# Canine and Feline Anesthesia and Co-Existing Disease

Lindsey B.C. Snyder and
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This book is dedicated to our animal friends and families–many of which have coexisting disease.

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# Preface

In human anesthesiology, textbooks concerning anesthetic techniques and protocols associated with specific disease states have been published since 1983 (*Stoelting's Anesthesia and Co-Existing Disease*, 1st edition – currently in its 6th edition). *Canine and Feline Anesthesia and Co-Existing Disease* is the first attempt to compile similar information about our veterinary species into one source and was developed to discuss the most current concepts in the fields of veterinary anesthesia and analgesia, especially with regards to patients with coexisting disease.

No longer is a successful anesthetic procedure defined as one which the patient simply recovers from unconsciousness. The goal of current anesthetic techniques should not just be to have the patient "wake up" from anesthesia but to have them recover from anesthesia with no lasting physiologic or psychologic detrimental effects from the anesthetic procedure itself. To this end, knowledge concerning veterinary anesthesia and analgesia is greatly expanding and continually developing as the breadth and depth of our profession are evolving with the emergence of species- and disease-specific research. Accordingly, changes in case management must also evolve as our cases become more challenging and our patient populations are growing older with more complex disease states. This book was developed to provide foundational information for veterinary professionals to build on (along with their own individual experiences and knowledge) in order to manage each veterinary case safely and successfully.

# 1 Cardiovascular disease

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## Introduction

The most critical function of the cardiovascular system is to circulate blood continuously, ensuring the adequate delivery of oxygen and survival of cells and tissues. The body can survive deprivation of food and water far longer than it can survive deprivation of oxygen and lack of perfusion; lack of oxygen delivery can trigger the complicated cascade that leads to temporary, permanent, or irreversible cell death.[1] As such, the simplest definition of cardiovascular disease is the decreased ability of this system to ensure adequate oxygen delivery for day-to-day survival.

Nearly all anesthetic drugs compromise cardiovascular function via a single or multiple mechanism(s) and can severely compromise oxygen delivery in patients with underlying cardiac disease.[2] Cardiovascular goals during anesthesia include maintenance of oxygen delivery and homeostasis when using drugs that knowingly disturb the system. However, this goal becomes complicated in patients with underlying cardiovascular disease and increasingly more difficult when severe pathology is present. In patients with significant cardiovascular disease, the optimization of oxygen delivery requires a complete understanding of the mechanisms underlying the pathology, as well as the anesthetic drugs, patient support, and monitoring tools available. The most difficult challenge when faced with these patients is how to balance the pathophysiology of disease against the effects of anesthetic drugs and to subsequently individualize an anesthetic plan that minimizes cardiovascular compromise.

It is difficult to predict all possible combinations of patient signalment and temperament, cardiovascular and comorbid conditions, clinicopathologic abnormalities, surgical procedures, and their effects on anesthetic drug choices. Thus, studies have tended to focus more on describing the specific cardiac disease or cardiac effects of specific anesthetics and less on their combinations. This approach leaves the difficult task of knowing how to choose the appropriate anesthetic plan for an individual patient. The goal of this chapter is to provide an overview of cardiovascular physiology and pathophysiology; anesthetic agents; and cardiovascular patient evaluation, monitoring, and support during anesthesia to help the clinician prepare anesthetic plans for patients with mild to significant cardiovascular disease.

## Cardiovascular physiology

### Tissue perfusion and oxygen delivery

The mathematical definition of oxygen delivery ($DO_2$) is the product of oxygen content ($CaO_2$, ml $O_2$ $dl^{-1}$ blood) and cardiac output (CO, l $min^{-1}$; Figure 1.1).[3]

Perfusion and the ability to deliver oxygen suffer either if the ability of the heart to eject blood (CO) is compromised or if the ability of the blood to carry oxygen ($CaO_2$) is reduced. Although decreases in $CaO_2$ significantly affect tissue oxygenation, the focus of this chapter is on treating reductions in CO associated with cardiac disease.

| Oxygen delivery "$DO_2$" | = | Cardiac output "CO" | X | Oxygen content "$CaO_2$" |
|---|---|---|---|---|
| ml $O_2$ delivered $min^{-1}$ | | Liters ejected/min | | ml $O_2$ carried/$dl^{-1}$ blood |

**Figure 1.1** Determinants of oxygen delivery.

*Canine and Feline Anesthesia and Co-Existing Disease*, First Edition. Edited by Lindsey B.C. Snyder and Rebecca A. Johnson.

## Blood pressure and cardiac output

It is critical to monitor blood pressure (BP) during anesthesia and is our best, yet indirect, clinical indicator of perfusion.[4] BP helps determine how anesthesia affects the patients' ability to perfuse their tissues and, as such, is used as a tool to treat perfusion abnormalities. However, BP is not a component of the mathematical definition of oxygen delivery: $DO_2 = CO \times CaO_2$. It is useful to assess BP in an attempt to estimate changes in CO, as CO is rarely measured in nonresearch patients.

Systolic arterial pressure (SAP) is the peak pressure measured in the artery or arteriole during one cardiac cycle and is due to a number of variables, including stroke volume (SV, volume ejected during one ventricular contraction), velocity of left ventricular ejection, arterial resistance, and the viscosity of blood.[5] Diastolic arterial pressure (DAP) is the lowest arterial pressure measured during the cycle and is affected by blood viscosity, arterial compliance, and length of the cardiac cycle.[5] Mean arterial pressure (MAP) is not the arithmetic mean pressure in the vessel and is always a calculated number. Various formulae exist to calculate MAP as follows: (1) MAP = DAP + 1/3 (SAP-DAP) or (2) MAP = (SAP + (2 × DAP)/3). In regards to perfusion, the most important of these values is MAP, as the time during the cardiac cycle spent at SAP is very short, whereas the time spent at MAP is much longer (Figure 1.2).[6]

## Mean arterial pressure and autoregulation

Autoregulation is the automatic adjustment of blood flow through a tissue regardless of the MAP driving blood through the tissue (Figure 1.3).[7] In other words, autoregulation is the unconscious adjustment of arterial and arteriolar smooth muscle tone to maintain a constant blood flow through a tissue across a wide range of pressures. Classically, this is thought to occur between MAPs of ~60–160 mmHg and is due to adaptive metabolic, myogenic, and neurogenic feedback mechanisms. Outside of this interval, tissue or organ blood flow is substantially altered, potentially resulting in reduced or nonuniform perfusion patterns.[8]

## Hypotension

MAPs <60 mmHg (or SAP <90 mmHg) have historically been considered the minimum recommended pressures in small animals associated with adequate tissue oxygen delivery.[9] However, a MAP of ~60 mmHg may not actually reflect adequate perfusion for a number of reasons. Firstly, studies investigating autoregulation are routinely performed in nonanesthetized patients.[10] Neurogenic mechanisms for autoregulation depend on sympathetic nervous system (SNS) input. Anesthetic agents depress both the conscious and unconscious (autonomic) nervous systems. Since the SNS tone is substantially reduced during

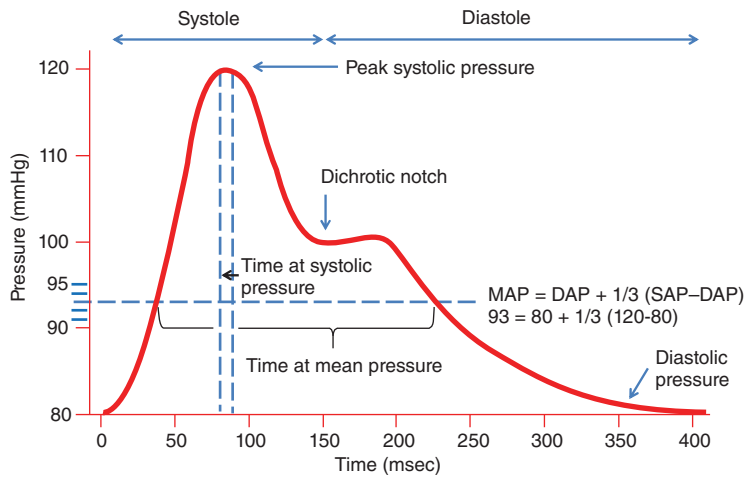


**Figure 1.2** Diagram of arterial pulse waveform. Mathematically, mean arterial pressure is 1/3 the difference between systolic arterial pressure and diastolic arterial pressure, added to the diastolic arterial pressure. Mean arterial pressure is considered the pressure of perfusion, as more time in the cardiac cycle is spent closer to mean arterial pressure as compared to systolic arterial pressure. Total cycle length is estimated at 400 ms for illustration and determined by the heart rate and other cardiovascular variables.

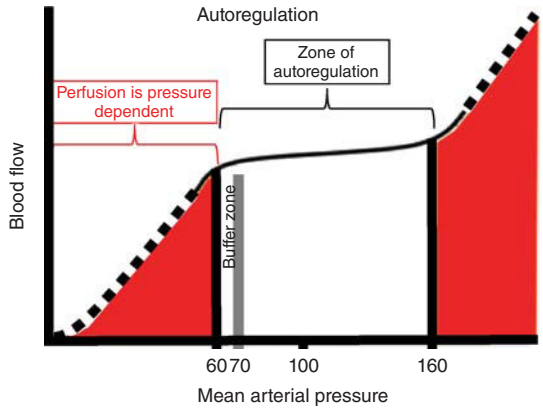


**Figure 1.3** Principles of autoregulation. Between mean arterial pressures (MAPs) of ~60 and 160 mmHg, blood flow through a tissue capillary bed is held constant by autoregulatory mechanisms. At MAP > ~160 mmHg and at MAP < ~60 mmHg, autoregulation of blood flow is lost and blood flow through capillary beds becomes pressure dependent; tissues are either overperfused or underperfused.

anesthesia, autoregulatory mechanisms are unavoidably depressed, either partially or completely, and autoregulation is impaired. Secondly, if a MAP of ~60 mmHg is considered the minimum acceptable BP and not hypotension, then treatments for patients assessed as hypotensive (i.e. MAP < 60 mmHg) will not begin until the patient is in a state wherein oxygen delivery is pressure dependent (i.e. to the left of thex autoregulatory curve). As all hypotensive therapies are not instantaneously acting, there is concern that the patient may become increasingly hypotensive before treatments are efficacious. Thus, a MAP of 70 mmHg (or SAP of 90 mmHg) should be considered the minimum acceptable BP to build in a buffer zone so that treatments for hypotension can be applied and take effect before tissue perfusion is severely compromised, taking into account both altered autoregulatory mechanisms and the time-dependent treatment effects.

## Relationship between mean arterial pressure (MAP) and cardiac output (CO)

When considering the relationship of measured BP to the definition of oxygen delivery, one must understand the components that derive a measured BP.[4] MAP is the product of CO (l $min^{-1}$) and SVR (dynes $s^{-1}$ $cm^{1}$). SVR is considered the degree of vasodilation (which reduces SVR) or vasoconstriction (which increases SVR) present in the systemic circulation. CO is the product of heart rate (HR, beats per minute) and SV (milliliter ejected per heart beat). SV is determined by preload (the venous return during diastole preloading the ventricle before contraction/ejection), afterload (the resistance that ventricular contraction must overcome in order to eject blood), and contractility (the force of contraction of ventricular muscle, independent of preload and afterload; Figure 1.4).

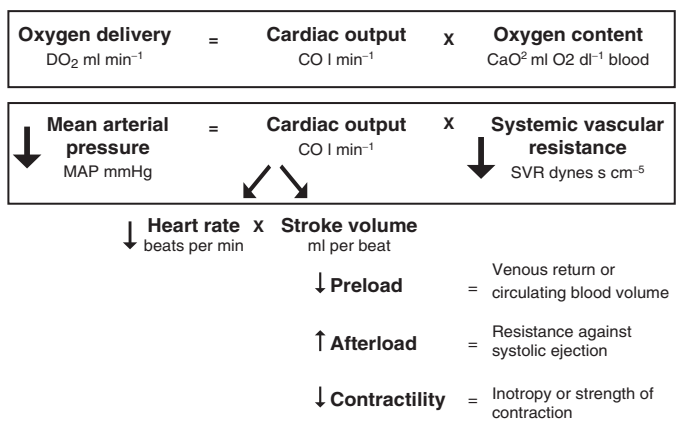


**Figure 1.4** Determinants of mean arterial blood pressure. Mean arterial blood pressure (MAP) is the product of cardiac output (CO), the volume of blood ejected by the heart per minute, and systemic vascular resistance (SVR), the degree of vasodilation (decreased SVR) or vasoconstriction (increased SVR). Note that MAP is not a component of oxygen delivery. Cardiac output is the product of heart rate (HR) and stroke volume (SV), the volume of blood ejected from the heart per cardiac cycle. Stroke volume is determined by the volume of blood returning to the heart during diastole (preload), the resistance to ejection of blood during systole (afterload), and the strength of cardiac muscle contraction (contractility).

Increases in SVR, SV, preload, and contractility tend to increase BP, whereas increases in afterload tend to decrease SV, CO, and MAP. As MAP is a mathematical product, one cannot definitively determine if a decrease or increase in MAP is due to a decrease or increase in CO or SVR, as CO or SVR are not routinely measured in clinical patients. Choosing which mechanism for hypotension or hypertension is driving the change in pressure for a given patient requires understanding the effects of anesthetic drugs, autonomic physiology, and underlying pathophysiology, among many others.

The four mechanisms based on this algorithm are vasodilation, bradycardia, decreases in cardiac preload, and a decrease in myocardial contractility (Figure 1.4). These mechanisms of hypotension each have a variety of causes (Figures 1.5–1.8) and treatments (Figure 1.9).

For example, vasodilation can be treated either with (1) fluid boluses (crystalloids or colloids) to expand vascular volume to "fill" the vasdodilated vasculature or with (2) administration of vasoconstricting agents to "offset" the vasodilation (phenylephrine, vasopressin, norepinephrine, etc.) or a positive inotrope that has vasoconstrictive properties (e.g. dopamine). Bradycardia can be treated with anticholinergics for sinus bradycardia or second-degree atrioventricular (AV) block or with other antiarrhythmics directed at specific bradyarrhythmias. Decreases in cardiac filling can be treated with blood volume expansion (crystalloid or colloid boluses) or with reversal or removal of

**Causes of bradycardia**

Normal for breed/species
Loss of SNS tone with anesthesia
Arrhythmias
Hypothermia
Opioids
Alpha-2 adrenergic agonists
Beta- receptor blocking agents
Excessive anesthetic depth
High vagal tone or stimulation
Hypoxia (fetus, neonate)
Low-dose anticholinergic
Oculocardiac reflex
Cushings reflex
Hyperkalemia

**Figure 1.5** Causes of bradycardia. Example causes of decreased heart rate either via disease, complications of a procedure (e.g. ocular or vagal stimulation), or via drug side effects. Note that this list can be used not only to treat a cause of bradycardia, but also to predict potential bradycardia from patient comorbidities or procedures for management before or during anesthesia.

**Causes of vasodilation**
(decreased SVR = vasodilation)

Propofol
Acepromazine
Inhalant anesthetics
Hypothermia
Cardiac drugs
- Nitroprusside
- Nitroglycerine
- Pimobendan
- Hydralazine
- ACE Inhibitors
- Amlodipine

Sepsis
Anaphylaxis
Hypercapnia

**Figure 1.6** Causes of vasodilation. Example causes of decreased systemic vascular resistance, either via disease, complications of a procedure (e.g. septic shock or anaphylaxis), or via drug side effects. Similar to Figure 1.5, this list can be used not only to treat a cause of vasodilation, but also to predict potential vasodilation from patient comorbidities or diseases for management before or during anesthesia.

**Causes of decreased preload**

Low total body water (geriatric)
Dehydration (vomiting, diarrhea)
3rd spacing (effusions, ascites, GI fluid)
Hemorrhage
Hypovolemia
Vascular occlusion
Vascular compression/obstruction
Positive pressure ventilation
Vasodilation

**Figure 1.7** Causes of decreased preload. Example causes of decreased venous return (i.e. preload), either via disease or via complications from drug side effects.

| Causes of decreased or poor contractility |
|---|
| Neonates/juveniles/pediatrics |
| Dilated cardiomyopathy |
| Seconday cardiomyopathies |
| Isoflurane (dose-dependent) |
| Propofol |
| Hypocalcemia |
| Acidosis |
| Beta-receptor blocking agents |
| Calcium channel blockers |

**Figure 1.8** Causes of decreased contractility. Example causes of decreased contractility (or inotropy) via either disease, complications of a disease, or drug side effects. Note that this list can be used not only to treat a cause of decreased contractility, but also to predict potential negative inotropy from patient comorbidities or anesthetics for management before or during anesthesia.

obstructions or compression of the cranial and caudal vena cava. Lastly, decreases in myocardial contractility from any cause can be treated either by reducing or removing the cause or with positive inotropes that improve contractility. As inhalant anesthetics are moderately to severely depressant on myocardial contractility (depending on dose), reducing the inhaled anesthetic dose (or requirement) of a patient can dramatically improve contractility and improve hypotension.

It is critical to understand that these mechanism(s) and cause(s) exist not only in the anesthetized patient, but also in the patient with preexisting disease or abnormal physiology (e.g. pregnancy, neonates, and geriatrics), and this approach can be used not only in the anesthetized patient, but also in planning ahead for hypotension and other complications under anesthesia.

## Preanesthetic patient assessment

The presence of underlying cardiac disease necessitates a more extensive patient evaluation compared to noncardiac patients.[11,12] For example, patient history should include previous cardiovascular diagnoses, medications, and any recent changes in medication dosages. Historical radiographs, electrocardiography (ECG), or Holter monitor evaluation, BP, and echocardiogram findings should be available. Patients with severe disease should be evaluated within 1–2 weeks of a planned anesthetic procedure.

Although a complete physical examination (PE) should be performed before and on the day of anesthesia, particular attention must be paid to the cardiovascular and respiratory systems. The localization and characterization of heart murmurs, changes in lung sounds, increases in respiratory rate and effort, poor color and refill of mucous membranes, presence

| Mechanism of hypotension | Treatment(s) |
|---|---|
| 1. Vasodilation | 1a. Fluid volume<br>1b. Vasoconstrictors or “pressors” |
| 2. Bradycardia | 2a. Anticholinergics<br>2b. Antiarrhythmics |
| 3. Decreased preload | 3. Volume bolus, decrease ventilation, relieve obstruction/compression |
| 4. Decreased contractility | 4a. Positive inotropes<br>4b. Reduce inspired inhalant levels |

**Figure 1.9** Causes of decreased contractility. Example causes of decreased contractility (or inotropy) via either disease, complications of a disease, or drug side effects. Note that this list can be used not only to treat a cause of decreased contractility, but also to predict potential negative inotropy from patient comorbidities or anesthetics for management before or during anesthesia.

of jugular pulsations, and pulse irregularities or pulse deficits are obvious indicators of potential heart disease or changes in the patient's cardiovascular status.

A minimum database for cardiac disease should include assessments of organ function with a blood chemistry panel, electrolytes, and a complete blood count. Patients with cardiac disease should have some combination of preanesthetic ECG, BP, thoracic radiographs, and echocardiogram depending on the type of cardiac disease. Ideally, the entire workup should be completed for patients presenting with a cardiac murmur or arrhythmia and previously unrecognized cardiac disease.

## Functional classification of cardiac disease

Previous texts[12] have established a functional classification of cardiac disease on the basis of clinical signs in an effort to help the clinician recognize which patients may have a higher risk of anesthetic complications and for whom anesthesia should be avoided until the patient has stabilized. If the presenting complaint necessitates anesthesia, this classification alerts the clinician to the high risk nature of such patients for owner counseling, preanesthesia preparation, requirements for intensive patient monitoring, and patient support.

*Classification I* comprises all nonclinical patients with preexisting cardiac disease and can be anesthetized with no preanesthetic stabilization. *Classification II* includes patients who have preexisting cardiac disease with mild to moderate clinical signs of disease at rest or with exercise. These patients require significant stabilization with medications and/or hospitalization before anesthesia can be considered. If anesthesia is required for a life-saving procedure, immediate stabilization with parenteral medications before anesthesia is required. Aggressive and invasive monitoring is necessary due to their fragile nature. *Classification III* includes patients with ongoing, fulminant heart failure. Anesthesia is contraindicated until the patient can be stabilized. If anesthesia cannot be avoided due to a life-saving procedure, they carry the highest risk of anesthetic complications, including severe debilitation, morbidity, and mortality.

The American Society of Anesthesiologists (ASA) patient status classification scheme has been adopted by The American College of Veterinary Anesthesia and Analgesia (ACVAA; Table 1.1). The ASA patient status value is not intended to be a risk assessment; however, the assignment of a patient status implies only the presence or absence of disease and that the clinician has evaluated the health status of the patient. The ASA physical status classification has limitations and can be seen as overly vague. However, the ASA does not (and presumably will not, as these definitions were accepted in 1963) expand on these limited definitions. Therefore, assignment of a particular patient to cardiac disease must be determined by the individual clinician (Table 1.1). Some authors have suggested

**Table 1.1** American Society of Anesthesiologists (ASA) physical status.

| Category | Physical status | Clinical examples |
|---|---|---|
| I | Normal healthy patients | No detectable disease; patients presenting with ovariohysterectomy or castration |
| II | Patients with mild systemic disease | Skin tumor, fracture without shock, uncomplicated hernia, cryptorchidectomy, localized infection, or compensated cardiac disease |
| III | Patients with severe systemic disease | Fever, dehydration, anemia, cachexia, or moderate hypovolemia |
| IV | Patients with severe systemic disease that is a constant threat to life | Uremia, toxemia, severe dehydration and hypovolemia, anemia, cardiac decompensation, emaciation, or high fever |
| V | Morbiund patients who are not expected to survive 24 h without operation | Extreme shock, dehydration, terminal malignancy or infection, severe trauma |

Patient physical status adapted from the American Society of Anesthesthesiologists (ASA) physical status classification. According to the ASA guidelines, "There is no additional information that will help you further define these categories." Clinical examples have been suggested by some authors, however, patient classification is highly variable and must be determined by the individual clinician.

classic types of patients who may be categorized into a particular physical status to help guide clinicians in the determination of ASA physical status.[13]

## Sedation versus general anesthesia

Sedation is defined as "a state characterized by central depression accompanied by drowsiness. The patient is generally unaware of his or her surroundings but is responsive to painful manipulation."[14] General anesthesia is defined as "drug-induced unconsciousness that is characterized by controlled but reversible depression of the central nervous system (CNS) and analgesia. In this state, the patient is not aroused by noxious stimulation. Sensory, motor, and autonomic reflexes are attenuated."[14] Surgical anesthesia is defined as "the state/plane of general anesthesia that provides unconsciousness, muscular relaxation, and analgesia sufficient for painless surgery."[14] The choice between whether to simply sedate a patient for a procedure or to use general anesthesia is important to consider. The degree of CNS depression that accompanies general anesthesia also depresses autonomic reflexes; the effects of which may be avoided if sedation is an acceptable alternative for the planned procedure. Systemic sedation that is appropriate for the patient's temperament and underlying disease in combination with locoregional analgesia may be sufficient for surgical analgesia in some cases.[15–17]

Although sedation may appear to be a universally safer option due to the avoidance of CNS/autonomic depression, sedatives such as alpha-2 agonists and phenothiazines may be absolutely contraindicated with some types of cardiac disease.[18,19] Moreover, the degree of cardiovascular depression may be difficult to treat (particularly in the case of the alpha-2 adrenergic agonists) without reversal of the sedative with an antagonist reversal agent. In some cases, however, sedation may be preferred. However, general anesthesia with cardiovascular-sparing protocols and appropriate patient monitoring and support may be the safer option. There is no single ideal anesthetic agent or anesthetic protocol for all cardiovascular disease; no one plan that will work for all patients and all procedures. All anesthetic plans should be individualized for the patient's heart disease and coexisting disease. Optimizing the plan requires a complete understanding of anesthetic drug effects and side effects, as well as pathophysiology of disease, so as to combine the two for optimal outcome.

## Anesthetic and analgesic agents

### Premedications

Premedication is an extremely important step in the process of anesthetizing patients because it provides sedation, analgesia, and a reduction in induction and maintenance drug doses.[2] As the induction and maintenance agents frequently are associated with severely depressant cardiovascular effects (albeit drug and dose-dependent in most cases), a large step toward cardiovascular stability can be provided with good to very good sedation with appropriate premedication.

#### Opioids

Opioids are a mainstay of premedication, induction, and maintenance of anesthesia in patients with cardiac disease, as they have minimal cardiovascular effects.[20–23] Bradycardia is the major consequence of opioid use, as opioids have minimal to no effects on cardiac contractility or vascular tone.[24,25] Bradycardia can be controlled with treatment or concomitant premedication with an anticholinergic (such as atropine or glycopyrrolate). Differences among the large number of opioids can cause confusion in choosing the most appropriate drug in this class. As a general rule, opioids will produce better sedation in the very young, old, or compromised patient as compared to a normally healthy adult patient. This rule is especially important consider in debilitated patients with cardiac disease.

#### Morphine

Morphine is considered the basis for comparison of all other opioids. Morphine is a full mu-opioid receptor agonist and provides very good sedation, often perceived as the best sedating choice in this class of drugs. It is also the most likely drug to induce vomiting.[26] It is absorbed rapidly when given intramuscularly,[27] and its duration is ~ 4–6 h. Intravenous (IV) administration is not recommended due to the risk of histamine release.[28] Morphine can, however, be delivered by low dose constant rate infusion and provides significant reductions in inhaled maintenance anesthetic requirements.

### Hydromorphone/oxymorphone

Hydromorphone and oxymorphone have very similar profiles in small animals.[29,30] Both are full mu-opioid agonists and provide excellent analgesia. They are moderately sedating opioids and are less likely to induce vomiting compared to morphine.[26] Hydromorphone (as well as morphine) may cause panting in clinical canine patients, which may be undesirable for sedated procedures. Hydromorphone has also been reported to cause postoperative hyperthermia in cats at standard clinical doses[31]; however, the clinical relevance of this is unclear.[32]

### Fentanyl

Fentanyl is a synthetic full mu-opioid agonist that is 80–100 times more potent than morphine, implying that an equally effective dose is 80–100 times less than morphine.[33] Owing to its short duration of action (~20–30 min after bolus administration), fentanyl is most useful for IV premedication, induction, or delivery by constant rate infusion.[23] Fentanyl is minimally sedating and is extremely unlikely to induce vomiting. It is very well suited for use as a sole anesthetic induction agent at high doses or as part of a multidrug induction protocol.

### Butorphanol

Butorphanol is a mixed opioid agonist–antagonist; it is an agonist at the kappa-opioid receptor and an antagonist at the mu-opioid receptor.[33] Therefore, it is only indicated for mild to weakly moderate pain, as it has analgesic effects only at the kappa receptor and is a very poor analgesic for moderate to severe pain.[34] Although it has a relatively short duration of action (~45–90 min), it can be sedative in small animals and thus used for conscious procedures either as a sole IV sedative or in combination with other more potent sedatives, depending on the requirements. Bradycardia is less likely to occur after butorphanol administration than with full mu-opioid agonists. It is very unlikely to cause vomiting and demonstrates a ceiling effect in which no further sedation or analgesia is seen beyond 0.8 mg $kg^{-1}$.[35,36]

### Buprenorphine

Buprenorphine is unique among the common opioids in that it is a partial mu-opioid receptor agonist. Buprenorphine has an extremely high affinity for the mu-opioid receptor, such that it outcompetes other opioids for receptor binding, but cannot evoke a full mu-opioid response.[37] Therefore, it is not equally efficacious compared to full mu-opioid agonists. It also demonstrates a ceiling effect in that doses above 0.04 mg $kg^{-1}$ do not provide additional analgesia or sedation. Owing to receptor binding, buprenorphine is poorly reversible to irreversible with opioid antagonists.[38] It is very unlikely to cause bradycardia and vomiting and is a relatively poor sedative.

## Phenothiazines

Acepromazine is a common premedication and is an excellent tranquilizer in small animals. However, it is a potent alpha-1 adrenergic receptor antagonist and will lead to peripheral vasodilation and hypotension[39] and so must be used with caution in patients with cardiac disease. Patients with stable, nonclinical disease may be able to compensate for the vasodilatory effects. However, it is prudent to avoid acepromazine in patients with moderate to severe cardiac disease. Hypotension may lead to a compensatory increase in HR, which can increase myocardial oxygen consumption. Acepromazine will protect the myocardium from epinephrine and barbiturate-induced arrhythmias.[40] However, this benefit must be weighed against the hypotensive effects.

## Anticholinergics

Atropine and glycopyrrolate are parasympatholytic anticholinergic agents used to increase HR associated with vagal-mediated sinus bradycardia and AV block. Atropine has a faster onset time (~1–2 min IV), shorter duration of action (~20–30 min IV), and is more likely to incite tachyarrhythmias.[41] Glycopyrrolate has a longer onset time (~2–4 min IV), longer duration of action (~1 h IV), and may be less likely to cause tachyarrhythmias.[41] Low doses of atropine and glycopyrrolate can initially precipitate second-degree AV block (see the following sections), which may require additional doses of anticholinergic for treatment.

## Benzodiazepines

Benzodiazepines (diazepam and midazolam) are good choices for sedation in patients with cardiac disease. They have minimal to no effects on HR, contractility, or vasomotor tone[42] and do not lead to hypotension across a wide range of doses (0.5–2.5 mg $kg^{-1}$ IV). Although respiratory rate decreases, arterial blood gas values do not change appreciably.[43] The major

disadvantage of benzodiazepines is that they are inconsistent sedatives in dogs[44,45] and may be poor sedatives in cats. For example, IV premedication doses can lead to dysphoria, excitement, ataxia, arousal, and, potentially, violent aggression.[44] Combinations of butorphanol and midazolam fail to provide sedation in healthy cats.[45] Although benzodiazepines decrease inhaled anesthetic requirements, this benefit can be achieved when they are combined with induction agents during the induction protocol as opposed to risking excitement when used as premedicants.[46,47]

### Alpha-2 adrenergic receptor agonists

Alpha-2 adrenergic receptor agonists (dexmedetomidine, medetomidine, xylazine, etc.) are usually contraindicated in patients with cardiac disease. Alpha-2 agonists cause intense peripheral vasoconstriction and decrease sympathetic outflow from the CNS. The severe increase in SVR leads to a marked increase in BP, a significant increase in myocardial afterload, and a baroreceptor-mediated reflex bradycardia. Some patients may demonstrate a period of vasodilation and arterial hypotension after the initial hypertension. This is commonly seen with xylazine in horses but appears to be less common with longer acting agents such as dexmedetomidine.[48,49] The initial baroreceptor-mediated bradycardia is exacerbated by a decrease in centrally mediated descending sympathetic tone. Alpha-2 adrenergic agonists can also produce AV blockade and ventricular escape cardiac rhythms. At sedative doses, these mechanisms will decrease CO by ~50–60%; dexmedetomidine at ≥5 mg $kg^{-1}$ IV will decrease CO by 50–60%,[50] and medetomidine at 20 mcg $kg^{-1}$ IV will decrease CO by at least 60%.[51] The increase in afterload from vasoconstriction, increase in left atrial pressure from centralization of blood volume, and decrease in CO are all mechanisms that can be detrimental to the function of a heart with underlying disease. Although alpha-2 adrenergic agonists are extremely reliable sedatives, the cardiovascular side effects are so profound that the depth of sedation may be better sacrificed in the interest of cardiovascular safety.

## Induction agents

### Propofol

The main advantage of propofol is a rapid onset (~15–20 s) and short duration of action (~6–10 min of anesthesia) from an IV bolus that allows intubation.[52] Its main mechanism of action[53] is stimulation of the gamma aminobutyric acid (GABA, the main inhibitory neurotransmitter in the CNS) receptor away from the binding site for other anesthetics such as thiopental.[54] Recoveries from propofol administration are extremely smooth. However, propofol is a significant dose-dependent vasodilator[55] and can precipitate significant hypotension at moderate to doses. While patients with mild cardiac disease may tolerate hypotension associated with propofol, those with more severe disease or in whom a decrease in SVR will worsen cardiac function should be cautiously induced with propofol.

### Dissociative anesthetics

Dissociative anesthetics such as ketamine and tiletamine produce anesthesia by interrupting neuronal transmission, thus "dissociating" the centers responsible for consciousness and unconsciousness from the peripheral ascending inputs. The cardiovascular effects of dissociative anesthetics result from stimulation of the SNS, increasing HR, contractility and MAP, with little change in SVR.[56] This leads to an increase in myocardial work and myocardial oxygen demand that is compensated for by increased CO and coronary blood flow.[57] The increase in oxygen demand in patients with cardiac disease may worsen cardiac function or arrhythmias. Thus, ketamine is contraindicated in hypertrophic cardiomyopathy (HCM) and is frequently avoided in any patient with other forms of cardiomyopathy and valvular cardiac disease (see the following section) or in those with severe systemic illness.[58]

### Etomidate

Etomidate is a nonopioid, nonbarbiturate sedative hypnotic drug that works similar to propofol and barbiturates in that it enhances inhibitory GABA effects.[59] Etomidate has the distinct advantage of having minimal to no cardiovascular depression because it does not significantly change HR, contractility, afterload, or venous return. However, it has several drawbacks. Etomidate has a very high osmolarity (~4800 mOsm $l^{-1}$) and can lead to osmolar shifting, causing possible phlebitis, pain at the injection site, red blood cell crenation, and potential hemolysis, as well as adrenocortical suppression.[60] Etomidate causes a reliable but relatively slow transition to unconsciousness when compared to propofol. Etomidate has poor muscle relaxation and

can stimulate myoclonus and so should be given with a benzodiazepine or fentanyl to facilitate a smooth induction period.[61]

### High dose opioids

High dose, full mu-agonist opioids such as fentanyl can be extremely effective in producing general anesthesia with uncomplicated placement of an endotracheal tube. High dose opioids have the disadvantage of moderate to severe respiratory depression and bradycardia; however, both are easily controlled with intubation and anticholinergics, respectively. Unfortunately, transition to unconsciousness with fentanyl appears somewhat less reliable and slower compared to propofol[62] or etomidate. Patients who are bright and energetic or are stimulated during the induction process by sound, touch, or pain may attempt to "override" the induction process, leading to poorer quality induction. In these cases, a rescue induction agent (typically propofol for speed of onset, but etomidate is an alternative option) can help push such a patient into unconsciousness. Quiet, dimly lit environments with little stimuli are ideal for fentanyl inductions, and fentanyl inductions usually work best in debilitated, older animals. Fentanyl should be given with a benzodiazepine for improved muscle relaxation.

## Anesthetic maintenance

### Inhaled anesthetics

Inhaled anesthetics are the most commonly chosen drugs for maintenance of anesthesia. Although injectable protocols for maintenance of anesthesia exist, referred to as total intravenous anesthesia (TIVA) protocols, inhaled anesthetics provide a number of unique advantages. Their pharmacokinetic properties allow for careful titration of and rapid changes in the anesthetic depth. The use of inhaled anesthetics requires the use of an anesthetic vaporizer that requires a carrier gas flow (nearly always 100% oxygen), which supports maximal arterial blood oxygenation. The need for an anesthesia machine requires endotracheal intubation, which allows for more accurate monitoring of ventilation. In addition, ventilation can also be supplemented and/or supported easily with this equipment. The ability to monitor expired gases such as carbon dioxide or exhaled anesthetic concentrations allows for more robust patient monitoring and support. Unfortunately, inhaled anesthetics depress cardiovascular function, leading to dose-dependent CO and BP depression.[63] This is due to a moderate to severe dose-dependent reduction in myocardial contractility (e.g. negative inotropy) and subsequent decreases in SV and CO.[63–66] Isoflurane also decreases SVR, resulting in vasodilation, which can incite or predispose to hypotension. Generally, these cardiovascular side effects are managed either by minimizing the dose administered or by counteracting the side effects with interventions aimed at providing cardiovascular support. Many strategies are available to allow reductions ("MAC reduction") in inhaled anesthetic drug requirements (MAC, the Minimum Alveolar Concentration of inhaled anesthetic required to produce lack of response to a supra-maximal noxious stimulus applied to a patient 50% of the time.) and include use of premedications, induction agents, bolus or infusion-dose analgesics or sedatives, and local/regional anesthesia techniques. The hypotensive effects of inhaled anesthetic agents can be treated by a variety of mechanisms, including optimizing HR and rhythm, judicious use of IV fluids (if not contraindicated by cardiovascular disease), and directly increasing contractility (to oppose the inhaled agents effects) with positive inotropic drugs (Figure 1.9).

## Anesthetic adjuncts

One major goal of adjunctive techniques or interventions is to increase cardiovascular stability and maximize CO and BP. In practice, this can be generally summarized as applying a technique that has fewer negative cardiovascular side effects as compared to patient management without that particular technique. As an example, fentanyl infusions have been shown to reduce the requirement for enflurane by as much as 65%[67] and of isoflurane by ~50%[68] at 0.8 mcg $kg^{-1}$ $min^{-1}$ and 0.3 mcg $kg^{-1}$ $min^{-1}$, respectively. As the primary cardiovascular effect of opioid infusions is bradycardia, which is easily corrected with anticholinergics, these infusions allow for decreased inspired concentrations of inhalant anesthetics, therefore reducing their cardiovascular compromise. This is presumed to be safer by providing improved cardiovascular stability than using higher doses of inhalants alone. Other anesthetic adjunctive techniques, including nonopioid analgesic constant rate infusions (lidocaine and ketamine) and local and regional anesthesia (epidurals, peripheral nerve blocks, and local anesthetics), are aimed at reducing the requirement of maintenance anesthetics in the interest of cardiovascular stability.

### Local and regional analgesia

Local anesthetics have the distinct advantage of blocking peripheral nerve function as compared to other analgesic drug classes (opioids and nonsteroidal anti-inflammatory drugs) that modulate the ascending nociceptive stimuli. If nociceptive stimuli are completely prevented from reaching higher centers, then, theoretically, a patient would not require general anesthesia despite painful surgery or procedures. Although this may not be practical for most procedures, it reminds us that local anesthetics are a powerful tool in preventing pain perception or ascending nociceptive information. For patients under general anesthesia, local or regional anesthesia/analgesia can dramatically reduce systemic and inhaled anesthetic drug requirements. As local anesthetics have minimal cardiovascular compromise at appropriate doses, the reduction in systemic and inhaled anesthetic drug levels can minimize or prevent the cardiovascular depressant effects of these anesthetics, leading to a more stable patient. Numerous studies have shown a significant reduction in inhaled anesthetic requirements due to application of regional anesthesia techniques, including the infraorbital nerve block,[69] and methadone epidurals[70] in dogs and morphine/buprenorphine epidurals in cats[71] as some examples. However, the use of local anesthetic administration can result in toxicity. For example, the dose of IV lidocaine at which canine patients will develop neurologic signs of toxicity (i.e. convulsions) is ~22 mg $kg^{-1}$.[72] Bupivacaine has a much lower therapeutic index in that cardiotoxicity and neurotoxicity can be seen at doses between 4.3[73] and 5.0 mg $kg^{-1}$ IV.[72]

### Systemic analgesic infusions

Much like local and regional techniques, systemically delivered analgesic infusions have the significant potential for reducing inhaled anesthetic drug doses and responsiveness to painful stimuli. Provided that the cardiovascular side effects of the infusion(s) are not more detrimental than the inhaled anesthetic, the reduction in inhaled anesthetic dose can lead to a significant reduction in their negative consequences, such as negative inotropy, vasodilation, and respiratory depression, thus improving cardiovascular performance. As mentioned previously, IV opioid infusions are particularly beneficial in reducing inhaled anesthetic requirements (Tables 1.2 and 1.3)[67,68] and are extremely safe cardiovascular infusions, as their primary side effect is bradycardia, easily treatable with anticholinergics. In horses anesthetized with sevoflurane, an IV lidocaine bolus of 1.3 mg $kg^{-1}$ followed by a constant rate infusion of 50 mcg $kg^{-1}$ $min^{-1}$ reduced sevoflurane MAC by 27%.[88] IV lidocaine infusions have been studied in dogs repeatedly for their benefits in reducing both isoflurane and sevoflurane inhaled anesthetic concentrations. Lidocaine at 50 mcg $kg^{-1}$ $min^{-1}$ reduced isoflurane MAC by 29%[78] and sevoflurane MAC by 22.6%[82] in dogs (Tables 1.2 and 1.3). In another study, at 50 and 200 mcg $kg^{-1}$ $min^{-1}$, no changes in cardiovascular parameters due to lidocaine infusion(s) were identified, and inhalant MAC was reduced by 15% and 37%, respectively.[83]

## Inotropes and vasopressors

Terminology and definitions confuse these classifications of drugs not only because the term vasopressor is used to refer to both drug categories, but also because of overlapping drug effects. Inotropes or positive inotropes are drugs that increase myocardial contractility by actions on the beta-1 adrenergic receptors and are used to improve SV, CO, and BP. By way of their actions on the beta-1 receptor, these drugs also tend to increase HR, although this is not a positive inotropic effect by the strictest definition. This would be a positive chronotropic effect. Regardless, these drugs are typically referred to by their positive effects on myocardial contractility. Vasopressor is the term applied to drugs that increase SVR via alpha-1 adrenergic or other receptor-mediated vasoconstriction, which subsequently increases BP. Although some drugs are uniquely suited to a single category, an inotrope or a vasopressor, many pharmacologic agents affect multiple receptor subtypes or have varying effects on the basis of dose, and their use in the spectrum of cardiovascular disease is difficult to generalize (Table 1.4).

### Dopamine and dobutamine

Dopamine and dobutamine are some of the most commonly applied positive inotropic drugs during veterinary anesthesia. As inhaled anesthetic agents cause dose-dependent suppression of myocardial contractility and decrease SVR, these drugs are highly efficacious for the management of inhaled anesthetic-mediated hypotension.

Dopamine is the immediate precursor to norepinephrine and has dose-dependent positive inotropic

**Table 1.2** MAC-reducing effects of common infusions in dogs.

| Study | Loading dose (mg kg$^{-1}$) | Infusion dose (mcg kg$^{-1}$ min$^{-1}$) | Inhalant | MAC (%) | MAC reduction | MAC-reduction percentage |
|---|---|---|---|---|---|---|
| ***Fentanyl*** | | | | | | |
| Ueyama 2009[74] | 0.005 | 0.15 | Isoflurane | 1.42 ± 0.08 | 0.93 ± 0.04 | −35% |
| Hellyer 2001[68] | 0.01 | 0.3 | Isoflurane | 1.8 ± 0.21 | 0.85 ± 0.14 | −53% |
| ***Remifentanil*** | | | | | | |
| Michelsen 1996[75] | None | 1.0 | Enflurane | 2.1 ± 0.2 | NR | −63 ± 10.4% |
| Allweiler 2007[76] | None | 0.1 | Isoflurane | 1.28 ± 0.13 | 0.78 ± 0.17 | −40% |
| | None | 0.25 | Isoflurane | 1.28 ± 0.13 | 0.65 ± 0.16 | −50% |
| Monteiro 2010[77] | None | 0.15 | Isoflurane | 1.24 ± 0.18 | NR | −43 ± 10% |
| | None | 0.3 | Isoflurane | 1.24 ± 0.18 | NR | −59 ± 10% |
| | None | 0.6 | Isoflurane | 1.24 ± 0.18 | NR | −66 ± 9% |
| | None | 0.9 | Isoflurane | 1.24 ± 0.18 | NR | −71 ± 9% |
| ***Ketamine*** | | | | | | |
| Muir 2003[78] | None | 10 | Isoflurane | 1.38 ± 0.08 | 1.03 ± 0.07 | −25% |
| Queiroz-Castro 2006[a, 79] | 1.0 | 25 | Isoflurane | 1.06 ± 0.02 | 0.73 ± 0.04 | −28.7 ± 3.7% |
| Doherty 2007[a, 80] | 1.5 | 50 | Isoflurane | 1.11 ± 0.05 | 0.56 ± 0.04 | −49.6% |
| Love 2011[b, 81] | 0.5 | 6.25 | Sevoflurane | 2.62 ± 0.21 | 2.61 ± 0.22 | −0.4 ± 4% |
| | 1.0 | 12.5 | Sevoflurane | 2.62 ± 0.21 | 2.06 ± 0.22 | −22 ± 4% |
| | 2.0 | 25 | Sevoflurane | 2.91 ± 0.21 | 2.64 ± 0.22 | −12 ± 4% |
| | 3.0 | 50 | Sevoflurane | 2.91 ± 0.21 | 2.44 ± 0.22 | −18 ± 4% |
| Wilson 2008[82] | 3.0 | 50 | Sevoflurane | 1.9 ± 0.2 | 1.1 ± 0.1 | −40 ± 3.5% |
| | 3.0 | 100 | Sevoflurane | 1.7 ± 0.2 | 0.9 ± 0.1 | −44.7 ± 3.5% |
| ***Lidocaine*** | | | | | | |
| Muir 2003[78] | None | 50 | Isoflurane | 1.38 ± 0.08 | 0.97 ± 0.04 | −29% |
| Doherty 2007[80] | 2.5 | 100 | Isoflurane | 1.20 ± 0.04 | 0.98 ± 0.06 | −18.3% |
| Matsubara 2009[83] | 2.0 | 50 | Sevoflurane | 2.30 ± 0.19 | 1.95 ± 0.23 | −15% |
| | 2.0 | 200 | Sevoflurane | 2.30 ± 0.19 | 1.45 ± 0.21 | −37% |
| Wilson 2008[82] | 2.0 | 50 | Sevoflurane | 2.0 ± 0.2 | 1.6 ± 0.1 | −22.6 ± 3.6% |
| | 2.0 | 100 | Sevoflurane | 1.8 ± 0.2 | 1.3 ± 0.1 | −29 ± 3.5% |
| | 2.0 | 200 | Sevoflurane | 2.0 ± 0.2 | 1.1 ± 0.1 | −39.6 ± 3.5% |
| Valverde 2004[84] | 2.0 | 50 | Isoflurane | 1.34 ± 0.11 | 1.09 ± 0.13 | −18.7% |
| | 2.0 | 200 | Isoflurane | 1.34 ± 0.11 | 0.76 ± 0.1 | −43.3% |

[a]Study performed in goats.

[b]Study evaluated MAC-BAR, the physiologic response to stimulus rather than evaluating for purposeful movement.

effects. The infusion dose of dopamine for beta-1 adrenergic-mediated increases in myocardial contractility, and HR is 5–10 mcg kg$^{-1}$ min$^{-1}$. The recommended dose for improvement of CO is 7 mcg kg$^{-1}$ min$^{-1}$.[89] Dopamine actions are unique, as doses above 10 mcg kg$^{-1}$ min$^{-1}$ likely stimulate alpha-1 receptors, leading to an increase in SVR. Although this can also be beneficial for BP, it must be noted that this increase in myocardial afterload may, in fact, worsen cardiovascular performance and may be contraindicated in patients with specific cardiovascular diseases such as dilated cardiomyopathy (DCM), HCM, and regurgitant valvular disease. Specific comments regarding positive inotropes and vasopressors are included in the sections of this chapter for each type of heart disease.

Dobutamine is a nonspecific beta-adrenergic agonist, activating both beta-1 and beta-2 receptors and will increase both HR and contractility similar to the beta-1 effects of dopamine. The general recommended dose for dobutamine to achieve beta-1 effects is 1–5 mcg kg$^{-1}$ min$^{-1}$. However, it is critically important to understand that dobutamine is also a beta-2 agonist and will induce a decrease in SVR, leading to beta-2-mediated vasodilation. Research has shown that

**Table 1.3** MAC-reducing effects of common infusions in cats.

| Study | Drug | Loading dose (mg kg$^{-1}$) | Infusion dose (mcg kg$^{-1}$ min$^{-1}$) | Inhalant | MAC (%) | MAC reduction | MAC-reduction percentage |
|---|---|---|---|---|---|---|---|
| Brosnan 2009[85] | Remifentanil | none | 0.0625–16 | Isoflurane | 1.94 ± 0.8 | None | None |
| | | | 0.125 | Isoflurane | | | |
| Ferreira 2009[86] | Remifentanil | | 0.25 | Isoflurane | 1.66 ± 0.08 | 1.27 ± 0.13 | −23 ± 7.9 |
| | | | 0.5 | Isoflurane | 1.66 ± 0.08 | 1.16 ± 0.17 | −29.8 ± 8.3 |
| | | | 1.0 | Isoflurane | 1.66 ± 0.08 | 1.22 ± 0.15 | −26 ± 9.4 |
| Pascoe 2007[87] | Ketamine | 2.0 | 23 | Isoflurane | 1.51 ± 0.23 | 0.84 ± 0.33 | −45 ± 17 |
| | | 2.0 | 46 | Isoflurane | 1.51 ± 0.23 | 0.57 ± 0.35 | −63 ± 18 |
| | | 16.0 | 115 | Isoflurane | 1.51 ± 0.23 | 0.41 ± 0.35 | −75 ± 17 |

**Table 1.4** Inotropes and vasopressors.

| | Sympathetic nervous system receptor activation | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Alpha-1** | **Alpha-2** | **Beta-1** | **Beta-2** | **Dopamine** | **Vasopressin** | **Dose** |
| Effect | Vasoconstriction | Vasoconstriction Bradycardia | Inotropic Chronotropic | Vasodilation Bronchodilation | D1 receptor | Vasoconstriction | |
| Drug | | | | | | | |
| Dopamine | +++ High dose | + | +++ Low dose | + Low dose | +++ | – | Inf: Low 5–10 mcg kg$^{-1}$ min$^{-1}$ Inf: High 10–20 mcg kg$^{-1}$ min$^{-1}$ |
| Dobutamine | – | – | +++ | ++ | – | – | Inf: 1–10 mcg kg$^{-1}$ min$^{-1}$ |
| Epinephrine | +++ | +++ | ++ | ++ | – | – | Bolus: 0.01–0.1 mg kg$^{-1}$ IV Inf: 0.01–1.0 mcg kg$^{-1}$ min$^{-1}$ |
| Ephedrine | + | + | + | + | – | – | Bolus: 0.03–0.1 mg kg$^{-1}$ IV |
| Isoproteronol | – | – | +++ | +++ | – | – | Inf: 0.01–0.1 mcg kg$^{-1}$ min$^{-1}$ |
| Norepinephrine | +++ | – | ++ | +++ | – | – | Inf: 0.05–2.0 mcg kg$^{-1}$ min$^{-1}$ |
| Phenylephrine | +++ | – | – | – | – | – | B: 1–5 mcg kg$^{-1}$ IV Inf: 0.5–3 mcg kg$^{-1}$ min$^{-1}$ |
| Vasopressin | – | – | – | – | – | V1 +++ | Bolus: 0.1–0.6 units kg$^{-1}$ IV Inf: 1–4 mU kg$^{-1}$ min$^{-1}$ (dogs) |

the increase in HR and contractility may be offset by the vasodilation, and no change in BP may occur.[89]

### Epinephrine

Epinephrine is a potent alpha- and beta-adrenergic agonist leading to intense peripheral vasoconstriction and increases in HR and contractility, respectively. It dramatically increases myocardial oxygen demand and is highly arrhythmogenic. It is not possible to discriminate effects (i.e. beta effects without alpha effects) with epinephrine and is therefore a poor choice for an inotropic agent, particularly due to the increase in oxygen demand and potential for arrhythmias. Epinephrine should be limited to use for cardiopulmonary cerebral resuscitation (CPCR).

### Ephedrine

Ephedrine is similar to an alpha- and beta-adrenergic receptor agonist. However, its effects appear weaker at these receptors. Ephedrine is one of the few inotropic/vasopressive agents that can be delivered by bolus injection, rather than by infusion, as the half-life for activity is longer than most other drugs in this category. Ephedrine bolus leads to increases in BP, cardiac index, and oxygen delivery in dogs anesthetized with isoflurane.[90] Onset time is very rapid, and the duration of the increase in BP is shorter than that of the increase in CO. As such, it is useful for short-term treatment of hypotension.

### Vasopressin

Vasopressin is the hormone arginine vasopressin (antidiuretic hormone, ADH) and acts as a vasopressor because it increases SVR and has no effect on HR or myocardial contractility. However, it is unique, as it does not affect adrenergic receptors but works through the vasopressin-1 receptor located on peripheral vasculature. Actions at the vasopressin-2 receptor are responsible for the renal effects.[91] Since it is not a catecholamine, it is not arrhythmogenic, a significant advantage over other drugs in this group. Vasopressin has been shown to be comparable to phenylephrine for the treatment of hypotension in an endotoxic shock model.[92] Although intentionally titrated vasoconstriction can be an important strategy for treatment of refractory hypotension, high levels of SVR may potentially decrease CO and oxygen delivery, particularly in patients with heart disease for which increases in afterload can be severely detrimental such as with DCM.

### Phenylephrine and norepinephrine

Phenylephrine and norepinephrine function as vasopressors. Phenylephrine is a pure alpha-1 adrenergic agonist that leads to dose-dependent vasoconstriction and carries the benefits and drawbacks of pure vasoconstrictors as described previously. Norepinephrine has both alpha-1 and beta-adrenergic effects, although in practice, the vasoconstrictive effects predominate, as the beta-2 and beta-1 effects are variable and typically overwhelmed by the alpha response.

## Patient monitoring and support

### Fluid therapy

As decreases in cardiovascular function and CO are inevitable effects of anesthetics, fluid therapy is recommended to maintain perfusion despite cardiovascular depression. Patients who present with compensated heart disease with no overt clinical signs may tolerate typical rates of IV fluids (balanced electrolyte solutions) during anesthesia, usually in the range of 5–10 ml $kg^{-1}$ $h^{-1}$. Patients with evidence of non-compensated cardiovascular disease are often at risk for failure due to poor cardiac function or the cascade of neurohormonal mechanisms that lead to an increase in circulating blood volume such as activation of the renin–aldosterone–angiotensin system (RAAS) and increased secretion of ADH. Patients with a history of heart failure and/or chronic volume overload (mitral, tricuspid, and aortic valve insufficiency, left to right shunts including patent ductus arteriosus [PDA], and ventricular septal defects [VSD]) may be less likely to tolerate high fluid rates during surgery, and so lower fluid rates should be used in these patients. Usually, 3–5 ml $kg^{-1}$ $h^{-1}$ is sufficient to meet maintenance metabolic needs but not increase blood volume and risk precipitating heart failure. Furosemide may be used for its' diuretic effects if the patient receives an excessive amount of IV crystalloid solution. The administration of synthetic colloids (i.e. hetastarch, pentastarch, dextran, and hemoglobin glutamer-200) is often avoided in patients with cardiac disease, as colloids can expand plasma volume for significantly longer periods and are more difficult to treat/reverse with diuretics.

## Patient preoxygenation

Most anesthetic premedications and induction agents are respiratory depressants; the most significant of which are the opioids, propofol, and inhaled anesthetic agents. Ketamine is considered a mild respiratory depressant[93] as is etomidate.[94] The onset of respiratory depression can be very rapid, which can result in patient desaturation and cyanosis. The alveolar partial pressure of oxygen ($PAO_2$) is predicted by the alveolar gas equation (Table 1.5).

The following equations are examples of differing conditions during normoxia

$$PAO_2 = FIO_2(Patm - PH_2O) - PaCO_2/0.8 \quad (1.1)$$

$$PAO_2 = 0.21(760 - 47) - 40/0.8 = 99.7 \text{ mmHg} \quad (1.2)$$

$$PAO_2 = 0.21(760 - 47) - 60/0.8 = 74.7 \text{ mmHg} \quad (1.3)$$

and hypoxemia

$$PAO_2 = 0.40(760 - 47) - 40/0.8 = 235.2 \text{ mmHg} \quad (1.4)$$

$$PAO_2 = 0.40(760 - 47) - 60/0.8 = 210.2 \text{ mmHg} \quad (1.5)$$

where $FIO_2$ refers to the inspired fraction of oxygen, Patm is the atmospheric pressure, $PH_2O$ is the partial pressure of water vapor, and $PaCO_2$ is the arterial partial pressure of carbon dioxide. In animals that are ventilating normally with a normal $PaCO_2$ of 40 mmHg (Table 1.5, Equation 1.2), the $PAO_2$ is ~100 mmHg. This pressure represents the alveolar pressure of oxygen able to diffuse down the oxygen concentration gradient into pulmonary arterial blood.

As patients hypoventilate, $PaCO_2$ increases which decreases the alveolar partial pressure of oxygen ($PAO_2$) and can result in clinical hypoxemia when $PAO_2$ is less than 80 mmHg. (Table 1.5, Equation 1.3). When providing supplemental oxygen via a tight-fitting facemask (estimated to be a $FIO_2$ of ~40%), $PAO_2$ is subsequently increased (Table 1.5, Equation 1.4), which can blunt the effects of hypoxemia due to hypoventilation (Table 1.5, Equation 1.5). Thus, preoxygenation can be a critical component of maintaining a high $PAO_2$ and arterial partial pressure of oxygen ($PaO_2$) subsequent to anesthetic-related respiratory depression from premedication through the induction process. The general recommendation is to provide oxygen via a tight-fitting facemask for a minimum of 3 min before induction of anesthesia.[96] This can be easily performed as monitoring equipment (ECG, noninvasive BP, capnometry) is placed before induction of anesthesia.

## Blood pressure (BP)

BP is the most reliable clinical indicator of perfusion, despite the disadvantage that it is not a clear indicator of CO. BP is a standard monitoring tool for all anesthetized patients and has been the standard of care in humans for decades. The ACVAA Guidelines on Small Animal

**Table 1.5** Alveolar to arterial pressure gradient calculations.

| $ETCO_2$ | 30 | | 40 | | 60 | | 80 | |
|---|---|---|---|---|---|---|---|---|
| $FIO_2$ (%) | $PAO_2$ | $PaO_2$ | $PAO_2$ | $PaO_2$ | $PAO_2$ | $PaO_2$ | $PAO_2$ | $PaO_2$ |
| 21 | 112.2 | 101.0 | 99.7[B] | 89.8 | 74.7[C] | 67.3 | 49.7 | 44.8 |
| 30 | 176.4 | 158.8 | 163.9 | 147.5 | 138.9 | 125.0 | 113.9 | 102.5 |
| 40 | 247.7 | 222.9 | 235.2[D] | 211.7 | 210.2[E] | 189.2 | 185.2 | 166.7 |
| 100 | 675.5 | 608.0 | 663.0 | 596.7 | 638.0 | 574.2 | 613.0 | 551.7 |

Alveolar partial pressure of oxygen is calculated using the alveolar gas equation: $PAO_2 = FIO_2(Patm\text{-}PH_2O) - PaCO_2/0.8$. $PAO_2$ is the alveolar partial pressure of oxygen. $FIO_2$ is the fraction of inspired oxygen. Patm is atmospheric barometric pressure specific to the elevation at or above sea level. $PH_2O$ is the vapor pressure of water, which varies by patient temperature but is generally assumed to be ~47 mmHg. $PaCO_2$ is the patient's current arterial partial pressure of carbon dioxide. $PaCO_2$ divided by 0.8 is the respiratory quotient, which is the ratio of $CO_2$ molecules produced for $O_2$ molecules consumed by the body. The normal alveolar to arterial gradient is <10–15% [95] in room air and the $PaO_2$ values calculated in Table 1.5 assume a 10% difference between alveolar and arterial partial pressures. $PaO_2$ is a measured variable with arterial blood gases; the numbers in the above table are calculated as expected normal values on the basis of $FIO_2$ and $PaCO_2$ and measurement at sea level (Patm = 760 mmHg). Refer to equations for values 1.2–1.5 in the body of the text.

Patient Monitoring[97] recommends measurement of BP as part of basic patient care during anesthesia.

Methods of arterial BP monitoring include both noninvasive and invasive techniques. Noninvasive methods include automated oscillometric BP monitors and manual Doppler BP monitoring. Invasive (direct) BP monitoring involves the placement of a catheter into a peripheral artery with connection to a fluid-filled pressure transducer system. All of the techniques have both advantages and disadvantages regarding the ease of placement, frequency and speed of measurement, invasive nature, and technical skill required for measurement and accuracy of measurement.

Invasive BP monitoring is the gold standard with which all other forms of BP measurement are compared.[98–104] Direct monitoring is the most accurate BP measurement and offers additional benefits of being a continuous, second-to-second monitor for SAP, DAP, and MAP. Acute changes in the patient's hemodynamic status can be appreciated rapidly, and alterations in the arterial pressure waveform can also provide information about patient status. The placement of an indwelling arterial catheter also allows for sampling of arterial blood for arterial blood gas analysis. Invasive BP monitoring has significant drawbacks, including the skill in placing arterial catheters in potentially hypotensive, unstable patients, the requirement for a multiparameter patient monitor with the capability of connecting to a fluid filled transducer system, the understanding of what causes error in the transducer system, and troubleshooting of the system.[105] There is the risk of hemorrhage and reduced perfusion to tissues distal to the catheterization site. Despite these complexities, invasive pressure management is a mainstay of advanced cardiovascular monitoring.

Noninvasive pressure monitoring includes both automated oscillometric monitoring devices and Doppler ultrasound BP monitoring.[106] Oscillometric monitoring devices use the principle of oscillometry to determine BP. An automated cuff is inflated above SAP, occluding arterial blood flow. As cuff pressure is reduced, the arterial pulse begins to generate oscillations in the arterial wall that are transmitted to the cuff. These oscillations increase and then decrease in amplitude as cuff pressure is reduced, and eventually the oscillations are eliminated as blood flow becomes laminar. Although technology and calculation algorithms vary between oscillometric devices, generally, the onset of oscillations is considered SAP, maximal oscillation amplitude MAP, and the cessation of oscillations DAP. Oscillometry carries the advantage of automation and ease of use. However, oscillometric devices are fraught with error, including inappropriate cuff size. The cuff should be ~40% of limb circumference; overlarge cuffs lead to inappropriately low readings, and inappropriately small ones lead to falsely elevated measurements.[106] Other issues with oscillometric devices include motion artifacts and interference from high HRs or potentially cardiac arrhythmias.[107] Studies comparing the accuracy of oscillometric BP cuffs to direct BPs found limited agreement with MAP and DAP in anesthetized dogs: "67% and 95% of readings were within 10 and 20 mmHg of invasive pressure values, respectively."[106] Another study found poor correlation such that a 25-mmHg bias was identified between invasive and oscillometric pressure in anesthetized cats.[99] Oscillometric BP devices also carry the disadvantages of slow performance compared to continuous arterial catheters.

Doppler BP devices use a BP cuff that is manually inflated over SAP. A Doppler crystal is placed over a peripheral artery, and blood flow is audibly demonstrated with appropriate Doppler sound. Inflation of the cuff occludes flow, and the Doppler signal is lost. As the cuff is manually deflated, blood flow begins to pass through the cuff and is again audible via the Doppler crystal. This is generally interpreted as the peak pressure or SAP. Doppler BPs can be checked manually more frequently than oscillometric devices, carry more confidence for the user in that the user can hear blood flow, provide an audible signal to the anesthetist that there is a blood flow (a comforting sound for many anesthetists), and are simple to use. A Doppler crystal placed over a peripheral artery provides the anesthetist with an audible signal for blood flow, which can be a strong comfort for those moments the anesthetist's attention cannot be on the patient or patient monitor. The placement of Doppler crystal also allows for a second assessment of BP should an arterial catheter fail. Disadvantages of Doppler crystals include that they are somewhat fragile, require more skill for placement to obtain an audible signal, and show inability to accurately predict SAP. For example, multiple studies have evaluated the assessment of SAP with Doppler noninvasive measurement compared to invasive BPs.[98,99,103] In cats, poor agreement was found between invasive SAP and Doppler BPs, such that the Doppler underestimated SAP by ~14 mmHg[98,99,103]

to −25 mmHg.[98,99] Doppler BP measurement was not recommended when accuracy is desired. However, in rabbits, direct SAP was found to have good agreement with Doppler BP.[107]

## Electrocardiography (ECG)

ECG monitoring allows analysis of the cardiac rhythm. Understanding the components of the cardiac rhythm and how it relates to mechanical function of the heart allows the anesthetist to analyze the rhythm for changes that would indicate abnormalities. These abnormalities might imply that there is asynchrony in mechanical function of the heart and further correction may improve mechanical function, CO, and perfusion. Although ECG monitoring does not "prove the patient is alive," as there can be dissociation between the electrical and mechanical activity (termed pulseless electrical activity, PEA), it is nevertheless a basic requirement of patient monitoring during anesthesia.

## Pulse oximetry

Saturation of hemoglobin in arterial blood is an important component of the $CaO_2$ equation. As the vast majority of oxygen is carried in the hemoglobin molecule, the degree to which hemoglobin is saturated with oxygenated blood is a critical variable in oxygen delivery. The pulse oximeter is a simple tool that measures the oxygen saturation of arterial blood ($SpO_2$). Hemoglobin saturation of ~90% is correlated with a $PaO_2$ of ~60 mmHg, well into the hypoxic range. Therefore, a hemoglobin saturation of >93–94% is required to ensure normoxia. Many variables can interfere with the ability of the pulse oximeter to provide an accurate arterial saturation (Table 1.6).[110]

**Table 1.6** Pulse oximetry: sources of error.[138–140]

| |
|---|
| Motion artifact |
| Thickness of tissue |
| Tissue hypoperfusion/hypotension |
| Vasoconstriction |
| Hypothermia |
| Tissue pigment |
| Met-hemoglobinemia (tends to 85% when Met-Hgb ~30%) |
| Carboxy-hemoglobinemia (tends toward 90%) |
| Intravenous dye injections (indocyanine green, methylene blue) |
| Ambient light at 660, 920 nm wavelength(s) |
| Severe anemia (hemoglobin < 5 g $dl^{-1}$) |

## Core body temperature

Hypothermia has varying effects on the basis of the degree of body temperature loss.[2] Essentially, all patients will become hypothermic to some degree due to the effects of premedication and induction of anesthesia, unless active heat support is provided. Causes of hypothermia include, but are not limited to, opioid, phenothiazine and alpha-2 adrenergic-mediated changes in thermoregulation, high surface area to body mass ratio, high cold-compressed oxygen flow rates, open body cavities, cold surfaces, room temperature IV fluids, cold scrub solutions, and body cavity lavage (especially orogastric lavage with fluids below body temperature). Mechanisms for heat loss include evaporation, conduction, and convection and heat loss from respiration and radiant heat loss.[111] Anesthetized patients also have decreased heat production due to central depression and inability to shiver in response to hypothermia. It is far easier to prevent than it is to treat hypothermia, as the peripheral vasoconstrictive effects of hypothermia make external rewarming difficult and inefficient. Consideration of the aforementioned variables for an individual patient or procedure will help the anesthetist generate a robust heat loss prevention or rewarming plan.

The physiologic effects of hypothermia vary with severity and include catecholamine release, decreased cerebral metabolic rate of oxygen consumption and intracranial pressure, and altered electroencephalogram and arterial blood gas results.[112,113] At moderate levels, hypothermia decreases inhalant requirements, reduces concentrations of inhalant required to produce apnea, decreases CO and BP, and increases SVR. In addition, moderate hypothermia results in bradycardia, prolonged clotting times, decreased drug metabolism, prolonged nerve conduction and muscle contraction, and a right shift of the oxygen–hemoglobin dissociation curve (which favors hemoglobin loading).[114] With these profound physiologic changes, it is clear that body temperature should be controlled in any anesthetized patient and especially in one who may have preexisting cardiovascular compromise, as they may lack the reserves to compensate.

## Capnometry and ventilation

Capnometry is the assessment of exhaled carbon dioxide as an indicator of ventilatory adequacy. Capnometry refers to the measurement of end-exhalation (end-tidal)

$CO_2$; a capnograph provides a visual waveform display of the measurement of $CO_2$ over time. However, the term capnography is often used to imply all of these components. Hypoventilation is defined by an increase in the $PaCO_2$ with a subsequent increase in end-tidal $CO_2$ levels. Hypoventilation leads to respiratory acidosis and should be avoided in patients with cardiac disease, as ideal cardiac function occurs at normal blood pH; acute respiratory acidosis has been shown to increase HR and CO but decrease myocardial contractility and SVR.[115] Hypercapnia increases catecholamine release[116,117] and can result in tachyarrhythmias from the combination of acidosis, electrolyte changes due to acidosis, and carbon dioxide-mediated increases in catecholamine release.[118,119] It is possible to roughly estimate the change in pH on the basis of the increase in $PaCO_2$; for every 10–20 mmHg increase in $PaCO_2$, arterial pH will decrease by ~0.1 pH unit.[120]

Assisted or controlled ventilation can be helpful in maintaining normoventilation, to optimize oxygenation ($SpO_2$ or $PaO_2$) and improve inhaled anesthetic depth. Mechanical ventilation can be provided either with a controlled mechanical ventilator or with intermittent assisted manual ventilation ("bagging"). It is nearly impossible to provide the same consistency, tidal volume, respiratory rate, peak inspiratory pressure, and duration of inspiration with manual ventilation as compared to mechanical ventilation, and the use of mechanical ventilators is strongly recommended to maintain this consistency and allow the anesthetist to attend to other tasks.

However, mechanical ventilation can and very often will decrease BP by one of three mechanisms.[121] Firstly, tidal volume via mechanical ventilation is very likely to be larger than that of a spontaneously taken breath. Therefore, mechanical ventilation represents an increase in anesthetic delivery via a larger number of isoflurane molecules being delivered with a larger tidal volume. Inhaled anesthetics subsequently cause dose-dependent decreases in BP, mediated by decreases in myocardial contractility and SVR. Secondly, increases in intrathoracic pressure during positive pressure ventilation decrease venous return (i.e. preload), leading to reduced SV, CO, and BP. The effects on CO are more pronounced with more frequent respiratory rates, longer inspiratory phase duration, and larger tidal volumes.[122] Lastly, high $PaCO_2$ can increase sympathetic tone and improve BP, an effect that is reduced when patients are ventilated to a normal or even low end-tidal $CO_2$.[123,124]

## Arterial blood gases

Arterial blood gas analysis is a useful direct measurement of $PaO_2$ and $PaCO_2$ to evaluate pulmonary function and quality of ventilation. Serial monitoring of arterial blood gases can allow the anesthetist to better direct adjustments in ventilation to maintain oxygenation and normal carbon dioxide levels. The availability of arterial catheters allows for continuous invasive pressure monitoring, as well as serial blood sampling for clinical pathology. Normal values for arterial blood gas values are presented in Table 1.5.

## Central venous pressure (CVP)

Central venous pressure (CVP) is the intraluminal pressure measured in the intrathoracic vena cava immediately outside the right atrium.[125,126] CVP is the difference in pressure between the atmosphere and IV at this location. It is often used as an indicator of right ventricular preload and overall patient intravascular volume status,[127] as well as in assessment of right heart function and critical patient care monitoring.[128] However, right ventricular preload is truly defined by the difference between the intracardiac (i.e. right ventricular) and extracardiac transmural pressure gradient.[125] A variety of factors can reduce preload but lead to an increase in measured CVP, which may lead the clinician to erroneously interpret an increase in preload. These include changes in intrathoracic pressure (changes in stage of ventilation, pleural effusion, and abdominal hypertension) and blood volume or cardiac arrhythmias. Decreases in right ventricular compliance also can increase CVP, as end-diastolic filling pressures can be elevated with a "stiff" ventricle, pericardial disease, or pericardial tamponade. Ultimately, CVP represents the balance between volume return to the heart and cardiac function. There are many excellent, in-depth published reviews of CVP monitoring.[125–128] Although CVP monitoring requires a complete understanding of these variables and the ability to trend values over time, it can be a valuable tool in monitoring patients under anesthesia in select cases.

## Anesthetic and pharmacologic recommendations for specific cardiac diseases

### Valvular heart disease

#### Introduction

Valvular heart disease accounts for over 50% of congenital heart disease in dogs; chronic AV valvular disease is the most common cardiac disease in dogs, whereas mitral valve insufficiency is in the top three causes of cardiac disease in cats.[129] The prevalence of valvular disease in small animals necessitates a complete understanding of these comorbidities and how they affect and dictate the perianesthetic plan.

#### Preanesthetic evaluation

A common misconception is that most heart murmurs do not definitively require complete cardiac evaluation before anesthesia is planned and that all patients with heart disease must be managed similarly when anesthetized. As with any anesthetic patient, patients with underlying cardiac disease should be evaluated with a complete history (detailing both the long- and short-term changes in underlying disease), PE, and minimum database of bloodwork/urinalysis relevant for their signalment. In addition, patients with cardiac disease should be evaluated with thoracic radiographs, ECG, BP, and ECG, which are aimed at not only documenting presence of disease, but also assessing the severity of disease and possible response to previous treatments. As one of the main goals of perianesthetic management is maintenance of homeostasis, especially perfusion and oxygen delivery, preanesthetic cardiac evaluation should include assessments for cardiac pump function.

#### Degenerative mitral valve disease (dMVD)

##### Incidence and pathophysiology

Degenerative mitral valve disease (dMVD) is the most common cardiac disease in dogs, found in as much as 30% of the geriatric canine population.[130] dMVD can also be referred to as myxomatous mitral valve degeneration, endocardiosis, degenerative valvular disease, and myxomatous degeneration; all these terms describe the same constellation of pathophysiologic and clinical signs.

dMVD is grossly seen as an idiopathic development of nodular irregularities on the free edge of mitral valve leaflets. These nodules consist of deposition of mucopolysaccharides in the layers of the valve leaflet, which can increase in size and number over time. Pathophysiology of dMVD[131] may also include distortion of the chordae tendineae such that they lengthen and/or thicken. When valve changes are severe, this leads to curling of the valve leaflet and subsequent AV valve incompetence. The valve may degenerate to the point at which valve leaflets can prolapse[132] into the left atrium. When valvular changes are sufficient that leaflets do not oppose one another during ventricular systole, regurgitant flow of blood into the left atrium results. Mitral valve regurgitation may be trivial or severe, and volume of regurgitation is dictated by the size of the space between the valve leaflets, the pressure gradient between ventricle and atria, and the duration of systole.[133] Mitral regurgitation leads to a volume overload on the left atrium, as pulmonary venous return is complemented by regurgitant flow. CO suffers as regurgitant flow increases, and the body compensates with renal, neurohormonal, and cardiac remodeling (left ventricular eccentric hypertrophy). High atrial pressures due to volume overload lead to atrial dilation, as well as increases in pulmonary vein pressures and congestion of pulmonary venous flow, which will eventually lead to pulmonary edema. Congestive heart failure (CHF) is the end result of chronic volume overload to the left atrium and pulmonary veins with eventual failure of adaptive mechanisms.

##### Physical examination findings

Dogs may present with lethargy, cough, exercise intolerance, weight loss, respiratory difficulty, or collapse.[134] Patients may also present with other complaints, and a murmur may be auscultated in a patient with no previous history of cardiac disease. It is these patients who often require a more cautious approach to evaluation and anesthesia planning, a lack of clinical signs may provide a false sense of security with regards to potential anesthetic complications. The classic heart murmur for dMVD is a holosystolic murmur, loudest over the left apex of the heart. The intensity of the murmur tends to be consistent over the duration of

systole, with no increase or decrease in the loudness of the murmur. Often, the second heart sound is inaudible. The intensity of the murmur is not correlated with the severity of regurgitant flow, but in general, louder murmurs indicate worse regurgitation. Prolapse of the mitral valve may result in a midsystolic click.

### Anesthetic management

Anesthetic management can cover the spectrum from patients with fully compensated, nonclinical disease to those at high risk for heart failure. No consensus statements exist regarding the management of either end of this spectrum. Patients with stable, compensated disease with no left atrial enlargement and no clinical signs of pulmonary edema or heart failure generally do not require intensive management. As a portion of left ventricular ejection regurgitates into the left atrium, CO is compromised, and the patient with dMVD is thought to compensate for this with increases in HR.[130] Normal to high normal HRs are recommended for any particular signalment. Therefore, it is optimal to consider anticholinergics in the anesthesia plan, particularly if opioids are to be administered. Opioids are considered to be extremely safe as part of an anesthesia plan for a patient with dMVD, as the cardiovascular effects are primarily limited to bradycardia, which is easily treated or prevented with the use of anticholinergic. Hypothermia should be avoided by using supplemental heat support to avoid hypothermia-related bradycardia. Stable patients should tolerate inductions with ketamine and diazepam/midazolam. Alternatively, they should tolerate the dose-dependent vasodilation with propofol induction; however, the dose of propofol should be minimized using preanesthetic sedatives and/or combining propofol with benzodiazepines and/or opioids during induction. The severe negative inotropic effects and mild to moderate vasodilation associated with inhaled anesthetics can be minimized by additional use of local, regional, or systemic sedatives and analgesics. Opioids are well suited for this purpose. Alpha-2 adrenergic agonists are contraindicated due to the severe increase in afterload and the potential for increased regurgitant flow, as well as severe decreases in HR and CO.

Unstable patients, such as those at significant risk for onset of heart failure or a previous history of heart failure, those with arrhythmias, or those with preexisting cardiovascular compromise must be handled with extreme caution. Preinduction stabilization of heart failure, hypotension, and arrhythmias must be attempted. Complete cardiac evaluation (PE, thoracic radiographs, ECG, BP, and echocardiogram) is optimal. Anesthetic management includes all efforts made to minimize or mitigate the cardiovascular compromise due to inhaled anesthetics and reliance on balanced anesthesia. As stated previously, alpha-2 adrenergic agonists are contraindicated. Sedation with opioids and benzodiazepines is recommended, as they have minimal effects on cardiovascular function; opioid-mediated bradycardia can be minimized or prevented with anticholinergics. Although optimal sedation is ideal, oftentimes, good sedation has to be sacrificed in the name of cardiovascular stability, as induction of anesthesia is approached. Midazolam followed quickly by etomidate is a good induction choice because they have minimal to no cardiovascular side effects. Fentanyl and midazolam may also be used for induction, provided opioid-associated bradycardias (and respiratory depression) are controlled and the patient is sufficiently sedated beforehand or is quite compromised. Alternatively, some patients may require induction with propofol despite the risk of dose-dependent vasodilation and hypotension. In these situations, reducing the dose of propofol with preinduction sedation and/or combining propofol with one (i.e. midazolam) or two (i.e. midazolam/fentanyl) additional induction drugs can minimize propofol doses. Inhaled anesthetic dose should similarly be minimized with additional local, regional, or systemic analgesics and sedatives. Monitoring in patients with severe mitral valve disease should include either Doppler noninvasive BPs or invasive BP monitoring.

## Mitral valve stenosis (MVS)

### Incidence and pathophysiology

Mitral valve stenosis (MVS) is a rare finding in dogs, with only 12 reported cases in a 10-year period in one reference.[135] Stenotic lesions may involve the valve annulus, leaflets, chordae tendineae, or papillary muscles and present as a valvular or supravalvular lesion.[136] The heart murmur associated with MVS is a mid-diastolic low frequency murmur and possibly a split S2. The stenotic lesion creates a pressure gradient across the valve and leads to an increase in left atrial pressure, which is transmitted to the pulmonary vasculature and can lead to pulmonary edema with

severe stenosis.[129] Diagnosis of MVS may be made only when a patient presents with left heart failure and the defect is identified with echocardiography. The treatment for MVS is frequently medical, as surgical options are extremely high risk and should only be considered when all alternatives have been exhausted. The goal of medical intervention is to manage signs of left-sided heart failure and to decrease left atrial pressure and signs of left heart failure with diuretics and angiotensin-converting enzyme (ACE) inhibitors. Sodium restriction is recommended in humans and small animals. Additional treatment may be required for supraventricular arrhythmias such as atrial fibrillation or supraventricular tachycardia (SVT).

### Anesthetic management

Anesthetic management of these patients largely depends on the severity of clinical presentation.[137,138] The anesthetic goal is to prevent any situation wherein CO is significantly impaired or they are put at risk of development of pulmonary edema. With MVS, CO can be decreased by multiple mechanisms. For example, as MVS worsens in severity, ventricular filling depends increasingly on diastolic filling time and right atrial pressure. Tachycardia or tachyarrhythmias will decrease diastolic filling time and worsen ventricular filling and subsequently CO. Loss of association between atrial depolarization or the atrial kick boosting end-diastolic volume (10–30% of end diastolic volume) and ventricular contraction/ejection will worsen CO. Therefore, arrhythmias affecting AV coordination should be treated rapidly in these cases. Atrial fibrillation and SVTs can develop, while anesthetized and the ECG should be evaluated before and through induction of anesthesia. Acute vasodilation and decreases in atrial preload may worsen ventricular filling, as the normal response to acute hypotension is tachycardia. Lastly, the pressure overload to the pulmonary vasculature from MVS can precipitate pulmonary edema.[139] Avoidance of increases in blood volume that has the potential for precipitating CHF is strongly recommended.

Patients with mild MVS can likely be managed with any anesthetic plan with the exception of ketamine and tiletamine. Both dissociative agents will increase catecholamine release, which increases sympathetic tone, leading to tachycardia and increases in myocardial contractility. If diastolic filling time decreases significantly, CO can drop precipitously. Similarly, tachycardia from patient stress, anxiety, and pain can decrease CO. Good preanesthetic sedation is optimal to prevent tachycardia. Opioids and benzodiazepines are attractive options, as they do not significantly decrease HR, contractility, or vascular tone. While some opioids are good sedatives, benzodiazepines are inconsistent sedatives in small animals and can precipitate mild dysphoria or excitement in dogs and undesirable behavioral changes including potentially aggression in cats.[44,45] Anticholinergic agents are controversial in that they can precipitate tachycardia. However, anticholinergics can be indicated if there is a preexisting bradycardia or second-degree AV block. Patients with mild disease can likely tolerate the vasodilation associated with propofol for induction, but combination with an opioid (propofol-fentanyl) or benzodiazepine (propofol-midazolam) is recommended to reduce the total dose of propofol. If patients have severe disease with significant cardiovascular compromise, anesthetic induction can be achieved with etomidate or fentanyl in combination with a benzodiazepine. Monitoring of patients with MVS also depends on their degree of disease and anticipated complications. Patients with mild disease can likely be monitored as for any patient. Patients with advanced disease may require invasive BP monitoring, arterial blood gas assessment to evaluate pulmonary function, and CVPs. Patients with severe disease may warrant referral to specialty centers for consultations with veterinary cardiologists and anesthesiologists for management.

## Tricuspid valve stenosis (TVS)

### Incidence and pathophysiology

Tricuspid valve stenosis (TVS) as an independent finding is rare in small animals, and tricuspid valve incompetence is far more often due to tricuspid valve dysplasia or is the result of underlying cardiac disease. Similar to MVS, it may result from abnormalities of the annulus, valve leaflets, or papillary muscles. Labradors or breeds at risk for AV valve disease such as Newfoundlands and Bull terriers may be at higher risk.[95]

### Anesthetic management

Should TVS be identified as an isolated finding, recommendations for anesthetic management are the same as MVS. Given the rarity of isolated TVS, other causes for tricuspid valve incompetence must be investigated in patients who have suspicion of tricuspid valve disease.

## Aortic stenosis (AS)

### Incidence and pathophysiology

Aortic stenosis (AS) is the most common congenital cardiac disease of large breed dogs such as Boxers, Great Danes, Rottweilers, Golden Retrievers, German Shepherds, English Bulldogs, and Bouvier des Flandres and has been described as heritable in Newfoundlands.[129] Subvalvular aortic stenosis (SAS) can be due to valvular, supravalvular, and subvalvular lesions; however, SAS is the most common finding in dogs representing more than 95% of lesions identified. The site of SAS is the left ventricular outflow tract (LVOT), which comprises the membranous and muscular portions of the basilar interventricular septum, the craniolateral left ventricular free wall, and the anterior mitral valve leaflet.

AS can be described as fixed or dynamic. Fixed SAS is due to an anatomic abnormality creating the stenotic lesion; the severity of the obstruction does not change with rate or velocity of flow through the area. Fixed SAS has been graded in cadavers depending on the anatomic findings. For example, grade 1 has minor changes (endothelial nodules) in the subaortic endocardial surface, grade 2 has a narrow fibrous band around part of the LVOT, and grade 3 has a complete band of tissue surrounding the entire LVOT.[108] Dynamic SAS is an obstruction in the LVOT that changes on the basis of the rate of flow through the subaortic outflow tract. Increases in HR or cardiac contractility lead to a decrease in intraluminal pressure (on the basis of the Bernoulli principle) and an increase in the degree of LVOT obstruction (LVOTO). Dynamic SAS is most commonly identified in HCM and can be referred to as hypertrophic obstructive cardiomyopathy (HOCM).

The principal hemodynamic consequence of outflow tract obstruction is an increase in resistance to systolic ejection of blood from the ventricle, thereby decreasing flow through the outflow tract, increasing pressure across the stenosis, or both.[109] Left ventricular pressure is increased and results in compensatory concentric hypertrophy to maintain left ventricular output. The ejection of blood through the stenotic area results in turbulence of blood during systole and a resultant systolic murmur, typically described as an ejection murmur that increases and then decreases (crescendo-decrescendo) through systole.[140] SAS and LVOTO along with the left ventricular hypertrophy typically do not lead to left-sided heart failure. However, left ventricular hypertrophy, a decrease in capillary density, and increased wall tension predispose to myocardial ischemia. Patients who develop this pathophysiology are at risk for syncope, ventricular arrhythmias, and sudden death, although it is unclear which of these is the definitive cause of death. Another possible explanation for sudden death is exercise-induced increases in left ventricular pressure (in addition to pathologically high resting left ventricular pressure) and activation of ventricular mechanoreceptors that lead to vasodilation and bradycardia; the Bezold-Jarisch reflex.[138] Damage to aortic valve leaflets from high velocity regurgitant jet flow can predispose the valves to bacterial endocarditis associated with bacterial shower from surgical or dental procedures or from concurrent noncardiac infectious causing bacteremia. Prophylactic antibiotics are recommended for all anesthetized procedures to minimize the risk of endocarditis.

### Anesthetic management

Anesthetic management in patients with SAS can become very complicated and requires intensive monitoring and antiarrhythmic treatments to maintain normal ventricular filling and optimal CO. Patients should remain in a normal sinus rhythm without sinus tachycardia or bradycardia, and one should be prepared to treat ventricular ectopy or atrial fibrillation. For example, left ventricular CO is dependent on the organization of atrial and ventricular contraction. Thus, AV blocks or atrial fibrillation will lead to loss of the atrial kick and reduction of left ventricular end-diastolic volume. Sinus tachycardia prevents diastolic filling time and should be avoided. Sinus bradycardia leads to poor CO and hypotension, subsequently leading to poor coronary and myocardial perfusion in a thickened left ventricle. Thus, HR should be kept in the normal range to prevent decreased tissue perfusion. Ventricular premature complexes (VPCs) cause contraction before complete ventricular filling and lead to a decrease in CO. Prompt treatment of ventricular ectopy is important, as the presence of ventricular rhythms can be a risk factor for sudden death.[141]

Premedication in patients with moderate to severe AS should provide adequate sedation/analgesia to prevent anxiety, pain, or stress-related tachyarrhythmias. Anticholinergic agents are indicated to prevent bradycardia and AV blocks. The administration of Acepromazine is controversial due to long acting vasodilation but may be tolerated in the minimally affected patient if anxiety is

present and tranquilization is required. Anesthetic drugs contraindicated in AS include dissociative anesthetics (ketamine and tiletamine) and alpha-2 adrenergic agonists (xylazine, medetomidine, and dexmedetomidine). High dose anticholinergic agents are controversial in that it is difficult to predict the maximum HR a patient may develop in response to a typical dose of anticholinergic. It is worth considering titrating lower doses of anticholinergic agents for patients developing sinus bradycardia and assessing the response to low doses, rather than risk-inducing tachyarrhythmias with standard or high doses of atropine or glycopyrrolate. Induction of anesthesia can be accomplished with propofol, etomidate, or opioid-benzodiazepine combinations.

### Pulmonic stenosis (PS)

#### Incidence and pathophysiology

Pulmonic stenosis (PS) is rarely identified in cats, but is the third most common cardiac defect identified in dogs.[142] PS is the most common abnormality, with supravalvular and subvalvular stenosis being less common. PS is commonly identified as a sole lesion in dogs, but can be identified in combination with other cardiac abnormalities such as Tetralogy of Fallot (TOF). It is heritable in Beagles and Keeshonds, and a variety of breeds have increased risk for PS, including English bulldogs, Cocker Spaniels, Mastiffs, Samoyeds and Miniature Schnauzers, Chihuahuas, and Chow Chows.[142]

Pulmonic stenosis is due to variable congenital deformations and fusion of pulmonic valve leaflets. The degree of anatomical change and severity of pulmonary outflow tract obstruction are graded as either grade 1 with minimal to mild fusion and trivial to mild outflow obstruction or grade 2 that has moderate to severe valve deformation and fusion, with severe outflow obstruction.[143] Severe obstruction leads to poststenotic main pulmonary artery dilation in response to the turbulent blood flow downstream from the affected valve. The primary pathophysiologic hemodynamic effect of PS is an increase in resistance to right ventricular systolic ejection, leading to increased right ventricular pressure. This pressure overload leads to concentric hypertrophy of the right ventricle as a compensatory response, thereby returning right ventricular output to normal or near-normal. The degree of pressure overload is related to the pressure gradient across the pulmonic valve and is correlated with the severity of disease. Right ventricular hypertrophy decreases right ventricular compliance, reduces ventricular filling, and leads to an increase in right atrial pressure. This mechanism also underlies the tricuspid regurgitation in patients with tricuspid dysplasia (whether preexisting or as a result of change in right ventricular size), which can result in right heart failure, jugular distension/pulsations, ascites, and pleural effusion.

#### Anesthetic management

Definitive anesthetic recommendations for mild PS are lacking, but patients with clinically insignificant PS can likely be anesthetized with any technique. IV crystalloid administration during anesthesia should be limited (2–5 ml $kg^{-1}$ $h^{-1}$), and synthetic colloids should be avoided, as volume overload and right heart failure could be a concern, particularly in patients with concurrent tricuspid dysplasia. Patients with severe PS should be treated cautiously, and anesthetic management should be designed to minimize cardiovascular depression. Alpha-2 adrenergic agonists are contraindicated due to the significant increase in right atrial pressure. Acepromazine is controversial due to the long lasting, irreversible vasodilation, hypotension, and reduced right atrial preload. However, opioids for patient analgesia and sedation, as well as anticholinergics to prevent or treat opioid-associated bradycardia are recommended. Induction agents that preserve cardiac function and CO are preferred; combinations of etomidate or fentanyl with benzodiazepines have minimal cardiovascular depression, provided patients do not become bradycardic. Dissociative anesthetics are controversial and may be contraindicated in severe PS due to increases in SVR. Inhaled anesthetic doses should be minimized by opioid infusions to minimize vasodilation and significant decreases in contractility. Local and regional anesthetic techniques should be employed to reduce systemic and inhaled anesthetic requirements. Monitoring should consist of standard ECG, $SpO_2$, temperature, and capnography, as well as invasive BP management to allow observation in minute-to-minute changes in patient status.

## Congenital cardiac disease

Congenital cardiac defects can be grouped according to their pathophysiologic mechanisms.[144] The most common examples include those with left-to-right shunting

of blood and volume overload (PDA and VSD), pressure overload (PS and SAS), and those which present for cyanosis (TOF, PDA, and VSD with shunt reversal [right-to-left]).

## Patent ductus arteriosus (PDA)

### Incidence and pathophysiology

PDA is one of the most common congenital abnormalities identified in dogs but is rare in cats. Predisposed breeds include the Chihuahua, Bichon Frise, Collie, Cocker Spaniel, Keeshond, Maltese, Miniature Poodle, Pomeranian, and Yorkshire terrier, among others.[145] The defect is genetic in the Miniature Poodle. The ductus arteriosus is a fetal structure that allows shunting of blood (80–90% of total flow) from the pulmonary artery to the aorta necessary to avoid blood flow through the high vascular resistance of the fetal lungs. Increases in oxygen tension in the ductus with neonatal ventilation should lead to constriction of the ductus and closure within the first week of life.[146] A PDA is the persistence of this fetal structure in the neonatal and juvenile patient. Morphology of a PDA can vary from a diverticular, funnel-shaped structure to a cylindrical tube between the pulmonary artery and vena cava. Blood flow for a left-to-right shunt is determined by the diameter in the shunt and the pressure gradient between the aorta and pulmonary artery.[147]

Left-to-right shunting of blood occurs continuously in patients with PDA throughout the cardiac cycle because of higher systemic BP, as compared to pulmonary BP and is a function of relative resistances in the aorta as compared to pulmonary vascular resistance. This leads to constant volume overload of the left ventricle as shunt flow is added to normal pulmonary venous return. The volume overload leads to atrial and ventricular dilation and ventricular hypertrophy. When pulmonary vascular resistance increases and exceeds SVR, shunt flow will reverse and become right-to-left, leading to clinical cyanosis, as shunt flow does not circulate through the lungs.[146]

### Anesthetic management

Owing to the risk of shunt reversal, cyanosis, development of heart failure, arrhythmias, and other complications, it is recommended that patients with PDA be anesthetized by individuals intimately familiar with the pathophysiology of disease and the surgical/interventional procedures required to ligate/occlude PDA shunts; evaluation and treatment by veterinary specialists trained to safely handle these patients are strongly recommended.

Anesthetic factors to consider are primarily directed at the patients' age and size. Neonatal or juvenile physiology leads to a variety of unique pharmacokinetic and pharmacodynamic alterations. For example, the cardiovascular system has lower myocardial contractile mass, low cardiac reserve, and high cardiac index; CO is HR-dependent primarily due to poor vasomotor control.[148] The ability to increase contractility or vasoconstrict may be reduced, and treatments aimed at increasing contractility or providing vasoconstriction may be reduced or ineffective. The respiratory system is very compliant with high elastic forces, leading to increased airway resistance. Respiratory rates and minute ventilation are greater than in the adult. The hepatic and renal systems are immature, and drug effects may be pronounced or prolonged in these patients. Young patients have high body weight to surface area ratios and will lose body heat rapidly. Thus, heat support is critical in these patients. High body water content may lead to lower than adult packed cell volume (PCV) and albumin levels. Blood glucose regulation may be impaired; patient fasting should be shorter than adults, and supplemental dextrose may be warranted.[148]

Patient size may present special challenges because they are usually quite small at presentation. Placement of monitoring equipment may be difficult, and the ability to access the patient during surgery may be limited. Venous access may be challenging, and access tubing should be confirmed and clearly labeled if the patient cannot be clearly visualized. Anticipated surgical or procedural complications can include hemorrhage, as well as complications from thoracotomy (pain, hypoventilation, hypoxia, ventilation/perfusion imbalance, etc.). Interventional catheterization carries the risk of hemorrhage, migration of the occlusive device into the pulmonary artery, and failure to occlude the PDA with conversion to thoracotomy.

Anesthetic drug selection is generally dictated by the unique neonatal/juvenile physiology; short acting, reversible drugs are recommended. For example, a combination of opioids, benzodiazepines, and anticholinergics is frequently used for sedation, analgesia, and HR support. Examples for premedication may

include hydromorphone, oxymorphone, methadone or morphine with or without atropine. In very young patients, additional sedation may be achieved with midazolam or diazepam. Anticholinergics are recommended, as CO is HR dependent and bradycardia can lead to significant hypotension. Acepromazine is not recommended, as juvenile patients are relatively more vasodilated than adults, have difficulties in increasing cardiac contractility and SVR, and diastolic runoff through the PDA leads to very low DAPs. Induction agents including ketamine, etomidate, and fentanyl/benzodiazepine are recommended. Propofol is not recommended as a primary induction agent because of the dose-dependent vasodilation. The requirement of maintenance agent can be reduced by concurrent infusions of opioids and/or lidocaine. Arterial pressure monitoring is recommended, although Doppler BP measurement is a reasonable alternative, given the difficulty of arterial catheter placement in these patients. Regional anesthesia including intercostal or intrapleural nerve blocks can be considered as a part of a balanced analgesic plan for patients undergoing thoracotomy. Intercostal nerve blocks are performed by intercostal intramuscular injection of local anesthetic along the caudal margin of the ribs, dorsal to the length of the incision, and two to three intercostal spaces cranial and caudal to the incision location for lateral thoracotomy.[149] Total dose of lidocaine or bupivacaine is recommended to not exceed 2 mg $kg^{-1}$, as the highest plasma concentration of local anesthetics is seen after intercostal nerve blocks, suggesting significant drug uptake from intercostal injection.[150] Intrapleural analgesia can also be obtained by direct intrapleural infiltration of local anesthetic, again, not exceeding the 2 mg $kg^{-1}$ maximum dose. Typically, bupivacaine is chosen for these regional techniques for the longer duration of action compared to lidocaine. Supplemental dextrose at 1.25–2.5% in maintenance IV fluids can be considered, and glucose monitoring is recommended. Additional complications of hemorrhage, arrhythmias, hypothermia, and others are treated as needed.

## Tetralogy of Fallot (TOF)

### Incidence and pathophysiology

TOF is a common congenital anatomic malformation, which can cause cyanosis.[151] Predisposed breeds include the English bulldog, Keeshond, Miniature Poodle, and Schnauzer, as well as other breeds and cats. TOF is a combination of four anatomic derangements as follows: (1) VSD, (2) dextrorotation with an overriding aorta, (3) PS, and (4) right ventricular hypertrophy due to obstruction in the right ventricular outflow tract (RVOT).[152]

Hemodynamic alterations are dependent on the degree of shunt through the VSD and the consequences of the PS. If PS is mild and resistance to RVOT flow is mild, then right ventricular pressures should be lower than left ventricular pressures and flow should be left-to-right.[142,152] If PS is severe and represents significant outflow obstruction, then elevated right ventricular pressures can shunt blood right-to-left and lead to clinical cyanosis. Clinical cyanosis results in erythropoietin release and secondary polycythemia. Polycythemia (PCV >70–75%) can lead to increased blood viscosity and poor perfusion because of sludging of blood flow.[153] Patients may seizure because of polycythemia.

### Anesthetic management

The primary consideration for anesthesia in a patient with TOF is maintenance of normal systemic BPs to prevent reduction in left ventricular pressure. Decreases in left ventricular pressure can lead to shunt reversal (i.e. right-to-left) if right ventricular pressures are higher than left ventricular pressures. Right ventricular desaturated blood can subsequently enter the systemic circulation, resulting in cyanosis and decreased oxygen delivery. Premedication, induction, and maintenance anesthetic agents should be selected to prevent systemic hypotension as much as possible. Avoiding or minimizing doses of propofol (vasodilation) and inhaled anesthetics (negative inotrope and mild vasodilator) is recommended. Opioids are a mainstay of anesthetic management used to reduce inhaled anesthetic requirements. BP should be supported and hypotension rapidly treated to prevent further right-to-left shunting; this may include positive inotropic agents such as dopamine or dobutamine or vasopressors such as phenylephrine or norepinephrine. Invasive arterial pressure monitoring is recommended for patients with significant cyanosis or right-to-left shunting for both gold-standard monitoring of systemic BP and arterial blood gas sampling in the event of desaturation. Preoxygenation and postoxygenation are strongly recommended.

### Ventricular septal defect (VSD)

#### Incidence and pathophysiology

VSD represent failures of complete development of the membranous or muscular interventricular septum. They are more likely seen in Keeshond and English Bulldogs but have been identified in a large number of breeds.[154] The incidence in cats is unknown, but the prevalence in dogs and cats is low. VSDs can vary in size and pathophysiology, and clinical presentation depends on the degree and direction of shunting. Simple VSDs show left-to-right shunting in both phases of the cardiac cycle, and volume of flow is dependent on the shunt diameter.[154] Small-to-medium size defects exhibit resistance to flow across the VSD, which typically minimizes the increase in right ventricular volume and does not result in increases in pulmonary circulation or pulmonary pressures. Large VSDs that do not cause resistance to flow across the VSD lead to pulmonary overcirculation and pulmonary hypertension (PHT). PHT can then increase right ventricular pressure and, if higher than left ventricular pressure, may lead to right-to-left shunting and clinical cyanosis. Increased pulmonary flow leading to increased left ventricular preload can lead to left ventricular hypertrophy and pulmonary edema because of the inability of the left ventricle to eject the increased pulmonary venous return.

#### Anesthetic management

Similar to TOF, anesthetic management is directed at preventing right-to-left shunting by maintenance of systemic BP. Anesthetic plans should be designed to minimally impact BP, and rapid support for hypotension should be available with positive inotropic agents (dopamine and dobutamine) or vasopressors (phenylephrine and norepinephrine) if needed. Monitoring and interventions for patients are similar to those for TOF.

## Abnormalities of cardiac conduction and cardiac rhythm

The importance of a normal cardiac rhythm cannot be overstated. The essential function of the cardiovascular system is to provide tissues with oxygen and nutrients while removing the waste products of metabolism. More than any other, the one essential micronutrient that the body cannot survive without is oxygen. As previously discussed, oxygen delivery is the product of CO (l $min^{-1}$) and $CaO_2$ (ml $O_2$ 100 ml $blood^{-1}$). $CaO_2$ is the sum of oxygen bound by saturated hemoglobin and the $PaO_2$. CO is the product of HR and SV (milliliters blood ejected per heart beat). In order to maximize CO and optimize oxygen delivery, the contraction and relaxation of the heart must be sufficiently coordinated to allow diastolic ventricular filling and systolic ejection of blood. Cardiac arrhythmias, by definition, are disorganizations of the coordinated electrophysiologic and mechanical function of the heart and can rapidly lead to life-threatening reductions in CO and perfusion.[154] Identification and treatment of arrhythmias are critical components of the management of patients before and during anesthetic events, as well as into the recovery period.

The behavior of electrical impulses and of the cardiac rhythm is largely determined by the shape of the action potential. The ECG is the electrical representation of the summation of all cardiac vectors measured in standard Lead I, II, or III configurations at the limb electrodes placed on the patient, graphed in voltage versus time. Changes in the shape of the cardiac action potential or ECG are determined by shifts of ions, particularly sodium, potassium, and calcium across the cardiac myocyte cell membrane. The movement of ions is determined by cell surface receptors and the electrochemical gradients of these ions across the membrane and is extensively reviewed elsewhere.[155]

### Electrophysiology of the conduction system

The cardiac action potential is described in four phases, labeled as Phase 0 through 4 during the progression of the cardiac cycle (Figure 1.10).[156] Phase 4 represents the resting phase and is described by the resting membrane potential (RMP), the voltage measured across the myocyte cell membrane during the unstimulated state. RMP varies by the type of myocyte; specialized myocytes such as the sinoatrial (SA) nodal cells (Figure 1.10) and AV nodal cells have a different RMP as compared to a nonspecialized working cardiac myocyte.

The transmembrane RMP measured in the generic cardiac myocyte is −90 mV but can vary from −50 to −90 mV depending on the type of cardiac myocyte. In Phase 4, the cell membrane is relatively permeable to potassium (inwardly rectifying potassium current, IK1) and impermeable to sodium and calcium; therefore, the RMP is determined mostly by potassium as it moves out

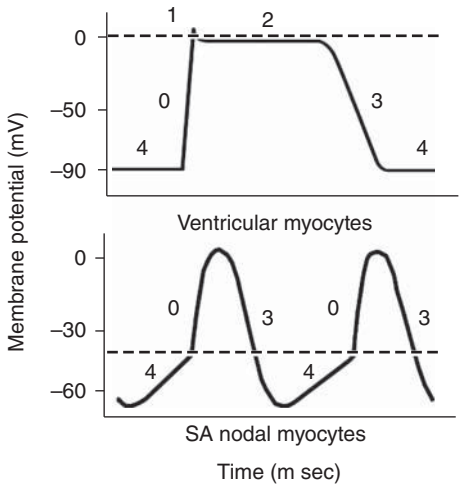


**Figure 1.10** Example myocardial action potentials. Representative membrane potential tracings of a ventricular myocyte (top) and SA nodal myocyte (bottom). Phase 4: resting membrane potential. Phase 0: rapid depolarization. Phase 1: initial repolarization. Phase 2: plateau phase. Phase 3: repolarization.

of the cell along the electrical and chemical gradients. The term "resting state" is somewhat misleading, as the RMP is also an active process due to the action of the basolateral sodium/potassium/ATPase pump, which actively moves sodium out of the cell against the concentration gradient.

Phase 0 is characterized by the depolarization of the myocyte cell membrane due to the rapid influx of sodium through rapidly opening voltage-gated sodium channels, down the electrochemical and concentration gradients such that the transmembrane potential reaches a positive value of ~+30 mV.[157] The reversal in polarity to positive in cell membrane potential opens the L-type calcium channels, allowing the onset of inward conductance of calcium that becomes important through Phase 2. The slope of Phase 0 represents the speed of depolarization of a single myocyte, and as conduction of the action potential through one myocyte dictates conduction to adjacent myocytes and spread of the action potential, the slope of Phase 0 determines conduction velocity through the heart. Pathologic states that slow sodium influx during Phase 0 reduce the speed of conduction of single myocytes and through the heart and can be the origin of cardiac arrhythmias or reentry circuits.

Phase 1 results from the return of the RMP toward neutral due to the inactivation of Phase 0 voltage-gated sodium currents, the onset of inward movement of calcium through L-type calcium channels, as well as transient inwardly rectifying potassium currents via voltage-gated potassium channels (IK-to).

Phase 2 is the sustained depolarization of the cardiac myocyte termed "the plateau phase," which is a unique feature in electrically excitable tissues. The plateau is the balance of the inward movement of calcium via L-type calcium channels and the outward movement of potassium through a sodium/potassium exchanger current.

Phase 3 is the final repolarization of the cardiac myocyte and is primarily due to the increase in outward potassium conductance across the cell membrane via multiple slow, rapid, and delayed rectifier currents. At the same time, conductance of sodium and calcium decreases, allowing overall net movement of positive charge out of the cell and re-establishment of RMP at ~−50 to −90 mV. Another mechanism of arrhythmia generation is the reduction in overall potassium outward movement during Phase 3 in the failing heart, leading to events such as early afterdepolarizations.

After the end of Phase 3, the cardiac myocyte enters a refractory period, wherein further stimulation cannot result in the generation of an action potential. The refractory period allows the heart to relax during diastole and the ventricles to reach an appropriate end-diastolic volume such that when the refractory period ends and the heart is again able to contract, a normal volume of blood is ejected and SV/CO is maintained. The refractory period prevents cardiac tetany and depolarization of one myocyte from the adjacent. This appropriately propagates the action potential in one direction, rather than allowing the passage of an action potential between two adjacent myocytes. The duration of the refractory period is roughly that the action potential, such that the myocyte cannot be restimulated until the end of Phase 3. The refractory period can be divided into an (early) absolute refractory period, wherein no degree of stimulation can lead to depolarization, and a (later) relative refractory period, wherein a higher than normal stimulus has the potential to depolarize the myocyte.

### Mechanisms eliciting cardiac arrhythmias

Cardiac arrhythmias can be classified on the basis of the electrophysiologic mechanism underlying the

generation of the abnormal rhythm. These mechanisms include disorders of impulse generation and impulse conduction and combined disorders. Specific arrhythmias of these classes are separated into sinus, supraventricular, and ventricular origin arrhythmias (Table 1.7).[152]

**Table 1.7** Classification of cardiac arrhythmias by mechanism.

| |
|---|
| Normal sinus impulse formation |
| • Normal sinus rhythm |
| • Sinus arrhythmia |
| • Wandering sinus pacemaker |
| Disturbances of sinus impulse formation |
| • Sinus arrest |
| • Sinus bradycardia |
| • Sinus tachycardia |
| Disturbances of supraventricular impulse formation |
| • Atrial premature complexes |
| • Atrial tachycardia |
| • Atrial flutter |
| • Atrial fibrillation |
| • Atrioventricular junctional rhythm |
| Disturbances of ventricular impulse formation |
| • Ventricular premature complexes |
| • Ventricular tachycardia |
| • Ventricular asystole |
| • Ventricular fibrillation |
| Disturbances of impulse conduction |
| • Sinoatrial block |
| • Persistent atrial standstill ("silent" atrium) |
| • Atrial standstill (hyperkalemia) |
| • Ventricular pre-excitation |
| • First-degree AV block |
| • Second-degree AV block |
| • Complete AV block (third degree) |
| • Bundle branch blocks |
| Disturbances of both impulse formation and impulse conduction |
| • Sick sinus syndrome |
| • Ventricular pre-excitation and the Wolff-Parkinson-White (WPW) syndrome |
| • Atrial premature complexes with aberrant ventricular conduction |
| Escape rhythms |
| • Junctional escape rhythms |
| • Ventricular escape rhythms (idioventricular rhythm) |

Source: Adapted from Tilley LP, Smith FW. 2008. Electrocardiography. In: Tilley EP, Smith FWK, Oyama MA, Sleeper MM, editors. *Manual of Canine and Feline Cardiology*. 4th ed. p. 62 (Box 3-2). St. Louis: Saunders Elsevier.

## Normal sinus impulse formation

The normal ECG waveform is generated from the coordinated conduction of the action potential from the SA node across the atria to the AV node, through the AV node to the Bundle of His, and into the ventricular Purkinje system. The conduction is subsequently carried rapidly through the ventricles, leading to coordinated muscular contraction of the ventricles. Repolarization of the ventricular myocardium is the terminal event of a single ECG complex.

Atrial depolarization is seen as the P wave. P wave amplitude and duration can vary with changes in body position relative to electrode position, vagal tone, and with arrhythmias or cardiac disease. Conduction of the action potential through the AV node is represented by the P–R interval. Shortened P–R intervals can be due to accessory atrial pathways increasing rate of atrial conduction. Prolongation of the P–R interval is the classic finding for first-degree AV block. Atrial repolarization occurs during ventricular depolarization and is not seen on the ECG waveform. The QRS complex is formed from ventricular depolarization (ventricular septum, left and right ventricular free walls; Figure 1.11). The S–T segment is the time between the end of ventricular depolarization and beginning of ventricular repolarization. Both S–T segment elevation and depression can be abnormal findings; elevation can be due to myocardial hypoxia, pericardial effusion or digoxin toxicity (cats), and S–T segment depression due to hypoxia, hyper/hypokalemia, infarction, or digoxin

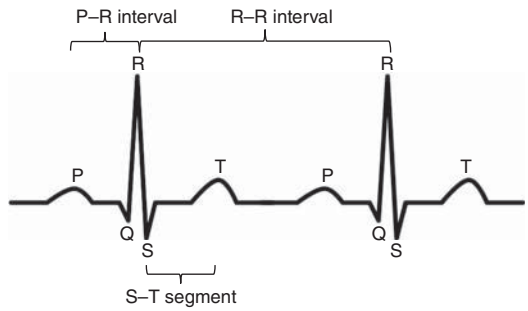


**Figure 1.11** Sample Lead II ECG tracing. Representative ECG tracing to identify named peaks. The P wave represents atrial depolarization. The P–R interval represents AV nodal delay in conduction. The QRS complex represents ventricular depolarization. The T wave represents ventricular repolarization. The R–R interval determines overall heart rate and is evaluated for regularity during ECG assessment.

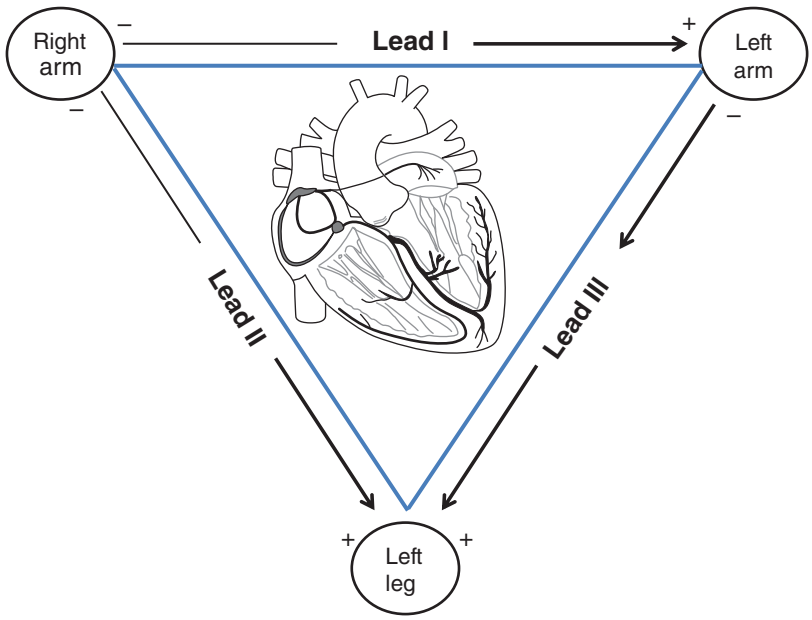


**Figure 1.12** Einthoven's triangle. Einthoven's triangle illustrates the vectors of electrical measurements through the heart on the basis of lead selection. The physics of electrical potential measurement states that the highest amplitude measurement occurs when the vector of measurement is parallel to that of electrical potentials. Electrical potentials that are perpendicular to the vector of measurement have a measured amplitude of zero. Myocardial potentials that are oblique to the vector of measurement have an amplitude between these extremes. A Lead II ECG shows the highest amplitude tracings as Lead II parallels electrical potentials from SA to AV node and through the His-Purkinje system to the ventricular myocardium. As the normal left ventricular myocardium has more mass than the right ventricular myocardium, it has a larger sum of electrical activity/potentials, and the overall direction of electrical potentials is from SA to AV node to the left ventricle. For this reason, Lead II is the most common ECG tracing used during general anesthesia. Source: Cardiac image courtesy of D. Altman, www.ECGguru.com.

toxicity.[150] Ventricular repolarization occurs after the QRS complex and is represented by the T wave.

### Evaluation of the ECG rhythm

Clinical evaluation of the ECG during anesthesia is typically performed in a Lead II arrangement. Each lead arrangement has a positive and negative electrode, described by Einthoven's triangle (Figure 1.12). The principal cardiac vector during normal sinus rhythm is from the SA node to the left ventricular free wall. Lead II ECG (negative right arm to positive left leg) measures parallel to this vector, typically resulting in the largest amplitude ECG waveform.

Evaluation of the ECG for arrhythmias requires a systematic approach to ensure arriving at an accurate diagnosis, and it is a common mistake to interpret the ECG and diagnose an arrhythmia with an "at-a-glance" approach. The following variables should be evaluated to identify ECG abnormalities.

#### Heart rate (HR)

HR will be averaged by the patient monitor over a specific duration of time, typically 6–10 s. Although this may be sufficient for some arrhythmias, manual calculation of the HR, whether an average over time or a calculated instantaneous rate (HR between two consecutive complexes), is recommended as a patient monitor can incorrectly calculate HR with irregular rhythms. HR allows classification of tachyarrhythmias and bradyarrhythmias, which are species dependent.

#### P–QRS relationship

The anesthetist must ensure that there is a QRS present for every P wave and a P wave for every QRS complex. P waves not followed by a QRS are typical of second and third-degree AV block. In small animals, the P wave has a positive deflection. Rounded P waves indicate an abnormality in the SA node, and P waves of different or variable morphology may represent ectopic atrial

contractions. Absence of P waves is seen with hyperkalemia, atrial standstill, atrial fibrillation, or P waves lost within a dissociated QRS complex (third-degree AV block). Inverted P waves (negative in Lead II) indicate that the P wave origin is near the AV node and travel toward the Lead II negative electrode (right arm).

Rhythm regularity is assessed by measuring the R–R interval between two successive QRS complexes, most easily accomplished with calipers. A regular rhythm is one in which the R–R interval is consistent. Regular rhythms with a consistent R–R interval include normal sinus rhythm, sinus tachycardia, sinus bradycardia, SVT, and ventricular tachycardia. Irregularity can be described as "regularly irregular" where there is irregularity with a pattern (AV blocks, sinus arrhythmias, and wandering pacemakers) or as "irregularly irregular" where there is no pattern to the rhythm (e.g. atrial fibrillation). Usually, the faster the rhythm, the more difficult it is to detect regularity or irregularity. Printing ECG strips at faster paper speeds (e.g. 50 mm $s^{-1}$) can assist in unmasking irregularity if difficult to determine compared to slower paper speeds (12.5 or 25 mm $s^{-1}$).

### QRS morphology

Morphology of the QRS complex can aid in identification of supraventricular or ventricular origin waveforms. Ventricular origin ectopic complexes rarely conduct through the Purkinje system, and therefore the wave of depolarization must spread cell to cell. Cell-to-cell conduction is far slower (~1 m $s^{-1}$) compared to conduction rates of the Purkinje system (~100 $ms^{-1}$), and therefore the ECG trace of an ectopic ventricular complex is wide and bizarre. Narrow complex QRS morphology is consistent with supraventricular origin complexes that pass through the AV node and spread via the Purkinje fibers and lead to extremely rapid (and therefore narrow) QRS complexes.

### Periodicity

Periodicity is the frequency of an arrhythmia and is described as either a sustained, incessant abnormality or nonsustained, paroxysmal rhythm. The term paroxysm is often reserved for an arrhythmia that converts from totally normal to totally abnormal between two QRS complexes, for example, the sudden, acute paroxysm of SVT or ventricular tachycardia.

## Specific arrhythmias

### Sinus arrhythmia

Sinus arrhythmia is the most commonly seen regularly irregular sinus rhythm during the respiratory cycle, wherein HR increases with inspiration and decreases with expiration.[158] This is due to changes in underlying vagal tone through the respiratory cycle and the effect of changing vagal tone on HR. It is common in the canine but is abnormal in the feline. If required, treatment is directed at increasing sympathetic tone or normalizing HR if bradycardic. Owing to the effects of premedication and induction agents and subsequent effects on parasympathetic tone, sinus arrhythmia can be a normal finding while anesthetized.

### Wandering sinus pacemaker

A wandering pacemaker is a sinus rhythm with variation in the origin of the P wave within the SA node and is likely due to the effects of variable vagal tone to the SA node.[159] It is seen as a cyclic variation in P wave configuration in the midst of a normal sinus rhythm. The P wave may occasionally be isoelectric and therefore undetected on the ECG trace.

### Sinus arrest

Sinus arrest is the failure of the SA node to produce a depolarization and subsequent PQRST complex due to severely depressed automaticity of the SA node.[160] For a diagnosis of sinus arrest to be made, the R–R interval of the period of arrest must be a minimum of twice the R–R interval of the underlying sinus rhythm. However, pauses of 5–12 s are not impossible and can be terminated by an escape ventricular complex, junctional escape complex, or sinus complex. Sinus arrest can result in clinical signs of weakness or syncope. Possible causes of sinus arrest include carotid sinus or ocular stimulation, SA nodal fibrosis, drug effects (digoxin, beta-blockers), or hyperexcitability of the vagus nerve ("vagotonia") with intrathoracic or cervical mass manipulation. Treatment of sinus arrest can include termination of the stimulating cause and attempts at anticholinergic therapy; however, if severe, mechanical pacemaker implantation may be required.

### Sinus bradycardia

Sinus bradycardia is a normal sinus rhythm of lower than normal expected rate. Assessment of normal HR varies with species and breeds. It may be a normal

finding in a very calm, athletic, or sleeping patient but can also be a consequence of drug therapy (opioids, alpha-2 adrenergic agonists, propofol, beta-blockers, calcium channel blockers, and digoxin), pathophysiologic (hypothyroidism and hypothermia), or a result of cardiac disease (sick sinus syndrome) or elevations in vagal tone. Treatment for sinus bradycardia is recommended if there are signs of reduced perfusion, CO, or BP. If no contraindications exist, a bradycardic animal that is hypotensive should have the HR increased with anticholinergic therapy to improve CO and BP before other treatments to improve BP are attempted.

**Sinus tachycardia**

Sinus tachycardia is a sinus rhythm in excess of the normal range, typically HR >160 beats per minute in dogs and >200–220 beats per minute in cats.[161] It can be a normal physiologic response to pain, stress, or anxiety, due to drug overdoses of anticholinergics, catecholamines, their derivatives (positive inotropes such as dopamine and dobutamine), or thyroid oversupplementation. Pathologic sinus tachycardia can be seen with pain, hyperthyroidism, fever, shock, CHF, and early stages of hypoxia (hypoxic, ischemic, hypemic, and/or histiotoxic). Treatment of sinus tachycardia before or during anesthesia requires ruling out possible causes of tachycardia and treating as needed. Light planes of anesthesia have been associated with sudden onsets of tachycardia and are due to increases in catecholamines as the patient mounts a physiologic response to noxious stimuli. Improvement of depth of anesthesia or administration of analgesics typically resolves tachycardia because of this etiology. Rarely, beta-blockers may be required to treat a pathologic sinus tachycardia; however, identification and treatment of underlying causes should be the focus of treatment.

**Atrial premature complexes (APCs)**

Atrial premature complexes (APCs) are ectopic foci of depolarization in the atria, which lead to premature atrial contractions.[157] Atrial contraction has been described as providing an atrial kick, increasing end-diastolic volume by 10–30%.[162] Loss of coordination and timing of the atrial contraction prevents this increase in end-diastolic volume and leads to a decrease in CO if sufficiently frequent. APCs are most frequently caused by cardiac disease, most commonly atrial enlargement secondary to AV valvular disease, valvular dysplasia, and PDA but can also be seen with metabolic, neoplastic, and/or inflammatory diseases that affect the atria.[163] Any cause of atrial volume overload may lead to atrial enlargement and development of APCs. APCs may also precede worsening atrial arrhythmias such as atrial tachycardia, atrial flutter, or SVT.

The presence of APCs typically does not warrant specific treatment, provided overall perfusion is adequate, but when identified should alert the anesthetist to the possibility of occult cardiac disease and may suggest the need for further cardiac evaluation (thoracic radiographs, BP measurements, and/or echocardiogram) or the possibility that APCs could degrade into atrial tachycardia or atrial fibrillation.

**Atrial flutter**

Atrial flutter is an atrial tachyarrhythmia (>300 beats per minute) in which P waves are replaced by a "saw-tooth pattern" of atrial depolarization, referred to as flutter or "f" waves.[164] Conduction of these flutter waves to the ventricles is variable, so that there may be a 4:1 ratio of atrial f waves to ventricular complexes or a 1:1 ratio that is difficult to differentiate from atrial tachycardia. Causes of atrial flutter are the same as those for other atrial tachyarrhythmias, particularly those causing atrial enlargement. Reentry rhythms can underlie atrial flutter, as can feline restrictive or HCM and ruptured chordae tendinae. Treatment of atrial flutter is not well described in veterinary medicine but is aimed at slowing ventricular rate. Options include diltiazem or digoxin administration, direct current cardioversion, or precordial thump in an emergency situation.

**Atrial fibrillation**

Atrial fibrillation is a common rhythm in dogs and tends to be a sustained rhythm, although paroxysms have been described.[165] It is the classic "irregularly irregular" rhythm noted on auscultation, pulse palpation, or ECG analysis. There is complete loss of P waves, replaced by a chaotic isoelectric line of fibrillatory waves and irregular R–R intervals. It is characterized mechanically by complete lack of coordinated atrial activity. Loss of all atrial coordination prevents the atrial kick in most if not all cardiac cycles and leads to significantly reduced CO when combined with the high ventricular rates. Atrial fibrillation is often the rhythm associated with DCM of large breed dogs, severe atrial enlargement of any cause, and cases with severe mitral regurgitation;

"lone" atrial fibrillation is seen in giant breed dogs that have atrial fibrillation but no structural cardiac disease.

Treatment of atrial fibrillation focuses on medical therapy for rate control and includes digoxin, beta blockers, and calcium channel blockers. Slowing of ventricular rate is important to prevent the development of heart failure and as a means to extend diastolic filling time and improve CO. However, long-term conversion from atrial fibrillation to a sinus rhythm is often not possible with severe underlying cardiac disease. In cases with minimal underlying structural cardiac disease (typically those with lone atrial fibrillation and atrial enlargement only), cardioversion to a sinus rhythm may be considered. The decision to attempt cardioversion (medically or with electric cardioversion) is controversial, and there are no clear criteria for attempting cardioversion.

**Atrioventricular junctional tachycardia**

AV junctional tachycardia is due to the presence of an ectopic focus of depolarization in the AV node. Intrinsic automaticity rate of the AV node is 40–60 beats per minute. Therefore, an AV nodal tachycardia has only to be faster than this rate to be termed a tachycardia. The mechanism underlying this rhythm is most commonly a reentry circuit. As the depolarization occurs in the AV node, the ventricular portion of the complex tends to be narrow. A noted variation in this rhythm is the presence of inverted P waves that can be seen before, during, or after the QRS complex. It may not be possible to distinguish this rhythm from an atrial tachycardia at very high HRs, so the term SVT can be used to identify either rhythm. Treatment is aimed at breaking the reentry circuit with a calcium channel blocker (e.g. diltiazem) to reduce calcium entry into the myocyte and therefore reduce HR.

**Ventricular premature complexes (VPCs)**

VPCs are due to ectopic foci of depolarization located in the ventricular myocardium. They occur before the next expected QRS complex on the basis of the underlying R–R interval. Depolarization spreads cell to cell, and a wide QRS complex results. Unifocal VPCs are individual wide QRS complexes with the same morphology, indicating they come from the same focus of depolarization.[166] Multifocal VPCs have differing morphology and can be positive with different morphology, negative with different morphology, or both. Couplets (two consecutive wide complexes) and triplets are terms used to describe multiple VPCs occurring consecutively. A rhythm of alternating VPCs and sinus-origin beats is referred to as ventricular bigeminy. There is often a compensatory pause after the VPC, due to the refractory period of the VPC. When the VPC does not affect the R–R interval of the underlying sinus rhythm, it is referred to as an "interpolated VPC." R-on-T phenomenon occurs when the VPC occurs on the T wave of the previous sinus beat and can predispose to development of ventricular fibrillation (VFib).[167]

The first-line treatment of VPCs is a class 1b antiarrhythmic such as IV lidocaine. Recommended IV doses range from 1 to 2 mg $kg^{-1}$ in dogs or 0.25 to 1.0 mg $kg^{-1}$ (up to 4 mg) for cats. Oral sotalol has also been recommended in cats but is not an option during anesthesia. Other therapies for ventricular arrhythmias have largely been unproven in the cat.[162] Mexilitine is an alternative for long-term management, as it is only available as an oral preparation. Class 1b antiarrhythmic drugs are believed to shorten the refractory period and terminate reentry rhythms by this mechanism. Triggers for treatment include multifocal VPCs (as more of the heart is presumed to be diseased/affected, and degradation to a worsening rhythm likely), runs of couplets/triplets/ventricular tachycardia, R-on-T phenomenon, or any ventricular rhythm that has hemodynamic consequences.

Causes of VPCs include hypoxia, cardiac disease (myocarditis, arrhythmogenic right ventricular cardiomyopathy, neoplasia, trauma, and structural cardiac disease), splenic/hepatic neoplasia, gastric dilatation volvulus syndrome, acidosis, pain, and catecholamine or sympathomimetic therapy. Treatment of VPCs and ventricular rhythms must include evaluation, monitoring, and treatment of these mechanisms in addition to treatment for the arrhythmia itself.

**Ventricular tachycardia**

Ventricular tachycardia is defined as a ventricular rhythm in excess of 160–180 beats per minute in dogs, whether paroxysmal or sustained.[166] Idioventricular rhythm is the ventricular escape rhythm seen with loss of supraventricular input such as in complete (third degree) AV block, typically a pulse rate of 40–60 $min^{-1}$ in dogs and 60–80 $min^{-1}$ in cats. The most appropriate term for complete ventricular rhythm with rates between 60 and 160 $min^{-1}$ (in dogs) is an accelerated

idioventricular rhythm; a ventricular rhythm that is not quite tachycardic. The major hemodynamic difference between accelerated idioventricular rhythm and ventricular tachycardia is the decrease in diastolic filling time as HR increases past 160–180 beats per minute, as well as the decrease in CO that results. Causes of ventricular tachycardia are the same as for VPCs, and the same considerations apply for treatment.

**Ventricular fibrillation**

VFib is a chaotic organization of coarsely wandering electrical potentials of variable duration and amplitude with no PQRST organization. It is a nonperfusing rhythm, creating no mechanical activity in the heart, and CO is near zero. VFib is a terminal rhythm and can be the end result of severe ventricular tachycardia or severe systemic or cardiac disease, the result of general anesthetics or cardiac surgery. The only treatment with a reasonable chance of converting VFib to a perfusing rhythm is electrical defibrillation. However, the ability to convert to a sinus rhythm is often temporary, and fibrillation frequently recurs in minutes to hours.

**Sinoatrial block**

SA block is failure of a normally generated SA nodal action potential to appropriately conduct to the atria and lead to atrial depolarization.[163] SA block differs from sinus arrest in that SA block is a failure of conduction, while sinus arrest is failure of the SA node to depolarize (failure of impulse generation). It can be difficult to distinguish between them with routine Lead II ECG analysis in anesthetized patients. First-degree SA block is a prolonged period from SA nodal firing and atrial depolarization. This is undetectable on ECG, as SA nodal firing is not recorded. Second-degree SA block is identified by a pause after a sinus beat or beats, wherein the duration of the pause is an exact multiple of that of the underlying normal sinus rhythm P–P interval. SA block appears otherwise identical to sinus arrest. Sinus block can be the result of atrial disease (enlargement, fibrosis, cardiomyopathy, and neoplasia), drug toxicity (beta and calcium channel blockers), or potentially sick sinus syndrome. SA nodal blocks typically do not require treatment. However, if severe bradycardia develops, treatment should be considered, as they may be responsive to atropine. If the rhythm fails to respond to anticholinergics and the patient is clinical for the arrhythmia, transcutaneous or transjugular cardiac pacing may be required.

**Persistent atrial standstill**

Atrial standstill is failure of normally generated SA nodal potentials to depolarize the atria. The ECG appears as a flat line with no P waves. Atrial standstill can be due to diseased atrial myocardium that is unable to depolarize normally, or more commonly, electrolyte disturbances such as hyperkalemia, where elevated serum potassium levels are sufficiently high to prevent atrial depolarization.[161] Common causes of hyperkalemia include urinary obstruction, renal failure, uroabdomen, and hypoadrenocorticism. At moderate to severe serum potassium levels, the SA node and ventricular myocardium maintains their ability to depolarize, albeit slowly, but no P waves are seen on the ECG; slowed and widened QRS complexes can be seen. Elevations in serum potassium are not correlated to the severity of arrhythmias; alterations in the ECG can be seen at severe hyperkalemia, and classic changes in the ECG waveform can be seen with low serum potassium levels. However, typically as potassium increases, the T waves become "tall and tented," P waves become flattened, and the P–R interval increases in duration, progressing to atrial standstill followed by widening of the QRS complex until the ECG appears as a sine wave. Ventricular arrhythmias may also present at any time.

Treatment for hyperkalemia is focused on identification and treatment of the underlying cause.[168] Immediate stabilization of the hyperkalemic patient involves decreasing serum potassium levels and treating underlying acid–base disturbances to move potassium intracellularly. These mechanisms are critically important in reducing serum potassium levels in a patient who requires general anesthesia to treat the underlying disease.

Calcium gluconate (50–100 mg $kg^{-1}$ as a slow 5-min IV bolus) or calcium chloride (10 mg $kg^{-1}$ as a similar bolus) can be given to counteract the electrochemical effects of hyperkalemia on resting membrane hyperpolarization and rapidly treat the ECG side effects of hyperkalemia. Improvements in ECG can be seen within minutes of administration and can last between 30 and 60 min, allowing time for other treatments to reduce the hyperkalemia. Calcium given too rapidly can cause bradycardia and worsen the rhythm, and so

should be given slowly while monitoring the patient with an ECG placed.

Sodium bicarbonate can be used to buffer an underlying acidosis and reverse the shift of transmembrane antiport of hydrogen ions and potassium, thus moving potassium back into cells. Once venous or arterial blood gas analysis is complete (pH, base excess, bicarbonate, and $PCO_2$), total bicarbonate deficit can be estimated with the formula: total deficit = 0.3 × base excess × body weight (kilograms). If bicarbonate therapy is appropriate, it is recommended to replace no more than 1/3–1/2 of the deficit. Administration of a larger dose of bicarbonate risks overcorrection and development of an alkalosis. One of the more significant buffering mechanisms for bicarbonate therapy is the generation of $CO_2$ based on the carbonic anhydrase equation: $HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$, where carbonic anhydrase catalyzes the reaction from carbonic acid to $CO_2$ and water. The patient must be capable of ventilating off the generated $CO_2$, an estimate of which is possible on the basis of a normal or low partial pressure of $CO_2$ on blood gas analysis. If hypercapnic, further elevations in $CO_2$ associated with bicarbonate administration will generate a respiratory acidosis and can worsen blood pH. Slow administration of bicarbonate is thus recommended. If the patient is anesthetized during bicarbonate administration, the anesthetist should be aware of the impending increase in $CO_2$ and adjust ventilation as necessary to maintain normal end-tidal $CO_2$. Lastly, the administration of sodium bicarbonate will increase measured serum sodium and may potentially lead to increases in serum osmolarity, where calculated osmolarity = $2[Na^+ + K^+]$ + BUN/2.8 + Glucose/18. Clinical signs of hyperosmolarity are not typically seen until osmolarity is >340 $mOsml^{-1}$. Although it is unlikely that serum osmolarity will increase to this extent with sodium bicarbonate, if the patient is at risk for hyperosmolarity (unregulated diabetes, severe azotemia, etc.), bicarbonate must be carefully titrated and serum osmolarity monitored.

A third strategy for decreasing serum potassium in the hyperkalemic patient is to cotransport potassium with glucose into cells under the influence of insulin. Recommendations for insulin/dextrose therapy are 0.25 units $kg^{-1}$ of regular insulin IV given with 1–2 g of dextrose for every full unit of insulin administered. Serial glucose monitoring is recommended, and patients may require a dextrose infusion (1.25–2.5%) to prevent hypoglycemia. In humans, onset time of insulin/dextrose therapy is 20 min, with a duration of 30–60 min.[168]

### First-degree AV block

First-degree AV block is defined as the prolongation of the P–R interval due to slowed conduction of atrial depolarization action potentials through the AV node to >0.13 s in dogs and 0.09 s in cats.[160] Causes include AV nodal disease (fibrosis, ischemia, and cardiomyopathy), vagal stimulation, electrolyte imbalance (hyperkalemia and hypokalemia), and drug side effects (propranolol and digitalis toxicity). First-degree AV block is not usually clinically significant. However, it may be an indication of underlying disease or a predictor of worsening AV nodal function.

### Second-degree AV block

Second-degree AV block is characterized by intermittent failure or delay in the association of the atrial depolarization through the AV node to the Bundle of His and subsequent ventricular depolarization. This appears as one or more isolated P waves that are not followed by QRS complexes.

Second-degree AV blocks are described either as Mobitz Type I or II or as low or high grade. Mobitz Type I is characterized by the increase in the duration of the P–R interval in successive sinus beats until a P wave is completely blocked and is not conducted through the AV node. Most Mobitz Type I blocks are due to altered AV nodal physiology, AV nodal disease (as for first-degree AV block), or drug side effects (low dose anticholinergics, digitalis toxicity, and alpha-2 agonists). Mobitz Type I blocks may be normal in high vagal tone species such as the very athletic dog, juvenile animals, and horses.[169]

Mobitz Type II second-degree AV block is acute, intermittent failure of conduction of a P wave through the AV node, but the P–R intervals of successfully conducted P waves are of normal duration. If there are many P waves that are not conducted so that a P–R interval is not able to be assessed, the term "high grade" second-degree AV block is applied, especially when there are four or more nonconducted P waves for every conducted P wave and QRS complex. High grade second-degree AV block can be due to the same causes as less severe AV blocks but may be a sign that AV nodal disease is severe and may degrade into complete AV dissociation (third-degree AV block). High grade second-degree AV block may be more

resistant to treatment and may require the placement of a permanent ventricular pacemaker.

#### Third-degree AV block

Third degree AV block is complete failure of AV nodal conduction and subsequent dissociation.[161] While SA nodal function, atrial conduction pathways, and atrial depolarization are normal, the wave of depolarization is not conducted through to the ventricles. The cause of third-degree AV block is often idiopathic. The characteristic findings on ECG are normal P wave generation, with a regular P–P interval at a normal sinus rate. Owing to the lack of supraventricular input, the ventricles depolarize because of ventricular automaticity (~30–50 beats per minute in dogs and 60–80 beats per minute in cats), and there develops a superimposed ventricular rhythm (a wide QRS ventricular escape rhythm) that has no association to the P waves, often with a regular R–R interval. It is critical that this escape rhythm not be interpreted and treated as VPCs, and the ECG be carefully evaluated for association between P waves and QRS complexes. If no association exists, third-degree AV block must be strongly considered and ruled out before antiarrhythmics are considered. If the ventricular escape rhythm is treated with lidocaine, it may suppress the escape rhythm and lead to cardiac arrest.

Treatment for third-degree AV block most commonly requires placement of a permanent ventricular pacemaker. Temporary measures to support (ventricular) HR, CO, and perfusion include transcutaneous, transesophageal, or transvenous temporary cardiac pacing. Medical interventions have included isoproterenol infusion, epinephrine, atropine, dopamine infusions, and dobutamine infusions.[170]

#### Bundle branch blocks

The bundle branches are the first two divisions of the Bundle of His as the conduction system travels from the AV node down the interventricular septum toward the ventricular myocardium. The left bundle branch divides into one anterior and one posterior fascicle. Bundle branch or fascicular blocks are the result of loss of rapid conduction through one or more of these bundles and result from combined rapid and slow conduction through the ventricular myocardium; the bundle branch that remains unblocked allows conduction through the bundle and into the Purkinje system, causing rapid depolarization of the ventricle and a narrow QRS complex. The block of bundle conduction from the AV node results in the cell-to-cell spread of depolarization and a resultant slow, wide QRS complex. The combination of rapid and slow conduction leads to a QRS complex that appears wide and bizarre but typically not as wide as a VPC.

Left bundle branch blocks can be due to significant underlying disease, including cardiomyopathy, degenerative conduction system disease, ischemia, AS, and drug toxicity (i.e. adriamycin) and can be secondary to left ventricular hypertrophy. Right bundle branch blocks can be normal in dogs and cats but can also develop because of right ventricular conduction abnormalities or because of right ventricular hypertrophy, in association with VSD, cardiomyopathy, and heartworm disease. Concurrent left and right bundle branch blocks have the same appearance and effects as third-degree AV block.

Bundle branch blocks will have a P wave present before the widened QRS complex, as supraventricular and AV nodal function are normal. This is an important distinction from a VPC. Bundle branch blocks typically do not lead to impairment of cardiac performance, CO, and perfusion, but should alert the anesthetist to evaluate the patient for possible underlying causes of cardiac disease.

## Systemic and pulmonary arterial hypertension

### Systemic hypertension

#### Incidence and pathophysiology

Systemic hypertension is defined as a persistently elevated BP. Most authors agree that SAPs >160–180 mmHg and DAPs >90–100 mmHg define systemic hypertension.[171,172] Systemic hypertension is often classified as either essential hypertension or secondary hypertension. Essential hypertension is defined as consistent, measurably repeatable high BPs for which a cause cannot be identified despite a thorough diagnostic workup. Secondary hypertension is due to a known cause that changes either the components of CO or SVR.

Most patients with hypertension present during middle age. However, hypertension can also be caused by or is seen concurrent with many geriatric diseases. An important breed exception is greyhounds, which have higher BP and CO due to cardiac hypertrophy unrelated

to disease that does not lead to patient morbidity.[173] Essential hypertension has also been reported in a line of Siberian Huskies[174], which might be due to their selection for endurance.

Common causes for hypertension include chronic renal disease, hyperthyroidism, hyperadrenocorticism, and a variety of miscellaneous uncommon to rare causes, including pheochromocytoma, hyperadrenocorticism, polycythemia, diabetes mellitus, increases in intracranial pressure (Cushings response), and hypercholesterolemia.[175] Drugs can also cause elevations in BP and include steroids, cyclosporine, phenylpropanolamine, and erythropoietin. Toxicities can also increase BP and include, but are not limited to, high salt, lead, nicotine and Vitamin D intake, alpha and beta-1 agonist administration, and steroid use.[9]

As noted earlier, MAP is the product of CO and SVR. CO increases with increases in HR, vascular volume (preload), or myocardial contractility (Figure 1.4). Hypertension is caused by either increases in one variable contributing to CO or increases in SVR. Renal disease leads to neurohormonal activation, which increases sympathetic system activation and has direct effects on angiotensin II and RAAS, as well as changes in body fluid balance. Thyroid hormones increase HR (positive chronotropic effect) and result most commonly in a sinus tachycardia with hypertension.[175,176] Thyrotoxicosis also leads to increases in contractility and peripheral vasodilation; yet, despite the decrease in SVR, the major cardiovascular side effect of hyperthyroidism is a significant increase in CO.[175] Increases in circulating glucocorticoids, whether endogenous due to hyperadrenocorticism or exogenously administered, lead to salt and water retention with subsequent increases in preload and CO and potential overproduction of renin with subsequent increases in SVR.[174] Pheochromocytoma is a malignant tumor of the catecholamine-producing chromaffin cells of the adrenal medulla. Secretion of epinephrine and norepinephrine is intermittent and is thought to be unrelated to stressors; the increase in circulating catecholamines leads to hypertension and tachyarrhythmias among other clinical signs unrelated to hypertension.[176] Any medications that increase SVR (alpha-1 adrenergic agonists or vasopressin-1 receptor agonists) or HR and contractility (beta-1 adrenergic agonists) have the potential to increase BP dramatically because of toxicity or inadvertent overdose.

Unfortunately, consequences of systemic hypertension can often go unrecognized for long periods, given the difficulty in recognizing and interpreting signs of hypertension by patient owners. Often, secondary hypertension is not recognized until signs of the primary disease are recognized.[177] Ophthalmic consequences of hypertension include acute blindness, retinal detachment, hyphema, retinal atrophy, or rarely corneal ulcers. Renal hypertension can lead to potential pressure diuresis, glomerulonephritis, and renal failure. The cardiovascular system can exhibit gallop rhythms, heart murmurs, or other arrhythmias; patients can show exercise intolerance, dyspnea, and, rarely, CHF. The vascular system remodels the intimal and medial layers, resulting in atherosclerosis and vascular stiffening and can lead to hemorrhage exhibited as hyphema, epistaxis, or bleeding in other locations. Neurologic symptoms of hypertension can include stroke, infarcts, or hemorrhage and can lead to head tilt, seizures, paresis, or other neurologic signs.

**Anesthetic management**

Treatment for hypertension should be aimed at identification and treatment of the underlying cause and of potential or identified consequences of hypertension and may subsequently be based on the severity of hypertension. Treatment of the underlying cause in itself may lead to resolution of the hypertension, and antihypertensive medication(s) may not be required. However, if hypertension is severe or if organ damage is identified (ophthalmic, cardiovascular, neurologic, renal, or vascular), treatment with antihypertensive agents may be necessary despite treatment of the underlying cause.[177]

Antihypertensive agent options include vasodilators (arteriodilators or venodilators), beta-adrenergic blockers, diuretics, ACE inhibitors, calcium channel blockers, and combinations of these. The choice of initial therapy has largely been extrapolated from human protocols and is a matter of species, identification of the underlying cause, and personal experience.[171] Generally, ACE inhibitors are recommended when hypertension is identified with chronic renal disease. ACE inhibitors will inhibit RAAS-mediated vasoconstriction and are indirect vasodilators. Alternatively, amlodipine is a calcium channel blocker, which also reduces SVR. Amlodipine has a slow onset of action and carries a lower risk for acute hypotension. Hydralazine is a direct

arteriodilator and is generally not a first-line treatment for hypertension but is added to combination therapy for refractory hypertension.

Recommendations for anesthetic management of patients with systemic hypertension in veterinary patients are lacking. Human guidelines for anesthetic management are well accepted and can serve as guidelines for management of veterinary patients. Thus, recommendations for anesthetic management include evaluation for magnitude of preanesthetic hypertension, evaluation for end-organ damage due to hypertension, administration of prescribed antihypertensive agents according to treatment schedule before induction of anesthesia, and close monitoring of patient BP during anesthesia.[178]

Most anesthetics reduce BP by multiple mechanisms, including inducing bradycardia, peripheral vasodilation, and/or negative inotropy. It is generally accepted that the minimum acceptable MAP is >60–70 mmHg for healthy patients. However, it is unknown if higher minimum MAPs are required for veterinary patients with preexisting hypertension. The literature discussing anesthetic care for human patients with preexisting hypertension offers no consensus[179] aside from recognizing that patients with preexisting hypertension are at higher risk for cardiovascular instability under anesthesia. Minimum acceptable BP for these veterinary patients remains an area for future research. However, anesthetic drugs that increase BP are generally avoided in patients with preexisting hypertension, including alpha-2 adrenergic agonists and dissociative anesthetics. Excitement, stress, pain, and other causes of catecholamine release should be minimized, with sufficient sedation and analgesia throughout all phases of anesthesia. The choice of anesthetic agents for patients with systemic hypertension is equally reliant on the degree of hypertension, as well as any underlying disease(s).

## Pulmonary arterial hypertension

### Incidence

PHT is defined as an abnormally high pressure in the blood vessels of the pulmonary circulation and can be due to either an increase in blood flow, an increase in blood viscosity, or an increase in pulmonary vascular resistance (i.e. pulmonary vasoconstriction). Pulmonary artery pressure >25–35 mmHg is considered abnormally high.[180,181] Normal systolic pulmonary arterial pressure averages 15–25 mmHg, and normal diastolic pulmonary artery pressure averages 5–10 mmHg.[126] Classification of PHT can be divided by the mechanisms of disease and includes primary pulmonary arterial hypertension (PAH), PAH due to left heart disease, pulmonary hypoxia, or thrombotic/embolic disease.

Typical breeds presenting with PHT are small to toy breed dogs and are typically middle age to older.[181] Primary PHT can be difficult to distinguish from those of underlying cardiac and pulmonary disease. Clinical features can include cough, dyspnea, lethargy, syncope or collapse, exercise intolerance, heart murmurs, and/or ascites.[180,181] Signs of underlying disease may also be present and most commonly include those of right heart failure, heartworm disease, cyanosis, and/or tachypnea. Cardiopulmonary examination may reveal tricuspid or mitral murmurs, split heart sounds, increased bronchovesicular sounds, or crackles and abdominal fluid wave due to ascites.

Diagnosis of PHT is aimed at determining the magnitude of PHT and the underlying cause and, most importantly, should include thoracic radiography and echocardiography. Thoracic radiography helps to identify underlying cardiorespiratory diseases that predispose to PHT. Right ventricular enlargement and dilated pulmonary arteries should increase suspicion of PHT. Characteristic echocardiographic findings include concentric right ventricular hypertrophy and dilation of the main pulmonary artery, although identification of underlying cardiac pathology can help assist in the identification of predisposing diseases.[181] Echocardiography also allows for grading of the severity of PHT from mild to severe by assessment of tricuspid valve regurgitation velocity, a number that estimates pulmonary artery systolic pressure. ECG can often be normal and may identify only arrhythmias because of underlying cardiac disease rather than be specific for PHT.[181]

Treatment for PHT is aimed at reducing clinical signs, improving exercise tolerance, decreasing pulmonary arterial pressure, and identifying and treating underlying causes. Unfortunately, treatment often fails unless the specific underlying cause can be identified and addressed before pulmonary vascular remodeling occurs and pulmonary vascular resistance becomes fixed. Vessel remodeling is characterized by vessel intimal proliferation, medial hypertrophy, and decreased compliance.[181] If the cause cannot be immediately identified, treatment is generally aimed at reducing pulmonary vascular resistance and controlling right

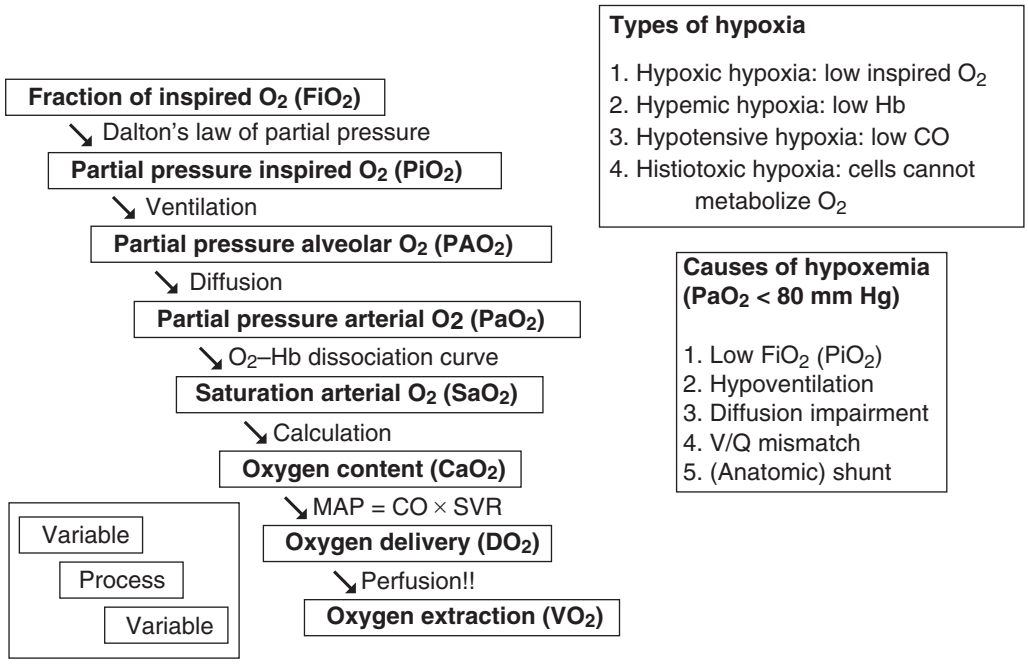


**Figure 1.13** The oxygen pathway. The oxygen pathway represents the major mechanisms, principles, and calculations that determine how a molecule of oxygen from the inspired gas arrives at the tissues. Understanding this pathway allows the clinician to evaluate causes of poor oxygen delivery and intervene where appropriate.

ventricular pressure overload. The primary pulmonary vasodilator currently used in veterinary medicine is sildenafil, which appears to provide benefits by a number of pathways, of which, direct pulmonary vasodilation is the most significant.[182,183] Sildenafil has been shown to improve survival and quality of life in dogs with PHT.[182]

### Anesthetic management

The most important factor in planning anesthesia for patients with PHT is to be aware of the potential cardiopulmonary derangement associated with the disease. This assessment is based on PE, potential clinical signs consistent with PHT, and results of diagnostic tests. Treatment and stabilization of underlying diseases are optimal. Currently, no peer-reviewed publications exist regarding anesthetic management of PHT in veterinary patients; however, the topic has been extensively reviewed in human medicine.[183–187] Therefore, symptomatic treatment is recommended on the basis of the possible mechanisms of PHT. For example, providing oxygen by facemask before anesthetic induction will increase the $FIO_2$, partial pressure of inspired oxygen, $PAO_2$, and $PaO_2$, as described by the oxygen pathway (Figure 1.13).

Maintenance of anesthesia with 100% oxygen is recommended, as oxygen is also a pulmonary vasodilator via stimulation of nitric oxide production.[180] The goals of anesthesia are to maintain CO by optimizing preload and contractility and minimizing decreases in SVR. To that end, choosing anesthetic premedications, induction, and maintenance agents should be done to minimize cardiovascular depression, as outlined previously in this chapter. It is crucial to avoid worsening or increasing pulmonary vascular resistance by preventing acidosis, hypoxia, hypercapnia, agitation, pain, and hypothermia.[183] Invasive BP monitoring should be strongly considered, as it provides a continuous monitor of BP, as well as enables arterial blood gas sampling. Good sedation with premedications is ideal to prevent stress and pain, which lead to increases in catecholamine release and systemic and pulmonary

**Table 1.8** Mechanisms of heart failure.

| Mechanism of heart failure | Categories of etiology | Differentials |
|---|---|---|
| Myocardial failure | | |
| – Primary | | Dilated cardiomyopathy |
| – Secondary | Infectious | Bacterial, viral, protozoal, fungal |
| | Drug | Doxorubricin |
| | Trauma | Physical trauma, heat stroke, electrocution |
| | Infiltrative | Neoplasia |
| | Metabolic | Hypothyroidism, hyperthryoidism, uremia |
| | Other | Valvular insufficiency, shunt |
| Pressure overload | Hypertension | Systemic or pulmonary hypertension |
| | Outflow obstruction – anatomic | Aortic stenosis, pulmonic stenosis |
| | Outflow obstruction – dynamic | Hypertrophic, obstructive cardiomyopathy |
| Volume overload | Valvular insufficiency | Mitral insufficiency |
| | Left to right shunt | PDA, VSD |
| | High output state | Hyperthyroidism, anemia |
| Decreased ventricular filling | Pericardial disease | Pericardial effusion, constrictive pericarditis |
| | Diastolic dysfunction | Hypertrophic cardiomyopathy, Restrictive pericarditis |
| | A-V valve obstruction | Mitral stenosis, tricuspid Stenosis |
| | Space-occupying lesions | Right atrial neoplasia, RVOT masses |

Source: Adapted from: Kittleson MD, Kienle RD. 1998. Classification of heart disease by echocardiographic determination of functional status. In: Kittleson MD, Kienle RD, editors. *Small Animal Cardiovascular Medicine*. p. 134. St. Louis: Mosby Publishing.

vasoconstriction. Similarly, balanced anesthesia with a reliance on opioids (repeat boluses or infusions) is important to prevent catecholamine release due to nociception. Sildenafil is also recommended to be given 1–2 h before the induction of anesthesia.

## Heart failure

### Introduction

Heart failure is defined as the inability of the heart to function as a pump and create forward flow (i.e. normal CO to meet tissue oxygen demands and systemic BP). It represents a final common pathway of a number of cardiac or pulmonary diseases and is associated with activation of neurohormonal and vascular mechanisms that compensate for the lack of forward flow. Initially, these mechanisms are beneficial in that they improve BP and perfusion but eventually become detrimental as heart failure worsens. CHF is defined as the failure of the left or right ventricle and the subsequent mechanisms that lead to fluid accumulation in the lungs (pulmonary edema with left heart failure) or abdomen (ascites with right heart failure).[188]

### Pathophysiology

The causes of heart failure or CHF are numerous but can be the end result for a wide variety of cardiac diseases. The underlying mechanisms for heart failure can be classified into four categories as follows: (i) myocardial failure (primary or secondary), (ii) pressure overload, (iii) volume overload, and (iv) decreased ventricular filling due to poor venous return or abnormal ventricular compliance (Table 1.8).

Myocardial failure is characterized by loss of contractile strength of the heart, whether primary (DCM)or secondary to other etiologies. Myocardial failure leads to activation of compensatory mechanisms that increase circulating blood volume through sodium and water retention that increases end-diastolic volume and leads to ventricular dilation. SV is initially maintained despite ventricular dilation, which can lead to AV valve insufficiency.

A pressure overload is due to an increase in myocardial wall stress subsequent to increases in ventricular systolic pressures. Most commonly, this results from valvular stenosis (PS and AS) or increases in systemic

or pulmonary vascular resistance from either systemic hypertension or PHT, respectively. Pressure overload leads to concentric hypertrophy of the ventricle that can be identified on echocardiogram. Inner layers of hypertrophied muscle may be underperfused and become ischemic, which can lead to ventricular arrhythmias, fibrillation, and sudden death.

A volume overload is most commonly seen with valvular insufficiency (usually AV valvular insufficiency) or anatomic shunts such as a PDA or VSD. It is defined as an increase in end-diastolic chamber size but normal end-systolic chamber size, an indicator that contractility is normal and SV has increased. Volume overload leads to eccentric hypertrophy to manage the increase in ventricular volume and increase forward flow. Anatomic shunts also increase ventricular volume, as they allow an increase in ventricular filling. For example, a PDA allows aortic blood to backflow into the pulmonary artery, increasing left atrial and left ventricular blood volume. Eventually, myocardial failure can result.

Reduced ventricular filling occurs when there is a physical obstruction to blood flow, blood volume is reduced, or there is impaired relaxation and filling of the ventricle. Physical obstruction to blood flow can occur because of enlarged abdominal organs (gastric dilatation volvulus, liver or splenic neoplasia, insufflation of hollow viscera, gravid uterus, etc.), surgical manipulation of vasculature responsible for venous return (cranial and caudal vena cava and tributaries), and positive pressure ventilation, among others. Reduced preload can be acute or chronic depending on the cause. For example, reduced blood volume can occur with dehydration, third spacing of fluids, or blood loss. Reductions in ventricular compliance occur with HCM and constrictive pericarditis, where the ventricle cannot relax normally, and stiffening due to muscular hypertrophy or a thickened pericardium that prevents diastolic relaxation. Compliance is the pressure–volume relationship in the ventricle; poor compliance leads to abnormally high filling pressure with relatively normal filling volumes. Abnormally high ventricular pressure leads to backup of blood to the atria and eventually organ congestion and/or edema.

Aside from the mechanisms for heart disease and pathophysiology briefly described, compensatory mechanisms exist to maintain homeostasis in the face of poor heart function to maintain BP and tissue perfusion. While they have been extensively described elsewhere,[189–191] a brief review is presented in this section. Compensatory mechanisms include the Frank–Starling mechanism and activation of the SNS, RAAS, and neuroendocrine pathways, which include endothelin and natriuretic peptides. In the acute phase of hypotension, decreased myocardial function activates baroreceptor responses to increase SNS tone, leading to vasoconstriction and increases in contractility and HR. The SNS also stimulates ADH and renin release. ADH causes fluid reabsorption in the kidneys, and renin stimulates the RAAS. The RAAS is further stimulated by reduced renal perfusion, SNS activation, and decreased sodium delivery to the macula densa. These mechanisms provide vasoconstriction and increase blood volume and venous return to return perfusion to normal. Although beneficial in the short term, chronic stimulation of these mechanisms is detrimental to homeostasis.

The New York Heart Association classifications[192] for heart failure have been adapted for veterinary use (Source: American Heart Association, Inc.) as follows: *Class I:* heart disease without clinical signs of heart disease such as exercise intolerance, *Class II:* patients who present with mild exercise intolerance but may not have radiographic evidence of disease, and *Class III:* veterinary patients who have clinical signs of heart failure during normal activity and have multiple radiographic signs of heart failure, including cardiomegaly, pulmonary edema, distended vasculature, and left atrial enlargement; Class IV patients are in obvious distress with signs of heart failure at rest. Radiographs have the aforementioned signs along with severe pulmonary infiltrates and potentially pleural or abdominal effusion.[190] Treatment strategies vary on the basis of the degree of heart disease and clinical signs along the spectrum of patients who present from mild to severe disease.

### Anesthetic management

Planning in advance for and responding to complications during an anesthetic event in a patient at risk for heart failure, one who has recently been treated for heart failure, or one how has evidence of heart failure tests the knowledge and skill of the anesthetist. Patients can present anywhere along the spectrum of classification for heart failure from minimal to severe risks for anesthesia.

Preoperative assessment of patient status is a critical step in assessing risks and planning for potential

complications, as well as choosing appropriate premedication/induction agents and preparing appropriate monitoring tools. It should include a complete history and PE, focusing on clinical signs of dyspnea, exercise intolerance, collapse, coughing, weakness, and other signs relevant to cardiopulmonary function. Of most importance are any recent changes in patient behavior. All medications for heart disease as well as the most recent dosing regimen should be noted. Although it is controversial to feed a patient anything before anesthesia, ensuring that the patient received morning doses of medications is prudent. PE should focus on parameters indicative of cardiopulmonary function such as mucous membrane color and refill, thoracic and cardiac auscultation, pulse rhythm and intensity, presence of jugular pulsations, and palpation/ballottement for organomegaly and/or fluid waves. Diagnostic procedures may consist of preanesthetic ECG, BP, thoracic radiography, abdominal ultrasonography, and echocardiography. Any abnormalities should prompt further investigation, as patient status may have changed since last examined. If the patient presenting with anesthesia is under the care of a veterinary cardiologist, patient reevaluation may be suggested and/or pursued.

The veterinary adaptation of the New York Heart Association classes of heart failure can be very useful in placing patients into an ASA status (Table 1.1). Although no classification system is optimal, and ASA status is not formally an assessment of risk of complications, it is reasonable to expect that as heart failure classification becomes more serious, ASA status will increase. The general strategies listed in the following section are intended to be specific to a patient presenting with heart failure. Obviously, if the nature of the procedure or the presence of comorbidities presents higher risk to the patient independent of the nature of their heart disease, ASA status would be higher than for the heart disease alone.

Patients who are *Class I* will likely be ASA status I and can likely be anesthetized with any combination of premedications (opioids, anticholinergics, benzodiazepines, ketamine, and acepromazine) and induction agents (ketamine/benzodiazepine, propofol +/−benzodiazepine), with the possible caveat that alpha-2 adrenergic agonists would be best avoided. Standard monitoring of ECG, BP, $SpO_2$, and temperature is likely to be sufficient. Standard IV fluids administered at 5–10 ml $kg^{-1}$ $min^{-1}$ are likely to be tolerated well.

Patients who are *Class II* present a higher potential for complications and are likely to be an ASA status III and should be treated accordingly. Acepromazine and alpha-2 adrenergic agonists should likely be avoided as premedications; reliance on opioids for sedation and dose reduction is recommended. Older, less stable patients may sedate well with a combination of an opioid and benzodiazepine. Induction agent dose, whether propofol or ketamine is used, should be reduced with good sedation from premedication and combination with a benzodiazepine. Inhaled anesthetic agent dose requirements should be reduced as much as possible with the combination of premedications, opioid, or possibly other analgesic infusions (lidocaine and ketamine), as well as local or regional anesthesia techniques. Maintenance fluid rates may be normal or reduced depending on patient status. Positive inotropic agents should be available in case of hypotension unresponsive to reducing inhalant dose and optimization of HR and rhythm. Standard anesthetic monitoring may be sufficient; however, advanced monitoring (invasive BP and CVP) may be required for unstable patients or for the nature of the procedure.

Patients who are *Class III and IV* present serious potential for decompensation and severe complications under anesthesia and are likely to be ASA status IV or V. The need for an anesthetic event must be carefully weighed against the benefit of a procedure, as the potential for life-threatening complications can be very high. These patients are very critical and require the highest level of intensive monitoring and support, including invasive BP monitoring, evaluation of arterial blood gases for oxygenation and acid–base balance, CVP monitoring, and advanced ECG interpretation. Positive inotropic agents, vasopressors, and antiarrhythmic agents should be available, and the anesthetist should be comfortable with their use. CPCR status should be discussed and known to the anesthesia team. Mechanical ventilation is extremely beneficial in optimizing ventilation and oxygenation, as well as preventing respiratory acidosis and the pH-related changes in cardiac function and electrolyte shifting. Premedication, induction, and maintenance phases of anesthesia should be aimed at minimally impacting cardiovascular function. Agents with short durations of action and/or reversibility are recommended should the patient decompensate. For this reason, opioids are good choices as premedication and induction agents. Acepromazine, ketamine, and

alpha-2 adrenergic agonists should be avoided, whereas benzodiazepines and possibly anticholinergics are also recommended. Induction of anesthesia is accomplished with combinations of opioids and benzodiazepines such as fentanyl and or etomidate and midazolam.

Chamber or "box" inductions with inhaled anesthetics are not recommended because anesthetic induction and transition through the excitement phase are slow, monitoring of vital parameters is impossible, airway access is slow and poor, and the dose of inhaled anesthetic required for intubation is higher (deeper) than is required for surgical procedures. These doses of inhaled anesthetics invariably lead to moderate to severe cardiovascular depression, however short they may (or may not) be. Chamber inductions are a last-choice option for patients with severe cardiovascular disease and should only be considered for severely fractious patients for whom handling and premedication may lead to detrimental stress, catecholamine release, and potential arrhythmogenic effects. If a chamber induction cannot be avoided, it is recommended that patients not be anesthetized to the point of intubation (owing to depth required and cardiovascular depression) but rather to the point of safe handling (immediately deep to the excitement phase) and then removed to place a facemask of inhalant only. At that point, the patient can be removed, monitoring equipment and an IV catheter can be placed, and the induction completed with a less cardiovascular depressant option such as low dose propofol or etomidate/benzodiazepine. This typically leads to a more satisfactory and efficient intubation as compared to inhalant only.

Inhaled anesthetic agent requirements should be reduced to the lowest possible levels with the application of constant rate infusions (Tables 1.2 and 1.3) and local/regional anesthesia techniques. Fluid rates should be significantly reduced to minimize the risk of volume overload; meeting metabolic requirements at 2–5 ml $kg^{-1}$ $h^{-1}$ is recommended. Fluid boluses and colloids should be avoided or administered cautiously to avoid precipitating or worsening heart failure and pulmonary edema/ascites.

## Canine and feline cardiomyopathies

Cardiomyopathy is a general term applied to diseases of the cardiac muscle tissue leading to structural impairment and subsequent decrease in cardiac function. This separates cardiomyopathies from valvular, congenital, electrical or conduction abnormalities, and traumatic or metabolic disturbances. A primary cardiomyopathy is due to intrinsic disease of the muscle; a secondary cardiomyopathy is due to derangements in a different organ system with secondary effects in the heart.

### Hypertrophic cardiomyopathy

#### Pathophysiology

HCM is due to idiopathic concentric thickening of the cardiac muscle, leading to stiffening of the myocardium and a failure of relaxation, a form of diastolic dysfunction wherein the heart fails to relax normally. It is known to be autosomal dominant in Maine Coon cats and is hereditary in Persians and some American Short Hair cats.[193] Disease onset can be seen as early as 6 months of age. Cats may be nonclinical even with severe disease, and sudden death is possible at any time.

HCM tends to affect the left ventricular free wall and interventricular septum/papillary muscles preferentially. The etiology in most cases is idiopathic; however, other possible causes include hyperthyroidism, hypergonadotropism, and secondary to hypertension. This thickening leads to a decrease in the internal volume of the ventricle when relaxed (end diastolic volume), and this inability to accept venous return leads to an eventual increase in left atrial pressure, mitral regurgitation, pulmonary edema, and the cascade of events leading to left heart failure. HOCM is a variant in which muscular hypertrophy can pull the anterior mitral valve leaflet into the LVOT and lead to dynamic obstruction of ventricular outflow. It is believed that increases in HR and velocity of blood flow through the LVOT can also predispose to systolic anterior motion (SAM) of the mitral valve leaflet and worsening of left ventricular CO. Systolic anterior motion may also worsen mitral regurgitation. Poor blood flow due to poor ventricular diastolic compliance leads to blood stasis and thrombus formation typically in the left atrium, leading to the potential for pulmonary thromboembolism. Diagnosis of HCM is typically due to identification of septal or free wall thickening in a nondilated ventricle with echocardiography. Poor diastolic ventricular filling also leads to poor CO and BP.

#### Treatment

Treatment for HCM typically involves identification and treatment of the underlying cause. No definitive treatments have been shown to achieve reversal of

hypertrophy, although many veterinary cardiologists recommend empirical beta-adrenergic blocker or calcium channel blocker therapy. Therefore, management is typically directed at treating the sequelae of reduced ventricular compliance: preventing myocardial ischemia, treatment of congestion and secondary arrhythmias, and potentially improving diastolic dysfunction.

**Anesthetic management**

Anesthetic management of HCM varies on the basis of the severity of disease. Patients with occult disease may fail detection and are likely successfully anesthetized with all combinations of anesthetic drugs. Patients with mild disease and heart murmurs with minimal structural change can similarly be anesthetized with nearly any combinations of anesthetics. However, the use of dissociative anesthetics such as ketamine and tiletamine is more controversial in mild cardiac disease. Dissociatives are generally considered contraindicated in more severe HCM, particularly if elevated BP or increased afterload is detrimental to heart function.[193] Dissociative anesthetics cause an increase in HR, myocardial contractility, and BP due to SNS stimulation and increased sympathetic discharge.[194,195] This stimulation leads to an increase in myocardial work and oxygen demand. HCM is characterized by thickening of the myocardium leading to diastolic dysfunction, potential systolic anterior motion, and LVOTO.[196,197] Increases in velocity of blood flow through the LVOT may worsen SAM and lead to obstruction of ventricular ejection. Therefore, the sympathomimetic effects of dissociative anesthetics can be quite detrimental to ventricular outflow, and ketamine and tiletamine are likely better off avoided in these cases. In addition, the increase in cardiac oxygen demand may not be met by tissues that are underperfused as a result of the pathologic remodeling of myocardial tissue, increasing the risk for myocardial ischemia and possible arrhythmias. Patients with severe disease characterized by previous history of CHF, arrhythmias, or HOCM require intensive monitoring and a complete understanding of strategies for management.

Regardless of disease severity, the primary focus for management should be to optimize perfusion and minimize myocardial oxygen demand. Typical treatments for hypotension include the following: (i) optimizing HR and rhythm, (ii) decreasing inspired inhaled anesthetic concentrations, (iii) providing adequate fluid therapy and volume, and (iv) administering positive inotropic agents or vasopressors (Figure 1.9).

Optimizing HR and rhythm is a combination of recognizing and treating bradycardia and underling arrhythmias (SVT, ventricular ectopy, or ventricular tachycardia) while weighing the risks of anticholinergic therapy. Hypotensive cats with a sinus rhythm may be considered for anticholinergic therapy to improve CO and BP, and doses should be titrated to avoid inducing tachycardia. Although tachycardia may be less risky in cats with mild disease, patients with moderate to severe thickening or HOCM/systolic anterior motion may have severe increases in myocardial oxygen demand (in poorly perfused, thickened muscle) due to tachyarrhythmias. Careful titration of anticholinergic therapy to prevent tachyarrhythmias is critical in these patients. Treatment for ventricular arrhythmias with lidocaine boluses (0.25–1.0 mg $kg^{-1}$ with a total per cat dose of 4 mg IV)[141] or SVT (diltiazem 25–50 mcg $kg^{-1}$ titrated to lowest effective dose) should be considered. Invasive arterial BP monitoring is recommended in moderately to severely affected cats.

Fluid therapy and boluses are intended to improve venous return and are controversial in patients with mild HCM, as diastolic compliance, if affected, may not be able to tolerate additional venous return. In patients with severe disease, particularly with a history of CHF, high fluid rates and boluses are contraindicated, as the increase in preload may precipitate congestion and pulmonary edema. Colloids are contraindicated, as fluid overload with colloids is more difficult to treat compared to volume overload due to crystalloids because colloids have a long duration of action and rely on liver metabolism for elimination.[198,199]

Reduction in inhaled anesthetic concentrations is a critical tool in preventing anesthetic induced hypotension. The anesthetist should consider all strategies to reduce inhaled anesthetic requirement, including analgesic boluses or infusions, local and regional analgesia, and potential for avoidance of general anesthesia if possible. Positive inotrope administration is controversial in cats with HCM. While positive inotropes improve contractility, HCM is mainly associated with diastolic dysfunction (lusitropy, not inotropy), and typically systolic function is not reduced. Increasing contractility may be detrimental, as it increases cardiac work (and myocardial oxygen demand in thickened,

poorly perfused myocardium) and can worsen systolic anterior motion in HOCM by increasing the velocity of flow through the LVOT. Positive inotropes can also be arrhythmogenic and can precipitate or worsen underlying cardiac arrhythmias. For these reasons, vasopressors used to increase SVR have been recommended. Although new research has questioned these conclusions, more investigation is required.

Premedication of cats with HCM typically includes opioids for mild sedation, facilitation of catheter placement, and reduced anesthetic induction doses. Acepromazine is controversial because it leads to long acting vasodilation that is not reversible and can precipitate hypotension. Alpha-2 adrenergic agonists are contraindicated due to the severe increase in afterload and decrease in CO. Benzodiazepines are very safe choices for patients with cardiac disease due to lack of cardiovascular effects but can be variable sedatives in cats and may lead to excitement and aggression.

Induction of anesthesia can be achieved with combinations of propofol with a benzodiazepine to reduce total propofol dose in patients with mild to moderate disease. Patients with more severe disease can be induced with combinations of etomidate with a benzodiazepine. Although combinations of fentanyl with a benzodiazepine are attractive in that they cause minimal cardiovascular depression, the slow transition to unconsciousness (and potential to be overridden with sufficient stimuli), as well as the potential for severe dysphoria in cats, makes this combination successful in only the most debilitated cats. However, in these patients, it may offer an advantage if etomidate is unavailable.

As discussed previously, for patients with moderate to severe cardiovascular disease, mask, chamber, or "box" inductions with inhaled anesthetics are not recommended. Induction of anesthesia is prolonged, and transition through excitement is slow, which could lead to patient stress. Intensive monitoring that these patients require is impossible; ability to intubate is brief, slow to achieve, and poor in quality, and the dose of inhaled anesthetic for intubation causes moderate to severe cardiovascular depression for the duration of the slow induction process. Chamber inductions should only be considered for severely fractious patients for whom handling and premedication may lead to detrimental stress, catecholamine release, and potential arrhythmogenic effects.

Opioid infusions can be used to provide analgesia, as well as reduce inhaled anesthetic requirements. Doses may need to be lowered toward the end of anesthesia to allow metabolism and prevent dysphoria in recovery. Local and/or regional anesthesia techniques are strongly encouraged to reduce systemic drug requirements. Hypotension can be treated as stated previously. Ventilation should be supplemented to prevent respiratory acidosis, and patients with arrhythmias should be monitored with continuous ECG waveform. Pulse oximetry should be used to monitor for oxygen saturation in all patients with cardiac disease. Invasive arterial BP monitoring and arterial blood gas analysis is the gold standard of monitoring, and should be strongly considered in patients with a recent or current history of CHF. Patients with CHF should be medically stabilized before anesthesia, provided it is not an emergency situation. Referral to a cardiologist or anesthesiologist may be considered for severe cases.

## Dilated cardiomyopathy (DCM)

### Incidence and pathophysiology

DCM is the most common cardiovascular disease diagnosed in dogs, followed by mitral valve and heartworm diseases. It is most commonly found in large breed dogs, including the Doberman Pinscher, Great Dane, Irish Wolfhound, Boxer dogs, and less commonly in mixed breed dogs, with male dogs appearing to be more affected than the female dogs.[200] Although not proven, it is likely that there is a heritable component to canine DCM.

DCM is characterized by an idiopathic primary loss of myocardial contractility. Secondary causes of DCM exist and include nutritional deficiency (taurine-deficiency-associated DCM in Cocker Spaniels and potentially in Labradors and Golden Retrievers), tachycardia-induced DCM (secondary to SVT or atrial flutter), and adriamycin toxicity.[201] Loss of contractility leads to systolic dysfunction associated with reduced ejection fraction, fractional shortening, and rate of ejection, as well as an increase in end-systolic volume. These changes lead to progressive dilation of the ventricle followed by left-sided or biventricular CHF. The term "occult" DCM is used before clinical signs are seen and is characterized by the loss of contractility and ventricular remodeling. Clinical signs may include irregular pulse rhythm, decreased intensity of cardiac sounds, weak pulses, or jugular distension. The overt phase of DCM

presents with clinical signs relative to onset of CHF, including lethargy, syncope, pulse deficits, dyspnea, cough, and/or abdominal distension. Patients can easily present with heart failure or sudden death as the first sign of DCM. Diagnosis is via demonstration of loss of systolic function without an identifiable cause. Patients may present with SVT, ventricular ectopy, atrial flutter, or atrial fibrillation.

**Anesthetic management**

The goal of DCM treatment is to prevent or reverse the remodeling associated with the loss of contractility. Unfortunately, as most cases are idiopathic, therapy is limited to treatment/prevention of heart failure, treatment of cardiac arrhythmias, and improving quality of life. Treatment of heart failure must be tailored to the individual, as no one treatment strategy is sufficient for all patients; however, common strategies include diuretics, positive inotropes, phosphodiesterase inhibitors, pimobendan, and antiarrhythmics. Long-term management may include diuretics, beta-adrenergic blockers, ACE inhibitors, pimobendan, and/or oral antiarrhythmics.

Anesthetic management of patients diagnosed with DCM is multifactorial and includes planning for and maintenance of systolic function, prevention of heart failure, management of arrhythmias, and inotropic support. Since even nonclinical patients may already have significant loss of systolic function and remodeling, the following techniques can likely be applied to all patients with occult or overt DCM. Patients presenting with heart failure are at severe anesthetic risks, and anesthesia should be postponed until the patient is stabilized.

Patients with overt DCM with reduced systolic function and forward flow develop heart failure, as they cannot eject diastolic preload. Therefore, perianesthetic fluid therapy should be titrated to the lowest effective dose for hydration and ongoing losses. Balanced electrolyte crystalloid administration rates should be ~3–5 ml $kg^{-1}$ $h^{-1}$; higher fluid rates may precipitate volume overload and heart failure. Colloids are contraindicated as previously discussed.

Common arrhythmias associated with DCM include VPCs, couplets, triplets, or more complicated ventricular ectopy, atrial fibrillation, and, rarely, atrial flutter or SVT. ECG monitoring should begin before induction of anesthesia, and the cardiac rhythm should be stabilized before anesthesia if possible. Antiarrhythmic agents including, but not limited to, lidocaine and diltiazem should be available.

For inotropic support, dobutamine is the clear choice over dopamine to increase contractility, SV, CO, and BP. While dopamine activates beta-1 adrenergic receptors and is a positive inotrope when delivered between 5 and 10 mcg $kg^{-1}$ $min^{-1}$, dopamine will cross to the alpha-1 adrenergic receptors at higher doses, subsequently inducing vasoconstriction and increasing afterload, which may severely reduce fractional shortening and CO. Dobutamine is preferred in these patients, as it has limited alpha-1 adrenergic effects. Dobutamine increases HR and contractility as a result of nonspecific beta-adrenergic (mainly beta-1) agonist effects.

Common premedication techniques for patients with DCM often include opioids because of their cardiovascular safety. Opioid-induced bradycardia may be treated with anticholinergics if necessary. Benzodiazepines are inconsistent sedatives in dogs. However, sedation with benzodiazepines is improved when combined with an opioid. Acepromazine is not recommended, as it leads to long acting, irreversible vasodilation and can easily precipitate hypotension with variable effects on contractility and HR. Alpha-2 adrenergic agonists are absolutely contraindicated due to the severe increase in afterload, as well as the decrease in CO.

Nearly all anesthetic induction agents are negative inotropes to some degree, and will reduce contractility dose-dependently. Although patients with very mild disease may be successfully induced with propofol while maintaining cardiovascular function, those with mild, moderate, or severe disease can most safely be induced with either etomidate or fentanyl and a benzodiazepine (midazolam or diazepam) or fentanyl. Etomidate has a more reliable transition to unconsciousness compared to fentanyl but has other effects, including adrenocortical suppression, higher cost, lower availability, and very high osmolarity (~4800 mOsm $l^{-1}$).[60,202,203] While the sympathomimetic effects of ketamine will increase HR, contractility, and BP by increasing circulating norepinephrine concentrations, ketamine has a direct negative inotropic effect that is typically overwhelmed by the sympathomimetic effects.[194–196] The potential for further reductions in myocardial contractility in a patient with DCM may be severely detrimental to fractional shortening and ventricular ejection. As safer alternative induction options exist, ketamine is not

recommended for induction of anesthesia in patients with DCM.

Maintenance with inhaled anesthetics is often unavoidable. However, all inhaled anesthetics produce a moderate to severe dose-dependent reduction in contractility and subsequent decrease in SV and CO. All attempts to minimize (or avoid) inhaled anesthetic doses must be applied. These include opioid infusions as well as local and regional anesthesia/analgesia.

### Arrhythmogenic cardiomyopathy

#### Incidence and pathophysiology

Arrhythmogenic cardiomyopathy (ARVC) is a variant of canine cardiomyopathy seen in Boxer dogs.[204] Patients often present with syncope or exercise intolerance; however, pulse deficits and arrhythmias maybe identified incidentally. Unfortunately, sudden death may be the only identifier of the disease. A small percentage of dogs may develop systolic dysfunction and heart failure. Short periods of ECG monitoring may fail to identify abnormal ECG rhythms, and Holter monitoring is recommended to evaluate for extent of arrhythmogenic disease. Criteria for advanced diagnosis of occult ARVC are lacking. Treatment for affected dogs may not reverse or delay the onset of more severe clinical signs but may decrease syncopal events and is generally recommended for >1000 VPCs in a 24-h Holter period, if R-on-T phenomenon is identified or there are paroxysms of ventricular tachycardia.

#### Anesthetic management

Anesthetic management is similar to patients with DCM. Preinduction monitoring of the ECG and treatment of ventricular ectopy are recommended before induction. Increases in sympathetic tone due to pain, stress, or excitement are to be avoided to reduce the potential for arrhythmogenic effects of catecholamine release.

## Heartworm disease

### Incidence and pathophysiology

Heartworm disease is prevalent across the United States and can affect all dogs and cats, regardless of age, environment, or gender. It is most common within 150 miles of the Gulf and Atlantic coasts and along the Mississippi river valley, with up to 5% seroprevalence in the South.[205] Other areas of the United States can see infection rates in up to 5% of the unprotected population. All dogs must be viewed as susceptible, and heartworm preventative is a mainstay of prophylactic veterinary medicine.

Heartworm infection is due to the parasite Dirofilaria immitis and is transmitted between dogs by mosquitoes, which transmit a larval stage of the parasite. Newly infected dogs develop adult heartworms that reside in the heart and pulmonary vasculature within 5–6 months of infection. Adult heartworms induce endothelial and myointimal thickening of both small and large pulmonary arteries from antigenic stimulation. Inflammatory mediators reacting to exposed subendothelial collagen and to adult worms lead to endothelial proliferation and development of villi-like projections on the arterial luminal surface. Arteries dilate and become torturous, leading to the classic radiographic findings. Altogether, these changes along with obstruction of flow due to physical presence of worms leads to an increase in pulmonary vascular resistance and is the underlying cause of PHT. The development of PHT, if severe, can then lead to a pressure overload of the right ventricle, although the degree of PHT can vary from mild to severe. Right heart failure is an end result of fulminant heartworm disease, although it is unclear if this is a direct result of PHT or some other mechanism. The fragmentation of dying or dead heartworms can lead to pulmonary thromboembolism and severe ventilation/perfusion imbalances. Pulmonary parenchymal disease characterized by inflammatory-mediated interstitial edema and eventual pulmonary fibrosis from chronic inflammation may also be seen.

Clinical signs of heartworm disease are dependent on worm burden in the heart and lungs. Early and mild infections may not have recognizable clinical signs; however, dogs with moderate worm burdens typically present with exercise intolerance, cough, and abnormal lung sounds. Dogs with severe worm burden can present with signs because of cardiac, pulmonary, hepatic, or renal dysfunction, including cough, exercise intolerance, dyspnea, hepatomegaly, syncope, ascites, heart murmurs, signs of right-sided heart failure, and/or acute death. Severe cases may also have signs of hypoxemia. Heart murmurs can auscult as left basilar ejection murmurs, split S2 sounds, systolic clicks, or murmurs supportive of tricuspid insufficiency. Severe disease can also present with pulmonary thromboembolism, disseminated intravascular coagulation, hemoptysis, or signs of allergic reactions directed against adult worms. Abnormalities may include eosinophilia and

basophilia in mildly affected dogs. Severely affected dogs may show thrombocytopenia and anemia due to caval syndrome (see the following section), signs of organ damage due to hypoxemia, or decreased organ perfusion. Heartworm screening includes antigen and antibody testing in dogs.

### Feline heartworm disease

Feline heartworm disease is far less common, as cats are not a typical target for mosquitoes, and dose of microfilariae for clinical infection and disease is higher than dogs.[206] PEs of cats with feline heartworm disease are often normal. However, they may present with mild cough and may infrequently have heart murmurs, arrhythmias, or abnormal lung sounds. Cats may present with asthmatic signs owing to immune system response to adult worms. No single abnormality on serum chemistry and blood count is diagnostic for adult heartworm infection. Combined antigen and antibody testing is recommended in cats, and a positive antigen test confirms infection, although infected cats are often antigen negative.[206]

### Caval syndrome

Caval syndrome is a life-threatening presentation of advanced heartworm disease and is characterized by a severe burden of adult worms with associated severe tricuspid regurgitation, decreased CO, intravascular hemolysis, marked hemoglobinemia, and hemoglobinuria. Clinical signs are due to acute accumulation of heartworms in the right ventricle and across the tricuspid valve, leading to severe ventricular dysfunction and tricuspid valve incompetence. It is unknown why the mass of heartworms invades the right heart, but moderate to severe PHT and a large worm burden are precipitating factors. Heartworms typically do not invade the right ventricle, as they are quickly moved into the pulmonary arteries because of downstream blood flow. Severe decreases in forward flow due to experimental administration of beta-blockers or thiopental have the potential to allow adult worms to "fall into" the right ventricle and precipitate caval syndrome. This argues that any severe decrease in forward flow, particularly in patients with high worm burdens or signs of PHT, have the potential to acutely develop caval syndrome in response to sudden decreases in CO. The lack of forward flow is the reason heartworms can recede into the right ventricle post-mortem.

### Anesthetic management

In mildly to moderately affected dogs, no single anesthesia protocol appears to have significant advantages over others, and no particular anesthetics are contraindicated with positive heartworm antigen tests. As with any anesthetized patient, appropriate monitoring, including BP, pulse oximetry, and ECG is critically important to evaluating patient stability and changes over time. Cardiovascular support for hypotensive patients can likely be provided as in normal patients.

In severely affected patients with moderate to severe worm burdens, particularly in those at risk for caval syndrome due to sudden decreases in CO, optimizing anesthetic plans to maintain CO and minimize changes in cardiac function and perfusion is strongly recommended. For patients with signs of right heart failure, anesthetic management has been previously described in this chapter. In patients who present with either heart failure or caval syndrome, choosing anesthetic plans that have minimal effects on CO or effects that are readily treatable is safest. If possible, avoidance of general anesthesia with sedation and/or locoregional anesthesia/analgesia is preferred to avoid the risks associated with general anesthesia.

Whether for sedation alone or as premedication before general anesthesia, sedation with opioids and benzodiazepines is preferred in that they have minimal cardiovascular effects, provided the opioid-mediated bradycardia is minimal or prevented with concurrent administration of anticholinergics. Premedication with alpha-2 adrenergic agonists is contraindicated in patients at risk for caval syndrome or with high worm burdens due to the severe reductions in CO at typical premedication doses equal to or higher than 5 μg $kg^{-1}$. Acepromazine is controversial, as the alpha-1 adrenergic antagonist-mediated decrease in SVR can lead to decreases in BP that are long acting and irreversible.

Etomidate or fentanyl combined with a benzodiazepine have minimal effects on cardiac contractility and SVR and are ideal induction agents to maintain CO. Induction doses of opioids have the potential to significantly depress HR and ventilation, and these side effects must be controlled.

In addition to basic monitoring tools, advanced monitoring for severely affected patients is strongly recommended. Invasive arterial BP monitoring provides accurate, continuous BP monitoring. Access to arterial blood and availability of arterial blood gas analyses are

critical tools for the assessment of ventilation/perfusion imbalances and can assist in the diagnosis of pulmonary thromboembolism. Doppler crystal placement also allows for a second assessment of BP should an arterial catheter fail.

## Summary

The large variety of cardiovascular diseases and the wide range of severity and clinical presentation of cardiac diseases present a significant challenge to the clinician in planning for an anesthetic event. Thus, one of the most important concepts to understand is that the wide range of diagnoses and underlying pathophysiologies should prompt the clinician to investigate the nature of any sign of cardiovascular disease carefully and completely and use that information to design an appropriate anesthetic and analgesic plan to maximize the safety of the patient through the anesthetic process. This chapter presents appropriate information for the clinician to prepare an individually tailored anesthesia plan for each patient presenting with cardiac disease.

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# 2 Respiratory disease

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## Introduction

Safe anesthetic care requires adequate function and support of the respiratory system. It is one of the most critical body systems for safe anesthetic management. When patients are presented with coexisting diseases of the respiratory system, safe anesthesia becomes challenging and difficult. It is therefore important to understand the physiologic changes and pathologic progression of the coexisting disease.[1]

Dogs and cats may require sedation or anesthesia for diagnostic or surgical procedures with pulmonary diseases that are either related or unrelated to the primary problem. Fortunately, support of pulmonary functions is straightforward and can, in most cases, be performed with minimal special equipment.

## Ventilatory control

Ventilatory "drive" originates within respiratory centers of the CNS medulla (i.e. the ventral respiratory column). This brainstem circuitry of neurons and pathways is responsible for respiratory rhythm generation and pattern formation.[2] Although not completely understood, several models for this complex network have been proposed, many using reduced medullary slice preparations as models.[3] Respiratory rhythm and pattern are continuously altered by homeostatic control mechanisms that allow the animal to "adapt" to physiologic respiratory challenges (i.e. exercise and pregnancy) or pathologic conditions (i.e. neurologic or respiratory disease). This respiratory plasticity involves alterations via sensory (i.e. central and peripheral chemoreceptors and airway mechanoreceptors) and modulatory projections (i.e. serotonergic neurons), as well as many other conscious and unconscious processes that affect breathing (i.e. cortical inputs and cardiovascular disease). Collectively, inputs merge to form the spatiotemporal neural output that projects to the respiratory muscles. The primary inspiratory muscles are the diaphragm and inspiratory (external) intercostals, which move the ribs forward and outward. However, accessory inspiratory muscles also play a role in breathing, especially during respiratory stress or disease (i.e. upper airway muscles).[4] Altogether, synchronized respiratory muscle contraction generates a breath that ultimately drives alveolar ventilation and blood gas regulation (Figure 2.1).[5]

## Lung volumes and ventilation

Alveolar ventilation is primarily driven by the arterial partial pressure of carbon dioxide ($CO_2$) and is frequently measured as "minute ventilation" (MV). MV is composed of the tidal volume (volume of each breath; VT) and respiratory rate (*f*): $MV = VT \times f$. For most animals, the VT is approximated at 10–20 ml kg$^{-1}$. The frequency of breathing is highly variable in animals. Smaller animals usually breathe at higher rates than larger ones; however, birds are an exception, as they have relatively slower respiratory rates than other mammals with similar body sizes.[6] Typically, the respiratory rate of dogs and cats that are awake may vary between 10 and 50 breaths per minute. Under anesthesia,

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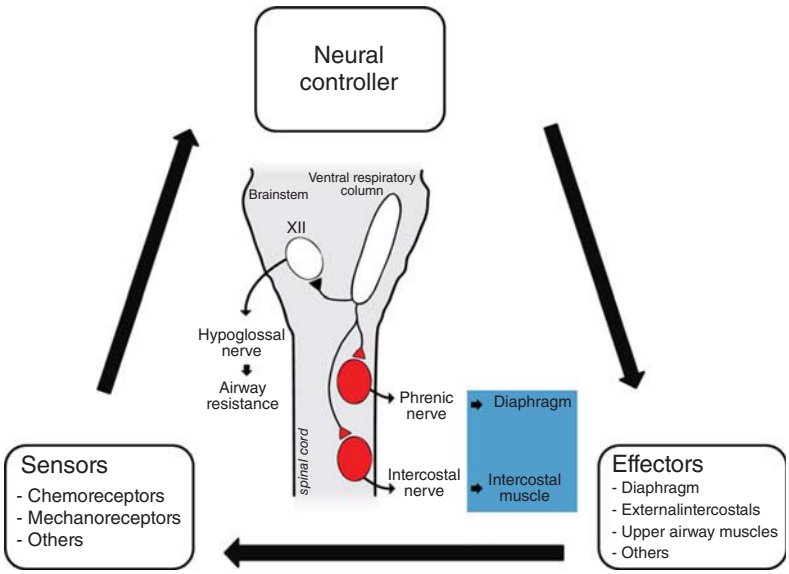


**Figure 2.1** Graphic representation of the respiratory control system. The respiratory rhythm is generated within the brainstem and is modulated by multiple afferent inputs from various sensors such as mechanoreceptors and chemoreceptors. The detailed spatiotemporal output is projected to primary (diaphragm, inspiratory intercostal) and secondary (upper airway) respiratory muscles, which contract to generate an adequate breath. During ventilation, respiratory mechanics and arterial oxygen and carbon dioxide levels change as conditions are altered, thus providing further sensory feedback to brainstem respiratory areas, which imparts the respiratory continuum.

however, respiratory rates are almost always decreased owing to drug-induced depression of the respiratory centers, hypothermia, body position, and other external factors such as bandages. An estimate of normal MV in small animals is ~100–200 ml $kg^{-1}$ $min^{-1}$.[7] However, during general anesthesia, small animals will usually breathe in the range of 8–25 breaths per minute, and tidal volume significantly decreases (see the following sections). Because of the high variability of respiratory rates, rate alone is not a good indicator of ventilatory function.

An important concept in the assessment of small animal ventilation is physiologic dead space (VD). For example, no gas exchange occurs in the upper or conductive airways of dogs and cats (i.e. nares, larynx, pharynx, trachea, bronchi, and nonrespiratory bronchioles). Thus, this portion of the VT is referred to as anatomic dead space ventilation. In addition, dead space also occurs in areas of the lung that are poorly perfused but adequately ventilated such that little to no gas exchange occurs (alveolar dead space ventilation). Physiologic dead space is the arithmetic sum of the anatomic and alveolar dead spaces, and the ratio of physiologic dead space to the tidal volume (VD/VT) has been classically calculated by the Bohr–Enghoff equation as follows: $VD/VT = (PaCO_2 - PECO_2)/PaCO_2$.[8,9] $PACO_2$ and $PaCO_2$ represent the alveolar and arterial partial pressures of $CO_2$, respectively; $PECO_2$ is the expired $CO_2$ tension. VD/VT in dogs that are awake is ~35% but increases during inhalant anesthesia (to ~50% or more).[10] Dead space ventilation is one reason that respiratory frequency should not be used as an assessment of adequacy of ventilation because small, frequent breaths primarily ventilate only the anatomic dead space, and alveolar ventilation may be inadequate. Rapid shallow ventilations may be effective for $CO_2$ removal that reaches the upper airways but not effective for the delivery of oxygen ($O_2$) to the alveoli. Slow deep ventilations are more likely to provide effective $CO_2$ removal and $O_2$ delivery. It is usually only the slow shallow ventilations that are easily recognized as ineffective by the anesthetist.

## Respiratory gases

The role of the pulmonary system is to effectively transfer $O_2$ and $CO_2$ between the atmosphere and the animal. Normally, the inspired air has only a trace percentage of $CO_2$, whereas the animal's blood contains ~5% $CO_2$. This differential creates a gradient that promotes the movement of $CO_2$ out of the animal. In contrast, the normal atmospheric $O_2$ content is ~21%, which is higher than that in the animal. Thus, $O_2$ normally moves into the blood via the lungs. Respiratory gases such as $O_2$, $CO_2$, and nitrogen are measured as a part of the total gases in the animal. Since the animal lives normally at a pressure of 1 atm (~760 mmHg at sea level), the units used to measure gases are also in millimeters of mercury. Evaluation of the pulmonary system requires an understanding of both $O_2$ and $CO_2$ transfer. Each gas is effectively independent of the other, and the assessment of pulmonary function requires measurement of both the gases. Thus, the "gold standard" for measuring adequacy of ventilation and patient oxygenation is the use of arterial blood gas analysis in both dogs and cats (Table 2.1).[11–13]

### Carbon dioxide ($CO_2$)

Although peripheral $CO_2$ receptors contribute to the $CO_2$-induced ventilator responses, the primary $CO_2$/pH sensitive chemoreceptors are located in the CNS throughout the brainstem (i.e. retrotrapezoid nuclei, serotonergic neurons in the raphé, noradrenergic neurons in the locus coeruleus, nucleus of the solitary tract, and pre-Bötzinger complex).[5] These chemoreceptors are extremely sensitive, and small deviations from a normal $PaCO_2$ of ~40 mmHg affect ventilation linearly and dramatically.

**Table 2.1** Normal arterial blood gas values in the unanesthetized dog and cat while breathing room air (~21% $O_2$)

| | |
|---|---|
| **Dog** | |
| pH | 7.41 (7.35–7.46) |
| $PCO_2$ (mmHg) | 36.8 (30.8–42.8) |
| $HCO_3^-$ (mEq $l^{-1}$) | 22.2 (18.8–25.6) |
| $PO_2$ (mmHg) | 92.1 (80.9–103.3) |
| **Cat** | |
| pH | 7.39 (7.31–7.46) |
| $PCO_2$ (mmHg) | 31.0 (25.2–36.8) |
| $HCO_3^-$ (mEq $l^{-1}$) | 18.0 (14.4–21.6) |
| $PO_2$ (mmHg) | 106.8 (95.4–118.2) |

Values are expressed as mean (range). When breathing 100% $O_2$ (such as during anesthesia), $PO_2$ values are expected to be >500 mmHg with ideal gas exchange.[11–13]
Source: Adapted with permission from Reference 13.

$CO_2$ diffuses rapidly from tissues into red blood cells wherein it forms bicarbonate according to the following reaction: $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$. The first reaction is slow in plasma but rapid inside the red blood cell due to the presence of carbonic anhydrase. $CO_2$ is then transported mostly as bicarbonate (~81%), with a small amount dissolved in plasma (~8%) and combined with amino groups of blood proteins (~11%).[2]

In the steady state, $PaCO_2$ is inversely proportional to alveolar ventilation ($\dot{V}A$) on the basis of the alveolar ventilation equation: $PaCO_2 = 0.863 \times (\dot{V}CO_2/\dot{V}A)$, where $\dot{V}CO_2$ is the metabolic production of $CO_2$, and 0.863 is a constant that corrects for dissimilar units. $CO_2$ is ~20–24 times more diffusible than oxygen, and, as such, there is complete equilibration across the alveolar membrane under normal situations. Thus, the $PaCO_2$ is essentially the same as the $PACO_2$ (within a few millimeters of mercury primarily due to a small amount of dead space ventilation).

Overall ventilation is a measure of the animal's ability to regulate the level of $CO_2$ within the body; it is the only route for elimination. Adequate ventilation occurs when $CO_2$ is maintained at an optimal partial pressure in arterial blood (~37–42 mmHg in dogs).[7,11,14] Accordingly, hyperventilation occurs when the $PaCO_2$ is <~37 mmHg, whereas hypoventilation is defined as $PaCO_2$ >~42 mmHg. Although blood gas analysis is the definite way to assess the adequacy of ventilation, noninvasive technology such as the use of end-tidal $CO_2$ capnometers has become increasingly popular in small animal (as well as exotic animal) practice, as they closely approximate alveolar $CO_2$ levels under normal situations and can be used in most species (Figure 2.2).

Since capnometry relies on adequate cardiac output to return $CO_2$ to the lungs, as well as pulmonary function to eliminate $CO_2$ from the body, it is an essential piece of equipment in any case wherein respiratory impairment or dysfunction is a concern and should become a routine monitor for any veterinary practice.


**Figure 2.2** Capnometry and pulse oximetry used during isoflurane anesthesia on a ring-tailed lemur (*Lemur catta*). Similarly to the procedure in cats and dogs, the end-tidal sample was drawn directly from the oral end of the endotracheal tube. The capnometer is reading an end-tidal $CO_2$ level of 37 mmHg and a respiratory rate of 26 breaths per minute in this lemur (seen on bottom left of tan monitor). The pulse oximetry probe was placed on the tongue and is reading a heart rate of 119 beats per minute and hemoglobin saturation of 98% (black/gray monitor). Inspired oxygen levels were ~100%.

## Oxygen

Once oxygen is carried from the conducting airways to the respiratory exchange tissues (respiratory bronchioles and alveoli), it quickly diffuses into the blood wherein it is carried dissolved in solution and bound to hemoglobin (Hb). Approximately 1.36–1.39 ml of $O_2$ can combine with 1 g of Hb compared to only a small amount that is dissolved in blood (0.003 ml per 100 ml blood per mmHg $PO_2$).[2,15] The total oxygen content of blood ($CaO_2$) is therefore calculated as follows: $CaO_2 = (1.39 \times Hb \times SaO_2) + (0.003 \times PaO_2)$, where $SaO_2$ is the oxygen saturation of Hb, and $PaO_2$ is the partial pressure of $O_2$ in the arterial blood. As determined by the oxygen–hemoglobin dissociation curve, the amount of $O_2$ carried by Hb increases rapidly until $PO_2$ reaches ~60–70 mmHg where the curve flattens off (Figure 2.3). Many factors affect the placement of this curve, including temperature, $PCO_2$, pH, and 2,3 DPG levels (Figure 2.3). In addition, the Haldane effect states that deoxygenation of Hb increases its ability to carry hydrogen ions, whereas the Bohr effect states that the affinity of Hb for $O_2$ decreases when the pH decreases or $CO_2$ concentration rises.

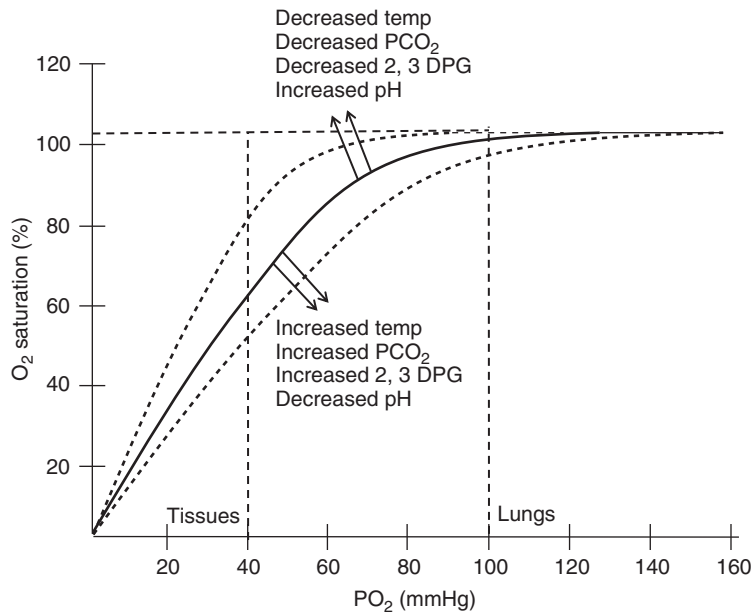


**Figure 2.3** Example oxygen–hemoglobin dissociation curves. The amount of $O_2$ carried by hemoglobin increases rapidly until $PO_2$ reaches ~60–70 mmHg when the curve flattens off. High levels of $PO_2$ and hemoglobin saturation occur in the lung, whereas lower values occur in the tissues (near the bottom of the curve). The curve is shifted right by increases in temperature, $PCO_2$ and 2,3 DPG levels and decreases in pH. Left shifts occur with opposite changes in temperature, $PCO_2$, pH, and 2,3 DPG levels.

Hemoglobin is normally nearly 100% saturated in healthy patients breathing room air (20.93% $O_2$) and should always be >90%.[16] In most normal anesthetized patients, the arterial partial pressure of oxygen ($PaO_2$) is very high due to 100% $O_2$ used as a carrier gas for the inhalant (frequently > 500 mmHg; Table 2.1). As per the oxygen–hemoglobin dissociation curve, a very high percentage of Hb will therefore be bound with $O_2$. Since arterial blood gas analysis may not be available to every practitioner, pulse oximetry is a standard, yet an indirect measure of oxygenation in anesthetized dogs and cats, which measures the Hb oxygen saturation ($SpO_2$; Figures 2.2 and 2.4). However, one must be cautious because significant pathology must exist for the $PaO_2$ to drop to a level wherein the pulse oximeter will alert the anesthetist; a $PaO_2$ of <100 mmHg (and $SpO_2$ <90%) only results from *significant* pathology in anesthetized patients (see the following sections). In addition, pulse oximetry does not indicate if adequate ventilation is present to remove $CO_2$ because the pulse oximeter only estimates the percentage of saturation of Hb with $O_2$. Although this has become one of the most widely used anesthetic monitors for a variety of species in veterinary medicine (Figures 2.2 and 2.4), it provides little information concerning the animal's ventilatory status during anesthesia unless severe pathology is present and should be used with care.

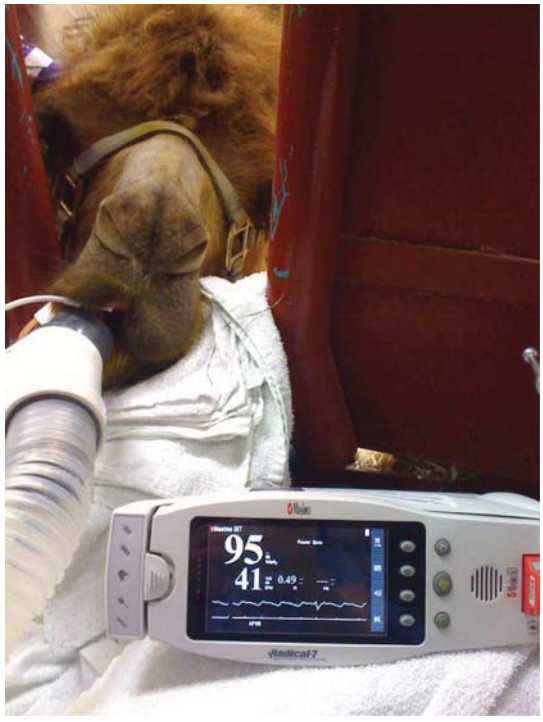


**Figure 2.4** Pulse oximetry used on an isoflurane-anesthetized dromedary (*Camelus dromedaries*). Pulse oximetry can be a valuable tool to measure oxygenation in a variety of species (including cats and dogs). As measured with a lingual probe, the heart rate was 41 beats per minute, and $SpO_2$ read 95%. Isoflurane in 100% $O_2$ was delivered via the anesthesia machine and a large animal mechanical ventilator.

Hypoxemia is commonly encountered in patients with respiratory impairment and is primarily due to one of five reasons: low inspired $O_2$ fraction, hypoventilation, diffusion impairments, ventilation–perfusion mismatching, and right-to-left shunts (cardiac or pulmonary). Discerning between these causes is sometimes difficult. However, some information can be obtained from the alveolar gas equation, which dictates that the arterial (a) or alveolar (A) $O_2$ tension will decrease with an increase in $PCO_2$: $PAO_2 = PIO_2 - (PACO_2/R)$, where $PIO_2$ is the inspired $O_2$ level, and R is the respiratory exchange ratio (~0.8 in normal animals). The difference between alveolar and arterial oxygen is defined as the (A – a) gradient. Substituting $PaCO_2$ for $PACO_2$, the (A – a) oxygen gradient equation becomes as follows: (A – a) $O_2$ gradient = $PACO_2 - PaCO_2 = (PIO_2 - 1.25PaCO_2) - PaCO_2$. Generally, values between 15 and 25 mmHg in animals breathing room air are considered normal.[2]

Hypoxemia due to low inspired $O_2$ levels (i.e. low atmospheric pressure and use of nitrous oxide without appropriate $O_2$ flows) does not usually result in increased (A – a) $O_2$ gradients, as there is a subsequent increase in alveolar ventilation (thus decreasing $PaCO_2$) secondary to hypoxemia. In addition, if hypoxemia is solely due to hypoventilation, the $PAO_2$ and $PaO_2$ decrease, whereas the $PaCO_2$ and $PACO_2$ must increase, and the (A – a) difference should not change. However, in the case of ventilation–perfusion abnormalities or right-to-left shunting (both very common during anesthesia), the (A – a) gradients are significantly elevated. These two are differentiated from each other, as administration of 100% $O_2$ to patients with ventilation–perfusion abnormalities significantly increases the $PaO_2$, whereas $PaO_2$ levels fail to return to normal in patients with significant shunting.[2]

## Phases of the ventilatory cycle

There are three phases of the ventilatory cycle as follows: inspiration, expiration, and an expiratory pause (which are important to understand in evaluating breathing or during adjustments of ventilatory support). Expiration is in most cases a passive process related to the elastic recoil of the chest. An exception is the horse in which expiration normally has an active phase even at rest.[17] Although some mechanical ventilators have the ability to augment the patient's expiration by facilitating air movement out of the chest, this adjustment is not normally available in veterinary medical ventilators.

The respiratory cycle is primarily changed by adjustments of the "pause" phase of the cycle (Figure 2.5). Ventilation rates are increased by decreasing the pause time between each inhalation and exhalation. Adjustment of the inspiration to expiration ratio (I : E) is possible in some ventilators and is important when changing the respiratory rate.

As a guideline, the inspiratory time should be less than or equal to the expiratory time. Thus, the I:E ratio will be at least 1:1 but may vary to a ratio as high as 1:5. As the respiratory rate is changed, the ratio will also change. If inspiratory time is keep at 1–2 s in duration and the respiratory rate is 10 breaths per minute, then the I:E ratio will be between 1:5 and 1:2. Typically, the I:E ratio is usually not set less than 1:1 to allow adequate time for lung filling and emptying.

## Intermittent positive pressure ventilation (IPPV)

Mechanical ventilation differs significantly from spontaneous ventilation. Normally, air enters the respiratory system because of contraction of inspiratory intercostal muscles and the diaphragm. During normal inspiration, the change in alveolar pressure is only about 1 cm of water pressure.[18] However, intermittent positive pressure ventilation (IPPV) is not a "normal" situation for the animal, as positive pressure is "forced" into the lungs; too much pressure can results in detrimental effects such as barotrauma (Figure 2.6).

Ultimately, the concern with IPPV is that the intermittent high pressure in the thorax can lead to tissue perfusion failure. For example, although during the positive pressure, breath pressurization of chest can augment cardiac ejection, increased intrathoracic pressure often exceeds central venous pressure, resulting in a decrease in venous return to the heart. The resulting decrease in ventricular filling may reduce cardiac output on the subsequent heart beat and often may decrease systolic arterial pressure.[19] To minimize the negative effects of IPPV, the inspiratory time should be kept short and should not exceed 2–3 s. In addition, the lowest peak inspiratory pressure (PIP) capable of inflating the lungs should be used. In many animals, a peak inspiratory pressure of $<15$ cm $H_2O$ will be sufficient to fully inflate the lungs. In mammals, the guideline is to keep the PIP below 20 cm $H_2O$; for reptiles and birds the guideline is a maximum of 15 cm $H_2O$.[20]

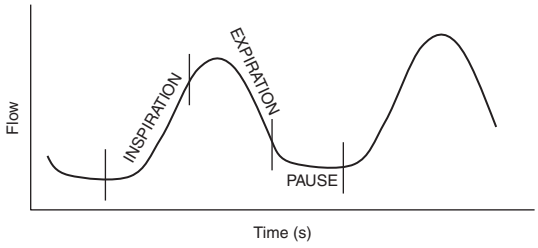


**Figure 2.5** Graphical depiction of the respiratory cycle, including the "pause." The inspiratory time is usually shorter than or equal to the expiratory time and pause to allow for appropriate cardiac and pulmonary physiology.

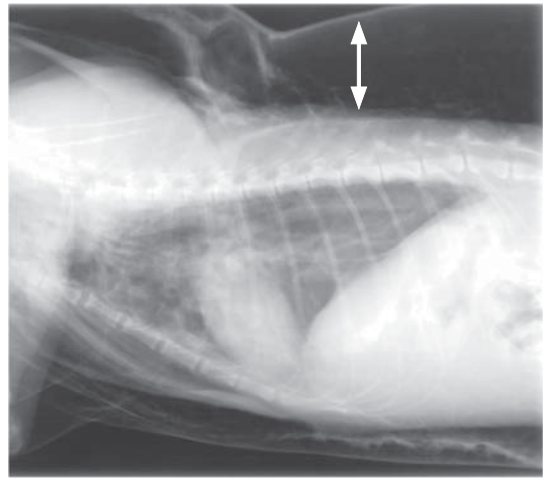

**Figure 2.6** Thoracic radiograph depicting subcutaneous emphysema secondary to barotrauma following excessive intrathoracic pressure delivered to cat. The skin has been separated from the body wall by a large volume of radiolucent air (white arrow).

Ventilatory support should be available to all animals during general anesthesia. Multiple factors contribute to an inability to adequately ventilate, including drug-induced respiratory depression, age, body weight, and pre-existing disease. Assisted or controlled ventilation is easy and safe for the patient when properly performed. Ventilation not only insures that the patient is oxygenated and $CO_2$ is removed, but also insures consistent delivery of anesthetic gases. Delivery, maintenance, and recovery from inhaled anesthetics uniquely depend on the movement of the agents through the lungs. Consistent and effective ventilation with controlled or assisted ventilation actually makes inhalant anesthesia more precise and easier to perform. Any patient can benefit from effective ventilatory support; however, it is essential in the patient with pre-existing respiratory disease.

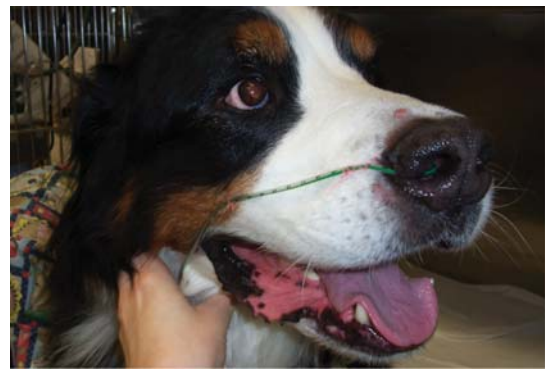

**Figure 2.7** Nasal oxygen cannula and supplementation in a dog. The tubing is secured to the lateral nasal area and upper lip to reduce the chances for dislodgment of the cannula. The tubing is further connected to an oxygen flowmeter to deliver gases enriched with oxygen.

## Oxygen ($O_2$) supplementation

In some patients with respiratory insufficiency, $O_2$ supplementation can be of benefit. Criteria for preoxygenation include animals that are marginal or unable to maintain $O_2$ saturation of their Hb when breathing room air. Cyanosis is a sign of an oxygenation crisis that warrants immediate $O_2$ supplementation via a mask or $O_2$ chamber. The ability to see cyanosis indicates that ~5 g of Hb is in the reduced form or not carrying $O_2$. However, it can be difficult to visually determine cyanosis in certain situations such as in poor lighting conditions or if the animal is severely anemic. Oxygen can be administered via a face mask, an $O_2$ chamber, or a nasal $O_2$ cannula (Figure 2.7).

However, inspired $O_2$ levels may not reach 100% with these techniques. For example, nasal insufflation with 100% $O_2$ only resulted in ~32–61% inspired $O_2$ and was dependent on insufflation and respiratory rate and tidal volume in cadaveric dog preparations.[21] In addition, mask oxygenation should not be forced on the patient if the process produces anxiety or stress owing to increased patient $O_2$ demands associated with struggling. Unless the animal is cyanotic, the benefit of preoxygenation is that it provides a longer time before a patient becomes hypoxic during apneic periods, for example, after anesthetic induction.[22,23] Specifically, 3 min of preoxygenation in dogs via face mask increased the time to Hb desaturation from ~70 s (room air) to 298 s ($O_2$ supplementation) after propofol induction.[22]

Preoxygenation with 100% delivered $O_2$ theoretically fills the alveolus with a higher than normal $O_2$ concentration. If the animal becomes apneic or if tracheal intubation is delayed, additional $O_2$ is then available to the pulmonary blood. It takes multiple minutes of preoxygenation to effectively wash out the gases normally found in the alveoli and replace them with a higher $O_2$ concentration[22], and any break in the breathing of the supplemental $O_2$ will require restarting of the oxygenation procedures. Thus, unless the animal is in respiratory distress and is hypoxic before anesthesia, preoxygenation may not benefit the animal and may actually precipitate additional failure through excitement or anxiety.

## Pharmacologic effects on the control of breathing

Since respiratory function is frequently diminished simply by the use of respiratory-depressant agents such as inhalants[24,25] and opioids in dogs and cats,[26] respiratory complications from coexisting diseases can impair ventilation even further. Anesthetic management of these cases should focus on keeping the patient oxygenated, ventilated, and perfused. Frequently, the anesthetic agents themselves are not as important as

the strict patient management associated with these high risk cases.

## Opioids

Many pure opioid analgesics depress MV via effects at mu-opioid receptors near and pathways projecting to brainstem respiratory centers. These dose-dependent effects can be seen as a reduction in respiratory frequency, tidal volume, or both[19] and are more pronounced with the pure mu-opioid receptor agonists when compared to the mixed agonist–antagonists or partial agonists.[27,28] Mixed agonists–antagonists such as butorphanol may actually be used to reverse, at least in part, the respiratory depression seen with pure mu-opioid agonists such as oxymorphone.[28,29] The ventilatory response to hypoxia is reduced, and the response to $CO_2$ is shifted to the right, and the slope is decreased, resulting in a rightward shift of the apneic threshold (level of $CO_2$ wherein breathing no longer occurs and the animal becomes apneic; Figure 2.8).[19,30]

Interestingly, ventilatory responsiveness may show maturational changes, as the newborn dog appears to have increased sensitivity to the respiratory-depressant effects of some opioids (e.g. morphine).[30] In addition, these effects may be reversed with opioid receptor antagonists such as naloxone or naltrexone.[19] In any small animal patient with significant respiratory disease, caution must be used when opioids are administered systemically; careful monitoring of ventilation ($PaCO_2$) and oxygenation ($PaO_2$) is highly recommended.

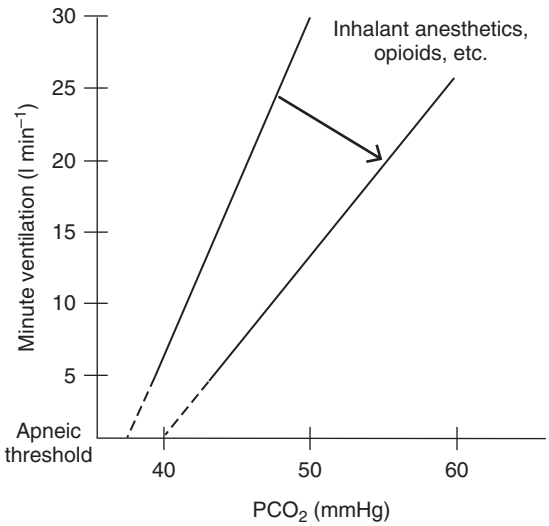


**Figure 2.8** Example ventilatory response curves to inspired $CO_2$ levels. As $CO_2$ levels rise, ventilation increases rapidly as the central chemoreceptor system is tightly regulated. Pharmacologic agents such as inhalants and opioid analgesics shift this curve to the right (decreasing sensitivity) and increase the apneic threshold (when ventilation ceases).

## Other sedatives and tranquilizers

Similarly to opioids, other sedatives and tranquilizers such as acepromazine[31] and alpha-2 adrenergic receptor agonists (e.g. medetomidine and dexmedetomidine)[32] may also have at least some respiratory-depressant effects in dogs and cats, although they appear to be minimal when sedative agents are used alone. For example, in dogs administered medetomidine (20 and 60 $\mu g\,kg^{-1}$), respiratory rate significantly decreased and $PaCO_2$ significantly increased, albeit with little effect on $PaO_2$.[27,33–36] However, in contrast, cats administered dexmedetomidine alone did not show decreased respiratory rates, and those administered medetomidine alone did not exhibit significantly altered arterial blood gas values.[37,38] It is important to recognize that the respiratory-depressant effects of the alpha-2 adrenergic agonists are likely to be exaggerated when used in combination with other anesthetic/analgesic agents (i.e. propofol and opioids).[36]

Acepromazine has minimal effects on the respiratory control system in unanesthetized patients, at least at clinical doses. Studies on small animals show a reduction in respiratory rate after acepromazine administration with minimal changes in MV, $PaO_2$, $PaCO_2$, and arterial pH.[28,39,40] Similarly, benzodiazepines (diazepam and midazolam) are associated with minimal pulmonary effects in small animals.[41] However, as always, in animals with respiratory disease, care should be used when administration of the agents is required; proper respiratory monitoring should be performed.

## Injectable and inhalant anesthetics

Similarly to the pure mu-opioid agonists, most induction and inhalational agents depress MV significantly. $PaCO_2$ increases as a result of decreased respiratory rates and volumes; these changes are frequently dose dependent. For example, propofol administered to small animals significantly reduces diaphragm contractility,[42] arterial pH, and $PaO_2$ while significantly increasing $PaCO_2$.[43] Propofol also suppresses carotid body chemoreceptor activity involved in hypoxia-induced

respiratory responses.[44] Intravenous ketamine administration appears to have less respiratory-depressant effects than other agents. Indeed, ketamine infusions improve respiratory (and cardiovascular) depressant effects associated with inhalant anesthetics in small animals when used as part of a balanced anesthesia technique.[45]

All inhalant agents shift the $CO_2$-ventilatory response curve to the right and reduce the slope in a dose-dependent manner (Figure 2.8).[46,47] In addition, the ventilatory response to hypoxia is also diminished via significantly depressed carotid body chemoreflexes.[48] When inhalant anesthetics are used in animals with respiratory disease (as well as in normal patients), the anesthetist should be ready to assist or control ventilation because the respiratory depression associated with the combination of anesthetic agents used (i.e. opioids along with sedatives and inhalants) is expected to result in significant respiratory depression in almost every anesthetized case.

## Anesthetic management of specific disorders

As previously stated, it may be that the choice of anesthetic/analgesic agents themselves is not as important as specific case management during respiratory disease (i.e. monitoring and ventilatory support) However, the following serves as examples of commonly occurring respiratory diseases in companion animal practice, and some suggested anesthetic management plans for both obstructive (e.g. asthma and laryngeal paralysis [may also be restrictive]) and restrictive lung disease (e.g. pneumonia and obesity). The main differences are that with obstructive lung disease, patients have difficultly exhaling a complete breath, whereas with restrictive lung disease, patients have difficulty in inhaling a complete lung volume.

### Asthma and heartworm-associated respiratory disease

#### Asthma

Asthma is a disease characterized by the obstruction of airflow due to constriction of the small airways, edema of the air passages, and inflammation. Since feline bronchial asthma is one of the most commonly diagnosed respiratory conditions of cats, practitioners encounter asthma regularly. Asthma can be diagnosed in cats of any age but is usually seen in young to middle-aged adults (mean: 4 years; range: 1–15 years).[49] Clinically, asthma results in increased efforts to move air into (and especially) out of the lungs; coughing and open mouth breathing are commonly observed in severe cases. However, many cats exhibit only mild, intermittent symptoms, whereas still others may develop life-threatening hypoxemia.[49] The diagnosis is based on history, clinical and radiographic signs, bronchoalveolar lavage, and response to therapy. Treatment focuses primarily on eliminating the inflammation and reversing bronchoconstriction and typically includes long-term glucocorticoid therapy, which can have significant consequences in itself.[50,51] Before sedation or anesthesia, it is recommended to insure that respiratory function of the animal is normalized as much as possible.

#### Heartworm-associated respiratory disease

Heartworm-associated respiratory disease (HARD) has recently been described as an inflammatory reaction to migrating heartworm dirofilaria. The acute respiratory signs thought to be associated with the death of immature heartworms in cats may mimic those of feline asthma. Interestingly, cats can also develop an inflammatory reaction to the immature stage of the canine heartworm.[52,53]

Although many cats remain asymptomatic after heartworm infection and are clinically normal, some develop clinical disease with signs of coughing, dyspnea, or intermittent vomiting not associated with eating. However, signs can sometimes be limited to weight loss or diarrhea without accompanying respiratory changes. When present, the respiratory signs can be similar to those observed with feline bronchial disease, which is frequently described as asthma by the owners. It is interesting to speculate that preventative therapy with selemectin may reduce the heartworm-associated respiratory inflammatory reaction in cats to microfilaria.

#### Anesthetic management

The primary approach to the asthmatic patient is to minimize excitement and stress. Calm, quiet handling of the patient is necessary to prevent worsening of clinical signs. One approach is to sedate the animal while it is with the owner and instruct the owner

as to the importance of preventing excitement. Handling of the animal during anesthesia preparation should be oriented to minimizing noise, handling, and unusual simulation. The use of analgesics and sedatives is recommended to limit excitement during handling and intravenous catheterization. Butorphanol at 0.2–0.5 mg kg$^{-1}$ intramuscular (IM) is an opioid agonist–antagonist analgesic in cats with a wide margin of safety that can be used to provide mild sedation and analgesia. Combinations of butorphanol with dexmedetomidine at 0.005–0.01 mg kg$^{-1}$ IM are more effective than each of these drugs used separately and produce sedation with more significant analgesia. Rapid induction and airway intubation allow for delivery of light levels of isoflurane or sevoflurane, which cause bronchodilation.[54] In addition, ketamine premedication or induction (~5–7 mg kg$^{-1}$) is often recommended because it is associated with bronchodilation via central release of catecholamines, stimulating beta-2 adrenergic receptors and inhibits vagal pathways, resulting in an anticholinergic effect on airway smooth muscle.[55,56] These drugs increase lower airway size and decrease the resistance to inflation of the alveoli. In most cases, asthmatic patients subsequently perform well under inhalation anesthetics.[54]

## Laryngeal paralysis

Laryngeal paralysis is a condition recognized mostly in older dogs that can develop slowly over a year or more until it reaches a stage that causes significant breathing problems or emergencies, as the larynx is unable to adduct properly to allow sufficient air flow into or out of the trachea (Figure 2.9).

Laryngeal paralysis can also be found in cats.[57] A complete physical examination and appropriate laboratory evaluation should be performed before general anesthesia unless the patient is in respiratory crisis. These animals become more dyspneic when frightened, nervous, or anxious, and the anesthetic management should be oriented toward reducing anxiety and stress. Patients are more likely to overheat under conditions that would not make a normal dog hyperthermic, and body temperature should be continuously monitored during the perianesthetic period.

Sedation with antianxiety drugs (i.e. acepromazine at 0.02–0.05 mg kg$^{-1}$ IM, intravenous (IV); dexmedetomidine at 0.002–0.007 mg kg$^{-1}$ IM, IV) and nonstressful handling are important during the preanesthetic period. Although laryngeal paralysis is not believed to be a painful condition, opioid analgesics are frequently administered (i.e. butorphanol at 0.02–0.05 mg kg$^{-1}$ IM, IV; hydromorphone at 0.1–0.2 mg kg$^{-1}$ IM, IV). The synergism of sedatives with the opioid often improves the animal's comfort with handling without significant respiratory depression. In addition, the goal of eliminating anxiety and struggling by the patient often improves breathing and facilitates anesthesia.

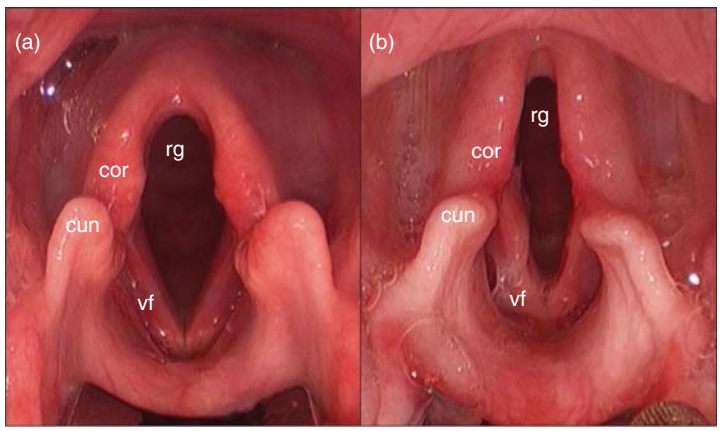


**Figure 2.9** Laryngoscopic view of the normal canine larynx (A) and a canine larynx with laryngeal paralysis (B) showing the cuniform (cun) and corniculate (cor) processes of the arytenoid cartilages. In the normal larynx, the arytenoid cartilages open, allowing sufficient air to move through the rima glottidis (rg) during a respiratory excursion (vf = vocal fold). With laryngeal paralysis, the arytenoid cartilages fail to adduct properly, resulting in a narrowed rima glottidis and increased resistance to breathing. Source: Photo courtesy of Dr. Robert Hardie.

Induction is frequently performed with short-acting intravenous anesthetics such as propofol (2–6 mg kg$^{-1}$ IV) or a dissociative/benzodiazepine combination (ketamine 4–5 mg kg$^{-1}$ with diazepam 0.1–0.2 mg kg$^{-1}$ IV). The recommendation is to titrate the dose of either of these techniques to allow the animal to relax and to facilitate examination of the larynx at the lightest anesthetic plane possible. Since all induction inhalants may affect laryngeal motion to at least some degree, there does not appear to be a clear choice for dogs and cats undergoing diagnostic airway exams.[58–61] In many patients, an initial dose of 2 mg kg$^{-1}$ IV of propofol will be sufficient for effective examination of the larynx if anesthesia is kept light enough. In addition, administration of doxapram (1.1 mg kg$^{-1}$ IV) may be useful for differentiating normal dogs from those with laryngeal paralysis.[62] Once diagnosis of laryngeal paralysis is confirmed, the dog can be intubated and maintained on inhalant anesthetics for the surgical procedure.

During a "tie back" laryngeal paralysis surgery, some surgeons examine the larynx through the mouth to assess the degree of lateralization of the arytenoids cartilages. The dog (or cat) will need to be briefly extubated, then reintubated for the remainder of the surgery and anesthesia; always keep extra induction agent available for this procedure and be aware of the possibility for aspiration of material into the trachea during this time.

At recovery, it is important to keep the animal quiet and comfortable. The goal is to have the patient regain full consciousness without pain or distress. Continuing pain management into the recovery is important. However, administration of pure mu-opioid agonists may result in overly sedate postoperative patients, which can result in aspiration pneumonia (~18–28% of dogs; for review see: reference [63]), a common consequence of the "tie back" surgery. Thus, butorphanol constant rate infusions are commonly performed in the postoperative period (0.2–0.4 mg kg$^{-1}$ h$^{-1}$ IV) to provide analgesia with minimal sedation. The anesthetist should stay with the animal until it is fully conscious and can maintain ventilation without assistance. The endotracheal tube should be left in the animal until they are able to swallow, and any blood or mucous should be cleared from the mouth or upper airway before extubation.

## Restrictive lung disease

Restrictive lung disease is characterized by diminished total lung capacity, which is volume of air in the lungs after maximal inspiration; it is the inspiratory capacity plus the functional residual capacity or vital capacity plus the residual volume after peak expiration (Figure 2.10).

This can be due to either changes in the lung tissue or in the chest wall such as muscle rigidity, obesity, or intra-abdominal changes. Normal breathing encompasses coordination of all structures in both the abdomen and the thorax. Synchronous contraction of the inspiratory intercostal muscles and the diaphragm lower the intrathoracic pressure, allowing air to move into the lungs. Any disease condition that interferes with this process results in impairment to breathing. Limitations in the movement of the diaphragm, chest wall, or abdomen are all integral to the breathing process and result in restriction of air movement. The clinical manifestation of restrictive lung disease is a decrease in the vital capacity of the lung (Figure 2.8); this is in contrast to obstructive lung disease wherein expiratory flow rates and volumes remain normal.[1] The fundamental issue is that the animal has increased difficulty in expanding the lungs.

### Aspiration pneumonia

One specific example of a restrictive lung disease is aspiration pneumonia. Aspiration pneumonia occurs when material enters the lung through the larynx,

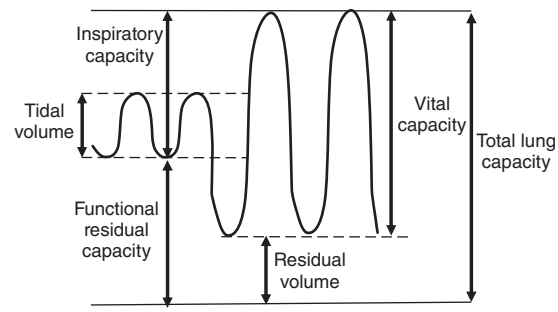


**Figure 2.10** Graphical representation of lung volumes. Total lung capacity is volume of air in the lungs after maximal inspiration; it is the inspiratory capacity plus the functional residual capacity or vital capacity plus the residual volume after peak expiration. A normal tidal volume represents only a small portion of the total lung capacity.

resulting in an inflammatory reaction in the airways. The most common type of aspiration pneumonia occurs when intestinal or foreign material enters the lung, resulting in irritation and inflammation of the tissues.

Although mild aspiration usually results in minor gas exchange problems, supplemental $O_2$ and symptomatic treatment are important to support the animal. Antibiotics should be administered to limit and eliminate infections. If aspiration pneumonia results from deposition of caustic or severely damaging material into the lung, severe tissue destruction will result; frequently, hypoxia and respiratory failure occur rapidly; treatment is usually ineffective, and death frequently occurs. When a large volume of foreign material enters the pulmonary system, physical obstruction of the airways is a concern. If removal is not rapidly performed, asphyxiation and death will occur.

Vomition, regurgitation, and aspiration of intestinal contents can occur during sedation and anesthesia.[64–68] Monitoring the patient for signs of fluid and/or intestinal contents in the mouth or airway is critical. If signs of regurgitation or vomiting are observed, the opening of the oral cavity should be lowered to facilitate gravitational drainage. Opening of the mouth and mechanical cleaning should be immediately performed, as well as examination of the oral cavity and pharynx followed by removal of any foreign material. A stomach tube can then be passed to facilitate removal of additional gastric material. Lavage with clean water and instillation of bicarbonate to increase esophageal pH are recommended.[68] Postanesthesia antibiotics are also recommended to decrease the likelihood of pneumonia.

Anesthetic management of patients with pre-existing pneumonia includes preoxygenation with quick and efficient tracheal intubation and mechanical ventilation. Arterial blood gases should be measured to ensure adequate oxygenation and ventilation. If blood gas analysis is not available, careful respiratory monitoring with a pulse oximeter and capnometer is recommended. The choice of anesthetic or analgesic agents is not as important as supportive patient care. However, caution with respiratory-depressant drugs (i.e. potent opioids and inhalants) should be used.

### Obesity

Another example of a restrictive lung disease is obesity. Obesity is the most common nutritional disorder in dogs and cats and one of the most common diagnosed overall health problems (see Chapter 9). Over half of pet dogs and cats are overweight, with ~25–35% of dogs and cats being clinically obese.[69] These animals are expected to have a shorter life span and increased incidence of osteoarthritis, diabetes mellitus, cardiovascular disease, pancreatitis, mammary tumors, and renal disease.[69] Although it is unknown what the actual increase in anesthetic risk is due to excessive body weight, it is generally believed that the likelihood of anesthetic complications will be greater in the overweight animal.

Obesity results in restrictive lung disease because of the presence of excessive visceral fat, adding pressure to abdominal organs and increasing the inhalational efforts of the animal. Ventilation is subsequently limited by the adipose tissue, and breathing is easily compromised by placing the animal in a recumbent position. Dorsal recumbency is the worst position, as it puts the largest portion of the lung in a dependent position.[69] Ventilation should be supported in all obese patients. This can be accomplished with manual ventilation or with a mechanical ventilator. Monitoring of the patient's arterial $CO_2$ and $O_2$ levels is used to determine the rate and volume of ventilation needed by the animal.

Additional concerns associated with excessive weight include calculation of the appropriate drug dosage. The dosage should be calculated on the basis of the animal's estimated ideal weight; dosing for the actual weight will frequently result in overdosage.[69] Drug dosages based on the body surface area are even more accurate and provide a better method for accurate effects (Table 2.2).

In addition, site of drug injection and the length of the needle should be chosen to insure that the drugs are injected into muscle rather than fat. Injections into fat will be absorbed more slowly than drugs administered intramuscularly. The slower onset can also result in longer duration of effect than is expected in the lean animal. In addition, the chosen muscle may also affect the speed and depth of sedation achieved.[70]

The route of administration depends on how the specific agent is administered and on the pharmacologic mechanism of action. For example, receptor-bound drugs obviously work at specific receptors on the cell membrane. For the most part, receptor numbers are not specifically associated with the animal's weight, and the dose does not necessarily need to be increased. Similarly, since the epidural space is reduced in obese animals, the volume of epidural drug administered will not increase as the animal become overweight. As

**Table 2.2** Sample weight-to-body surface area conversions

| Dogs | | Cats | |
|---|---|---|---|
| **Body weight (kg)** | **BSA ($m^2$)** | **Body weight (kg)** | **BSA ($m^2$)** |
| 1.0 | 0.101 | 0.5 | 0.063 |
| 5.0 | 0.295 | 1.0 | 0.100 |
| 10.0 | 0.469 | 2.0 | 0.159 |
| 15.0 | 0.614 | 3.0 | 0.208 |
| 20.0 | 0.744 | 4.0 | 0.252 |
| 25.0 | 0.864 | 5.0 | 0.292 |
| 30.0 | 0.975 | 6.0 | 0.330 |
| 35.0 | 1.081 | 7.0 | 0.366 |
| 40.0 | 1.181 | 8.0 | 0.400 |
| 45.0 | 1.371 | 9.0 | 0.433 |
| 50.0 | 1.371 | 10.0 | 0.464 |
| 55.0 | 1.461 | | |

Body surface area (BSA) in square meters = $K \times$ body weight in grams$^{2/3}) \times 10^{-4}$.
$K$ = constant (10.1 for dogs, 10.0 for cats).

a rule, similarly to systemic administration, epidural drugs should be administered on the lean animal's weight.

Frequently, the overweight animal is less active and is in poor condition. The cardiovascular system is both weaker and has a greater demand because of the increased animal's weight. The overweight animal also has more difficulty dissipating body heat, resulting in hyperthermia; monitoring of body temperature is critical to prevent overheating. However, hypothermia can also be a problem, and rewarming of the animal can be difficult.[69] Some breeds are classically associated with obesity. Bulldogs, Pugs, and Boston Terriers are frequently associated with Brachycephalic Airway Syndrome[71], which can worsen with excessive weight. Extra care should be taken to assure a patent airway is maintained in these animals.

Monitoring the overweight animal can be more challenging because normal physiologic parameters seen in ideal-weight patients are frequently altered. For example, the normal heart rate of the obese animal may be higher due to the increased cardiac work.[69] Ventilation will often be faster but shallower than for the lean animal due to reduced VT associated with excessive weight; end-tidal or arterial $CO_2$ analyses are excellent methods of assessing the adequacy of ventilation in all patients but are especially imperative in obese patients. Blood pressure should be similar to animals of normal weight, but caution should be taken to insure that all parts of the animal are well perfused, as some areas may experience additional pressure owing to excess fat. Checking pulses in each leg and the tongue aids in the assessment of blood flow to all areas.

Anesthetic recovery for the overweight animal is one of the critical aspects of anesthetic management. Make sure the animal is well padded and is positioned to prevent pressure points on the nerves and muscles. Positioning the patient to facilitate ventilation is also important. Remember that the overweight animal may not have normal respiratory muscle strength and may need more assistance in regaining sternal recumbency, as well as normal ventilatory efforts. Drug elimination and metabolism, as well as any respiratory-depressant effects, will likely be prolonged in the overweight animal, so timely discontinuation of the gas anesthetics should be performed.

In summary, when managing the overweight animal, it is important to have a well-prepared plan of action. Firstly, assess the patient's pain and sedation needs. Choose dosages on the basis of the ideal body weight and the temperament of the animal; quiet animals generally are sedated using lower dosages of drugs, whereas excited animals require higher dosages. Administer the drugs insuring that they are injected in a vascular muscle wherein absorption will be rapid. Be prepared to support ventilation during anesthesia. Induce general anesthesia with a dosage adjusted for the animal's ideal weight. During anesthesia, monitor to ensure excellent tissue perfusion and ventilation and keep maintenance anesthetic levels appropriate for the procedure. During recovery, support the patient's ventilation and make sure that the body temperature is returning to normal levels, and keep the animal comfortable throughout the return to consciousness.

## Summary

Anesthetic management of dogs and cats with respiratory diseases can usually be performed if care is provided to insure adequate oxygenation and $CO_2$ elimination. The most critical consideration is to minimize patient stress and anxiety during handling and induction; proper premedication with analgesics and sedatives should be a standard of anesthetic management of dogs

or cats with respiratory disease. Rapid control of the animal's airway with a properly placed endotracheal tube and ventilatory support is essential for the anesthetic care of animal with respiratory disease. Clinicians should review and be familiar with the normal function of the respiratory system and insure that the patient is stabilized before anesthesia. Capnometry should be a routine monitoring method of all animals during anesthesia and is especially essential for all animals with respiratory disease.

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# 3 Neurologic disease

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Patients with diseases involving the nervous system often require anesthesia for diagnostic imaging, sample collection, or treatment of the disease pathology. Others will require anesthesia for procedures unrelated to the disease of the nervous system. Understanding the physiology and pathology of the nervous system is important when considering an anesthetic plan during which the goal should be optimization of cerebral blood flow (CBF) and perfusion and prevention of increases in intracranial pressure (ICP).

## Brain physiology

### Cerebral blood flow

Blood flow to the brain is a function of the cerebral perfusion pressure (CPP) and the cerebral vascular resistance (CVR). Both of these variables are maintained by autoregulation, cerebral metabolic rate (often measured by the rate of oxygen consumption; $CMRO_2$), the arterial partial pressure of carbon dioxide ($PaCO_2$), the arterial partial pressure of oxygen ($PaO_2$), the central venous pressure (CVP), and the autonomic nervous system. Autoregulation of CBF ensures that the flow remains constant despite changes in CPP.[1]

In clinically normal canines, the CBF is approximately 67–90 ml $min^{-1}$ 100 g tissue.[1–3] In clinically normal felines, the CBF is approximately 40 ml $min^{-1}$ 100 g tissue.[1,2,4]

The brain is unique in that an intact, boney, noncompliant skull encases the intracranial structures. All intracranial structures (tissue, cerebral spinal fluid, and blood) must have a fixed volume to maintain normal intracranial volume. Any increases in the volume of tissue, cerebral spinal fluid, or blood without a concomitant decrease in the volume of another constituent will lead to an increase in intracranial volume and therefore an increase in ICP. This is illustrated by the Monro–Kellie Doctrine (Equation 3.1).[5]

Equation 3.1 Monro–Kellie Doctrine. Total volume ($V$) of intracranial constituents is equal to brain volume, cerebral spinal fluid volume, and blood volume combined.

$$V_{\text{intracranial}} = V_{\text{brain}} + V_{\text{CSF}} + V_{\text{blood}} \qquad (3.1)$$

If ICP continues to increase, herniation of brain tissue from its normal position within the skull may occur. Signs of brain herniation may include increasing systolic and pulse pressures, bradycardia, and irregular breathing, collectively known as the Cushing response.[6] Efforts at preventing and treating increased ICP should be aimed at decreasing the volume of the intracranial constituents. This can be achieved with therapeutic interventions such as hyperventilation, hyperosmotic therapy, or diuretics.

### Autoregulation

Under normal conditions, CBF is strictly autoregulated, keeping it constant over a wide range of CPPs and mean arterial pressures (MAPs, 60–140 mmHg) (Figure 3.1). When systemic pressure increases, cerebral arterial constriction occurs, and when systemic pressure decreases, cerebral arterial vasodilation occurs.[1] These active vascular responses maintain a constant CBF despite the wide range in perfusion pressures. Several disease processes, including hypertension, intracranial masses, traumatic brain injury (TBI), and the presence of volatile anesthetics, affect autoregulation. Thus, blood flow patterns may be altered by the disease process itself in addition to general anesthetics.

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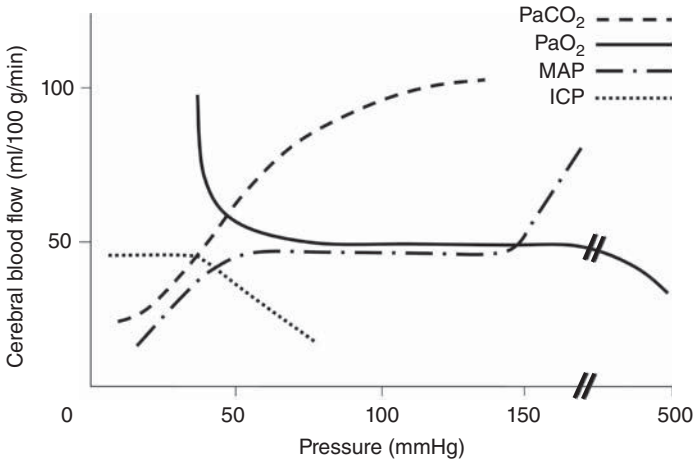


**Figure 3.1** Impact of the intracranial pressure (ICP), partial pressure of oxygen ($PaO_2$), partial pressure of carbon dioxide ($PaCO_2$), and mean arterial pressure (MAP) on cerebral blood flow in milliliters per 100 grams of brain tissue per minute.[1,7] Source: Image courtesy of Kristen Cooley, BS, CVT (anes).

### Cerebral perfusion pressure and mean arterial pressure

Cerebral perfusion pressure has a large effect on CBF. CPP is defined as the difference between MAP and ICP (Equation 3.2). Normal values for humans include a MAP range from 60 to 160 mmHg and ICP from 5 to 10 mmHg. Therefore CPP is 55–150 mmHg.[1] Although subtle species differences in these values may exist, the concept remains as follows: when ICP increases, MAP must also increase to maintain CPP. Since hypotension is not uncommon during anesthesia, MAP must be monitored vigilantly and treated aggressively.

Equation 3.2 CPP is the difference between MAP and ICP.

$$CPP = MAP - ICP \quad (3.2)$$

### Cerebral metabolic rate

Typically, the CBF and the cerebral metabolic requirement of oxygen ($CMRO_2$) are directly related. As CBF increases or decreases, $CMRO_2$ changes in the same direction. This relationship is referred to as CBF/$CMRO_2$ coupling. The $CMRO_2$ is influenced by several factors, including temperature and anesthetic drugs such as inhalants, sedatives, and analgesics.[1]

### Arterial partial pressure of carbon dioxide and oxygen

The $PaCO_2$ rapidly affects CBF; therefore $CO_2$ is often targeted in the treatment of increased ICP (Figure 3.1). CBF increases by approximately 2 $ml\,min^{-1}$ 100 $g^{-1}$ of brain tissue for every 1 mmHg increase in arterial carbon dioxide over the range of $PaCO_2$ from 20 to 80 mmHg.[8] This is mediated by the changes in the pH of the cerebrospinal fluid (CSF) surrounding the arterioles. As the pH decreases with hypercapnia, vasodilation and increased ICP result. Thus, it is important to maintain normocapnia or mild hypocapnia ($PaCO_2$ between 30 and 35 mmHg) to prevent or treat intracranial vasodilation. Normocapnia or mild hypocapnia is achieved through mechanical ventilation. Controlling $PaCO_2$ can be instrumental in controlling cerebral blood volume and ICP in the short term.

The $PaO_2$ has an effect on CBF as well, but not until levels are below 50 mmHg (Figure 3.1). At this level of hypoxemia, cerebral vasodilation will occur, increasing CBF and ICP. Although monitoring oxygenation with arterial blood gases is the definitive way to accurately determine $PaO_2$, it may not be available. As such, pulse oximetry can be used with the understanding that recognition of hypoxemia may be delayed while on 100% oxygen, according to the oxygen–hemoglobin dissociation curve.[9]

### Central venous pressure

Blood flows continuously out of the brain when ICP is higher than CVP. Under normal conditions, CVP has almost no effect on CBF. In situations wherein CVP is increased, however, CBF will also increase.

## Anesthesia

### Preanesthetic considerations

For patients who are unstable before anesthesia, extracranial stabilization should be the first priority. Stabilizing hemodynamic parameters such as cardiac output and blood pressure by initiating adequate volume replacement is of utmost importance. Head trauma may affect ventilatory centers; therefore, adequate oxygenation and ventilation must also be a priority. After the most life-threatening problems have been addressed, intracranial stabilization should follow shortly. This includes maintaining normal CBF, CPP, and ICP.

#### Glycemic control

Hyperglycemia is a common sequela to head trauma and is significantly associated with the severity of injury in both dogs and cats.[10] Numerous reports have shown that hyperglycemia in the face of head trauma leads to higher mortality rates and worse neurologic outcomes.[11–13] Glucose levels above 180 mg $dl^{-1}$, specifically, are associated with poorer outcomes in patients with brain injuries.[14] However, because glucose is essential to cerebral metabolism and mental alertness, levels below 60 mg $dl^{-1}$ should be treated with glucose supplementation.[15]

#### Methods to manage increased intracranial pressure

It is not practical to measure ICP in veterinary patients, so changes in clinical signs that suggest increases in ICP must be assessed before anesthesia and closely monitored during and after anesthesia. Absent or abnormal pupillary reflexes and mentation and ventilatory pattern changes may be appreciated on physical examination. The Cushing response is a result of increased sympathetic discharge to the peripheral vasculature and a reflex increase in parasympathetic discharge to the heart, respectively.[6] These events occur as a result of increasing ICP and happen in an attempt to maintain cerebral perfusion.

##### Posture

It has been proposed that in human patients with head injury, a head elevation of 30° may help prevent further increases in ICP by encouraging venous outflow.[16–19]

##### Hyperventilation

Hyperventilation, thus lowering $PaCO_2$, is the most effective method for rapidly reducing ICP by decreasing CBF.[20–22] A common recommendation is to maintain the $PaCO_2$ near 30–35 mmHg.[1] Hypocapnia, however, can worsen cerebral ischemia in cases of traumatic brain injuries[23] so this approach should be limited to emergency management of increased ICP.

##### Hyperosmotic therapy

Mannitol may be used to reduce ICP in patients with previously elevated ICP.[24] Mannitol increases plasma osmolarity, causing a movement of water down an osmotic gradient from the intracellular and interstitial areas of neuronal tissue to the intravascular space within the brain and ultimately to the systemic circulation. Mannitol may also reduce ICP by increasing cerebral perfusion, causing cerebral vasoconstriction[25,26] and by decreasing the production of CSF.[27] Despite its many mechanisms of ICP reduction, mannitol may cause elevations in ICP through reversal of the initial plasma-to-blood osmotic gradient in patients without an intact blood–brain barrier.[28] In these cases, hypertonic saline may be a viable alternative.

Hypertonic saline works similarly to mannitol, causing a net loss of water from intracranial structures to the systemic circulation. It may be used in patients with intracranial pathology to reduce or prevent increases in ICP.[29–31] In cases of TBI, hypertonic saline is more effective than mannitol in treating elevated ICP.[32–34] The effect on decreasing intracranial volume may be limited, however, to <90 min,[35] limiting its use for long-term control of elevated ICP.

### Anesthetic management

#### Sedatives and analgesics

Acepromazine has historically been implicated in decreasing the seizure threshold in patients with a history of seizure activity. A retrospective study has since indicated that acepromazine can be used without the risk of increasing the likelihood of seizure.[36] Since acepromazine exerts antagonist effects on alpha-1 adrenergic receptors leading to vasodilation and subsequent hypotension, this sedative should be used with caution in patients with intracranial pathology (Table 3.1). MAPs should be closely monitored in order to maintain CPP (Equation 3.1).

**Table 3.1** Effects of opioids, sedatives, and anesthetics on intracranial pressure (ICP).

| Drug or drug class | Effect on ICP |
|---|---|
| Opioids | Decrease, however, can indirectly cause increases through hypoventilation/hypercapnia or emesis |
| Benzodiazepines | No change or decrease |
| Acepromazine | Potential increase secondary to cerebral vasodilation and increase CBF |
| Alpha-2 adrenergic agonists | No change |
| Propofol | Decrease |
| Etomidate | Decrease, however, may cause increases secondary to retching |
| Barbiturates | Decrease |
| Ketamine | Increases, however, may cause no change if used with other sedatives and controlled ventilation |
| Isoflurane, sevoflurane, desflurane | In general, no change if <1 MAC, increase if >1 MAC or if hypercapnia occurs |
| Nitrous oxide | Profound increase |

Both dexmedetomidine and midazolam appear to be rational choices in patients with intracranial disease. Dexmedetomidine decreases CBF in dogs anesthetized with halothane or isoflurane.[37,38] Midazolam reduces CBF by decreasing the cerebral metabolic rate of oxygen consumption.[39] Opioids are an acceptable choice for premedication and analgesia in neurologic patients, as they have minimal direct effects on CBF and ICP.[40] Opioids, however, can indirectly increase ICP. Opioids as premedicants may cause emesis[41,42] which can cause increases in ICP. They can also cause hypoventilation, leading to an increase in ICP secondary to hypercapnia; therefore, assisted or mechanical ventilation during general anesthesia is recommended.[43] Because pain can also cause respiratory depression, avoiding the use of opioids as analgesics in these situations cannot be recommended.

### Injectable anesthetics

Barbiturates, etomidate, and propofol all decrease CBF and ICP and contribute to the decrease in $CMRO_2$ seen with CNS depression.[43–48] The use of ketamine in patients with intracranial pathology is controversial. Unlike other injectable anesthetics, ketamine does not reduce CBF, ICP, or $CMRO_2$.[7] Early studies examining ketamine's effect on intracranial hemodynamics were performed in humans without concurrent sedation or mechanical ventilation. The use of ketamine in patients with controlled ventilation in combination with other sedative agents has demonstrated no increase in ICP[49] and may be a reasonable choice in veterinary patients when used under these circumstances.

### Inhalant anesthetics

In general, inhalant anesthetics increase CBF and decrease $CMRO_2$. The effect on CBF is a result of opposing actions on cerebral vasculature; vasodilation due to direct action on vascular smooth muscle vs decreases in blood flow due to a reduction in $CMRO_2$.[50] Most volatile anesthetics minimally affect CBF when used at concentrations below 1 minimum alveolar concentration (MAC). Above the MAC, however, cerebral blood vessels will continue to dilate and cause increased CBF and possible increased ICP. The changes in CBF are inhalant and dose specific. Sixty percent nitrous oxide increases CBF and $CMRO_2$ by up to 203% in dogs.[51] Of the volatile anesthetics, halothane appears to have the most effect on CBF, whereas enflurane, isoflurane, sevoflurane, and desflurane are similar in their effect on CBF.[52] Halothane produces significant increases in CBF at 0.5–1.5 times the MAC in cats, whereas isoflurane does not.[53] Sevoflurane and isoflurane have minimal effects on CBF at concentrations of anesthetic up to 2.15 MAC in anesthetized dogs.[54] Similarly, desflurane concentrations from 0.5 to 1.5 MAC cause dose-dependent increases in the CBF of anesthetized dogs.[55] The magnitude of $CMRO_2$ reduction is least with halothane but similar with isoflurane, sevoflurane, and desflurane.[53–57] In mechanically ventilated anesthetized dogs, both isoflurane and sevoflurane significantly decrease CPP at two times the MAC, with mean CPP lower during isoflurane anesthesia at all MAC tested.[58] The inhalant anesthetics increase ICP in parallel to the increases in CBF.[56,59] These effects, however, can by minimized by hyperventilating to mild

hypocapnia.[60] Thus, it is important to use a balanced or multimodal approach to anesthesia, which will permit reduction in the inhalant levels required for a surgical anesthetic plane but minimally affect the oxygen supply to the CNS.

## Anesthetic management of specific disease processes

### Traumatic brain injury

Traumatic brain injury is divided into primary and secondary events. Primary injuries are the result of the initial traumatic event and irreversible, whereas secondary injuries occur after and can lead to the death of more neuronal tissue. The etiology of secondary brain injury includes hypoxemia, hypotension, increased ICP, and decreased CBF.[61–63]

Diagnostic imaging, such as computed tomography (CT), may be performed in these patients after initial stabilization. Other procedures requiring anesthesia may be necessary, such as the management of intrathoracic and intra-abdominal injuries or fracture stabilization. The goals of anesthesia should be aimed at maintaining oxygenation, systemic blood pressure, and CPP, while preventing further increases in ICP.

Premedication should focus on providing analgesia and decreasing induction doses of injectable drugs and inhalant concentrations. Rarely is a sedative indicated. Anesthetic agents that increase CBF (halothane and nitrous oxide) should be avoided. Most injectable anesthetics (barbiturates, propofol, and etomidate) reduce $CMRO_2$ and decrease CBF, therefore are reasonable induction choices for patients with TBI. Rapid intubation with minimal laryngeal stimulation, as to not provoke coughing, and a resultant increase in ICP should be performed. If a difficult intubation is suspected, preoxygenation (100 $ml\,kg^{-1}\,min^{-1}$) of the patient with a tight-fitting mask for 3 min will avoid desaturation of hemoglobin for ~5 min.[64] Assisted or mechanical ventilation should be instituted to avoid hypercapnia and cerebral vasodilation. Hypocapnia should also be avoided, as it can worsen cerebral ischemia in TBI.[23] Maintenance of anesthesia may include continuous infusions of intravenous analgesics such as a combination of fentanyl and propofol or low dose volatile anesthetics.

In the recovery period, continuous monitoring of neurologic status is prudent. The use of standardized scoring systems for neurologic injury and outcome, such as the Glasgow coma scale, have been validated and widely used in human patients. A modified Glasgow coma scale has been used in veterinary medicine with some success.[65] More typically, veterinary clinicians rely on serial neurologic assessments and response to treatment to predict the severity of injury and the prognosis.

### Intracranial tumors

Tumors found within the brain may be primary or metastatic. Meningiomas are the most common primary intracranial tumor in dogs and cats followed closely by astrocytomas and oligodendrogliomas in dogs and lymphoma in cats.[66–68] The most common dog breeds affected are Golden Retrievers and Boxers[67,69] whereas domestic shorthaired cats seem to be predisposed.[66,68] Clinical signs can be extremely variable. Dogs present most frequently with seizures, changes in mentation, vestibular syndrome, blindness, and neck pain[67,69] whereas cats present with altered consciousness, circling, and seizures.[66,68,70]

Diagnosis of intracranial tumors requires the use of imaging techniques such as CT or magnetic resonance imaging (MRI), while treatment may require surgical intervention or radiation. All of the aforementioned require anesthesia for veterinary patients. If intramuscular premedication is necessary, drugs that have minimal effects on ICP should be used. Pure mu-agonists, such as morphine and hydromorphone, may cause emesis, which can increase ICP.

Anesthesia should be induced with drugs that induce unconsciousness rapidly and reliably without increasing the ICP. Laryngeal stimulation leading to coughing should be avoided, and the patient should be mechanically ventilated to avoid hypercapnia and cerebral vasodilation. Maintenance of anesthesia should be aimed at providing a balanced approach. Fluid therapy should be instituted with either isotonic crystalloids or hyperosmolar solutions, being careful to avoid hypervolemia. Monitoring should include the placement of an arterial catheter for the measurement of invasive blood pressures, as well as pulse oximetry, capnography, and electrocardiography. In the recovery period, the assessment of neurologic status may be postponed to ensure that the sedative effects of drugs given during

anesthesia are not exacerbating pre-existing neurologic conditions.

## Seizure disorders

Seizures are caused by transient, paroxysmal, and synchronous discharge of neurons in the brain.[1] Clinical presentations depend on the extent of brain involved and the specific area of the brain that is affected. Causes of seizures can be classified into two categories. Extracranial causes of seizures, such as metabolic disturbances, toxicosis, and systemic disease necessitate treatment of the underlying cause, which is often curative. Intracranial causes of seizures include many disorders such as degenerative, anomalous, neoplastic, infectious, inflammatory, idiopathic, traumatic, and vascular conditions. Treatment typically involves maintaining normal temperatures, ensuring adequate perfusion, oxygenation and ventilation, and instituting therapies to decrease the development of cerebral edema and stop any continued seizure activity.[71,72]

Managing anesthesia in patients with a history of seizures must include consideration of the effect of antiepileptic drugs on anesthesia. Anticonvulsants that result in sedation can have additive effects, whereas drugs that induce hepatic enzymes could alter the pharmacokinetics and pharmacodynamics of anesthetic drugs.[1] Avoid the use of epileptogenic drugs such as methohexital and enflurane. For many years, acepromazine was avoided owing to the suspected increase in seizure activity associated with administration. A retrospective study has since indicated that acepromazine does not potentiate seizure activity.[36] Opioids, benzodiazepines, propofol, and barbiturates are reasonable choices for the anesthetic period. During the recovery period, continued monitoring for seizure activity is important and treatment instituted if necessary.

## Intervertebral disc disease and other spinal injuries

Intervertebral disc disease and vertebral trauma leading to spinal cord dysfunction are major causes of neurologic injury in small animal patients. Traumatic injuries cause disruption of neural tissue leading to demyelination, axonal injury, and neuronal and axonal destruction.[73] Pain results either from instability of local tissues or from the compression of spinal structures.

Patients with suspected spinal cord compression may undergo some form of diagnostic imaging, either spinal radiography, myelography, CT, or MRI that necessitates the use of general anesthesia. They may also undergo surgical intervention.

Several goals should be addressed during this time. Sedation, induction and maintenance techniques, and drug choices should focus on providing necessary analgesia and using balanced anesthetic techniques. If a fracture or luxation is suspected, immobilization and stabilization of the spine before anesthesia are extremely important, as relaxation of paraspinal musculature can lead to instability and further damage. Maintaining physiologic parameters such as heart rate and blood pressure is imperative. Certain breeds of dogs, such as dachshunds, are more susceptible to developing bradycardia during spinal imaging.[74] The treatment of bradycardia with an anticholinergic such as glycopyrrolate may help maintain normal heart rates during anesthesia. Hypothermia is a frequent complication of anesthesia in veterinary patients.[75,76] The maintenance of normothermia can be challenging; however, using intravenous fluid warming devices[77] and forced air warming devices[78] may attenuate drops in temperature. Patients receiving radiographic imaging studies or myelography may undergo frequent position changes under anesthesia predisposing patients to tracheal trauma.[79,80] Paying particular attention to reducing endotracheal tube movement during patient positioning may decrease this risk.

Dogs anesthetized for the treatment of intervertebral disc disease are at risk for developing pneumonia postoperatively.[81] Efforts to shorten the duration of anesthesia and prevent postanesthetic vomiting and regurgitation may decrease this risk. Postmyelography seizures are reported in 3–14% of dogs.[82,83] Acute anticonvulsant therapy should be instituted and is described elsewhere.[71,72]

Patients with nervous system dysfunction or injury to nervous system tissues, similar to that which might occur in patients with intervertebral disk disease, are at risk for developing neuropathic pain. Reorganization of sensory transmission within the nervous system, including central sensitization, central disinhibition, and phenotypic changes to A-beta fibers, are the mechanisms thought to be responsible.[84] Because of this neurochemical transformation, perioperative analgesia regimes using opioids may not be sufficient for these patients. Adjunct analgesics, such as a ketamine constant rate infusion, are beneficial. The reader is referred

to an article by Mathews for an extensive review of the pathophysiology and treatment of neuropathic pain.[84]

### Chiari-like malformation and syringomyelia

Patients may present with a suspected Chiari-like malformation, diagnosed definitively with MRI. Some of the most common clinical signs in dogs with syringomyelia secondary to a Chiari-like malformation are cervical pain, allodynia, and dysesthesia.[84–87] When planning the anesthetic management of these patients, one must consider using a balanced anesthetic technique by providing adequate analgesia. Focus should also be on preventing increases in ICP.

### Other nervous system disorders

Dysautonomia is a rare idiopathic condition characterized by degeneration of neurons in the autonomic nervous system ganglia. Clinical signs and physical examination findings reflect the severity of degeneration in both sympathetic and parasympathetic nervous systems. Dysuria with a distended urinary bladder, mydriasis with absent pupillary light reflexes, xerostomia, decreased tear production, decreased anal tone, and vomiting or regurgitation were reported most commonly in dogs with dysautonomia.[88,89] In cats, lethargy, inappetence, vomiting, dysphagia, stranguria, mydriasis with absent pupillary light reflexes, xerostomia, prolapse of the nictitans, and bradycardia have been reported.[90] In general, dysautonomia has a grave prognosis with very high mortality rates in both dogs and cats.[88–90] Patients needing anesthesia should be managed similar to any critically ill patient, paying particular attention to heart rate and potential for regurgitation.

Myasthenia gravis is a congenital or an acquired autoimmune disease that causes a decrease in functional acetylcholine receptors at the neuromuscular junction. Clinical signs include muscle weakness and megaesophagus, making pulmonary aspiration of gastric contents a risk. Treatment includes anticholinesterase drugs in combination with immunosuppressive therapies when indicated. Patients with myasthenia gravis may need anesthesia for procedures unrelated to the disease. Special attention should be paid to the increased risk of aspiration of gastric contents. Patients should be induced and intubated rapidly. Extubation should be performed when a patient demonstrates the ability to adequately maintain respiration and to protect their airway via the return of the ability to swallow. Because of the decrease in functional acetylcholine receptors, these patients may have an increased sensitivity to nondepolarizing muscle relaxants such as atracurium.[91,92] If the use of nondepolarizing muscle relaxants is necessary, the dose should be reduced by one half to two thirds and the response monitored with a peripheral nerve stimulator.[93,94] Interestingly, human patients with myasthenia gravis are somewhat resistant to the effects of depolarizing muscle relaxants.[95] However, this has not been described in veterinary patients.

Peripheral neuropathies can be associated with several other conditions, including cancer[96] and diabetes mellitus.[97,98] Paraneoplastic peripheral neuropathies occur in patients with malignant disease and have been reported with several tumor types in the veterinary literature.[99–110] Patients with diabetes mellitus are more susceptible to peripheral nerve ischemia due to compression and stretching. During anesthesia, positioning and padding are extremely important to prevent further injury to nerves. In addition, peripheral neuropathies may increase the effects of nondepolarizing muscle relaxants because of neural damage and the possibility of denervation-induced upregulation.[111]

Nerve sheath tumors originate from nerve roots or peripheral nerves, most commonly the cervical nerve roots or brachial plexus.[112] Clinical signs are dependent on the tissues involved but commonly include unilateral forelimb lameness with varying degrees of pain. Muscle atrophy and neurologic deficits may also be present. Diagnostic imaging such as radiographs, CT, or MRI may be necessary for surgical planning. The goals of anesthetic management should focus on using a balanced, multimodal approach while providing adequate analgesia. Because these patients may be experiencing neuropathic pain, opioids alone may not be sufficient.[84]

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# 4 Hepatobiliary disease

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The liver is a highly complex organ that serves a number of vital functions. Hepatic disease can present a number of anesthetic challenges. Liver dysfunction can range from elevation of liver enzymes with no clinical disease to fulminant liver failure. Fortunately, veterinary patients rarely present for anesthesia with severe liver disorders leading to hepatic failure such as cirrhosis or hepatitis. However, many liver conditions require surgical interventions such as liver biopsy or portal venous shunt repair and thus require sedation or general anesthesia. The anesthetist must understand the extent of the disease, the abnormalities associated with the disease, and their repercussions on drug metabolism and patient homeostasis before formulating an anesthetic plan.

## Anatomy and physiology

Blood flow to the liver comprises 25–30% of total cardiac output and is provided via dual blood supplies: the hepatic artery and portal vein. The portal vein accounts for 75% of the blood flow but, owing to the relatively low oxygen saturation of portal venous blood, provides only 50–55% of hepatic oxygen requirements. However, the hepatic artery provides only 25% of blood flow but 45–50% of oxygen requirements. Owing to the constitutively high hepatic blood flow, increases in hepatic oxygen demand are met with increased oxygen extraction from the blood rather than further increases in blood flow to the organ itself.[1]

Under normal circumstances, decreases in cardiac output or systemic blood pressure with accompanying decreases in portal venous flow are usually compensated for by increases in hepatic arterial flow. The hepatic vasculature is richly innervated with α1-adrenergic receptors; sympathetic nervous system activation results in hepatic artery vasoconstriction and, therefore, reduced hepatic blood flow.[2] Hepatic blood flow is also decreased in the face of increased portal pressure and is directly related to central venous pressure (CVP); such increases in CVP may be associated with congestive heart failure or positive pressure ventilation. Circumstances such as these will impair outflow of blood from the liver, increasing portal venous pressure and decreasing hepatic blood flow.

In healthy animals, the liver provides multiple essential functions, which include bile formation and excretion, metabolic functions, synthesis of plasma proteins, and storage of glycogen. Although the liver serves a wide array of functions, it has substantial reserve, and significant disease may be present before clinical abnormalities are evident. Bile salts and acids are synthesized in hepatocytes, and bile is carried from hepatic lobules by bile ducts, with the gallbladder serving as a reservoir in most species. The common bile duct releases bile into the duodenum on relaxation of the sphincter of Oddi. The administration of morphine has been known to cause spasm of the sphincter of Oddi in several species and was once contraindicated in the face of acute pancreatitis.[3] Recent human research suggests that morphine is safe for analgesic use in acute pancreatitis and there is no clinical evidence to avoid the use of morphine in patients with hepatobiliary disease for this reason (see Opioids).[4]

Multiple enzymatic pathways are present in the liver, thereby metabolizing carbohydrates, proteins, fats, and pharmacological agents. Carbohydrate metabolism results in synthesis of glucose and its storage in the form of glycogen. Abnormalities in glucogenesis can lead to hypoglycemia, a common presenting complaint

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in patients with severe hepatic dysfunction. Protein metabolism through deamination provides further vital energy substrates to the organism but produces ammonia as a by-product. Under normal circumstances, ammonia is cleared from the body but can be elevated in certain hepatic disease states, leading to hepatic encephalopathy. Anesthetic and analgesic agent metabolism may also be impaired in the patient with hepatic disease, leading to prolonged drug effects. With few exceptions, most anesthetic agents undergo hepatic biotransformation to active or inactive compounds. Many of these reactions rely on the cytochrome P-450 enzyme (CYP) system of the liver. The hepatic CYP enzymes can be induced by the administration of drugs such as barbiturates and inhibited by the administration of multiple drugs such as ketoconazole and cimetidine (Table 4.1).[5] Enzyme induction can cause a degree of drug tolerance and cross-tolerance, thus requiring an increase in patient drug dosages, especially with chronic administration of enzyme inducers such as phenobarbital. Conversely, drug dosages should be decreased when enzyme inhibitors have been chronically administered, as enzyme inhibition may lead to a decrease in hepatic drug metabolism. Greyhounds appear to have decreased activity of the CYPs, accounting in part for the increased anesthetic drug duration observed in this breed.[6] This has been extrapolated to all members of the sighthound family; drugs that rely heavily on the CYP system for biotransformation, such as thiopental, should be avoided or decreased in dosage in these breeds.[7]

**Table 4.1** Enzyme inhibitors and inducers commonly encountered in veterinary medicine.

| Enzyme inhibitors | Enzyme inducers |
|---|---|
| Ciprofloxacin | Rifampicin |
| Erythromycin | Phenytoin |
| Chloramphenicol | Phenobarbital |
| Ketoconazole | Omeprazole |
| Itraconazole | St John's Wort |
| Fluconazole | Insulin |
| Fluoxetine | Dexamethasone |
| Omeprazole | Tramadol |
| Cimetidine | |
| Ranitidine | |
| Quinidine | |
| Amiodarone | |
| Chlorpromazine | |
| Methadone | |
| Propofol | |

Note that some pharmacological agents may act as both an enzyme inhibitor and an inducer, depending on the CYP enzyme form.[5]

One of the most vital roles of the liver is protein synthesis. Nearly all proteins are formed in the liver. This includes albumin, coagulation factors, and cholinesterase.[2] Albumin is critical in providing plasma oncotic pressure and transport of multiple substances including anesthetic drugs. Hypoalbuminemia, azotemia, and acidosis reduce drug binding to albumin. This subsequently increases the free, unbound drug portion and potentially increases the drug effect. Albumin has a half-life of ~21 days; due to this prolonged half-life, acute liver disease will not manifest with hypoalbuminemia.[1] In contrast, all coagulation factors except factor VIIC and von Willebrand factor are synthesized in the liver. However, unlike albumin, the coagulation factors have relatively short half-lives and may be affected by acute liver disease.[2,8] Patients with evidence of acute liver dysfunction should have coagulation testing performed before anesthesia and surgery.

## Markers of hepatic dysfunction

Unfortunately, biochemical markers of hepatic dysfunction can be both nonspecific and nonsensitive. Tests of liver function include measurements of serum albumin, blood glucose, bile acid quantification, prothrombin time (PT), blood urea nitrogen (BUN), and cholesterol.[9] Owing to variability in serum half-lives, deviations in these markers of hepatic function may not be present immediately. Owing to the relatively long half-life of albumin (~21 days), hypoalbuminemia may not be seen until hypoglycemia, hypocholesterolemia, and decreased BUN become evident. Coagulation factors have a relatively short half-life, and abnormal coagulation may, therefore, appear with acute disease. The status of the patient's overall coagulation is best performed by thromboelastography (TEG); however, clinically relevant coagulopathies can be detected by elevations in proteins induced by vitamin K antagonism (PIVKA) and PT.[10,11]

Elevations of hepatic enzymes suggest hepatocellular damage rather than true dysfunction.[9] Serum

aminotransferases such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are released with hepatocellular injury and are of some diagnostic use. For example, serum ALT is located only in the liver and, as such, is more specific for liver disease. In any case, the absolute values of these enzymes can be related to the extent of hepatocellular injury but not the reversibility of injury.[10] Serum alkaline phosphatase (ALP) is produced by the liver, bone, small intestine, and kidney. Mild elevations in this enzyme are consistent with hepatocellular injury, and elevations may be present in pediatric patients, patients with bone disease, or patients chronically administered drugs such as phenobarbital, phenytoin, and corticosteroids.[10] Increased γ-glutamyltransferase (GGT) in addition to ALP can be indicative of cholestasis.[9]

The most sensitive and specific test for hepatobiliary dysfunction is preprandial and postprandial measurement of bile acids. Elevations in preprandial and postprandial bile acids can be present in portal venous shunts, cirrhosis, hepatic necrosis and inflammation, steroid hepatopathy, cholestasis, and intestinal obstruction.[9]

Ultimately, it is difficult to definitively diagnose hepatobiliary disease solely on the basis of blood work. Diagnosis should be made by careful physical examination and clinical presentation in addition to biochemical evaluation. Diagnostic imaging, such as abdominal ultrasound, and hepatic biopsy may be necessary to provide a definitive diagnosis.

## Hepatic dysfunction and surgery

Intra-abdominal surgery can result in decreased hepatic blood flow because of the direct compression of hepatic vasculature by surgical manipulation, as well as from activation of the sympathetic nervous system associated with surgical stress and pain. The hepatic vasculature is richly innervated with α1-adrenergic receptors; the release of catecholamines from sympathetic nervous system activation causes an initial vasoconstriction, thereby reducing hepatic arterial flow.[2]

Furthermore, mechanical or assisted ventilation using high positive pressures and/or positive end-expiratory pressure (PEEP) reduces hepatic blood flow as a result of decreases in both cardiac output and portal blood flow.[12] In addition, hypercarbia, which can be associated with spontaneous ventilation under general anesthesia, can also decrease hepatic blood flow.[13] Since the liver and diaphragm/thoracic cavity are in close proximity, surgical manipulation may impinge on lung and thoracic wall excursions, resulting in hypoventilation. Care must be taken to reduce the mechanical restriction of breathing, especially in small patients. Mechanical ventilation may therefore be indicated in these cases. However, close monitoring of peak airway pressure is necessary to avoid barotrauma.

## Hepatic dysfunction and pharmacological agents

### Preanesthetic agents

#### Phenothiazines

Acepromazine is commonly used in veterinary medicine for its sedative and anxiolytic properties. Acepromazine is a phenothiazine derivative that causes blockade of dopaminergic and α1-adrenergic receptors, leading to vasodilation.[14] Drug metabolism is via hepatic biotransformation, and no antagonist is available. The direct effects of acepromazine on hepatic blood flow and hepatic function have not been well characterized in veterinary medicine. The administration of ketamine, xylazine, and acepromazine does not appear to have adverse effects on liver function, graft liver regeneration, inflammatory response, or hepatic pathologic changes in hepatic transplantation studies.[15] However, acepromazine should potentially be avoided in patients with hepatic disease. For example, the administration of acepromazine causes vasodilation due to antagonism of α1-adrenergic receptors, potentially leading to systemic hypotension.[14] In addition, patients with hypoalbuminemia may have pre-existing hypotension due to a decrease in colloidal osmotic pressure; the administration of acepromazine may further decrease systemic blood pressure. Furthermore, the coadministration of acepromazine and atropine has been shown to induce abnormalities in platelet aggregation.[16] Since patients with hepatic dysfunction may present with coagulopathies, the administration of acepromazine in the face of coagulation disorders is, therefore, contraindicated and that before procedures such as ultrasound-guided liver biopsy should be carefully questioned.

### α2-Adrenergic agonists

α2-Adrenergic agonists such as dexmedetomidine offer excellent sedative properties at the cost of significant cardiovascular depression. The α2-adrenergic agonists significantly decrease heart rate and cardiac output while increasing systemic vascular resistance.[17–19] However, hepatic blood flow may be fairly well preserved. For example, dogs undergoing thoracotomy under anesthesia did not demonstrate significant decreases in hepatic blood flow after administration of dexmedetomidine.[20] In addition, histopathology of liver tissue after administration of dexmedetomidine to rats with experimentally induced sepsis actually demonstrated a liver-protective effect of dexmedetomidine.[21] The metabolism of dexmedetomidine relies on hepatic biotransformation, but α2-adrenergic receptor antagonists such as atipamezole are available in the event of increased effect or duration of effects. Overall, dexmedetomidine does not appear to have negative effects on the liver and is not contraindicated in patients with liver disease. However, as this agent has not been extensively evaluated in clinical patients with pre-existing liver disease and can induce extreme sedation and cardiovascular depression, caution should be used in its administration.

### Benzodiazepines

The benzodiazepines, such as midazolam and diazepam, exert their sedative effect via enhancement of the actions of the endogenous inhibitory neurotransmitter, gamma amino butyric acid (GABA).[22] These agents have minimal cardiovascular effects and are generally well tolerated in patients with many disease states.[23] However, fulminant liver failure has been associated with oral administration of diazepam in cats.[24] This adverse event has not been reported after parenteral administration of diazepam or midazolam, and both are considered safe for administration in the perioperative period. Metabolism occurs through hepatic biotransformation, but a GABA receptor antagonist, flumazenil, is available if sedation is prolonged or excessive.

The administration of benzodiazepine for preoperative sedation of most patients with liver dysfunction is an excellent choice. However, care must be exercised in patients with hepatic encephalopathy. Neurons from animals with hepatic encephalopathy demonstrate increased sensitivity to benzodiazepines due to the presence of endogenous benzodiazepines, and the administration of exogenous benzodiazepines can aggravate hepatic encephalopathy.[25] The benzodiazepine antagonist flumazenil improves the symptoms of hepatic encephalopathy.[26] Owing to the effect of hepatic encephalopathy on the GABAergic tone, dosages of diazepam and midazolam should be greatly decreased or avoided in animals demonstrating symptoms of hepatic encephalopathy.

### Opioids

Opioids are classified on the basis of their effects on opioid receptors.[27] Mu-opioid agonists exert a pharmacological effect via activation of the mu-opioid receptor; these agents include, but are not limited to the following: morphine, hydromorphone, oxymorphone, fentanyl, methadone, and meperidine. Butorphanol, classified as an opioid agonist-antagonist, acts as an antagonist at the mu-opioid receptor and an agonist at the kappa-opioid receptor. Buprenorphine is a partial agonist at the mu-opioid receptor and, as such, exhibits a submaximal clinical response.

In general, opioids are considered safe for use in patients with liver disease. Most opioids rely on hepatic biotransformation, and the duration of effect may be prolonged in cases of liver dysfunction.[28] Naloxone, a nonselective opioid receptor antagonist, may be given if drug duration is prolonged or opioid agonist effects are profound. However, one must consider that analgesic effects will also be reversed with the administration of naloxone. As discussed previously, morphine causes contraction of the sphincter of Oddi in several species, increasing biliary pressure.[3] Although previously considered unsafe for use in patients with acute pancreatitis, human research suggests that morphine is safe for analgesic use in these patients.[4] At this time, there is no clinical evidence to suggest that morphine should be avoided in patients with hepatobiliary disease.

Most opioids primarily undergo hepatic biotransformation followed by renal excretion. Remifentanil is a notable exception; metabolism is entirely extrahepatic, via ester hydrolysis.[27] Subsequently, it has an ultrashort duration of ~5 min and should be administered as a constant rate infusion to provide analgesia of any appreciable duration.[29] Remifentanil is advantageous in animals with liver disease, as duration of effect should be unchanged in the presence of liver dysfunction. In humans, duration and drug clearance were unchanged

in severe, chronic liver disease and during the anhepatic phase of liver transplantation.[30,31] Remifentanil has been reported to have an isoflurane-sparing effect in both dogs and cats and has been used in combination with isoflurane to provide anesthesia for liver biopsy in dogs.[32–34] As significant respiratory depression and bradycardia can result with bolus administration, as well as during high constant rate infusions of remifentanil, close monitoring of cardiovascular and ventilatory status is imperative, as anticholinergic administration and positive pressure ventilation may be required.

### Nonsteroidal anti-inflammatory agents

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a critical component of most perioperative analgesic regimens and are administered chronically in many patients presenting for surgery and anesthesia. All NSAIDs have the potential to cause idiosyncratic hepatotoxicosis with clinical signs of hepatic dysfunction and liver enzyme elevation, largely due to oxidative stress.[35,36] Although not contraindicated, caution should be used when administering NSAIDs to animals with liver disease owing to the potential for this idiosyncratic hepatotoxicity. Furthermore, NSAIDs may adversely affect platelet aggregation. The administration of NSAID resulted in platelet dysfunction in dogs after the administration of deracoxib, but not aspirin, carprofen, or meloxicam.[37] Similarly, carprofen decreases clot strength and platelet aggregation, but deracoxib might actually increase strength; the clinical significance of these seemingly disparate data is not known.[38] As liver disease may be accompanied by impaired coagulation and multiple NSAIDs have been implicated in causing platelet dysfunction, it is prudent to avoid NSAIDs in cases of hepatic dysfunction with coagulopathy.

## Induction agents

### Barbiturates

Thiopental has little place in anesthetic induction for patients with significant liver disease. While anesthetic recovery largely relies on redistribution out of the central nervous system, metabolism is through hepatic biotransformation and may be dramatically slowed in the presence of liver dysfunction.[39] As better choices for anesthetic induction are currently available, thiopental should be avoided in cases of liver dysfunction.

### Propofol

Propofol similarly provides rapid induction and recovery after administration. However, it is rapidly metabolized in the liver to inactive metabolites; however, total body clearance exceeds hepatic blood flow, suggesting extrahepatic metabolism as well.[40] Bolus dosing of propofol is known to cause systemic hypotension, but hepatic arterial flow is increased due to vasodilation.[41] Thus, propofol is an excellent choice for anesthetic induction in patients with liver dysfunction. It does not exacerbate hepatic encephalopathy and has been found safe for use in human patients with cirrhosis.[42,43]

### Etomidate

Etomidate offers the advantage of greater cardiovascular stability as compared to other injectable agents.[40] Bolus dosing provides rapid anesthetic induction and recovery through precipitous redistribution out of the central nervous system. Metabolism is via ester hydrolysis, and drug clearance is not significantly altered in the presence of severe liver dysfunction.[44] Despite the cardiovascular stability offered by etomidate, hepatic blood flow and oxygen delivery are decreased after administration.[45] However, overall, etomidate is considered safe for use in patients with liver dysfunction due to its minimal cardiovascular effects and rapid recovery profile.

### Dissociatives

The dissociative agents ketamine and tiletamine rely on hepatic biotransformation for metabolism in most species. Cats, however, rely more extensively on renal excretion of dissociatives than other species.[46] After experimental administration of ketamine to dogs, hepatic arterial and portal venous flows were not significantly altered from baseline, although hepatic oxygen delivery was decreased.[47] Overall, dissociative agents are considered safe for use in patients with hepatic dysfunction. However, as propofol and etomidate offer smooth anesthetic induction and more rapid recovery than ketamine, these agents may be better alternatives.

## Inhalational agents

Historically, halothane was associated with hepatotoxicity in several animal species.[48–52] Modern anesthetics are not directly associated with hepatotoxicity, but a number of adverse physiologic effects can occur. In general, all halogenated anesthetics decrease hepatic blood flow to varying degrees.[53,54] Reduced hepatic

blood flow results in decreased drug clearance and hepatocellular damage. Dose-dependent hypotension from inhalant administration may further reduce hepatic blood flow. As hypercarbia also decreases hepatic blood flow, the dose-dependent respiratory depression associated with volatile anesthetics must additionally be considered.[13] Ventilatory status should be monitored and positive pressure ventilation instituted as necessary to maintain arterial $CO_2$ levels. All modern volatile anesthetics are minimally metabolized, and recovery is unaltered directly by hepatic dysfunction. These agents are considered safe, although elevations in ALT, AST, and GGT after anesthesia with isoflurane and sevoflurane have been reported.[55,56] Collectively, isoflurane, sevoflurane, and desflurane are all acceptable for use in patients with liver dysfunction.

The administration of nitrous oxide causes dose-dependent decreases in hepatic arterial and portal venous blood flow.[57] However, nitrous oxide is largely considered safe for patients with hepatic dysfunction, although centrilobular necrosis has been reported to occur in the hypoxic rat model; no such hepatotoxicity has been reported in clinical patients under normoxic conditions.[58] Nitrous oxide can be advantageous to decrease the amount of halogenated anesthetic needed, thus attenuating the adverse cardiorespiratory effects of these agents.

## Anesthetic management of patients with hepatic dysfunction

As previously mentioned, there can be a broad spectrum of hepatic dysfunction, ranging from nonclinical liver enzyme elevation detected on preoperative serum biochemistry profile to fulminant liver failure. A number of underlying disease processes can cause these abnormalities, and the case presentation can be quite variable. Table 4.2 lists the commonly encountered physiological abnormalities in patients with hepatic dysfunction. In veterinary medicine, patients presenting with fulminant liver failure for general anesthesia are fairly rare. The most common case presentations seen in veterinary medicine are portal venous shunts, surgical or ultrasound-guided liver biopsy, and patients presenting for surgery with unrelated liver dysfunction.

Animals presenting for liver biopsy for workup of liver enzyme elevation often have sufficient functional hepatic reserve and do not present many unexpected anesthetic challenges apart from what has been discussed previously. It is important, however, to consider that hepatic biotransformation of drugs may be impaired, and, as such, drug choice must be carefully considered. Most anesthetic agents that rely heavily on hepatic biotransformation for metabolism and duration of effect may be prolonged if liver function is impaired. Agents such as benzodiazepines and opioids are excellent choices, as they have minimal cardiovascular and respiratory depressant effects, and their receptors are easily antagonized in the event of profound or prolonged sedation. Depending on the patient's cardiovascular status, propofol or etomidate can be chosen to allow sufficient relaxation for endotracheal intubation. Both are excellent choices, as they allow rapid anesthetic induction and rely on redistribution followed by extrahepatic metabolism for recovery.[40] In the case of ultrasound-guided biopsy, preanesthetic sedation may be unnecessary. If the patient requires sedation or general anesthesia, an intravenous dose of butorphanol (0.1–0.3 mg $kg^{-1}$), a kappa-opioid agonist with mild sedative and analgesic properties, followed by propofol titrated to effect to allow relaxation may be adequate.

Patients presenting with portal venous shunts are typically the most severe cases of hepatic dysfunction encountered by the veterinary anesthetist. They often have clinical signs and laboratory abnormalities consistent with hepatic failure.[10] It is important to manage these abnormalities throughout the entire perioperative period, not just while on the operating table. These

**Table 4.2** Physiological abnormalities commonly associated with hepatic dysfunction and hepatic failure.

| Problems commonly associated with hepatic dysfunction |
|---|
| Hepatic encephalopathy |
| Hypokalemia |
| Hypoglycemia |
| Hypoalbuminemia |
| Ascites |
| Coagulopathy |
| Hypotension |
| Impaired drug biotransformation |

Note these abnormalities may or may not be present in the patient who presents for anesthesia with hepatic dysfunction.

patients are generally small due to their age, breed, and stunted growth. This small stature can make vascular cannulation difficult, and the application of local anesthetic cream such as EMLA (EMLA® Cream; APP Pharmaceuticals, LLP; Schaumburg, IL 60173) before intravenous catheterization can aid in patient comfort. Furthermore, small patients are highly prone to hypothermia, a contributing factor to prolonged anesthetic recovery.[59] Heat support should be provided on sedation and throughout the entire anesthetic period and patient temperature closely monitored.

Hypoglycemia is often present in patients with severe hepatic disease due to impaired hepatic glucose metabolism and should be closely monitored throughout the perioperative period. Blood glucose should be checked before anesthesia, at anesthetic induction, every 30–60 min while under anesthesia (if possible), and on recovery. Intravenous fluids should be supplemented with 2.5–5% dextrose as needed to maintain blood glucose above 70 mg $dl^{-1}$.[60] Hypoglycemia should be suspected and ruled out in the event of delayed anesthetic recovery.

Hypoalbuminemia due to either impaired protein synthesis or increased loss through ascitic fluid can cause several anesthetic challenges. Drug protein binding will be altered, and highly protein-bound drugs such as diazepam will exert a greater effect due to a greater proportion of unbound, active drug.[61] As many anesthetic agents have a high degree of protein binding, anesthetic drug dosages should be decreased in the face of significant hypoalbuminemia. Albumin plays a critical role in providing oncotic support to plasma; decreases in this oncotic support can lead to hypotension and edema. For example, severe hypoalbuminemia (albumin concentration <1.5 g $dl^{-1}$) can lead to pulmonary and/or peripheral edema with perioperative crystalloid administration.[62] The administration of plasma to increase albumin concentration can be attempted before anesthesia but may lead to volume overload owing to the large quantities of plasma needed. Human albumin can be used in extreme cases, but the possibility of untoward reactions must be considered, as severe reactions have been reported in both healthy and critically ill dogs.[63,64] Lyophilized canine-specific albumin (5%) is available, and delayed adverse events have not been reported as with the administration of human albumin.[65] Perioperative fluid administration should consist of colloidal solutions such as 6% hydroxyethyl starch in conjunction with crystalloids (5 ml $kg^{-1}$ $h^{-1}$ each) or as a sole fluid in cases of severe hypoalbuminemia. In severe cases of hypoalbuminemia, CVP should be measured to prevent volume overload. CVP should be maintained at approximately 3–5 cm $H_2O$; pressure exceeding 13–16 cm $H_2O$ is associated with an increased likelihood of pulmonary edema.[66]

Ascites can be present in animals with severe liver disease. A large volume of ascitic fluid will impair expansion of the lungs on recumbency. In these cases, fluid should be removed before anesthesia, with care to not remove large volumes of fluid rapidly. Ascitic fluid that is removed too rapidly can cause a shift in intravascular volume to the abdominal cavity, resulting in profound hypovolemia and potential cardiovascular collapse.[10] Animals with considerable ascitic fluid should be preoxygenated with 100% oxygen delivered by face mask before anesthetic induction, as time to desaturation with apnea may occur more rapidly in these patients.

Hypotension due to hypovolemia, hypoalbuminemia, and hypothermia is often encountered. Surgical manipulation in the abdomen of small patients can worsen hypotension by impeding venous return, resulting in sudden blood pressure swings. Invasive blood pressure measurement via arterial catheterization should be used in patients with severe liver disease, although the small size of many portal venous shunt patients can make this difficult. In the absence of invasive blood pressure measurement, a noninvasive blood pressure measurement should be noted every 5 min, either by a reliable oscillometric monitor or by Doppler ultrasonic sphygmomanometry. Hypotension (mean arterial blood pressure <60 mmHg) may be managed with colloid administration, positive inotropes such as dobutamine, and/or with vasoactive agents such as norepinephrine or vasopressin.

In any patient with liver dysfunction presenting for anesthesia and invasive procedures, it is important to check the coagulation status to rule out coagulopathy. At a minimum, PT should be checked before anesthesia. However, further coagulation testing may be warranted, as animals with hepatic disease may have high serum activity of PIVKA, which may be associated with bleeding tendencies.[10] Coagulopathy can be treated with fresh frozen plasma and administration of vitamin $K_1$.[67] Even in the event of normal coagulation times, the anesthetist should be prepared for hemorrhage with

all invasive procedures, as the liver is highly vascular. Blood products should be available, and the animal should be cross-matched as needed to blood donors.

Patients presenting with hepatic encephalopathy present unique challenges. Owing to a high concentration of endogenous benzodiazepine receptor agonists, these patients are uniquely sensitive to drugs that exert action through the GABA receptor such as benzodiazepines.[68] Profound sedation can result if drug dosages are not appropriately decreased.

Hypokalemia may be encountered preoperatively in patients with chronic vomiting owing to liver disease. Potassium levels <3.5 mEq $l^{-1}$ should be treated before anesthesia. This can be accomplished through intravenous fluid supplementation with potassium at a rate not to exceed 0.5 mEq $kg^{-1}$ $h^{-1}$ of supplementation.

## Monitoring the patient with hepatic dysfunction

Patients with hepatobiliary dysfunction should be carefully outfitted with anesthetic monitors before draping, especially in those of small stature that may become poorly accessible after surgical draping. Temperature, pulse oximetry, the electocardiogram, blood pressure, and end-tidal carbon dioxide should be closely monitored. Invasive arterial blood pressure measurement should be used in patients with baseline hypotension, severe hypoalbuminemia, or when intraoperative hemorrhage may occur. In patients with moderate to severe hypoalbuminemia, CVP should be monitored to prevent volume overload. As stated previously, CVP should be maintained at approximately 3–5 cm $H_2O$. Rapid increases in CVP (>4 cm $H_2O$) suggest that fluid administration should be slowed, whereas decreased CVP suggests inadequate fluid therapy.[66]

Although patients presenting for surgical treatment of biliary disease may not have abnormalities consistent with hepatic dysfunction, they can be highly unstable during surgery. There are numerous anecdotal reports of cardiovascular arrest under anesthesia in cats undergoing cholecystectomy. Autonomic dysfunction as well as hyperdynamic circulation, much analogous to a state of sepsis, has been described in human patients with chronic liver disease.[69,70] Patients with biliary disease undergoing cholecystectomies often demonstrate wide swings in blood pressure and heart rate, and close monitoring of cardiovascular parameters is indicated.

Postoperatively, it is important to carefully evaluate the patient with hepatic dysfunction. Blood pressure, temperature, hematocrit, albumin, and blood glucose should be measured to provide an immediate postoperative baseline measurement and to gauge therapy in the postoperative period. Delayed recovery from anesthesia can result from residual or prolonged drug effects, hypothermia, and hypoglycemia.[71] Drug antagonism, temperature support, and supplementation of dextrose should be provided as necessary.

Drug choice should be tailored to patient temperament, degree of hepatic dysfunction, and type of procedure. In general, it is safe to use a benzodiazepine/opioid combination either intramuscularly (IM) or intravenously (IV); when drugs are administered via the intravenous route, the lower end of the dosage range should be chosen.

## Conclusion

Hepatic disease does not preclude a patient from anesthesia with close, diligent monitoring. Examples of suggested premedication combinations include IV or IM midazolam (0.05–0.1 mg $kg^{-1}$) and hydromorphone (0.05–0.2 mg $kg^{-1}$) in dogs or midazolam (0.05–0.1 mg $kg^{-1}$) and oxymorphone (0.05–0.1 mg $kg^{-1}$) in cats. Anesthetic induction can be achieved using either propofol (2–6 mg $kg^{-1}$ IV) or etomidate (1–2 mg $kg^{-1}$ IV) to allow transition to gas anesthesia. Constant rate infusions of analgesics such as intravenous fentanyl (5–10 mcg $kg^{-1}$ $h^{-1}$) or remifentanil (2–5 mcg $kg^{-1}$ $h^{-1}$) can provide intraoperative analgesia and reduce minimum alveolar concentration (MAC) of inhalants as needed. Again, care must be taken to decrease drug dosages in cases of hypoalbuminemia and hepatic encephalopathy.

## Summary

Patients with liver disease can have highly variable case presentations; close attention to clinical abnormalities, with a plan for careful management of each is advised. The anesthetist must have a thorough understanding of the repercussions of liver dysfunction, as well as any

possible confounding issues of the procedure requiring anesthesia. Although true of all patients, it is especially important for patients with liver dysfunction to be carefully monitored not only intraoperatively, but also postoperatively. With careful attention, monitoring, and management, these patients can be successfully managed through the entire perioperative course.

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# 5 Gastrointestinal disease

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## Gastrointestinal tract function

The digestive system provides the body with a continual supply of water, electrolytes, and nutrients. In order to achieve these larger global functions, several physiological functions need to be occurring normally. Food must be appropriately apprehended, ingested, and moved through the gastrointestinal (GI) tract; the stomach must secrete digestive juices, and at the same time, the homeostatic function of the stomach must be maintained; nutrients, water, and electrolytes must be absorbed by the small intestines; circulation of the GI organs must be adequate to carry away the absorbed substances; and motility of the GI tract must be maintained.[1]

Any alteration in function or structure in the segments of the GI tract can disturb these physiological processes, resulting in anorexia, dehydration, hypovolemia, acid–base and electrolyte disturbances, protein loss, abdominal pain, and patient emaciation. All of these derangements can have significant implications in the anesthetic management of dogs and cats undergoing diagnostic procedures (e.g. endoscopy), feeding tube placement, or surgery.

## Oropharyngeal diseases

Oral cavity and pharyngeal diseases in dogs and cats that require surgical intervention include congenital and traumatic abnormalities, foreign bodies, neoplasia, and salivary gland and dental diseases.[2] Neoplasia in the oropharyngeal region is relatively common in dogs and cats, and treatment often requires surgical resection.[3]

### Oropharyngeal neoplasms

Dogs and cats with oropharyngeal neoplasms frequently require mandibulectomy or maxillectomy. Before anesthesia is performed, a thorough physical examination, complete blood cell count (CBC), serum biochemistry profile, and urinalysis should be performed. These surgeries can often result in significant hemorrhage from potential laceration or resection of major arteries.[2] Therefore, blood typing should be performed before surgery in dogs and cats to ensure safety, in case blood product transfusion is necessary. Blood cross-matching should always be performed in dogs and cats that have previously been transfused.[4]

### Clinical signs

Patients with large neoplasms in the oropharyngeal area may have abnormal prehension of food and dysphagia. Attempts to ingest food can cause trauma to the oropharyngeal mucosa, resulting in oral pain and bleeding. Difficulty associated with eating and swallowing can lead to weight loss and poor body condition score[2,3], which can compromise redistribution of lipid-soluble drugs such as thiopental.

In addition, animals with large oropharyngeal neoplasms can have difficulty opening their mouth or may be at risk of partial or complete airway obstruction.[2]

### Laboratory data

Complete blood cell (CBC) count and serum biochemical profile results can be nonspecific for these patients; however, low hematocrit values owing to continuous small bleeding from trauma of the oropharyngeal mucosa may be noted.[2]

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## Management of anesthesia

### Perianesthetic considerations

Anemic patients with packed cell volume (PCV) lower than 20% should receive a packed red blood cell (pRBC) transfusion before surgery because the oxygen-carrying capacity of blood and the oxygen delivery to tissue are significantly impaired below this point. pRBC transfusion must also be considered in patients with severe anemia undergoing mandibulectomy and maxillectomy owing to the increased risk of hemorrhage during these procedures. In this regard, the placement of two intravenous catheters may be prudent, as this allows simultaneous administration of blood, fluids, and inotropic support, if necessary.[2]

In patients with large neoplasms, visualization of the larynx is often difficult, and this may lead to difficulty in placing an endotracheal (ET) tube to secure and maintain a patent airway. General anesthesia without a secure airway may result in aspiration of gastric content and blood, which can lead to pneumonia[5] and small airway obstruction, respectively. In cases where ET intubation is expected to be complicated, preoxygenation with 100% oxygen via a mask should be considered before induction of anesthesia. In addition, diverse diameters of ET tubes, stylets, and laryngoscope blade sizes should be readily available. A surgical tracheostomy pack should also be readily available, as tracheostomy may be necessary if several attempts at ET intubation fail.

An orally placed ET tube can sometimes hinder oral cavity and oropharyngeal surgery. In these cases, the portion of the ET tube that remains in the oral cavity can be deviated through a pharyngotomy (Figure 5.1A and B) or tracheotomy incision (also see Chapter 11). For all methods of intubation, it is important that the ET tube and its cuff prevent blood and fluid from entering the lower airways. Gauze sponges are frequently placed in the oropharynx around the ET tube to help absorb fluids. However, these gauze sponges must be removed before the end of anesthesia and removal of the ET tube in order to prevent airway obstruction.[2]

### Preanesthetic medication

Selection of sedative drugs will depend on multiple factors, including patients' signalment, temperament, physical status, and localization of disease. In patients with partial airway obstruction and those in whom preoxygenation is included before induction of anesthesia, sedative drugs that decrease anxiety may be desired.

The potential for severe pain exits in patients undergoing mandibulectomy and maxillectomy, as bone and nerves will be resected during these procedures. Therefore, these cases warrant a multimodal approach for analgesia.[6] Full mu-opioid agonist drugs should

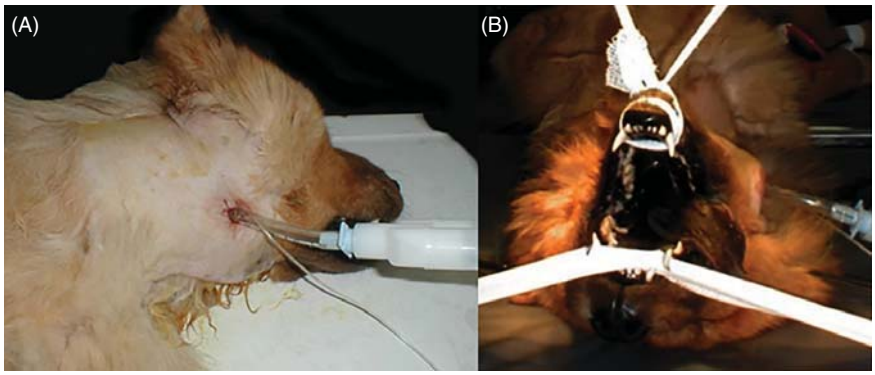


**Figure 5.1** (A) Introduction of the proximal end of the ET tube through a pharyngotomy. After the ET tube is orally placed and connected to the breathing system, inhalational anesthesia is started. A pharyngotomy is performed, and the adaptor of the ET tube is removed. A hemostat is inserted through the skin at the entry site of the pharyngotomy. The proximal end of the ET tube (without the adaptor) is grasped with the hemostat and pulled through the pharyngotomy. The adaptor is reattached to the ET tube, and the latter is reattached to the breathing system. Inhalational anesthesia can be continued at this time. Photo courtesy of Dr. M. Martinez, Dr. V. Cairoli and Dr. R. Bruhl Day. (B) Oral cavity access by the surgeon without hindrance of the ET tube. Source: Photo courtesy of Dr. M. Martinez, Dr. V. Cairoli, and Dr. R. Bruhl Day.

be included in the premedication with the goal of providing preemptive analgesia.

Vomiting after premedication should be avoided in patients with an inability to open the oral cavity and with partial airway obstruction. Therefore, drugs such as alpha2-agonists[7] and full mu-agonist opioids[8,9] should be used with caution. Meperidine (1.0–5.0 mg kg$^{-1}$ in dogs; 0.5–1.0 mg kg$^{-1}$ in cats) and methadone (0.5–1.0 mg kg$^{-1}$ in dogs; 0.1 mg kg$^{-1}$ in cats) are notable exceptions, as they are less likely to cause vomiting in small animal patients.[10,11] The advantage of using a full mu-opioid agonist (i.e. intense analgesia) must be weighed against several factors, including options of opioids available to the clinician, the level of pain caused by the procedure, and the risks associated with emesis. Therefore, in patients in whom vomiting is undesirable but analgesia is required, methadone may be a better premedication drug to administer.[10]

### Induction of anesthesia

In patients with airway obstruction or an inability to open the oral cavity, induction of anesthesia should be rapidly achieved without excitement. For this reason, intravenous anesthetic techniques (e.g. ketamine [5.0 mg kg$^{-1}$]-diazepam [0.25 mg kg$^{-1}$], propofol [4–8 mg kg$^{-1}$], thiopental [8.0–20 mg kg$^{-1}$]) are preferred to mask induction with inhalation anesthetics.

### Maintenance of anesthesia

The maintenance of anesthesia in patients undergoing mandibulectomy and maxillectomy should be achieved using inhalation anesthetics (e.g. isoflurane, sevoflurane, or desflurane). Intraoperative analgesia can be accomplished by combining nitrous oxide with the inhalation anesthetic or by using a multimodal approach. Depending on the area of resection, local anesthetic blocks of the infraorbital, maxillary, or mandibular nerves can be performed with the administration of 0.5–1.0 ml of lidocaine, bupivacaine, or ropivacaine.[12] The administration of a loading dose (LD) and continuous rate infusions (CRI) of lidocaine intravenously (LD: 1.0–2.0 mg kg$^{-1}$; CRI: 3.0 mg kg$^{-1}$ h$^{-1}$), ketamine (LD: 0.5 mg kg$^{-1}$, CRI: 0.6 mg kg$^{-1}$ h$^{-1}$), and/or morphine (CRI: 0.1–0.3 mg kg$^{-1}$ h$^{-1}$) provide the additional benefit of reducing the amount of inhalation anesthetic required, which will improve hemodynamic stability for the patient. Furthermore, these infusions may prevent windup of pain.[6,13]

Intraoperatively, a balanced isotonic crystalloid solution (e.g. Lactated Ringer's solution (LRS)) should be administered intravenously at a rate of 5–10 ml kg h$^{-1}$. The magnitude of the surgery and the likelihood of hemorrhage should be considered when selecting modalities of arterial blood pressure monitoring. Intra-arterial catheter placement with invasive arterial blood pressure measurements is preferred when large vascularized masses are excised. Seven percent hypertonic saline, 6% hetastarch 600/0.75 (Hespan®) or 6% hetastarch 130/0.4 (Vetstarch™), whole blood or pRBC, and fresh frozen plasma (FFP) should be available in the event of severe hemorrhage.[2] Studies on humans show that 6% hetastarch 130/0.4 is an equally efficacious plasma volume substitute as the other hetastarch formulation with a lesser effect on coagulation.[14] However, a recent systematic review and meta-analysis in human literature did not reach a conclusion regarding the benefits or risks of administering a lower versus a higher molecular weight of 6% hetastarch.[15] Vetstarch™ has recently been introduced in the veterinary market, and more studies regarding its adverse effects are warranted.

### Recovery from anesthesia

On termination of inhalation anesthetics, gauze sponges should be removed from the caudal pharynx and the oral cavity.[2] Postoperative swelling of the oral mucous membranes may cause airway obstruction. This can be minimized by the administration of corticosteroids (e.g. dexamethasone 0.1–0.2 mg kg$^{-1}$ IV).

Extubation should be delayed until a well-developed swallowing reflex is present. When the patient is ready for extubation, the ET tube should be removed with the cuff inflated to help ensure that blood clots and fluid are expelled through the mouth rather than being aspirated or swallowed.[16] During recovery, these patients should be monitored for signs of airway obstruction or pain.

Analgesics such as opioids (e.g. fentanyl [LD: 0.002–0.005 mg kg$^{-1}$, CRI: 0.002–0.005 mg kg$^{-1}$ h$^{-1}$], hydromorphone [0.05–0.1 mg kg$^{-1}$], methadone [0.1–0.5 mg kg$^{-1}$]) and nonsteroidal anti-inflammatory drug (NSAID) (e.g. carprofen [2.0–4.0 mg kg$^{-1}$ in dogs; 2.0–4.0 mg kg$^{-1}$ single dose in cats], meloxicam [0.2 mg kg$^{-1}$ in dogs; 0.1–0.2 mg kg$^{-1}$ single dose in cats]) should be provided as needed. However, if corticosteroids have been previously administered to

the patient, caution should be taken when deciding if NSAIDs are an appropriate analgesic to administer.

## Esophageal diseases

The esophagus carries food, water, and saliva from the pharynx to the stomach. Impairment of these functions can lead to regurgitation of the ingesta back to the oral cavity and aspiration of this content, resulting in pneumonia.[2]

Esophageal diseases in dogs and cats are related to obstructive, motility (e.g. megaesophagus), or inflammatory (e.g. esophagitis from chronic vomiting or gastroesophageal reflux (GER)) disorders.[17] In certain situations, these patients require anesthesia for feeding tube placement (e.g. percutaneous endoscopic gastrostomy (PEG) tube and gastrostomy tube), further diagnostics (e.g. esophagoscopy and biopsy), or treatment of the problem (e.g. esophagoscopy for foreign body removal, esophageal balloon dilation, and vascular ring anomaly correction).

### Anatomy of the esophagus

The esophagus is divided into cervical and thoracic portions. The upper esophageal sphincter (UES, composed of cricopharyngeus and thyropharyngeus muscle) is located at the proximal end of the esophagus. The lower esophageal sphincter (LES) is located at the distal end. The esophagus is the only visceral organ that contains striated muscle. In the dog, the muscular layers of the esophagus are made entirely of striated muscle, whereas in the cat, only the proximal two thirds contain striated muscle.[18,19]

### Esophageal obstruction

Esophageal obstruction usually occurs in dogs and cats because of foreign bodies, strictures, neoplasms, hiatal hernia, gastroesophageal intussusception, and vascular ring anomalies.[2]

Esophageal foreign bodies are relatively common in small animal patients. Foreign material usually lodges where the esophagus narrows. These locations include the thoracic inlet, the base of the heart, and the esophageal hiatus in the diaphragm. The extent of secondary esophageal injury depends on the type of object, its size and shape, and the duration in contact with the mucosa.[17] Previous unsuccessful attempts at endoscopic removal of foreign material can also lead to a significant increase in secondary esophageal injury. Esophageal perforation during foreign body removal can lead to significant morbidity and mortality because of pneumothorax and infection.[20]

Esophagitis and resulting esophageal strictures owing to GER during general anesthesia may occur when protective mechanisms are diminished by general anesthetic and analgesic drugs. The acidic gastric contents that come into contact with the esophageal mucosa can severely damage the esophagus if they are not neutralized by saliva or removed by peristalsis within a few minutes. Signs of regurgitation may occur within a few days or weeks after surgery because of stricture formation.[2] Scar formation and esophageal strictures may develop after esophageal injury. The incidence of GER associated with anesthesia varies from 16 to 55%.[21–26] In one study, the incidence of esophageal stricture after anesthesia was 0.07%. Despite the low incidence of esophagitis and stricture formation, the cost associated with diagnosis and treatment of these disorders is extremely high, with a subsequent high mortality rate.[27] These patients usually return for several subsequent anesthetic events in which esophageal bougienage or dilation with balloon catheters is performed to treat the strictures, thus further increasing the risk of GER. Thus, the use of aggressive medical therapy to decrease the acidity of gastric secretions combined with promotility drugs is recommended before future anesthetic events.[27]

### Megaesophagus

Megaesophagus may occur with motility disorders of the esophagus. The causes of esophageal hypomotility are extensive, varying from primarily idiopathic in origin in dogs (most common) or possibly secondary to neuromuscular, muscular, infectious, or autoimmune disorders. Patients with megaesophagus may require anesthesia for esophagoscopy or other diagnostic tests and procedures for the suspected primary disease. These may include electromyography and nerve conduction velocity, muscle biopsy, cerebrospinal fluid collection, or thymoma removal.[2,17]

### Clinical signs

Clinical signs of esophageal diseases include abnormalities of prehension and swallowing, regurgitation, and ptyalism. Vomiting can occur if both esophagus and

stomach have significant disease such as with hiatal hernia, gastroesophageal intussusception, or GER.[17] It is important to differentiate regurgitation from vomiting because regurgitation is more likely to occur in patients with primary esophageal disorders. In addition, the clinical consequences of vomiting and regurgitation may be different and, as such, can influence the clinician's anesthetic plan. Regurgitation is a passive flow of food, water, or saliva from the esophagus to the oral cavity.[28] It is most often associated with pharyngeal or esophageal diseases. The primary complication of regurgitation is aspiration pneumonia. Alternatively, vomiting is a forceful expulsion of gastroduodenal contents mediated by the central nervous system. The presence of vomiting usually indicates the presence of GI or systemic disease.[28,29] A chronic history of regurgitation in a patient can lead to anorexia, weight loss, depression, and emaciation.[2] Esophageal pain may be suspected when patients are observed having signs of neck stretching while swallowing and repeated swallowing.[27] Coughing, pulmonary crackles, and fever may suggest aspiration pneumonia secondary to regurgitation. Patients with disorders related to esophageal motility (e.g. megaesophagus) can also present with generalized muscle weakness or atrophy, neurologic deficits, and/or oropharyngeal dysphagia.[2,17]

## Laboratory data

A minimum database of tests, including CBC and serum biochemical profile, should be performed in patients with esophageal disease. PCV, total protein (TP), blood urea nitrogen (BUN), and creatinine may be elevated because of dehydration. A neutrophilia with left shift may be consistent with aspiration pneumonia. Metabolic acidosis with lactatemia can occur in dehydrated patients. Metabolic alkalosis can occur in patients with gastroesophageal disorders (e.g. hiatal hernia).[17]

Patients with megaesophagus secondary to hypoadrenocorticism may have electrolyte disturbances such as hyperkalemia and hyponatremia.[30]

## Management of anesthesia

### Perianesthetic considerations

Dogs and cats with esophageal disease should be fasted for 8–12 h before scheduled anesthetic procedures. However, esophageal foreign bodies are considered medical emergencies, and fasting is usually not possible. If patients are not fasted, preoperative and intraoperative regurgitation may occur with potential of aspiration.

Care must be taken in anesthetizing young animals (e.g. 8–16 weeks of age) for esophageal surgery such as ligation and transection of the ligamentum arteriosum in puppies and kittens with persistent right aortic arch (Figure 5.2).[2,19] Special anesthetic considerations regarding size and age must also be taken into account. For example, fasting of these animals should be limited to 4–6 h. In addition, perioperative hypoglycemia and hypothermia are common problems in these patients.[2,20]

Depending on the planned surgical and anesthetic event, medications to increase the pH of gastric secretions may be given preoperatively. By reducing gastric acidity, this may help to reduce esophageal mucosal damage and lung damage after aspiration if reflux does occur.[2] However, it should be noted that the efficacy of these drugs, when administered preoperatively, in reducing the frequency of GER events during anesthesia is equivocal, as several studies have shown conflicting results.[31,32] Cimetidine, ranitidine, and famotidine (histamine$_2$ [H2] antagonists) decrease gastric acid secretion and increase gastric pH. Famotidine has been shown to be significantly more effective in changing pH than ranitidine in dogs.[33] Proton pump inhibitor (PPI) drugs such as omeprazole and pantoprazol are also useful in increasing gastric secretion pH. However, therapy with PPIs should be started at least 2 days before

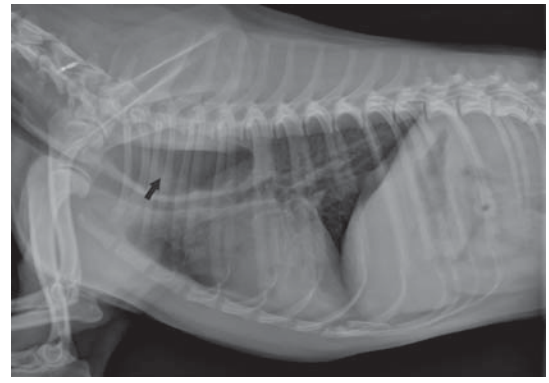

**Figure 5.2** Right lateral thoracic radiograph showing esophageal dilation cranial to the base of the heart (black arrow) secondary to a vascular ring anomaly (persistent right aortic arch in this case). Source: Photo courtesy Dr. G. Sepulveda.

anesthesia in order to be effective.[32,33] In a recent study on dogs undergoing orthopedic surgery, the administration of esomeprazole intravenously 12–18 h and 1–1.5 h before anesthetic induction significantly increased the gastric and esophageal pH. However, their administration did not decrease the frequency of GER in these patients. In contrast, the administration of esomeprazole intravenously combined with cisapride, a prokinetic drug, before anesthesia was associated with a significant decrease in GER events.[34]

Metoclopramide is a dopamine antagonist drug and has antiemetic properties. In addition, it increases the resting tone of the LES and promotes gastroduodenal motility. Clinically, metoclopramide has been recommended for patients who are at risk of GER and regurgitation. In one study, the administration of a high intravenous dose (1.0 mg kg$^{-1}$) followed by an infusion (1.0 mg kg$^{-1}$ h$^{-1}$) in healthy dogs undergoing orthopedic surgery decreased the risk of GER by 54%.[24] In another study, metoclopramide at the same infusion rate did not influence the incidence of GER in dogs undergoing ovariohysteretomy.[31] Therefore, the risk of GER still exists during anesthesia in healthy patients, and observation of clinical signs for esophagitis are warranted. In addition, care must be taken when extrapolating these data from healthy patients to patients with esophageal disorders who already have predisposition to GER and regurgitation in order to not give to the clinician a false sense of security.

In cases where the patient is emaciated, anesthesia should be postponed until the animal has an improvement in body condition score. However, in certain situations, treatment for nutritional debilitation requires the placement of a gastrostomy or PEG tube, both of which would require general anesthesia. [17] In these situations, the anesthesia period should be kept as short as possible.

Since regurgitation is commonly associated with esophageal disease, thoracic radiographs should be taken preoperatively to evaluate the presence of aspiration pneumonia. Patients with aspiration pneumonia should be treated aggressively before being anesthetized for esophagoscopy, surgery, or feeding tube placement. If anesthesia cannot be delayed until aspiration pneumonia resolves, oxygenation with 100% oxygen before induction of anesthesia is recommended.[2] In addition, the trachea should be immediately intubated after induction of anesthesia, and positive pressure ventilation should be instituted to maintain oxygen saturation above 90%.

Dogs presented with esophageal diseases that appear to be dehydrated or hypovolemic on the basis of physical examination, CBC, and serum biochemical variables should receive fluid resuscitation before anesthesia. Tachycardia, pale mucous membranes, prolonged capillary refill time, and cold extremities are signs of hypovolemic shock and should be treated with isotonic crystalloids (70–90 ml kg$^{-1}$ in one-quarter dose increments) and 6% hetastarch (5–20 ml kg$^{-1}$) and reassessed before the induction of anesthesia. It should be noted that cats in shock might present with bradycardia and hypothermia.[35] Treatment of acid–base and electrolyte disturbances should be initiated before anesthesia if possible (see Laboratory data of Gastric and small intestinal diseases).

### Preanesthetic medication

The GI effects of anticholinergic drugs have been well described. Atropine and glycopyrrolate decrease LES tone at doses commonly used for prevention or treatment of bradycardia.[21] However, high doses of these drugs are required to inhibit hydrogen ion secretion by gastric parietal cells, and at the standard recommended doses for preanesthetic medication, these drugs have minimal effect on the pH of gastric secretions in dogs.[36] Therefore, the argument for including anticholinergic drugs in the preanesthetic medication for the purpose of having a less acidic reflux is not justifiable due to the increased likelihood of reflux due to decreased LES tone.

The administration of drugs that may induce vomiting or GER (e.g. alpha2-agonists and full mu-opioids) in the preanesthetic period of patients with esophageal foreign body is questionable. Sharp foreign body objects may abrade or lacerate the esophageal mucosa, causing esophagitis. Sharp objects may also perforate the esophagus and, occasionally, the great vessels. If emesis is induced by preanesthetic drugs in these patients, further damage may occur.[2,37] Reflux of acidic gastric fluid can induce further damage to the esophagus. Even so, opioids are usually included in the preanesthetic medication of these patients to provide analgesia even if removal of the foreign body is performed with noninvasive techniques (e.g. esophagoscopy) wherein pain is less intense. However, opioids that do not cause vomiting[10] such as butorphanol (0.1–0.4 mg kg$^{-1}$),

buprenorphine (0.01–0.02 mg kg$^{-1}$), and methadone (0.1–1.0 mg kg$^{-1}$) have been recommended for this type of procedure.[20] The administration of morphine, hydromorphone, and oxymorphone has been shown to increase the risk of regurgitation, GER, or vomiting significantly.[9–11,23,38] Therefore, methadone is preferred in the case of esophageal surgery where pain is more likely to be more intense.

Acepromazine (0.02–0.05 mg kg$^{-1}$) can be administered to provide sedation in patients with esophageal foreign bodies that are hemodynamically stable. When administered a few minutes before opioids, acepromazine decreases the incidence of vomiting induced by opioids[9], although it increases the chances of GER.[11] Diazepam or midazolam (0.2 mg kg$^{-1}$) may be preferred in depressed and hypovolemic patients. Furthermore, diazepam has been associated with a significant reduction in GER episodes.[21]

Intense sedation or muscle relaxation should be avoided in patients with megaesophagus. Muscle relaxation of the striated muscle layer of the esophagus can increase the likelihood of regurgitation before anesthetic induction. Intense sedation may impair the patients' ability to protect their airway, increasing the chances of aspiration pneumonia. Acepromazine, alpha2-agonists, and benzodiazepines should be used with caution in these patients.

### Induction of anesthesia

Dogs and cats with esophageal disease are at high risk of regurgitation and aspiration pneumonia. For this reason, it is advised to have a suctioning system set up during the induction period. Induction of anesthesia should be rapid with immediate ET intubation. Therefore, mask induction with inhalation anesthetic should be avoided, and intravenous anesthetic techniques are preferred. Propofol (4.0–8.0 mg kg$^{-1}$ IV) produces rapid onset of action, and the airway can be immediately secured, particularly in patients with megaesophagus. Alternatively, other drugs with fast onset of action, such as ketamine-diazepam and thiopental, can be used in patients with esophageal disorders.[20]

Endotracheal intubation should be performed with the patient in sternal recumbency with the head elevated. Application of pressure to the cricoid region has been documented in humans to reduce regurgitation[39]; however, this has not been advocated for dogs and cats. If regurgitation is observed during induction, the airway of the patient should be secured with a cuffed ET tube and its cuff immediately inflated. The patient's head should be dropped below the thoracic inlet, and the airway and oropharynx should be suctioned. The ET tube should be connected to a breathing system and 100% oxygen supplemented. Oxygenation and ventilation with the aid of a pulse oximeter and capnograph should be monitored at this time. If the procedure can be delayed, it is advised to allow the patient to recover from anesthesia and be observed for signs of aspiration pneumonia.

### Maintenance of anesthesia

The maintenance of anesthesia in patients with esophageal obstruction or megaesophagus is achieved with inhalation anesthetics (e.g. isoflurane, sevoflurane, or desflurane) diluted in 100% oxygen. Nitrous oxide should be avoided in patients with esophageal obstruction, as it can accumulate in viscous organ and produce dilation of the portion of the esophagus distal to the obstruction.[2]

Owing to the striated muscle layer in the esophagus, especially in dogs, administration of central muscle relaxants (e.g. diazepam and midazolam) or short-acting neuromuscular blocking agents (e.g. atracurium, vecuronium −0.1 mg kg$^{-1}$ IV) may be indicated. These drugs may help to relax the striated muscular layer of the esophagus, reduce esophageal tone, and facilitate endoscopic manipulations and foreign body removal.[2,5,20] Positive pressure ventilation should be provided in this case, and, ideally, neuromuscular function should be monitored by means of train of four. Deep planes of anesthesia with inhalation anesthetics to achieve muscle relaxation should not be performed especially in patients who are hemodynamically unstable.

Intraoperatively, a balanced isotonic crystalloid solution (e.g. LRS) should be administered at a rate of 5–10 ml kg$^{-1}$ h$^{-1}$. Supplemental fluid boluses of isotonic crystalloids or synthetic colloids (e.g. 6% hetastarch) may be indicated depending on the patient's hydration and hemodynamic status. In most cases, blood pressure can be monitored noninvasively, and pulse oximeter and capnography can provide valuable information in the event of esophageal perforation or aspiration.[20]

Most general anesthetics can increase the chances of GER or regurgitation because of their effects on the LES tone in dogs and cats.[25,40,41] Although the incidence of regurgitation is low in healthy anesthetized

patients[22,23,25,38], it is more likely to occur in patients with esophageal disorders. Continuous monitoring for regurgitation during anesthetic maintenance, and immediate treatment (i.e. suction) if regurgitation occurs, can help prevent complications from occurring.

If regurgitation is observed, suctioning the refluxate from the oropharygeal cavity and esophagus can minimize the chances of the patient from aspirating. However, only suctioning of the refluxate from the esophagus has no impact on the pH within the lumen of the esophagus. It has been recommended that if regurgitation is observed, suctioning should be followed by lavage of the esophagus. The esophagus can be lavaged with tap water using a smooth tipped catheter. In addition, bicarbonate should be instilled into the esophageal lumen to attempt to raise the pH and therefore possibly minimizes the chances of future esophageal stricture.[26]

If aspiration of the refluxate is observed while the animal is anesthetized, the airway should be suctioned to remove irritants, and oxygen saturation and breathing patterns should be monitored. If oxygen saturation starts to drop, positive pressure ventilation should be instituted.[2] Peak inspiratory pressure generated by a normal tidal volume (10–20 $ml\,kg^{-1}$) should be observed. Generation of high peak inspiratory pressure (>20 cm $H_2O$) with a normal tidal volume can indicate bronchospasm. Blood gas analysis can help assess the degree of oxygen exchange impairment.

Esophageal perforation with life-threatening tension pneumothorax should be suspected if sudden changes in breathing patterns occur with subsequent drops in oxygen saturation, decreased breath sounds on thoracic auscultation, and increased resistance to manual ventilation.[20] If this occurs, immediate thoracocentesis should be performed and positive pressure ventilation instituted. A decision of exploratory thoracotomy should then be made in order to remove the esophageal foreign body and repair the esophagus.[2,17]

In cases of thoracotomy for esophageal surgery, positive pressure ventilation must be continued and appropriate pain management should be administered intraoperatively and postoperatively. Air and fluid must be evacuated via a thoracostomy tube or thoracocentesis after the procedure.

### Recovery from anesthesia

Observing for regurgitation and protection of the airway during recovery is still crucial. Premature extubation can lead to aspiration if regurgitation occurs. Patients should be maintained in sternal recumbency, with the head elevated until the animal regains full consciousness and laryngeal reflex. The ET tube cuff should be kept inflated during extubation in order to remove any fluid or content proximal to the ET tube cuff, which will minimize the chances of aspiration.[16] If the patient regurgitates on extubation, its head should be dropped below the thoracic inlet, and suctioning of the airway should be provided. Oxygenation with the aid of a pulse oximeter must be monitored during recovery from anesthesia.

Postoperative analgesia should be provided accordingly to the intensity of pain produced by the procedure and damage to the esophageal mucosa in the case of foreign bodies.

Recently, NSAIDs have been identified as a factor associated with intraoperative regurgitation[38]; therefore, these drugs should be avoided in patients with esophageal disorders.

## Gastric and small intestinal diseases

Gastric surgery is commonly performed to remove foreign bodies and to correct gastric dilatation-volvulus (GDV). Gastric foreign bodies usually cause vomiting as a result of either mechanical irritation to the mucosa, outflow tract obstruction, or gastric distention. Vomiting often is intermittent, occurring when the object is forced into the pyloric antrum.[2,29]

Gastric ulceration, hemorrhage, and neoplasia are less common indications for surgery. However, patients with these disorders may require endoscopic diagnostic procedures or feeding tube placement. Bleeding of the gastric mucosa should be considered in patients with gastroduodenal ulceration, or esophagitis due to chronic vomiting, and less often due to malignancy.[42]

Gastroscopy or gastrotomy is often indicated for the removal of large, sharp, or potentially toxic foreign bodies, whereas partial gastrectomy is performed for the removal of ulcers and neoplasms or necrosis from GDV. Pylorectomy with gastroduodenostomy is indicated for the removal of the pylorus due to neoplasm in this area, outflow tract obstruction caused by pyloric muscular hypertrophy, or ulceration of the gastric outflow tract.[2,29]

Surgery of the small intestines is most often indicated for GI obstruction such as foreign bodies. With intraluminal GI obstructions, the intestine orad to the lesion distends with gas and fluid. Fluid accumulation is caused both by retention of fluid in the intestinal lumen and by secretion of fluid by intestinal glands. During obstructions, secretion increases and absorption diminishes, and gas also accumulates. Eventually, fluid shifts not only into the lumen, but also from the serosa into the peritoneal cavity. Circulation in the mucosa and submucosa becomes impaired, and the mucosa becomes ischemic. Full thickness wall necrosis may occur at the obstruct site. Small intestinal stasis leads to luminal bacterial overgrowth. If the normal mucosal barrier is impaired by distention and ischemia, permeability may increase, with subsequent bacterial translocation and absorption of toxins into the systemic circulation or peritoneal cavity, or both.[2]

Other indications for small intestine surgery include trauma (e.g. perforation, ischemia), malpositioning (e.g. volvulus, intussusception), neoplasia, and diagnostic procedures (e.g. full thickness biopsy).

Patients with suspected protein-losing enteropathy require stomach and intestinal biopsies in order to confirm the diagnosis. These patients may undergo gastroduodenoscopy or exploratory laparotomy with gastrotomy and enterotomy.[43]

## Clinical signs

Visual examination provides the following information about dogs and cats with GI disease: the animal's mental state, temperament, nutritional state, and comfort. Most animals with gastric diseases have vomiting, anorexia, or depression and, occasionally, abdominal pain and weight loss. Patients with primary small intestinal disorders are usually presented for signs of vomiting, diarrhea, anorexia, depression, and/or weight loss.[2] Fever and abdominal pain may result from severe GI disease such as complete GI obstruction or perforation.[2,29] These patients usually become severely dehydrated as a result of fluid loss and a reduced fluid intake, resulting in acute volume depletion and signs of shock.[2,20,28]

Upper GI hemorrhage is an important cause of blood loss and anemia and potentially is a life-threatening condition in dogs.[42] Hematemesis or melena may indicate gastroduodenal ulceration or the presence of a coagulopathy.[2] If blood loss exceeds 25% of total blood volume, these patients may experience hypotension and tachycardia and may not be the best anesthetic candidates.

Coughing, dyspnea, and cyanosis can indicate that aspiration pneumonia has occurred in vomiting animals. However, aspiration pneumonia is a less common complication of vomiting than it is of regurgitation because reflex closure of the glottis occurs during emesis. Regurgitation may also occur because of esophagitis in chronic vomiting animals.[2,28]

## Laboratory data

A full CBC and serum biochemistry profile should be performed in any patient presented with vomiting and/or diarrhea undergoing anesthesia[28,43], as GI disease can lead to electrolyte and acid–base disturbances[20].

Laboratory parameters may be normal or may show only changes caused by dehydration (e.g. high PCV, TP, BUN, and creatinine), especially in animals with GI foreign bodies that are presented as soon as signs of disease are noted.[2] The metabolic consequences of vomiting because of foreign bodies are variable but can be severe.[29,44] The most common electrolyte and acid–base abnormality, regardless of the site (stomach or small intestine) or type of foreign body, is hypochloremic metabolic alkalosis with hypokalemia and paradoxical aciduria due to loss of acid-rich gastric secretions.[28,29] This also suggests that foreign bodies distal to the duodenum can produce metabolic alkalosis by increased secretion of chloride and potassium into the intestinal lumen. This, combined with vomiting of acid-rich gastric secretions, hypochloremia, hypokalemia, and volume contraction, all act to perpetuate any initial metabolic alkalosis.[44] However, metabolic acidosis may occur depending on the composition and volume of expelled GI contents and the degree of dehydration.[28,29] In patients with more chronic vomiting, hyperlactatemia with subsequent metabolic acidosis may occur because of GI ischemia or systemic hypoperfusion.[2,28]

Hematocrit in patients with acute and severe gastric bleeding may be normal early in the course of acute gastroduodenal hemorrhage due to insufficient time for equilibration of plasma volume. Once plasma volume is equilibrated and fluid resuscitation is administered, anemia becomes more overt.[29] Acute upper GI bleeding is associated with a normocytic normochromic regenerative anemia, whereas chronic blood loss is characterized by iron deficiency and microcytic hypochromic anemia.

In addition, a mild to moderate thrombocytosis may also be noted with chronic GI blood loss. With active bleeding, anemia is accompanied by hypoproteinemia.[29] BUN levels are typically increased in these cases because of the absorbed nitrogen load from the blood in the small intestine. A high BUN to creatinine ratio has been reported with upper GI hemorrhage.[42]

Gastrointestinal loss accounts for ~40% of the normal daily turnover of plasma proteins, and for this reason, protein-losing enteropathy (e.g. inflammatory bowel disease) can lead to hypoproteinemia.[45] The mechanism of protein loss may be related to inflammation or damage of the GI barrier. Albumin is one of the proteins lost into the GI tract, and as it contributes significantly to oncotic pressure, intravascular fluid loss can occur second to hypoalbuminemia.[28] As albumin decreases ($<1.5$ g dl$^{-1}$), effusions (e.g. pleural and peritoneal effusions) and edema can occur.[45]

## Management of anesthesia

### Perianesthetic considerations

The degree of dehydration should be evaluated on the basis of physical examination and laboratory findings. Ideally, correction of fluid deficit, electrolyte, and acid–base abnormalities should take place before anesthesia in order to improve the patient's hemodynamic stability throughout the anesthetic procedure.[20] Isotonic 0.9% saline is the fluid of choice for metabolic alkalosis. Since hypokalemia can lead to skeletal muscle weakness, decreased GI motility and ileus, and cardiac arrhythmias, it should be corrected with potassium chloride supplementation before anesthesia. When administered intravenously, potassium chloride generally should not be infused at rates $>0.5$ mEq kg$^{-1}$ h$^{-1}$ to avoid potential adverse cardiac effects.[46] Hypokalemia can also predispose the myocardium to become refractory to the effects of class I antiarrhythmic drugs such as lidocaine and procainamide. These drugs are commonly used during anesthesia in patients with diseases that can cause ventricular arrhythmias such as GDV. Hypokalemic patients in shock should be resuscitated with an isotonic crystalloid solution (e.g. 0.9% saline or Lactated Ringer's solution) before adding potassium chloride to the fluids. If a patient is severely hypokalemic (serum potassium $<2$ mEq), it is prudent to start potassium as a separate infusion and not with the resuscitation fluid bag, in order to not exceed the recommended potassium infusion rate (0.5 mEq kg$^{-1}$ h$^{-1}$).[28] Dehydration from vomiting in patients with metabolic acidosis should be corrected with a balanced isotonic crystalloid solution containing lactate or acetate. The administration of sodium bicarbonate is necessary only in the treatment of patients with severe metabolic acidosis who have not responded to fluid therapy (pH $<7.1–7.2$).[29] In these patients, bicarbonate deficit should be corrected with sodium bicarbonate according to the following equation:

$$\text{Bicarbonate deficit (mEq)} = 0.3 \times \text{base excess (mEq l}^{-1}) \times \text{body weight (kg)}$$

Initially, one-third to one-half of the calculate sodium bicarbonate should be administered slowly.[20] The administration of sodium bicarbonate should be withheld in hypokalemic patients.[28]

When possible, food should be withheld for 8–12 h to ensure gastric emptying. Patients with GI foreign bodies or GDV should have surgery performed as soon as possible after the animal's condition has been stabilized, and they should be assumed to have a full stomach when they come for surgery.[2]

Patients with signs of profuse GI bleeding (i.e. hematemesis or melena) should be hemodynamically stabilized with fluid resuscitation.[2,29,42] If PCV is <20%, these patients should be blood typed or cross-matched (if they have previously received blood transfusion), and pRBC or whole blood transfusions should be administered or at least started before gastroduodenoscopy or surgery.[2,29] These patients should also be evaluated for coagulation defects by measuring prothrombin time, activated partial thromboplastin time, platelet count, fibrinogen, and fibrin degradation products.[29] FFP transfusions should be considered if clotting times are prolonged or if albumin is $<1.5$ g dl$^{-1}$.[2] Medications known to cause ulcers (e.g. NSAIDs and steroids) should be discontinued.[42] Since ulceration is the most common cause of GI bleeding and GER may occur during general anesthesia, the administration of drugs that increase gastric secretion pH is advised.[33] Perianesthetic considerations for this problem are discussed in the esophageal disease section.

### Preanesthetic medications

The selection of sedative drugs for preanesthetic medications should be based on the patient's attitude and severity of disease. Debilitated animals do not

require drugs that produce intense sedation (e.g. alpha2-agonists). Alternatively, benzodiazepines combined with opioids should be considered for these patients because they produce good sedation and analgesia in depressed patients. Opioids are usually part of the premedication protocol for patients undergoing exploratory laparotomy because they produce analgesia and spare inhalational anesthetics.[20]

Acepromazine has central antiemetic effects and can be included in preanesthetic medications. However, caution should be taken when administering acepromazine to dehydrated or hypovolemic patients.[29]

In animals with gastric foreign bodies (Figure 5.3A–C), vomiting can be induced with preanesthetic medication in dogs and cats, but only if the object is small and has rounded edges. However, this should only be attempted when the clinician is confident the object will be expelled without causing harm to the esophagus. Trauma to the esophagus could be potentially life threatening or could lead to future esophageal stricture.[2] In dogs, xylazine is more likely to induce vomiting than medetomidine. In cats, both xylazine and medetomidine have a high incidence of inducing emesis.[7] Alpha2-agonist can be used as an emetic agent, provided that patients are hemodynamically stable.

Atropine and opioids agents may increase pyloric sphincter tone in dogs and cats. The effects of these drugs on the level of difficulty and time required to pass an endoscope into the proximal portion of the duodenum have been evaluated in dogs and cats. In dogs, morphine and atropine induced gastropyloric conditions that resulted in significant difficulty in passing an endoscope through the pylorus into the duodenum. Meperidine and acepromazine did not increase the difficulty of endoscopic intubation of the duodenum in dogs.[47] In cats, the administration of hydromorphone alone, hydromorphone and glycopyrrolate, medetomidine alone, or butorphanol alone in the premedication did not affect the duration and level of difficulty of passage of the endoscope through the pylorus.[48] However, some endoscopists have suggested that opioids should be avoided altogether in dogs and cats undergoing gastroduodenoscopy.[37]

## Induction of anesthesia

The selection of induction agent will depend on cardiovascular and nutritional status of the patient. If patients are hemodynamically stable, virtually any intravenous anesthetic technique can be used. In hemodynamically compromised patients, ketamine (5.0 mg kg$^{-1}$) and diazepam (0.25 mg kg$^{-1}$) should be considered. Neuroleptanalgesia technique with an opioid (e.g. fentanyl 0.005–0.01 mg kg$^{-1}$, oxymorphone 0.05–0.1 mg kg$^{-1}$, or hydromorphone 0.05–0.1 mg kg$^{-1}$) and benzodiazepines (diazepam 0.2 mg kg$^{-1}$ or midazolam 0.2 mg kg$^{-1}$) can also be administered intravenously in very debilitated dogs. Rapid induction and immediate intubation are essential if vomiting is a concern, and mask induction should be avoided.

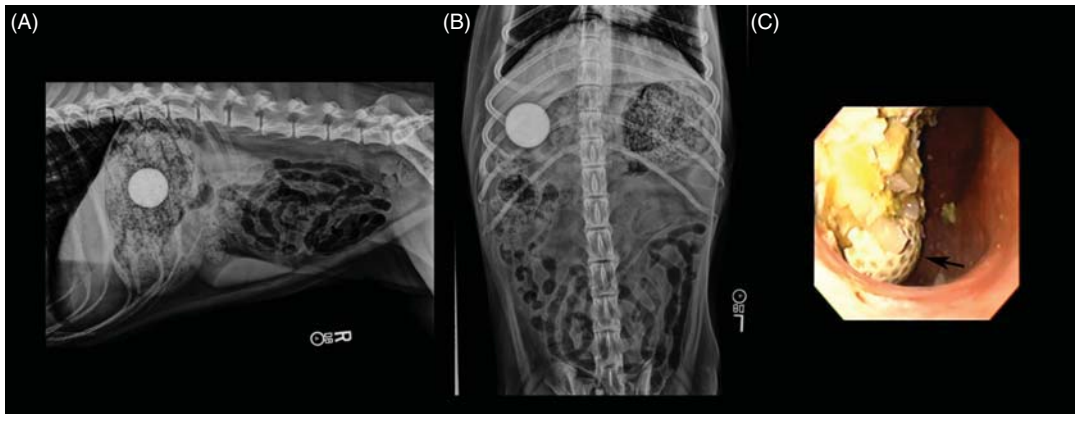


**Figure 5.3** (A) Lateral abdominal radiograph showing a round radiopaque foreign body in the stomach of a dog. (B) Ventrodorsal radiograph showing the same round radiopaque foreign body in the stomach of a dog. (C) Gastroscopic study of the dog revealing that the round radiopaque foreign body was a golf ball (black arrow).

## Maintenance of anesthesia

Any halogenated inhalational anesthetic can be administered for GI procedures commonly performed in small animals. However, it is preferred to maintain the concentration of these gases as low as possible in hypovolemic patients. This can be performed by using infusions of drugs that produce minimal cardiovascular depression and have inhalation anesthetic-sparing effects. CRIs of opioids (e.g. fentanyl or remifentanil 0.005–0.04 $mg\,kg^{-1}\,h^{-1}$) and lidocaine (3 $mg\,kg^{-1}\,h^{-1}$) can achieve this goal in dogs. Although lidocaine CRI decreases isoflurane requirement in cats, its use is not recommended in this species because of greater cardiovascular depression than an equipotent dose of isoflurane alone.[49]

Nitrous oxide increases the volume of air trapped in body viscera and therefore should be avoided in patients with intestinal obstruction.[2]

Body heat is lost from exposed viscera during abdominal surgery. This may lead to hypothermia, which may reduce the need for anesthesia. Care should be taken during surgery to try to maintain the patient's body temperature above 95°F (35°C), especially in nutritional debilitated animals with poor body condition scores.[2]

Routine anesthetic monitoring is recommended in these patients. Patients who are likely to be hypovolemic and are undergoing GI surgery of long duration will benefit from invasive blood pressure monitoring. During gastroscopy, gastric inflation and distention of the stomach can impair ventilation, oxygenation, and circulation.[20] Therefore, monitoring with capnography, pulse oximetry, noninvasive blood pressure, and heart rate can help the anesthetist to judge stomach inflation and prevent complications. In addition, the anesthetist should inform the endoscopist if the stomach is overinsufflated. The excessive amount of air in the stomach can be removed with the use of suction through the endoscope. Prolonged distention of the stomach can result in decreased venous return to the heart and vasovagal stimulation, leading to bradycardia.[37] A decrease in heart rate with a resultant decrease in blood pressure should be treated with anticholinergic agents.

A balanced isotonic crystalloid solution should be administered throughout surgery or endoscopic procedure at a maintenance rate of 5–10 $ml\,kg^{-1}\,h^{-1}$. Fluids supplemented with potassium that are used in hospitalized patients should be used with caution during anesthesia maintenance. These fluids often contain supplemental potassium chloride, so they may increase the risk of potassium chloride overdose if boluses of fluids are required. For this reason, if potassium supplementation is required in severely hypokalemic patients, it is advised to use a secondary intravenous line containing a potassium supplemented fluid. With this set up, a primary intravenous line containing nonsupplemented fluids can be used for the purpose of maintenance of fluids and/or administration of boluses of fluids. Alternatively, potassium can be supplemented with the aid of an infusion pump separate from the main fluid.

Patients with protein-losing enteropathy who are presented with hypoalbuminemia are more likely to become hypotensive because of decreased oncotic pressure and leakage of intravascular fluid to the interstitium. Six percent hetastarch (1–2 $ml\,kg^{-1}\,h^{-1}$) can also be administered perioperatively in hypoalbuminemic patients. Balanced isotonic crystalloid therapy for anesthesia maintenance should be decreased in these patients.

Intraoperative hypotension can be treated with balanced isotonic crystalloid boluses (e.g. LRS 10–20 $ml\,kg^{-1}$), 6% hetastarch (3–5 $ml\,kg^{-1}$), or inotropic drugs such as dopamine or dobutamine (starting at 5.0 $mcg\,kg^{-1}\,min^{-1}$).

## Recovery from anesthesia

Pain should be estimated and treated accordingly in patients recovering from laparotomy for gastrotomy, enterotomy, and intestinal resection and anastomosis. Fentanyl and lidocaine infusions can still be administered postoperatively. If these medications are discontinued, analgesia should be supplemented with hydromorphone or oxymorphone as needed.

Nonsteroidal anti-inflammatory drugs are a frequent cause of gastric ulceration. These drugs inhibit prostaglandin synthesis, which decreases mucosal blood flow and alters gastric mucus production, thus predisposing to ulceration.[29] In addition, inhibition of prostaglandin synthesis may impair renal blood flow in the event of hypovolemia and hypotension, potentially leading to renal ischemia and acute renal insufficiency. Therefore, NSAIDs are contraindicated for analgesia in patients with GI diseases, hypovolemia, or hypotension.

Body temperature should be continuously monitored during recovery. Hypothermia should be treated with a warm forced air blanket or a heating pad that is safe against burns.

## Gastric dilatation-volvulus

Gastric dilatation-volvulus is an acute, life-threatening disorder that affects 40,000 to 60,000 dogs (with increased risk in large breed) per year in the United States.[5,29,50,51] The disease refers to an acute distension of the stomach associated with rotation on its mesenteric axis, resulting in complete gastric outflow obstruction. Concurrent obstruction of the gastroesophageal junction precludes relief of fluid and gas accumulation by vomiting.[2,29,52] The GDV syndrome has a mortality rate of 10%–45% in treated animals.[51,53–57] Increased mortality is usually associated with septic shock or peritonitis secondary to gastric necrosis or perforation, gastrectomy and splenectomy, and preoperative cardiac arrhythmias.[2,55,57,58] Reperfusion injury has also been implicated as a factor associated with the high mortality from this condition.[2]

The initiating cause of the gastric distension is unknown; however, once the stomach dilates, normal physiological means of removing air (i.e. eructation, vomiting, and pyloric emptying) are hindered because the esophagus and pylorus become obstructed. The stomach becomes enlarged, as gas and fluid accumulate in the lumen. Normal gastric secretion and transudation of fluids into the gastric lumen as a result of venous congestion contribute to fluid accumulation. The stomach rotates and the duodenum, pylorus, and spleen are displaced (Figure 5.4A). Splenomegaly can occur secondary to displacement.[2] Impairment of venous return to the heart occurs as the caudal vena cava, portal vein, and splanchnic vasculature are compressed by massive gastric distention and an increase in intra-abdominal pressure.[29,52,59] This ultimately decreases cardiac output and systemic arterial pressures, causing myocardial ischemia and decreased tissue perfusion.[60] As a result, dogs with GDV can develop multiple types of shock, including obstructive, hypovolemic, and distributive shock. This ultimately leads to inadequate tissue perfusion and affects multiple organs, including the kidneys, heart, pancreas, stomach, and small intestines.[2]

In addition, gastric distention prevents caudal displacement of the diaphragm, decreasing pulmonary compliance and impeding normal thoracic expansion (Figure 5.4B). Respiratory rate and effort are increased as a compensatory mechanism. If these efforts are inadequate, then minute volume ventilation is decreased, and respiratory acidosis occurs.[52]

When GDV occurs, multiple factors can lead to gastric mucosal ulceration, hemorrhage, and necrosis. These factors include an increase in intragastric pressure, decreases in gastric mucosal perfusion, and increased gastric secretion. Bacterial translocation from the stomach or other portions of the poorly perfused GI tract may lead to septicemia. Necrosis and perforation can result in peritonitis.[52]

Cardiac arrhythmias such as sinus tachycardia, atrial fibrillation, idioventricular tachycardia, paroxysmal

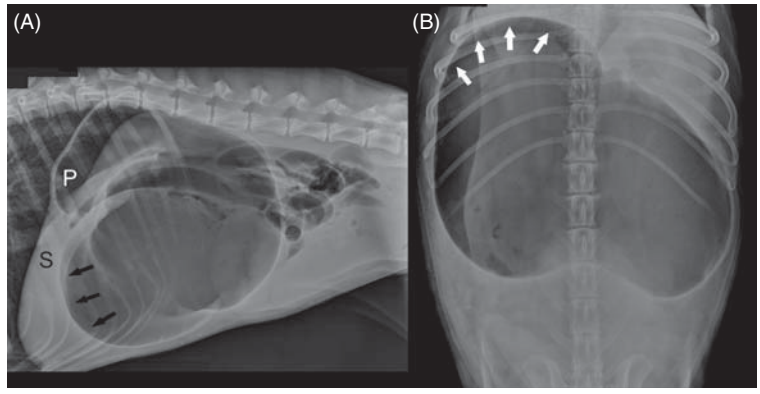


**Figure 5.4** (A) Right lateral radiographic view of a dog with gastric dilatation volvulus (GDV). The pylorus (P) and spleen (S) are displaced cranially. The major radiographic feature observed is accumulation of gas and distention of the stomach (black arrows). All of these abnormalities lead to decreased venous return from compression of the caudal vena cava, portal vein, and splanchnic vasculature, as well as cranial displacement of the diaphragm (shown in [B], white arrows) and respiratory compromise.
Source: Photo courtesy Dr. G. Sepulveda.

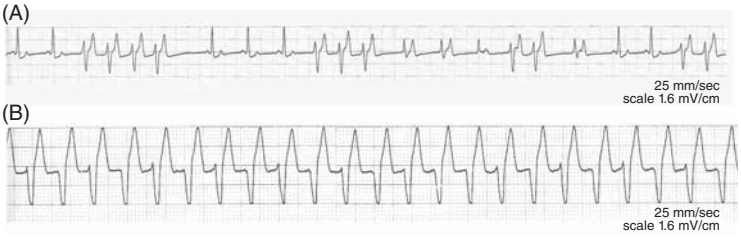


**Figure 5.5** (A) Paroxysmal ventricular tachycardia in a dog. (B) Ventricular tachycardia in a dog.

ventricular tachycardia, and ventricular tachycardia (Figure 5.5A and B) are frequently observed in dogs with GDV[53,61], particularly those with gastric necrosis[58]. Arrhythmias may contribute to mortality and require appropriate monitoring and treatment.[53] The cause of ventricular arrhythmias is unknown, but reduced cardiac output, myocardial ischemia, epinephrine release, and the release of myocardial depressant factor may be the contributing factors.[52,60,62]

## Clinical signs

Dogs with GDV are presented with acute onset of abdominal distention and may appear to have signs of abdominal pain (e.g. arched back). Nonproductive retching, hypersalivation, distended abdomen, restlessness, and respiratory distress are common. Clinical signs of shock may be present, including depressed mentation, weak peripheral pulses, tachycardia, prolonged capillary refill time, pale mucous membranes, or dyspnea. Arrhythmias can often be auscultated along with palpable pulse deficits. These arrhythmias are commonly ventricular in origin.[2,29,52,61]

## Laboratory data

Gastric dilatation-volvulus can be associated with multiple systemic problems with several metabolic and electrolyte derangements. These are not always consistently present.[63,64] In one study, hypokalemia was present in 33% of the dog with GDV; however, potassium may be elevated or normal. Hypochloremic metabolic alkalosis may develop from gastric sequestration of hydrogen and chloride ions.[64] Later in the course of the disease, metabolic acidosis may occur from decreased effective circulating blood volume, resulting in tissue hypoxia and lactate production. Plasma lactate concentrations below 6 mmol $l^{-1}$ at preresuscitation or more than 50% in decrease in lactate levels within 12 h from initial presenting concentration suggest that gastric necrosis is not present, and therefore a fair prognosis is warranted.[65–67]

Respiratory acidosis is likely to occur secondary to gastric impingement on the diaphragm and diminished ventilatory compliance. Once anesthesia is induced, respiratory acidosis may become severe because of the respiratory depressant effects of anesthetics. Hypoventilation combined with ventilation perfusion mismatch can lead to hypoxemia.

Blood glucose levels may also decrease in the later stages of shock, as energy demands cannot be met by the inefficient production of adenosine triphosphate through anaerobic metabolism.[52]

Packed cell volume and TP may reveal evidence of hemoconcentration. These patients may have increased BUN and creatinine owing to prerenal azotemia due to decreased renal perfusion.[52]

## Management of anesthesia

### Perianesthetic considerations

The gastric distention and compression of the abdominal vasculature lead to cardiopulmonary and GI compromise that can severely affect the stability of these dogs during anesthesia. Therefore, stabilizing the patient's condition is the initial goal before inducing anesthesia. At least two large-bore (14–18 gauge) intravenous catheters should be placed in either a jugular and cephalic vein or both cephalic veins. More than one catheter allows rapid fluid resuscitation and administration of several drugs simultaneously, some of which may be incompatible in the same line. Blood samples for CBC, serum biochemistry profile, and blood gas analysis can be collected at the same time of catheter placement.[2,29,68]

During the initial patient examination up to induction of anesthesia, oxygen should be supplemented via a mask if the patient will tolerate this. Restoration of circulating plasma volume should be initiated using

high volumes of isotonic solutions. These solutions can be given alone or with hypertonic saline solution or 6% hetastarch over 5–15 min.[2,52,69,70] The shock dose for isotonic crystalloid fluids is equivalent to the patient's blood volume (90 ml $kg^{-1}$) and should be calculated and administered in aliquots of one-third to one-quarter of the total dose. These aliquots can be administered in combination with 7% hypertonic saline (4–6 ml $kg^{-1}$) or aliquots of one-quarter of the daily 6% hetastarch dose (5 ml $kg^{-1}$). A small volume fluid resuscitation with a combination of hypertonic saline and synthetic colloid has been advocated as a more efficient method than high volume during resuscitation of dogs with GDV.[69,70] In this case, a mixture of ~7% saline and 6% hetastarch can be administered (calculate 1 ml $kg^{-1}$ 23.4% saline and 2 ml $kg^{-1}$ of 6% hetastarch, mix them in a same syringe and administer the total volume of 3 ml $kg^{-1}$ over 5 min). If 7% hypertonic saline and/or 6% hetastarch are administered, the rate of subsequent crystalloid administration must be adjusted. After initial resuscitation, cardiovascular parameters should be reassessed before further administration of fluids. Significant electrolyte and acid–base abnormalities should be corrected.[2,52]

Debilitated moribund dogs usually will allow catheterization of the dorsal pedal artery after the skin over the artery is desensitized with lidocaine (Figure 5.6A–F). Arterial catheterization will allow monitoring of arterial blood pressures and gas analysis, which can be used as a guide to fluid therapy before and during anesthesia.[68] If arterial catheterization is not possible before anesthesia, blood pressure should be monitored noninvasively with the aid of an oscillometric blood pressure device or an ultrasonic Doppler device combined with a sphygmomanometer.

Continuous electrocardiographic (ECG) monitoring will provide valuable information regarding the cardiac rhythm in these patients. Preoperative treatment of arrhythmias should include correction of hypovolemia and electrolyte imbalances. This is especially important if hypokalemia is present because lidocaine is ineffective when the animal is hypokalemic. If the arrhythmias interfere with cardiac output, they should be primarily treated with lidocaine initially with IV boluses of 2.0–4.0 mg $kg^{-1}$. Clinical findings that may suggest poor cardiac output due to arrhythmia may include poor blood pressure or lack of palpable pulse during tachycardia, multiform ventricular arrhythmias, the presence

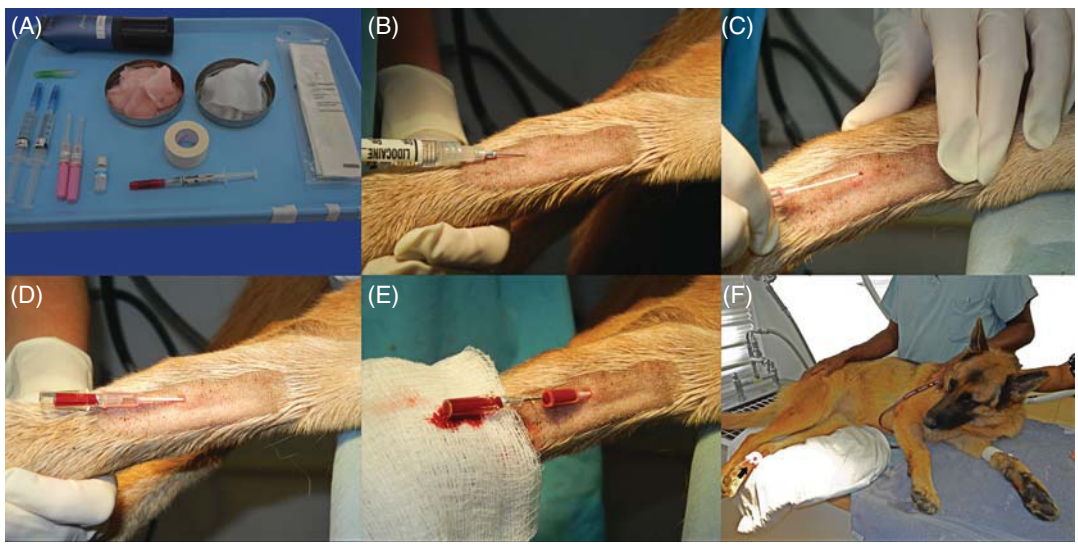


**Figure 5.6** Desensitization of the dorsal skin of the hock and catheter placement in the dorsal pedal artery before anesthetic induction. (A) All material required for arterial catheterization. (B) The hair of the skin over the dorsal pedal artery is clipped and aseptically prepared. Lidocaine (2%) is injected subcutaneously over the dorsal pedal artery. In order to avoid the artery and subsequent hematoma formation, the artery should be palpated and the skin over the artery pulled to the side before injection. (C) The dorsal pedal artery should be palpated before catheter placement. (D) The catheter and stylet are introduced into the artery. (E) The catheter is fed into the artery. (F) Successful arterial catheter placement in a dog with GDV before anesthetic induction.

of subsequent premature beats inscribed on the T wave of the previous complex (R on T), or a sustained ventricular rate of >160 beats per minute. After the initial boluses are given, treatment with lidocaine can be continued with a CRI of 3.0–4.5 mg kg$^{-1}$ h$^{-1}$.[61] Signs of lidocaine toxicity should be monitored in the awake patient. These signs may include muscle tremors, vomiting, and seizures. If any of these signs occur, lidocaine administration should be decreased or discontinued. If seizures occur, they should be treated with IV diazepam (0.5 mg kg$^{-1}$). Procainamide (0.5–1.0 mg kg$^{-1}$ IV bolus and CRI at 2.4 mg kg$^{-1}$ h$^{-1}$) may be administered if lidocaine fails to convert the rhythm back to a normal sinus rhythm, or if improvement in variables indicative of circulation (e.g. heart rate, peripheral pulse pressure quality, arterial blood pressure, mucous membrane colors, and capillary refill time) is not seen.[2,52,61]

Gastric decompression, preferably via an orogastric tube, should be performed to remove air and fluid from the stomach as soon as the dog is hemodynamically stabilized. Decompression of the stomach may improve the patient's cardiopulmonary status. Sedation may be needed in order to accomplish decompression. When an orogastric tube is placed, the clinician should have an ET tube and laryngoscope handy in order to protect the patient's airway. Reflux around the orogastric tube and aspiration may occur while the dog is extremely sedated and cannot protect its airway.[29,52]

Drugs that increase the gastric pH such as H-2 antagonists should be considered preoperatively.

### Sedation to pass orogastric tube and preanesthetic medication

Sedation may be necessary for gastric decompression via orogastric intubation or percutaneous gastrocentesis. However, drugs that produce moderate to intense sedation are not necessary because dogs presented with GDV are usually depressed and have decreased cardiac output. Therefore, the use of alpha2-agonists should be avoided in these cases because of their depressant effects on cardiac output, despite the initial increase in blood pressure.[7] Acepromazine should be avoided because its vasodilatory effect can further decrease venous return to the heart and lead to hypotension.[50]

Preanesthetic drugs that cause vomiting should be avoided because the central effects of these drugs will induce all reflexes for vomiting. However, these dogs may not be able to expel their gastric contents because of gastroesophageal obstruction. Increases in abdominal pressure may lead to stomach rupture and decrease in venous return to the heart.[59]

Intravenous administration of drugs is preferred because doses can be administered to effect and thus reduced, making their effect more predictable. The combination of diazepam (0.1–0.2 mg kg$^{-1}$) or midazolam (0.1–0.2 mg kg$^{-1}$) with butorphanol (0.2–0.4 mg kg$^{-1}$) has been commonly recommended for GDV because of the antiemetic properties of butorphanol and minimal cardiovascular effects of both drugs.[29,68] However, dogs with volvulus require surgery, and full mu-opioid agonists will produce more effective analgesia. Butorphanol is an agonist-antagonist with a 1–2 h duration of action and, if still present in therapeutic concentrations in the plasma at surgery, it can decrease the effectiveness of full mu-agonist. Full mu-agonists are the drugs of choice to minimize the amount of inhalation anesthetics because of their anesthetic-sparing effect and minimal cardiovascular effect. So, as an alternative to butorphanol, methadone (0.1–0.5 mg kg$^{-1}$), hydromorphone (0.05–0.1 mg kg$^{-1}$), oxymorphone (0.05–0.1 mg kg$^{-1}$), or fentanyl (0.002–0.005 mg kg$^{-1}$) combined with diazepam or midazolam can be used.[68]

### Induction of anesthesia

Agents selected for anesthesia should produce minimal cardiovascular depression. Drugs that produce significant vasodilation, myocardial depression, or are arrhythmogenic (e.g. thiopental or halothane) should be avoided.[20,50] Neuroleptanalgesic combinations such as diazepam (0.2–0.5 mg kg$^{-1}$ IV) and fentanyl (0.005–0.02 mg kg$^{-1}$ IV) administered to effect, produce minimal cardiovascular effects and are appropriate for anesthetic induction in dogs with unstable cardiovascular function. Propofol titrated to effect or ketamine (5.0 mg kg$^{-1}$) combined with diazepam (0.25 mg kg$^{-1}$) has also been suggested as appropriate options for induction of anesthesia.[68] Care must be taken when inducing severely sick patients with ketamine-diazepam because ketamine may potentially cause negative inotropy when depletion of sympathetic tone is present, which often occurs in the later stages of shock.[20]

Once the ET tube is placed into the trachea, the cuff should be inflated. An orogastric tube should be placed soon after induction to minimize the risk of regurgitation and aspiration.

### Maintenance of anesthesia

Because inhalation anesthetics produce dose-dependent vasodilation and myocardial depression, their concentrations during maintenance of anesthesia in dogs with GDV should be decreased by the use of balanced anesthetic techniques. Sevoflurane and desflurane can be considered in these cases because they are relatively insoluble agents and have the advantage of rapid change in end-expiratory concentration in the case of cardiovascular instability. However, it is also possible to achieve a rapid change of depth of anesthesia with isoflurane.[20] Nitrous oxide is contraindicated before permanent gastric decompression is achieved because it rapidly diffuses into gas-filled compartments, causing additional organ distention and increasing the intragastric volume. This can crowd the operative field, limit diaphragmatic movement, and compromise respiration.[2]

Fentanyl or remifentanil (LD: 0.002–0.005 mg $kg^{-1}$, CRI: 0.005–0.04 mg $kg^{-1}$ $h^{-1}$) and lidocaine (LD: 1.0–2.0 mg $kg^{-1}$, CRI: 3.0 mg $kg^{-1}$ $h^{-1}$) are usually administered for their anesthetic-sparing effects. In addition, fentanyl and remifentanil produce effective analgesia, whereas lidocaine has analgesic, antiarrhythmic, anti-inflammatory, and GI prokinetic effects. Furthermore, the administration of lidocaine as a bolus followed by a CRI starting before surgery in dogs with GDV decreased the occurrence of cardiac arrhythmias.[71] Benzodiazepines (e.g. diazepam 0.05–0.2 mg $kg^{-1}$ IV) or nondepolarizing neuromuscular blocking agents (NMBAs; e.g. atracurium 0.1–0.2 mg $kg^{-1}$ IV) can be supplemented as part of balanced anesthetic technique. If NMBAs are administered, ideally, neuromuscular function should be monitored by means of train of four.[20]

Intraoperatively, a balanced isotonic solution (e.g. lactated ringer's solution) should be administered at a rate of 10 ml $kg^{-1}$ $h^{-1}$. If an arterial catheter has not been placed before induction, an attempt should be made after induction for monitoring of invasive blood pressure because patients with GDV are often hypotensive.[59] Because a variety of acid–base abnormalities may occur during the maintenance of anesthesia, serial monitoring of arterial blood gases and electrolytes is advised. Any documented abnormalities should be corrected. Sodium bicarbonate should only be administered if severe acidosis occurs ($pH < 7.1–7.2$).[29] As discussed previously, the administration of sodium bicarbonate should be withheld in hypokalemic patients.[28]

Hypertonic saline, 6% hetastarch, and FFP should be available in the event that hypotension with tachycardia occurs. Fluid therapy during anesthesia should be continuously reassessed and modified on the basis of the monitoring of parameters such as central venous pressure, invasive arterial blood pressure, PCV, TP, heart rate, capillary refill time, and mucous membrane color.[50] Urine output can also be used as an assessment of renal perfusion, cardiac output, and fluid therapy efficacy. Therefore, it should be considered in hemodynamically compromised patients.

The administration of inotropic drugs such as dobutamine and dopamine (starting at 5.0 mcg $kg^{-1}$ $min^{-1}$ [2–20 mcg $kg^{-1}$ $min^{-1}$]) can help maintain mean arterial pressure above 60 mm Hg.[68] In patients with refractory response to fluids and inotropic support, administration of vasopressor drugs such as norepinephrine (0.05–2.0 mcg $kg^{-1}$ $min^{-1}$), phenylephrine (0.1–3.0 mcg $kg^{-1}$ $min^{-1}$), or vasopressin (0.5–2.0 mU $kg^{-1}$ $min^{-1}$) may be warranted.

Continuous monitoring of ECG will allow detection of arrhythmias and also help to evaluate efficacy of antiarrhythmic drugs when administered.

Positive pressure ventilation should be instituted to correct respiratory acidosis, as well to recruit collapsed alveoli and improve blood oxygenation. However, intrathoracic positive pressure may result in a decrease in venous return, thus worsening hypotension, especially in dogs with ineffective circulatory volume. Observation of invasive systolic blood pressure values or the pulse oximeter pulse pressure wave immediately after a delivered breath by the ventilator can provide early and noninvasive information regarding decreased venous return and stroke volume.[72,73] If drops in systolic arterial pressure occur with the ventilator breaths, decreases in tidal volume or peak inspiratory pressure are warranted, as well as the administration of a fluid challenge.

### Recovery from anesthesia

Mucous membrane color, capillary refill time, ECG, heart rate, blood pressure, and oxygen saturation should still be monitored in recovery. Packed blood cell volume and TP measurements can be helpful in determining if hemodilution produced by fluid therapy has occurred.

These measurements can also be used to determine if blood products will be needed postoperatively. Lactate and urine output are useful indicators of tissue perfusion and can guide with postoperative administration of fluids and cardioactive drugs.[52]

Acid–base and electrolytes abnormalities should still be monitored at the end of surgery or recovery from anesthesia. Prevention or correction of hypokalemia may decrease the incidence of muscle weakness in recovery from anesthesia.

Owing to the potential extensive gastric mucosal damage, NSAIDs should be avoided for analgesia. Analgesia in these patients can be achieved by the administration of fentanyl and lidocaine CRI. Partial reversal of opioid agonist drugs may be required with incremental doses of naloxone (0.001–0.002 mg kg$^{-1}$ IV) or butorphanol (0.1 mg kg$^{-1}$).

Temperature should still be monitored during recovery and treated accordingly, especially if the dog is experiencing a prolonged recovery.

## Surgeries of the large intestines, rectum, and perineum

Surgery of the large intestine is indicated for lesions associated with obstruction, perforation, colonic inertia, or chronic inflammation. In cats, subtotal colectomy has been a common procedure for the treatment of idiopathic megacolon (Figure 5.7A and B).[74] Rectal surgery is usually performed to resect masses and to repair rectal prolapse, perforation, or fistulae. Perineal surgery is most often performed to treat perineal hernias, anal sac disease, and neoplasms (Table 5.1).[2]

**Table 5.1** Most common large intestine surgical diseases in dogs and cats.

| Surgical diseases of the large intestine |
|---|
| Linear foreign body |
| Intestinal intussusception |
| Intestinal perforation |
| Intestinal neoplasms |
| Cecal inversion |
| Cecal-colic volvulus |
| Idiopathic megacolon |
| Rectal prolapse |
| Rectal fistulae |
| Perineal hernias |
| Anal sac neoplasm |
| Atresia ani |

### Clinical signs

Clinical signs of these diseases may include diarrhea, vomiting, anorexia, abdominal enlargement and pain, tenesmus, constipation, obstipation, and depression. Shock may occur in dogs and cats with perforated intestines or strangulating lesions.[2,50]

### Laboratory data

Laboratory data may reveal dehydration, electrolyte, acid–base, or serum biochemical abnormalities. Anemia and hypoalbuminemia are rare in these patients. If

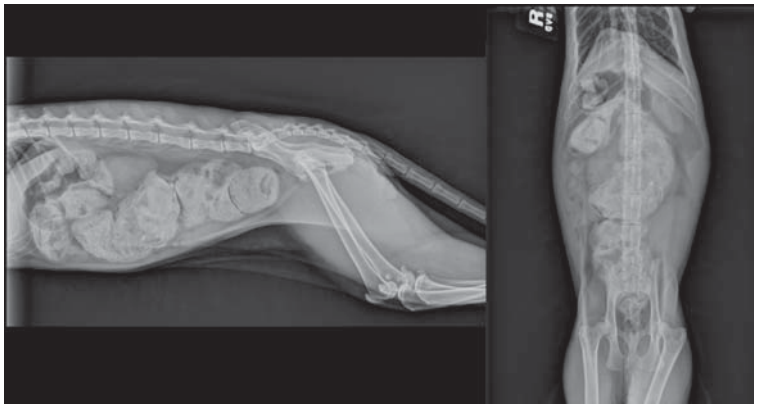

**Figure 5.7** (A) Right lateral abdominal radiographic view of a cat with megacolon. (B) Ventrodorsal abdominal radiographic view of a cat with megacolon. Source: Photo courtesy Dr. G. Sepulveda.

the patient is not rapidly deteriorating, hydration, acid–base, and electrolyte deficits should be corrected before induction of anesthesia.[2]

Neoplastic masses may be associated with hypoglycemia, hypercalcemia, anemia, and other paraneoplastic sydromes. Postrenal azotemia with or without hyperkalemia may occur with bladder entrapment caused by perineal hernia.

### Anesthetic considerations

Anesthetic complications may arise from uncorrected dehydration, electrolyte, or acid–base abnormalities. Therefore, correction of these abnormalities should be addressed before anesthesia whenever is possible.

Anal sac adenocarcinomas and apocrine gland adenocarcinomas are tumors that can produce parathyroid hormone-like hormone and hypercalcemia. Polyuria and polydipsia are usually only noted in dogs with hypercalcemia. Mildly to moderately hypercalcemic animals, on the basis of ionized calcium measurement, should be rehydrated and diuresed with a 0.9% saline solution.[2]

Hyperkalemia in patients with perineal hernia owing to bladder entrapment should be corrected with the administration of 0.9% NaCl solution, dextrose and insulin, or sodium bicarbonate. Administration of calcium gluconate or chloride should be considered in order to normalize the difference between resting and threshold potential of the myocardium, thus helping to restore membrane excitability.[46] The urinary bladder can be decompressed by cystocentesis or urethral catheterization.[2]

Anesthetic protocols should be created on the basis of the patient's signalment, attitude, blood work abnormalities, and level of severity of systemic clinical signs as previously discussed in this chapter. If there are no contraindications (e.g. sepsis, bleeding disorders, and hypovolemia), epidural administration of bupivacaine or ropivacaine alone (0.1 $ml\,kg^{-1}$) or combined with preservative free morphine (0.1 $mg\,kg^{-1}$) should be considered in dogs and cats in order to supplement balanced anesthesia and provide multimodal analgesia for rectal or perineal surgeries.[20]

All dogs and cats undergoing laparotomy for intestinal surgeries or perineal hernia repair or perineal surgeries require basic monitoring (e.g. noninvasive or invasive blood pressure, ECG, and body temperature). Patients requiring surgery for perineal hernia repair, anal gland sacullectomy, or perineal mass removal are positioned in ventral recumbency with their hind end elevated and their head down. This results in diaphragmatic compression and impaired ventilation. Positive pressure ventilation and devices to monitor ventilation (e.g. capnograph) and oxygenation (e.g. pulse oximeter) should be considered in these patients.[20]

## Secondary peritonitis

The recognition of peritonitis arising from perforation of the GI tract caused by necrosis or ulceration is critical and must be treated promptly and aggressively. In dogs undergoing GI tract surgery, low preoperative serum albumin and intraoperative hypotension were associated with increased risk to develop secondary peritonitis postoperatively.[75] Secondary peritonitis is the predominant form of peritonitis in dogs and usually is caused by bacteria. It is particularly common in young animals that have perforating foreign bodies and in those with abdominal trauma (e.g. hit by a car or bite wounds). In addition, older animals on chronic nonsteroidal anti-inflammatory therapy can have perforation of the GI tract with consequent peritonitis.[76] Once diagnosed, treatment of secondary peritonitis is directed toward the correction of electrolyte and fluid abnormalities, and exploratory laparotomy to determine and surgically correct the underlying cause of the peritonitis. Mortality rates with septic peritonitis secondary to leaking intestinal anastomosis may be as high as 70%.[74] With secondary peritonitis, most animals are presented for treatment of lethargy, anorexia, vomiting, diarrhea, and/or abdominal pain. Abdominal distention may be noted if sufficient fluid has accumulated. Prolonged capillary refill times, pale mucous membranes, and tachycardia may indicate that the animal is in shock. Dehydration and arrhythmias may also occur.[76] Massive fluid and protein movement to the peritoneal cavity result in a shift of fluid away from the intravascular space, causing hemoconcentration and eventual hypovolemic shock. The presence of large numbers of free bacteria or endotoxins causes massive shifts of neutrophils to the abdomen, vasodilation of the visceral vasculature, high hepatic energy demand

(hypoglycemia), metabolic acidosis, and often fatal septic shock.[74]

### Anesthetic considerations

Animals with secondary peritonitis often are endotoxic and hypotensive. Intravenous fluid resuscitation therapy should be initiated as soon as possible, particularly if the animal is dehydrated or appears to be in shock. Synthetic colloids such as 6% hetastarch may be beneficial, particularly if vasculitis is present and TP is under 4 $g\,dl^{-1}$ or albumin levels are under 1.5 $g\,dl^{-1}$.[76] Anesthetic management, preanesthetic and anesthetic drug selection, and inotropic and vasopressor support in patients with secondary peritonitis are similar to patients with GDV, as both syndromes produce acid–base and electrolyte abnormalities combined with hypovolemic and distributive shock.

## Summary

Canine and feline patients with diseases of the GI tract commonly require sedation and/or anesthesia for diagnostic and surgical procedures. These patients frequently have alteration in function and/or structure of the GI tract resulting in anorexia, dehydration, hypovolemia, acid–base and electrolyte disturbances, protein loss, abdominal pain, and emaciation. Since these changes can alter the anesthetic management of these patients, attempts should be made, if possible, to treat these derangements before general anesthesia.

Oropharyngeal neoplasia is a relatively common problem in dogs and cats, and treatment often requires surgical resection. Visualization of the larynx may be difficult in these patients because of the presence of a mass, so preoxygenation should be considered before orotracheal intubation is attempted. In addition, a surgical trachesostomy pack should be readily available should attempts at ET intubation fail. Significant hemorrhage can occur from laceration of major arteries, so blood products must also be readily available. Since mandibulectomy and maxillectomy may be required for these patients, a multimodal approach for analgesia is warranted. Extubation should be delayed in these patients until a well-developed swallowing reflex is present, and the tube should be removed with the cuff inflated to help avoid aspiration of any blood clots and fluid that may be present.

Common diseases of the esophagus include megaesophagus, foreign body, ulceration, neoplasia, and stricture formation. Patients with esophageal diseases are at an increased risk of aspiration, so they should be fasted, if possible, for 8–12 h before any anesthetic procedures. In addition, these patients should have thoracic radiographs performed before anesthesia to evaluate for the presence of aspiration pneumonia. Increasing gastric acidity by the use of medications may be helpful at reducing esophageal mucosal and lung damage should reflux and/or aspiration occur. Induction of anesthesia should be rapid in these patients followed by immediate intubation. Suction should always be available should regurgitation occur. Esophageal disease may result in esophageal perforation. This life-threatening complication should be suspected in patients with sudden changes in breathing patterns and subsequent drops in oxygen saturation, decreased breath sounds on thoracic auscultation, and increased resistance to manual ventilation. Thoracocentesis should be immediately performed followed by chest tube placement or thoracotomy. Once this is achieved, positive pressure ventilation should be instituted.

Common diseases of the stomach and small intestine include foreign bodies, ulceration, GDV, inflammatory disease (e.g. IBD) and neoplasia. Vomiting and diarrhea are common signs of gastric and small intestinal diseases, so fluid, electrolyte, and acid/base disturbances are common. Anemia may also be presented if significant ulceration is present. With diseases of the small intestinal, hypoalbuminemia may also be present. Ideally, these conditions should be treated before anesthesia if possible. GDV is an acute, life-threatening disorder in dogs and should be treated as an emergency. Significant hypovolemia is often present, so aggressive fluid therapy is warranted.

Common diseases of the large intestines, rectum, and perineum requiring anesthesia include neoplasia, idiopathic megacolon (cats), inflammatory disorders (e.g. IBD), anal sac disease, and perineal hernia. Anal sac adenocarcinoma may have concurrent paraneoplastic hypercalcemia, and this may result in cardiac and/or renal abnormalities. For this reason, this abnormality should be addressed before anesthesia. Perineal hernia may involve bladder entrapment, leading to azotemia and hyperkalemia. Hyperkalemia may result in significant cardiac changes (bradycardia, etc.), so treatment should be instituted before anesthesia.

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# 6 Renal disease

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General anesthesia has profound effects on the body, greatly affecting cardiac output, blood pressure, and perfusion of vital organs. The task of the anesthetist is to minimize these detrimental effects, with the goal of maximizing the resemblance to patient homeostasis. This is no simple task in the healthy patient and can be a daunting task in the face of disease. Renal disease is a common pathology faced when providing anesthesia to today's pet population.

Before anesthetizing a patient with either acute renal injury or chronic renal disease, it is paramount to understand the effects of renal dysfunction on the patient and the effects of anesthesia and surgery on the kidneys; only then can an anesthetic plan be tailored to the patient and the disease process. Although anesthetic procedures and drug choices may have profound effects on the kidneys, the maintenance of normotension, isovolemia, and adequate cardiac output sufficient to maintain renal perfusion has the greatest effect on the prevention of initial or ongoing renal insult.

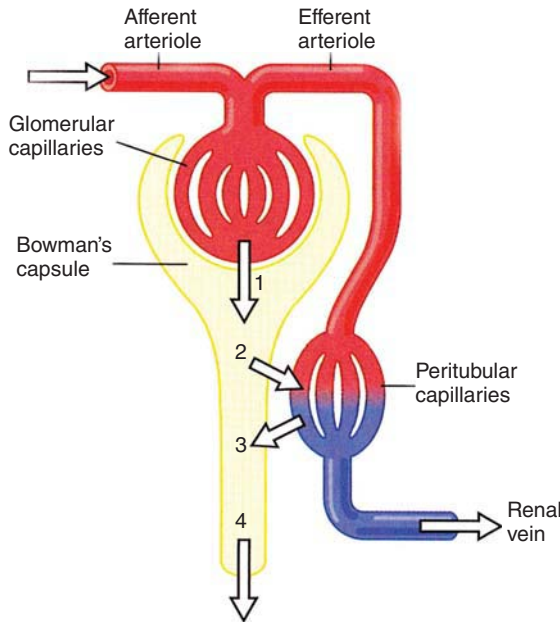


**Figure 6.1** Schematic representation of the nephron, including the glomerulus and renal tubule. (1) Filtration of blood at the level of the glomerulus. (2) Reabsorption of substances from renal tubules by peritubular capillaries. (3) Secretion of substances from peritubular capillaries into renal tubules. (4) Excretion of the urine. Urinary excretion = filtration − reabsorption + secretion. Source: Adapted from Guyton and Hall Textbook of Medical Physiology, 2011, with permission.

## Anatomy and physiology

The kidneys serve a number of functions, including excretion of metabolic waste products and toxins and regulation of blood volume, extracellular fluid volume, osmolality, and electrolyte balance. The kidneys also serve important roles in acid–base regulation, erythrocyte production, and hormone secretion.

Each kidney is divided into cortical and medullary portions and is made up of hundreds of thousands of nephrons, the functional kidney units.[1] The nephron comprises the glomerulus and the renal tubule (Figure 6.1). The glomerulus is a unique ball of capillaries interposed between two sets of arterioles with a high hydrostatic pressure, favoring fluid filtration. Fluid filtered from the glomerulus enters the renal tubule, where, depending on a number of factors, reabsorption and secretion occur, resulting in the end product of urine.

Despite their relatively small size, the kidneys receive an impressively high proportion of cardiac output,

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roughly 20–25%.[1,2] The vast majority (90–95%) of the blood flow is directed to the renal cortex, with the remainder perfusing the renal medulla.[2] High blood flow serves to match the extremely high oxygen consumption of the kidneys. On a per-gram basis, the kidneys have roughly twice the oxygen consumption of the brain but nearly seven times the blood flow.[1] As oxygen delivery to the kidneys exceeds the consumption under normal circumstances, the arteriovenous difference in the kidneys is relatively low.

In general, renal blood flow (RBF) is directly related to glomerular filtration rate (GFR). However, renal autoregulation serves to stabilize GFR, despite large swings in blood pressure (Figure 6.2). This occurs via a number of extrinsic and intrinsic mechanisms at mean arterial blood pressures from ~80 to 180 mmHg.[3] Although GFR is preserved within this autoregulatory range, a number of factors can alter this process and lead to renal ischemia, despite apparent normotension. For example, sympathetic activation, as occurs in the presence of pain or surgical stimulation, can lead to renal vasoconstriction and hypoperfusion of the kidney.[2] Although autoregulation is preserved with most anesthetics, anesthetic drugs may cause a redistribution of blood flow away from the renal cortex.[2] Autoregulation may also be altered in the presence of chronic hypertension, acute renal failure, and sepsis.[2] In the face of these disease processes, mean arterial pressure must be maintained at a higher range to preserve autoregulation of RBF.

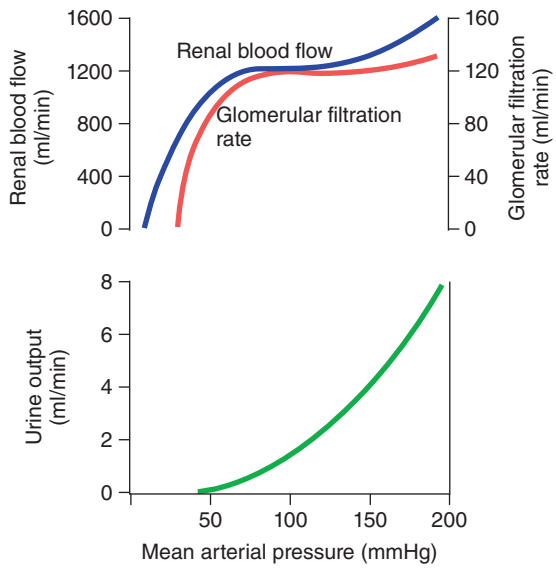


**Figure 6.2** Autoregulation of renal blood flow (RBF) and glomerular filtration rate (GFR) within the mean arterial pressure range of ~80–180 mmHg. Urine output is not autoregulated and is directly related to mean arterial pressure. Source: Adapted from Guyton and Hall Textbook of Medical Physiology, 2011, with permission.

## Pathophysiology

Renal disease is broadly classified as acute kidney injury (AKI) or chronic kidney disease (CKD). AKI can occur over a period of hours to days and is due to a number of processes, including toxicities, infection, and inflammatory conditions.[4] Some of the more common perioperative causes include urethral obstruction, sepsis, and infectious disease. These patients may present for any number of procedures, from brief placement of a urethral catheter to major exploratory laparotomy. AKI can also occur as a result of anesthesia and surgery. In human patients, this is often due to a combination of prerenal azotemia and acute tubular necrosis.[5] Fortunately, the healthy kidney is relatively tolerant to perioperative insults, and multiple and/or severe insults are generally required to produce injury enough to cause significant decrease in renal function.[5] Judicious use of fluids and maintenance of blood pressure, in addition to avoiding nephrotoxic agents and ischemia, are often sufficient to prevent perioperative AKI. However, AKI can present with coexisting abnormalities in acid–base status, electrolytes, and the biochemical profile that may affect patient anesthetic management (Table 6.1). Thus, before attempting general anesthesia, it is important to perform a thorough evaluation of the patient, including assessment of hydration, acid–base and cardiovascular status, blood pressure, and biochemical profile.

The prognosis of patients with AKI can be quite poor, with an overall mortality rate of ~50–60% in small animals.[4] The risks vs benefits of performing general anesthesia on patients with AKI need to be assessed, and, if necessary, anesthesia should be delayed until appropriate patient stabilization has been achieved. However, the reality is that many of the patients with AKI, such as the "blocked cat," may require general anesthesia in order to attain appropriate stabilization,

**Table 6.1** Physiological abnormalities commonly associated with acute renal injury[4,5]

| Abnormalities commonly associated with acute renal injury |
|---|
| ↑ BUN |
| ↑ creatinine |
| ↑, ↓ or - $Na^+$ |
| ↑ $K^+$ |
| ↑ P |
| ↑, ↓ or – urine output |
| Metabolic acidosis |
| ↑ Respiratory rate |
| Hypertension or hypotension |
| Cardiac dysrhythmias |
| Nausea and vomiting |

↑ and ↓ indicates an increase or decrease, respectfully, in a parameter, - indicates no change.

**Table 6.2** Physiological abnormalities commonly associated with chronic renal disease[4,5,7]

| Abnormalities commonly associated with chronic renal disease |
|---|
| ↑ BUN |
| ↑ creatinine |
| ↑ or ↓ $K^+$ |
| ↑Mg |
| ↓ $Ca^{2+}$ |
| ↑ P |
| Metabolic acidosis |
| ↑ Respiratory rate |
| Hypertension |
| Anemia |
| Uremic coagulopathy |
| Hypoalbuminemia |
| Dehydration |
| Nausea, vomiting |

↑ and ↓ indicates an increase or decrease, respectfully, in a parameter.

especially if sedation or regional anesthesia is not an option.

Chronic kidney disease is the structural or functional disease of one or both kidneys that has been present for a longer duration, generally 3 months and longer.[6] CKD is due to a myriad of underlying problems and, unlike AKI, is considered progressive and irreversible. The diagnosis can be made on the basis of a number of hallmark abnormalities, and a single test is generally insufficient to diagnose CKD. The International Renal Interest Society (IRIS) has developed guidelines to stage renal disease on a scale of 1–4 on the basis of renal function tests, proteinuria, and blood pressure. Complete guidelines for staging of renal disease, as well as current algorithms for staging in small animals can be found on the IRIS website (www.iris-kidney.com). On the basis of the animal's IRIS stage, appropriate prognosis and treatment can be pursued by the managing clinician. Animals presenting for general anesthesia with a history of CKD, especially those that have been assigned an IRIS stage, generally are accompanied by a history of diagnostic tests, as well as clinical management. Newly diagnosed patients should be staged and stabilized with medical treatment before undergoing general anesthesia. Unfortunately, this is not always the case. However, all patients with CKD should have baseline diagnostic tests performed before formulating an anesthetic plan, including a thorough evaluation of hydration, cardiovascular status, blood pressure, complete blood count, biochemical profile, and evaluation of acid–base status. It is important to realize that these patients can present with a number of abnormalities (Table 6.2). Comorbidities such as diabetes mellitus and cardiovascular disease are also frequently encountered.[5] Stabilization and management of sequelae of the primary disease, as well as any comorbidities, are keys to successful management of CKD.

## Renal disease and surgery

The stress and pain associated with surgery can have significant effects on the kidney. The release of catecholamines, renin, arginine vasopressin (AVP), and aldosterone associated with surgical stimulation often leads to an increase in renal vascular resistance and decreases in RBF and GFR.[7] The systemic use of analgesic drugs or regional anesthetic techniques may attenuate this response. For example, blockade of T4–T10 spinal segments via neuraxial administration of local anesthetics in humans suppresses the release of catecholamines, renin, and AVP.[8]

Surgical manipulation may compromise RBF either through direct compression of vasculature associated with the kidneys or through increases in intra-abdominal pressure. Pneumoperitoneum associated with the use of insufflation in laproscopic surgery

can increase intra-abdominal pressures sufficiently to induce oliguria in human patients owing to direct venous compression, decrease in cardiac output, and increased plasma levels of renin, aldosterone, and AVP.[7] In addition, any intervention that decreases cardiac output can similarly affect RBF and GFR. This includes positive pressure ventilation and positive end-expiratory pressure (PEEP).[5]

## Renal disease and pharmacologic agents

### Preanesthetic agents

#### Phenothiazines

Of the phenothiazines, acepromazine is the most relevant to modern veterinary practice, inducing sedation lasting anywhere from 1 to 6 h, depending on dosage[9]; no direct-acting drug antagonist is available. Acepromazine is a phenothiazine derivative that causes blockade of dopaminergic and alpha-1 adrenergic receptors, inducing vasodilation that may lead to hypotension below the range of renal autoregulation.[10,11] However, acepromazine may offer a renal protective effect, as RBF and GFR are preserved in dogs, despite systemic hypotension under general anesthesia.[10] As no antagonist is available, one must use caution in administration to patients who may not be able to tolerate the associated systemic hypotension. Careful blood pressure monitoring is advised following administration of acepromazine, especially to patients with existing renal disease.

#### Alpha-2 agonists

These pharmacologic agents include xylazine, dexmedetomidine, and medetomidine, the racemic mixture of dexmedetomidine and levomedetomidine isomers. Each of these agents significantly decreases heart rate and cardiac output while increasing systemic vascular resistance.[12–14] The administration of medetomidine, along with propofol induction, induced a ~60% decrease in cardiac output and ~50% decrease in RBF in dogs.[15] GFR was increased despite these changes. Another study evaluating the renal effects of medetomidine in dogs revealed variable effects dependent on the method of drug administration. For example, intramuscular administration of medetomidine induced decreases in RBF and GFR, whereas intravascular administration induced opposite effects, increasing RBF and GFR.[16] These contradictory effects may be attributed to the immediate systemic hypertension following intravenous administration, an effect not drastically observed with intramuscular administration.[16] Owing to wide blood pressure variations and significant decreases in cardiac output, caution should be used with alpha-2 agonist administration in renal disease. Furthermore, a diuretic effect is often observed with these agents owing to several possible mechanisms, including inhibition AVP and osmotic diuresis due to insulin inhibition and resulting hyperglycemia.[16] Therefore, the use of alpha-2 agonists in patients with unresolved urinary obstruction should be avoided.

#### Benzodiazepines

The benzodiazepines, midazolam and diazepam, exert a sedative effect via enhancement of the endogenous inhibitory neurotransmitter, gamma amino butyric acid (GABA).[17] Their cardiovascular effects are mild, and they are well tolerated in patients with many disease states, including renal disease.[18] Although use of benzodiazepines is generally recommended, caution must be exercised in using these agents in animals that may demonstrate paradoxical excitement on administration, such as juvenile patients and young cats.[19] Sole administration of benzodiazepines to most veterinary patients is generally not suggested for this reason, and, to improve sedation, coadministration with an opioid or other sedative is advised.

#### Opioids

The opioids can be broadly classified into agonists, agonist-antagonists, and partial agonists on the basis of their effects on opioid receptors.[20] Opioid agonists include, but are not limited to, morphine, hydromorphone, oxymorphone, fentanyl, methadone, and meperidine; these exert a pharmacologic effect via interaction with the mu-opioid receptor. Butorphanol is a commonly used agent in veterinary medicine and is classified as an opioid agonist-antagonist, acting as an antagonist at the mu-opioid receptor and an agonist at the kappa-opioid receptor. Buprenorphine, a partial agonist, acts as an agonist at the mu-opioid receptor but exhibits a submaximal response as compared to opioid agonists.[21] This submaximal response does not necessarily reflect analgesia, as buprenorphine has proven analgesic efficacy in a number of species, including cats

and dogs.[22,23] Renal effects of the opioids are generally mild and of little consequence for patients with renal disease.[24,25]

The profound analgesic effects of this pharmacologic class may attenuate the sympathetic response associated with surgical pain, thus minimizing renal vasoconstriction. Several studies have documented the reduction in minimal alveolar concentration (MAC) of volatile anesthetics associated with opioid use. For example, the administration of oxymorphone and hydromorphone decreased the MAC of isoflurane in dogs by ~45%.[26] Decreases in MAC associated with opioid use may attenuate the systemic hypotension associated with volatile anesthetics.

Multiple opioids are metabolized by extrarenal pathways, and duration and effect are largely unaffected by renal failure.[27,28] However, active metabolites of morphine and meperidine rely on renal excretion; significant renal disease may result in untoward effects such as prolonged sedation, respiratory depression, or neuroexcitation.[27,29–33] For example, morphine is metabolized in most species to morphine-3- and morphine-6-glucuronide, both eliminated by glomerular filtration. Morphine-6-glucuronide has similar activity to the parent drug, and significant renal impairment resulting in compromised excretion of this metabolite has been shown to lead to prolonged clinical effects in human patients.[29–31] Similarly, the metabolite of merperidine, normeperidine, has been reported to cause seizures in humans with renal impairment.[32,33]

### Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have the potential to cause detrimental effects in animals with renal disease, although they are generally considered safe in healthy animals. These agents exert their effects via inhibition of the cyclooxygenase and lipoxygenase enzymes that oxidize arachidonic acid to various prostaglandins and leukotrienes. The result is inhibition of important mediators of pain and inflammation, such as prostaglandin $E_2$ and prostacyclin.[34,35]

Prostaglandins serve several constitutive physiological functions. For instance, under conditions of stress such as that induced by general anesthesia and surgery, RBF can become prostaglandin dependent. Prostaglandins are thought to induce renal protection under conditions of renal ischemia. These protective prostaglandins are derived largely from the COX-1 enzyme, and, therefore, COX-1-sparing NSAIDs such as meloxicam and carprofen are considered more kidney sparing than nonpreferential NSAIDs such as aspirin.[36] Multiple studies evaluating these agents in healthy canine and feline patients have failed to reveal detrimental renal effects, even under conditions of moderate hypotension.[15,37–41] However, adverse effects have been reported, including renal insufficiency in cats following use of meloxicam, and the safety of these drugs in small animals with pre-existing renal disease has not been well characterized.[42] A definitive link between patient morbidity and perioperative use in animals with pre-existing disease has not been established; however, until NSAIDs can be definitively proven to be safe in animals with pre-existing renal disease, judicious use of these agents is advised.

## Induction agents

### Barbiturates

Thiopental is an ultrashort-acting barbiturate that exerts its anesthetic effect primarily via interactions with GABA receptors in the central nervous system (CNS).[17] This agent has been found to induce minor decreases in RBF and GFR in human patients without causing histologic evidence of renal damage.[43] Dogs anesthetized with thiopental, however, maintained GFR.[44] Recovery from thiopental anesthesia is achieved through redistribution out of the central nervous system followed by hepatic metabolism and renal excretion.[43] Although anesthetic emergence might be unchanged in patients with renal disease following a single thiopental bolus, overall recovery may be prolonged.[45] Furthermore, metabolic acidosis that may accompany renal dysfunction may induce an increase in sensitivity to thiopental owing to an increase in the nonionized fraction of barbiturate.[46] Other induction agents should be used or thiopental dosage decreased in patients with significant renal impairment and/or metabolic acidosis.

### Propofol

Propofol is a rapidly acting induction agent that potentiates GABA-induced chloride currents, thus creating a hypnotic effect.[17] Although data are not available for all species, propofol does not induce significant changes in RBF or GFR in dogs and is an excellent choice in patients with renal disease.[44,47] Furthermore, the pharmacokinetic profile of propofol is not significantly altered in

the face of chronic renal disease in human patients.[48] Hypotension can occur following bolus administration of propofol, potentially leading to decreases in RBF; this is a transient effect and can be attenuated by volume loading and preadministration of sedative agents and/or opioids.[49]

### Etomidate

Etomidate is widely considered the safest induction agent in patients with cardiovascular disease, exerting minimal cardiovascular effects following administration. Much analogous to thiopental and propofol, etomidate exerts its anesthetic effect via an interaction with the GABA receptor.[17] Etomidate does not induce decreases in RBF or GFR and is generally considered safe for use in patients with renal disease.[44,47] Drug dosage should be tailored to the severity of the underlying disease, as plasma protein binding of etomidate is markedly decreased in human patients with renal failure, potentially leading to an unexpected increase in drug effect; the lower end of the etomidate dosage range (1–2 mg $kg^{-1}$) should be used in patients with significant renal disease.[50]

### Ketamine

Ketamine is unique among anesthetic induction agents in its mode of action, causing immobilization via antagonism of the *N*-methyl-D-aspartate (NMDA) receptor.[51] Ketamine administration induces catecholamine release, increasing renal vascular resistance and creating hypertension, leading to an increase in RBF, with no change in GFR.[52] In humans, ketamine preserves RBF during hemorrhage, but this has never been demonstrated in veterinary species.[8] Ketamine is metabolized by the liver in most species; renal disease should have little effect on the metabolism of moderate doses of ketamine. However, elimination of ketamine relies more extensively on renal excretion in cats and, therefore, should be avoided in cats with renal disease to avoid impaired drug elimination.[53]

## Inhalational agents

All inhalational anesthetics cause a decrease in RBF and GFR, effects at least partially attenuated by preoperative hydration.[54,55] Historically, methoxyflurane was associated with nephrotoxicity due to metabolic breakdown to free fluoride ions.[56] Of the modern agents, sevoflurane is the most metabolized, ~5% as compared to ~0.2% and 0.02% for isoflurane and desflurane, respectively, leading to the release of inorganic fluoride ions.[57] These ions have the potential to induce nephrotoxicity, but there appears to be no relationship between serum inorganic fluoride concentration and renal toxicity following sevoflurane administration; renal toxicity as a direct result of sevoflurane anesthesia is not to be expected.[58,59] Sevoflurane also produces compound A, a potentially nephrotoxic agent that is formed by the reaction with potassium or sodium hydroxide found in sodalime or Baralyme® carbon dioxide absorbents.[60,61] However, modern carbon dioxide absorbents contain considerably lower levels of these chemicals, nearly eliminating degradation to compound A.[56] Although a study of healthy human volunteers administered sevoflurane for multiple hours did reveal some biochemical evidence of glomerular injury, a retrospective study of nearly 2000 human patients administered sevoflurane under normal clinical conditions failed to reveal evidence of renal injury.[62,63] The implications for most veterinary species are unknown, but there is not sufficient evidence to preclude the use of sevoflurane in patients with renal dysfunction. Higher fresh gas flows and avoidance of carbon dioxide absorbents containing potassium hydroxide and sodium hydroxide and carbon dioxide absorbent desiccation will greatly decrease formation of potential nephrotoxic degradation products.[64] Isoflurane and desflurane are minimally metabolized to inorganic fluoride and do not cause creation of compound A. Therefore, some practitioners choose these agents over sevoflurane. However, all of the modern volatile anesthetics are appropriate choices for anesthetic maintenance of patients with renal disease.

Nitrous oxide exerts mild decreases on RBF, but to a lesser extent than the other inhalants, and can be used safely in patients with renal disease.[65] However, in CKD with severe anemia, the use of nitrous oxide must be weighed against the need to provide supplemental oxygen. Nitrous oxide should be avoided if the patient cannot tolerate a fraction of inspired oxygen <0.7.

## Adjunctive drugs

Historically, the administration of a low dose infusion of dopamine (1–3 μg $kg^{-1}$ $min^{-1}$min) was commonly used in the management of patients with both AKI and CKD. Dopamine infused at these rates acts via the dopamine-1 (D1) and dopamine-2 (D2) receptors in multiple species to produce vasodilation of renal

arteries, leading to increased RBF and natriuresis via inhibition of $Na^+/K^+$ ATPase activity.[66–68] Dopamine has been used in several species, although some believe that dopamine is ineffective in cats due to a lack of intrarenal dopamine receptors. However, cats do possess a unique putative D1 receptor, and dopamine infusions for inotropic support are effective.[69,70] Despite these effects, a number of studies have found this regimen to be ineffective, and the use of low dose dopamine in the management of animals with renal disease is no longer recommended.[5,71–77] In fact, low dose dopamine might induce negative renal effects. For example, dopamine infusion inhibits renal tubuloglomerular feedback, a protective mechanism induced within the kidney under conditions of ischemia.[78] Furthermore, dopamine increases renal medullary blood flow, while the intrarenal partial pressure of oxygen remains unchanged, suggesting that dopamine increases tubular work and negatively impacts renal function.[79] Overall, there is insufficient evidence to suggest a positive effect of low dose dopamine in patients with renal disease, and the effects of low dose dopamine infusions may prove detrimental. However, higher doses of dopamine (5–10 μg $kg^{-1}$ $min^{-1}$) may be indicated for inotropic support in hypotensive patients.[5] Maintenance of blood pressure via dopamine infusions may support RBF through enhancement of cardiac output rather than direct renal effects.

Mannitol, however, induces natriuresis and causes renal arteriole dilation, decreased vascular resistance, increased urine output, and scavenging of oxygen-free radicals.[80] Mannitol also improves GFR and RBF in small animals as a bolus dose (0.5–0.8 g $kg^{-1}$ over 15 min) and continuous infusion (1 mg $kg^{-1}$ $min^{-1}$).[80,81] Mannitol-induced acute renal failure, however, has been reported in humans and animals from osmotic nephrosis, histologically appearing as vacuolization of the renal tubular epithelium.[82–85] Coadministration of cyclosporin A may potentiate mannitol toxicity.[86] It is a known complication, and coadminsitration of mannitol with cyclosporine A or other nephrotoxic agents should be avoided.

Furosemide has been suggested to increase RBF and reverse the redistribution of blood flow from the renal cortex to the medulla in humans.[7] Furosemide can be used to differentiate between oliguria of hypovolemia vs that from redistribution of RBF. The administration of furosemide increases urine output without increasing GFR. However, animal studies that provide definitive evidence for the benefit of furosemide in renal disease are lacking, and meta-analyses evaluating the use of furosemide for the management of renal disease in human patients revealed a lack of sufficient evidence for improved outcome in patients with renal disease administered with furosemide.[87]

## Anesthetic management of patients with renal disease

There is no single anesthetic plan when it comes to management of patients with renal disease. Although all anesthetic agents have effects on RBF and GFR, some more than others, there is no combination of drugs that has been proven to be far more effective in the management of these cases than other drugs. Rather than focusing on the perfect combination of anesthetic agents, it is instead more important to focus on management of the individual sequelae of the renal disease and any coexisting disease while striving to avoid significant depression of cardiac while maintaining normotension and isovolemia.

### Preanesthetic stabilization

With both AKI and CKD, it is extremely important to stabilize the patient as much as possible before sedation and general anesthesia. If stabilization cannot be achieved, the value of the procedure requiring anesthesia must be questioned when weighed against the risks of sedation and anesthesia. The case should be delayed or rescheduled until the patient has been sufficiently managed medically and presents less of an anesthetic risk. Unfortunately, this is often not a possibility, and general anesthesia must be induced in patients who are highly unstable, which increases the risk of significant morbidity and, in extreme cases, eventual mortality. Therefore, stabilization of the patient must be attempted quickly with prioritization of clinical signs and their threat to life.

Stabilization is geared toward each individual problem, discussed in the following sections; however, attaining adequate hydration status is often the most valuable step taken before anesthetic induction. This optimizes cardiac output and RBF while helping to attenuate variations in blood pressure that may accompany anesthetic induction and maintenance. A patient

with CKD presenting for an elective procedure should be admitted to the hospital and maintained on intravenous fluids for 12–24 h before anesthesia. Fluid rate should be calculated on the basis of maintenance fluids (40–60 ml $kg^{-1}$ $day^{-1}$) and replacement of any fluid deficit, replaced over the first 4–6 h, in addition to fluids to account for ongoing losses such as vomiting, if present.[88] Patients presenting for emergent conditions with either AKI or CKD should be administered fluids to, at minimum, replace fluid deficits. This can be estimated by assessing the patient's level of dehydration and replacing the deficit over 1–2 h or longer if time allows. For example, a 10-kg patient presenting with 7% dehydration should be administered 700 ml of intravenous fluids (10,000 g × 7% = 700 ml).[89] Fluid choice should be made on the basis of the patient's electrolyte status, but, typically, a polyionic balanced crystalloid, such as lactated ringers, is an excellent choice. Saline (0.9%) may be chosen if the patient is hyperkalemic, but care should be taken to avoid worsening any pre-existing metabolic acidosis with a large chloride load. Fluid administration should be carefully monitored to achieve adequate hydration while avoiding overhydration, especially in patients with concurrent cardiovascular disease. Depending on the severity of the patient's condition, this can be accomplished noninvasively by careful physical examination and thoracic auscultation or by more invasive means. For example, a urinary catheter can be placed in order to monitor urine output, normally 0.5–2.0 ml $kg^{-1}$ $h^{-1}$, and the amount of fluid administered vs eliminated is calculated.[89] Central venous pressure (CVP) can also be monitored and maintained at a normal value of 3–5 cm $H_2O$; values >10 cm $H_2O$ suggest volume overload or myocardial dysfunction, whereas values <3 cm $H_2O$ suggest inadequate fluid resuscitation. Response to fluid therapy can also be based on CVP measurement, and it is important to monitor CVP trends during the perioperative period; elevations of ≤2–4 cm $H_2O$ can be expected with a fluid bolus, whereas elevations >4 cm $H_2O$ from baseline suggest that fluid administration should be slowed.[89]

Tables 6.1 and 6.2 list problems often associated with AKI and CKD. Patient presentation is highly associated with underlying cause and management before requiring anesthesia. Although multiple abnormalities can be present, those that are most relevant to anesthetic management are azotemia, acidosis, hyperkalemia, and anemia.

Azotemia is often encountered with both AKI and CKD but may not reflect the severity of the disease process. Azostix® reagent strips (Santa Cruz Biotechnology, Dallas, Texas 75220, USA) may be used as a preoperative screening tool if a chemistry panel is impractical due to time or financial constraints. Azotemia may be due to dehydration in the case of prerenal azotemia or due to kidney damage in itself. Approximately 60–70% of nephrons must be damaged in order for azotemia to be evident; absence of azotemia does not rule out renal disease. Azotemia can alter the permeability of the blood–brain barrier.[90] This becomes clinically relevant in that anesthetic agents, which rely on passage across the blood–brain barrier into the central nervous system, can have more profound effects in the presence of azotemia. Azotemia, in addition to acidemia and hypoalbuminemia, causes a decrease in drug protein binding.[91] Highly protein-bound drugs such as diazepam, thiopental, and etomidate will exert more profound effects, as there will be more unbound, active drug in circulation. Taking these factors into account, the dosages of sedative and induction agents may need to be decreased in the azotemic patient, as well as those demonstrating acidosis and hypoalbuminemia.

Although multiple electrolyte abnormalities can accompany both AKI and CKD, hyperkalemia is the most life threatening and may require immediate correction. In the absence of serum potassium measurement, an electrocardiogram can aid in the diagnosis, as characteristic waveform changes are often associated with increased serum potassium. These changes are often progressive, with mild elevations in potassium (5.5–7.5 mEq $l^{-1}$), resulting in increased amplitude and narrowing of the T wave, or 'tenting', as well as shortening of the QT interval. Prolongation of the PR interval, widening of the QRS complex, and a decrease in amplitude and widening of the P wave are consistent with moderate hyperkalemia (7.0–8.0 mEq $l^{-1}$). In cases of severe hyperkalemia (8.0–9.0 mEq $l^{-1}$), P waves are absent, and bradycardia occurs (Figure 6.3A and B). Finally, in extreme cases (>10.0 mEq $l^{-1}$), a sine wave appearance on the ECG, ventricular fibrillation, or asystole may occur.[92,93] These electrical disturbances are due to an increase in the resting membrane potential of the cardiac myocyte from hyperkalemia, decreasing automaticity, conductivity,

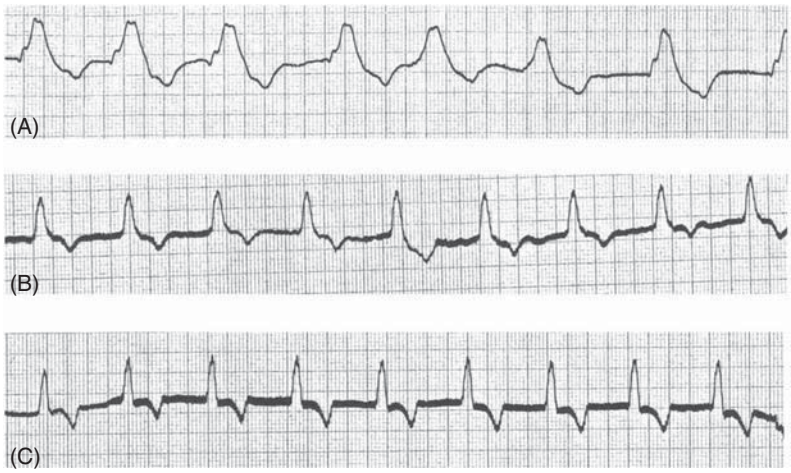


**Figure 6.3** (A) Electrocardiogram from a hyperkalemic cat ($[K^+]$ = 10 mEq $l^{-1}$) presenting with urinary obstruction and a heart rate ~58 beats per minute. Note the bradycardia, absence of P waves, and widened QRS complexes. (B) Electrocardiogram from the same patient after initial administration of calcium gluconate (0.5 mg $kg^{-1}$ IV; heart rate ~69 beats per minute). (C) Electrocardiogram after completion of calcium therapy (1.0 mg $kg^{-1}$ IV; heart rate ~73 beats per minute). Calcium was administered as initial therapy for its membrane stabilization effects; definitive treatment was administered after cardiovascular stabilization. Source: ECG courtesy of Dr. Jonathan Bach, DVM, DACVIM, DACVECC.

contractility, and excitability.[93] It is paramount to treat hyperkalemia immediately and closely monitor the ECG for characteristic changes and dysrhythmias. Induction of anesthesia should not be attempted in patients with serum potassium concentrations exceeding 6.0 mEq $l^{-1}$. Although ultimately the hyperkalemia may resolve with resolution of the underlying renal insult, treatment is geared toward shifting potassium intracellularly where it is not free to exert effects on cardiac action potentials. This can be accomplished through intravenous administration of regular insulin (0.55–1.1 U $kg^{-1}$) and dextrose (1–2 ml $kg^{-1}$ or 1–2 g per unit of administered insulin).[92] The presence of acidosis worsens hyperkalemia by shifting potassium extracellularly; acidosis should be treated either by mechanical hyperventilation to cause a mild compensatory respiratory alkalosis or by intravenous administration of sodium bicarbonate. Sodium bicarbonate dosage can be calculated as: total mEq of $NaHCO_3$ administered = base deficit × 0.3 × body weight (kg).[94] The administration of sodium bicarbonate is not frequently recommended or performed, and it is important to note that exogenous administration of bicarbonate will result in the production of carbon dioxide, potentially creating a respiratory acidosis if the patient is unable to ventilate appropriately. If bicarbonate is administered under anesthesia, only 1/3 of the calculated dose should be administered initially, and mechanical ventilation should be instituted. Although administration of calcium does not directly affect serum potassium concentration, the presence of hypocalcemia can potentiate the cardiovascular effects of hyperkalemia, and if cardiovascular effects are present, such as bradycardia or ECG changes, this should be the first line of therapy. To counteract adverse cardiac effects, 10% calcium gluconate can be slowly administered (0.5–1.0 mg $kg^{-1}$ IV; Figure 6.3B and C).[95]

Patients with both AKI and CKD often present with metabolic acidosis because of dehydration and hypoperfusion, leading to lactic acidosis, decreased urinary $H^+$ excretion, and decreased urinary $HCO_3^-$ reabsorption.[95] Acid–base disorders should be corrected before general anesthesia and dehydration corrected. Once anesthesia is induced, it is important to control ventilation in order to prevent worsening acidemia with a concurrent respiratory acidosis. End-tidal carbon dioxide should be monitored and maintained at ~30–35 mmHg, and in cases of moderate to severe metabolic acidosis, arterial blood–gas measurements should be taken.

Patients with CKD may have moderate to severe anemia owing to increased red blood cell fragility and decreased production of erythropoietin.[6] Anemia is often chronic and is fairly well tolerated. However,

with severe anemia (Hgb <7.0 g $dl^{-1}$), oxygen-carrying capacity can be critically impaired, and the animal may have a greater reliance on the dissolved fraction of oxygen.[96] Therefore, it is imperative that oxygen be supplemented throughout the entire case: before induction through recovery. Furthermore, hemoglobin levels < 7.0 g $dl^{-1}$ are consistent with critical decreases in oxygen-carrying capacity and may require transfusion of red blood cells to maintain adequate oxygen-carrying capacity.[96] Anesthesia should be delayed until the hemoglobin is >7.0 g $dl^{-1}$.

Hypertension can be present in patients with CKD and will cause shifts in individual organ autoregulatory ranges.[2,6] For instance, while RBF is autoregulated at blood pressures of ~80–180 mmHg in normal patients, the patient with chronic hypertension may have autoregulatory ranges shifted to a higher range from chronic compensation. These patients may not tolerate hypotension to the degree of a healthy patient and may require earlier intervention in the event of hypotension. Many patients with underlying renal disease are treated with angiotensin-converting enzyme inhibitors (ACEI), such as enalapril or benazepril. Anesthetic patients receiving treatment with ACEIs may be more prone to hypotension under anesthesia, and vigilant monitoring of blood pressure is required.[97,98] Cessation of ACEI therapy ~12 h before surgery was found to significantly decrease the incidence of induction-induced hypotension in human patients.[99] One must weigh the risks of potentially facing refractory hypotension under anesthesia vs risk of interrupting the medical management of the patient.

### Intraoperative management

There is no single protocol for all patients, and patient temperament must be taken into account. However, it is generally safe to use a benzodiazepine/opioid combination as a preanesthetic sedative. For instance, midazolam (0.05–0.2 mg $kg^{-1}$ IM) and hydromorphone (0.1–0.2 mg $kg^{-1}$ IM) may be administered to dogs or cats, or oxymorphone (0.05–0.1 mg $kg^{-1}$ IM) may be alternatively used. Lower ends of the dosage range should be used when administering drugs intravenously or in patients with moderate to severe disease. Following sedation and intravenous catheter placement, 100% oxygen should be supplemented by face mask for 5 min at a flow of 1–5 l $min^{-1}$, especially in anemic animals, wherein oxygen-carrying capacity is compromised. Anesthetic induction can be achieved with intravenous propofol (2–6 mg $kg^{-1}$ IV) to facilitate intubation and transition to gas anesthetic. Intravenous fluids should be supplemented at a rate of 20 ml $kg^{-1}$ $h^{-1}$ for the first hour and then decreased to 10 ml $kg^{-1}$ $h^{-1}$ for the remainder of the case if prior fluid overload is not present. The degree of anesthetic monitoring depends on the severity of the patient's condition and any coexisting disease. At a minimum, capnometry, pulse oximetry, and noninvasive blood pressure monitors should be placed. With coexisting hyperkalemia, an electrocardiogram should be closely monitored for dysrhythmias. If variations in blood pressure are anticipated, an arterial catheter should be placed to monitor beat-to-beat invasive blood pressure accurately, as well as measure arterial blood gas tensions. CVP and urine output should be measured where volume status is questionable, in patients with significant coexisting cardiovascular disease, or if pre-operative fluid resuscitation was insufficient.

## Summary

Although patients with renal disease can have highly variable underlying conditions and presentation, preanesthetic stabilization with careful tailoring of the anesthetic plan to the patient problem list, and close monitoring of the patient in order to maintain normotension and isovolemia will maximize patient management success in the perioperative period.

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# 7 Perioperative fluid, electrolyte, and acid–base disorders

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Alterations in body fluid volume, distribution, and composition, including disturbances in osmolality, electrolytes, and acid–base status are not uncommon in veterinary patients presenting for anesthesia, particularly in the emergency setting. This chapter focuses on the most common disturbances in body fluid volume and composition, their etiologies, and the impact of their change on the clinical management of patients before, during, and immediately after anesthesia. Additional literature addressing the physiology and pathophysiology of body fluid regulation and acid–base balance should be consulted for comprehensive reviews on this subject.[1,2]

In general, perturbations in a patient's hydration, intravascular fluid volume, electrolyte composition, and/or acid–base status may be a manifestation of a disorder that has overwhelmed the body's ability to compensate for losses or additions in its content or may be indicative of a failure in regulatory mechanisms responsible for maintaining fluid and electrolyte balance. A thorough patient history, physical examination, blood electrolyte, and gas analysis provide essential information during the assessment of body fluid disturbances. Consequences of abnormalities in body fluid volume and composition most commonly include alterations in central nervous system (CNS), cardiac, and neuromuscular function, all of which may alter the patient's response to drugs used in the anesthetic period. Several investigations on anesthetic-related morbidity and mortality have shown a negative impact of increasing American Society of Anesthesiologists (ASA) status on outcome.[3,4] While underlying conditions resulting in a patient being assigned an ASA status of III to IV are likely to be associated with fluid, electrolyte, and acid–base disturbances, specific details regarding patient hydration, intravascular volume, and acid–base and electrolyte status on anesthetic outcome in clinical veterinary patients are largely unknown. Current recommendations for patient management are therefore primarily based on clinician experiences, data from human trials, and experimental investigations in veterinary species rather than from prospective or retrospective studies in veterinary patient populations. In general, recommendations regarding the management of a patient's water, electrolyte, and acid–base disturbances in the perianesthetic period are heavily influenced by the severity of the disturbance, as well as the nature of the underlying and concurrent conditions.

In the normal animal, body fluid, volume and composition, including water and electrolytes, are regulated by several overlapping mechanisms (Table 7.1). Disturbances in a patient rarely occur in isolation; however, for purposes of discussion, the chapter is organized to address alterations in hydration, intravascular fluid volume, electrolytes, and then acid–base disturbances.

## Body fluids

Body fluids are composed of water and dissolved solutes. Water makes up ~60% of the total body weight of domestic animal species, with two-thirds located in the intracellular space (~40% of total body weight) and one-third in the extracellular space (~20% of total body weight). Of the extracellular water, ~two-thirds is located in the interstitial fluid space (~15% of total body weight) and one-third in the intravascular space (~5% of total body weight). Of note, the volume of

*Canine and Feline Anesthesia and Co-Existing Disease*, First Edition. Edited by Lindsey B.C. Snyder and Rebecca A. Johnson.

**Table 7.1** The major physiologic factors that regulate body water and electrolytes.[1,2]

| Variable | Regulatory mechanism | Primary stimulus | Primary effect |
|---|---|---|---|
| Water | ADH | Serum osmolality | Increase reabsorption of water in kidney |
| | Thirst | Serum osmolality | Increase water intake |
| Sodium | Aldosterone | Angiotensin II, hyperkalemia, ACTH | Increase $Na^+$ reabsorption in kidney |
| | Epinephrine | Sympathetic nervous system stimulation | Increase $Na^+$ reabsorption in kidney |
| | Angiotensin II | Renal perfusion | Increase $Na^+$ reabsorption in kidney |
| | ADH | Serum osmolality | Alter water reabsorption in kidney |
| Chloride | Kidney | Sodium, acid–base status | Alter the reabsorption of sodium and chloride |
| Potassium | Aldosterone | Hyperkalemia, angiotensin II | Decrease $K^+$ reabsorption in kidney |
| | Epinephrine | Sympathetic nervous system stimulation | Increase intracellular movement of $K^+$ |
| | Insulin | Serum glucose | Increase intracellular movement of $K^+$ |
| Calcium | Parathyroid hormone | Serum ionized calcium | Increase reabsorption of $Ca^+$ in kidney<br>Increase mobilization of $Ca^+$ from bone<br>Increase calcitriol synthesis |
| | Calcitriol | Parathyroid hormone | Increase intestinal absorption of $Ca^+$ |
| | Calcitonin | Serum ionized calcium | Reduce mobilization of $Ca^+$ from bone |

water in the intravascular space constitutes ~50–60% of the total blood volume.

In general, there are major differences in solute concentrations, notably electrolytes and negatively charged proteins, between intracellular and extracellular spaces, whereas small differences exist between the interstitial and intravascular spaces (Table 7.2).

The varying concentrations of the different solutes play a key role in the oncotic and osmotic pressures and the net electrical potential in each space. Water and solutes move between the different compartments via multiple mechanisms depending on the specific substance and the barrier separating the space. A semipermeable cell membrane, which is highly permeable to water but not solutes, separates the intracellular and extracellular spaces. Water moves between these spaces through the cell membrane as a result of an osmotic pressure gradient created by differences in the number of osmotically active particles in each space. The movement of solutes between the intracellular

**Table 7.2** Approximate electrolyte content in intracellular, interstitial, and intravascular fluid Spaces.[5]

| | Intracellular fluid (skeletal muscle cell) (mEq $l^{-1}$) | Interstitial fluid (mEq $l^{-1}$) | Intravascular fluid (plasma) (mEq $l^{-1}$) |
|---|---|---|---|
| $Na^+$ | 13 | 145 | 142 |
| $K^+$ | 155 | 4 | 5 |
| $Ca^{2+}$ | 4.0 | 2.4 | 2.5 |
| $Mg^{2+}$ | 35 | 2 | 2 |
| $Cl^-$ | 2 | 115 | 106 |
| $HCO_3^-$ | 10 | 30 | 24 |
| $HPO_4^{2-}$, $H_2PO_4^-$ | 113 | 2 | 2 |
| $Proteins^-$ | 50 | 0 | 14 |

Source: Adapted from Seeler DC. In: Tranquilli WJ, Thurmon JC, Grimm KA, editors. Lumb and Jones' Veterinary Anesthesia and Analgesia, 4th ed. Ames: Blackwell Publishing Professional 2007.

and extracellular space occurs through channels in the cell membrane. In some cases, solutes can flow passively through channels. However, in other cases, they require active transport. While the cell membrane separates the intracellular and extracellular spaces, the capillary membrane separates the extracellular space into interstitial and intravascular fluid spaces. The capillary membrane is freely permeable to water and low-molecular-weight particles such as ions, glucose, acetate, lactate, and bicarbonate. The hydrostatic and oncotic forces that exist in each of the spaces therefore determine the movement of fluid between the interstitial and intravascular compartments.

Water intake and loss from the body are regulated primarily by thirst and the impact of antidiuretic hormone (ADH), also known as vasopressin, on the kidney. In the healthy animal, an increase in serum osmolality results in stimulation of osmoreceptors in the anterior hypothalamus, which increases thirst and the release of ADH from the posterior pituitary. ADH, acting on receptors on the collecting ducts of the kidney, promotes the reabsorption of water, resulting in a decrease in serum osmolality. Alternatively, a decrease in serum osmolality results in a reduction in ADH secretion, decreasing the reabsorption of water from the urine. In addition to serum osmolality other factors can also influence ADH release from the posterior pituitary, including a decrease in blood volume or blood pressure. Several drugs, including morphine, phenothiazines, and barbiturates can also increase ADH section and alter body fluid dynamics. In humans and dogs, anesthesia and surgery increase serum ADH concentrations, a response attributed to shifts in intravascular fluid volumes and pressures.[6,7] Although changes in serum ADH levels were not measured, urine output in dogs was reduced and total body water increased during anesthesia with routine maintenance intravenous fluid strategies with, or without, surgery.[8,9] The clinical significance of the typical increase in body fluid in normal animals during anesthesia with routine fluid therapy is not known; however, the clinician should be aware that urine output alone is not a good indicator of body water volume status in the anesthetized patient.

## Dehydration and intravascular volume deficits

Dehydration occurs when body fluid losses are in excess of gains. Depending on the relative loss of water to electrolytes, the losses can result in hypertonic, hypotonic, or isotonic dehydration on the basis of the tonicity of the remaining body fluids.[10] Dehydration is typically quantified by the percent deficit of total body volume. For example, a patient is 10% dehydrated when the total body fluid deficit is equivalent to [0.1] × [body weight in kg]. Clinical signs of dehydration will depend on the type of dehydration and the concurrent electrolyte changes; however, in general, signs attributed to dehydration >5% include dry mucus membranes, decreased skin elasticity, sunken eyes, dull mentation, and increased heart rate. With >12% dehydration, significant cardiovascular consequences including inadequate tissue perfusion secondary to intravascular volume deficits occurs, and shock develops.[11]

Many anesthetic drugs and ventilatory support measures alter preload, afterload, or myocardial function, contributing to a reduction in cardiac output at surgical planes of anesthesia in normal patients. Owing to the intravascular volume deficits and reduction in cardiac output associated with dehydration, correction of volume deficits should occur before anesthesia, with the rate of fluid administration primarily dependent on clinical sign severity and the patient's cardiovascular reserve. Although recommended treatment of fluid volume replacements are focused on calculating fluid deficits, ongoing losses, and maintenance requirements, the clinician should recognize that these calculations are based on estimates, and, ultimately, fluid therapy should be guided by the patient's physiologic status as assessed by mentation, heart rate, arterial blood pressure, body temperature, and urine output. Of note, in the awake patient with adequate cardiac function, hypotension is likely indicative of inadequate vascular volume; however, due to the tremendous cardiovascular reserve in most patients, normal arterial blood pressure by itself is not a guarantee of normal vascular volume or blood flow. In the nonemergent situation, a patient's volume deficit should be replaced over 12–24 h; however, if this is not possible, it is ideal if anesthesia can be delayed until the patient's heart rate and arterial blood pressure are within normal ranges. General recommendations include replacing ~50% of the patient's volume deficit over 4–6 h before anesthesia, with the remaining deficit replaced more slowly. Choice of the specific fluid should be based on the patient's electrolyte, acid–base, and serum protein levels; however, a balanced electrolyte solution is generally the initial fluid of choice, with

adjustments made on the basis of the patient's response to treatment, including repeated evaluation of packed cell volume, total solids, blood gases, and electrolytes.

In addition to whole body dehydration, intravascular volume deficits can exist secondary to blood loss. In the normal awake patient, a ~10% loss of blood volume can reduce cardiac output. However, up to a 30% blood volume loss can occur before a decrease in arterial blood pressure is observed.[12] In the anesthetized patient, significant hemodynamic alterations including a reduction in arterial blood pressure can occur with as little as ~10% blood volume loss. Goals of therapy during blood loss include maintaining indicators of perfusion such as blood pressure, heart rate, urine output, and body temperature within normal ranges, maintaining oxygen delivery capacity by keeping the packed cell volume above 20% and preventing coagulopathies associated with excessive dilution of platelet and coagulation factors. Replacement of intravascular fluid losses with a balanced electrolyte solution is the recommended initial treatment, with rates as high as 90 ml $kg^{-1}$ $h^{-1}$ in dogs or 60 ml $kg^{-1}$ $h^{-1}$ in cats. Owing to the redistribution of crystalloids throughout the body fluid spaces, the volume of administration must be three times the estimated intravascular volume loss. When blood volume losses exceed 30% of the patient's total blood volume, synthetic or natural colloids are recommended, as patient outcome may be negatively affected if fluid therapy is restricted to crystalloids.[13] Fresh whole blood or packed red blood cells and fresh frozen plasma are indicated with blood loss in excess of 50% of the patient's vascular volume. Although the latter recommendations provide the clinician with guidelines, the individual patient's requirements will vary considerably, and therapy should be individualized on the basis of pre-existing conditions and the clinical response to treatment.

For hypovolemic patients requiring anesthesia, preoxygenation for 3–5 min is highly recommended before anesthetic induction to compensate for a potentially reduced cardiac output and/or reduced oxygen-carrying capacity secondary to decreased hemoglobin levels. Although no specific anesthetic regime is contraindicated in the hypovolemic or dehydrated patient, the dose of sedatives and anesthetic agents to achieve a desired clinical effect will be reduced. For example, the dose of propofol and ketamine when used in combination with diazepam was ~50% in hypovolemic dogs compared to normovolemic dogs.[14] In addition, the minimum alveolar concentration (MAC) of isoflurane was also reduced from 1.15% to 0.97% in healthy dogs after removal of 30 ml $kg^{-1}$ of blood.[15] Overall, the anesthetist should therefore be prepared for excessive CNS and cardiovascular depression during the anesthetic period in a patient with underlying hypovolemia at the time of anesthesia.

Alveolar hypoventilation and the associated increase in arterial carbon dioxide levels are not uncommon in compromised patients under general anesthesia, and ventilatory support is frequently required. The increase in intrathoracic pressure during inspiration associated with positive pressure ventilation most notably reduces right ventricular preload and increases left ventricular afterload.[16] In some patients, this can result in a significant decrease in cardiac output, systemic arterial pressure, and overall oxygen delivery. The magnitude of these changes is dependent on the ventilatory strategy used and the patient's hemodynamic status. Therefore, if ventilatory support measures are required during anesthesia of the hypovolemic patient, strategies that use a low tidal volume and have a long expiratory pause are recommended.

## Sodium

The majority of the total body sodium is located within the extracellular space, with only low quantities located in the intracellular space, a relationship that is maintained by the cell membrane's $Na^+$–$K^+$–ATPase pump. Dietary intake is the source of sodium for the body, with losses of sodium primarily occurring via the kidney in the normal dog and cat. In the kidney, sodium is freely filtered at the glomeruli, with reabsorption occurring to varying degrees in the renal tubules. Aldosterone is the major endogenous substance that controls the net quantity of sodium reabsorption. Factors that increase the production and release of aldosterone and, therefore, the reabsorption of sodium include angiotensin II (which is subsequently increased secondary to a decrease in renal perfusion), hyperkalemia, and adrenocorticotrophic hormone. Factors that inhibit the release of aldosterone include atrial natriuretic factor and dopamine. Although possessing a less significant effect than aldosterone on sodium reabsorption in the kidney, catecholamines and angiotensin II also directly impact sodium excretion. Specifically, catecholamines

directly and indirectly increase sodium reabsorption at the proximal tubule via alpha-1-receptor-mediated effects and through stimulation of renin, respectively. Angiotensin II also directly promotes sodium reabsorption by the kidney.

Serum (or plasma or whole blood) concentrations of sodium are strictly a reflection of the quantity of sodium relative to the amount of water in the extracellular space and not of total body sodium levels. Measured levels of sodium are a result of not only factors that impact its own excretion and reabsorption, but also factors that influence water homeostasis in the body. Specifically, sodium being the most plentiful ion in the extracellular fluid space contributes most of the effective osmoles in serum. Changes in serum sodium concentration therefore impact serum osmolality and water homeostasis indirectly as described previously. Abnormalities in serum sodium concentration are frequently associated with abnormalities in total body water balance and osmolality. The clinician should therefore consider the patient's serum osmolality and hydration or total body water status when presented with a hyponatremic or hypernatremic patient.

## Hyponatremia

Hyponatremia is defined as serum sodium concentrations <140 mEq $l^{-1}$ in dogs and 149 mEq $l^{-1}$ in cats. In veterinary patients requiring anesthesia, hyponatremia is most frequently associated with low plasma osmolality. However, it is possible for a patient to be hyponatremic and hyperosmolar if receiving mannitol or if severely hyperglycemic. Although rare, hyponatremic patients can also have a normal osmolality if they are hyperlipemic or severely hyperproteinemic. Generally, the clinical context provides the clinician with the most likely etiology and associated osmolality of the hyponatremia; however, in complex cases, the serum osmolality should be measured before treatment.

In addition to varying states of osmolality, patients can have different levels of hydration associated with low serum sodium levels. Hyponatremia with low plasma osmolality can be associated with hypovolemia, hypervolemia, or normovolemia depending on the underlying etiology.[17,18] Physical examination finding is crucial to determine which is present.

The primary disturbances resulting in hypovolemic hypotonic hyponatremia are rarely associated with primary sodium loss; rather, they are generally associated with isotonic or hypotonic fluid losses. Hyponatremia results from the compensatory mechanisms aimed at restoring blood volume. Gastrointestinal or third space losses are the most common extrarenal etiologies of hyponatremia in dogs and cats (Table 7.3).

Clinical signs associated with hyponatremia are primarily related to CNS dysfunction. In the hyponatremic patient with low extracellular osmolality, CNS signs can develop as a result of water shifting from the extracellular to the intracellular space due to the osmolality gradient. Brain cells can compensate if the changes occur slowly, by shifting other solutes out of the brain cell to minimize the accumulation of water. However, if the changes occur rapidly or are excessive, CNS signs such as depression, ataxia, coma, and seizures can develop. Clinical signs of CNS dysfunction tend to occur with sodium levels <120 mEq $l^{-1}$ or if the rate of decrease is >0.5 mEq $h^{-1}$.[10]

The major concerns in the perioperative period for patients with hyponatremia relate to the effects of the electrolyte disturbance on the patient's CNS and volume status. The therapeutic approach before anesthesia should be dependent on the severity of clinical signs and the chronicity of the disorder. If possible, significant hyponatremia should be corrected before anesthesia. The patient's clinical signs and the chronicity of the hyponatremia should guide the rate and volume of the intravenous therapy. In urgent situations, treatment should be started before anesthesia and continued throughout the anesthetic period and into recovery. Intravenous physiologic saline (0.9%) or a balanced electrolyte solution is recommended to correct volume deficits in the acutely hypovolemic hyponatremic patient. In the latter case, volume replacement can occur rapidly to re-establish extracellular fluid status. However, with chronic hyponatremia, serum sodium should be increased by 0.5 mEq $l^{-1}$ $h^{-1}$ at a maximum to avoid the risk of osmotic nervous system demyelination. Serial serum sodium measurements can be used to guide the rate of replacement solution administration. In the normovolemic or hypervolemic hyponatremic patient who requires anesthesia, management will be heavily dependent on the underlying cause of the electrolyte disturbance; restriction of intravenous fluid administration and possibly diuretic administration will be necessary in the perianesthetic period if the patient develops clinical signs associated with the hypervolemic state. Serum hypoosmolality has been shown

**Table 7.3** Common causes of electrolyte disorders in dogs and cats.[2]

| | Hyponatremia | Hypernatremia | Hypochloremia corrected | Hyperchloremia corrected | Hypokalemia | Hyperkalemia | Hypocalcemia | Hypercalcemia |
|---|---|---|---|---|---|---|---|---|
| Altered losses | *Increased loss of Na*<br>GI loss<br>• Vomiting, diarrhea<br>Cutaneous loss<br>• Burns<br>Gain of free water<br>• Drugs<br>• Congestive heart failure<br>• Liver disease<br>• Renal disease<br>• Psychogenic polydipsia | *Increased loss of water relative to Na*<br>GI loss<br>• Vomiting, diarrhea<br>Renal loss<br>• Diuresis<br>• Renal disease<br>• Diabetes inspidius<br>Cutaneous loss<br>• Burns<br>Respiratory losses<br>• Panting<br>Fever<br>*Decreased intake of water*<br>Water deprivation<br><br>*Decreased loss of Na*<br>Hyperadrenocorticism | *Increased loss*<br>GI<br>• Vomiting, diarrhea<br>Renal loss<br>• In response to chronic elevation in $PaCO_2$ | *Decreased loss*<br>Renal chloride retention<br>• Renal disease<br>• Hypoadreno-corticism<br>• Diabetes mellitus<br>• Respiratory alkalosis<br><br>*Increased loss of $Na^+$ relative to $Cl^-$* GI Diarrhea | *Increased loss*<br>GI loss<br>• Vomiting, diarrhea<br>Renal loss | *Decreased loss*<br>Decreased renal excretion<br>• Renal disease<br>• Urethral obstruction<br>• Uroabdomen<br>• Hypoadreno-corticism | *Increased loss*<br>GI Loss<br>• Phosphate enemas<br>Renal loss<br>• Renal failure<br>Loss-other<br>• Puerperal tetany | *Decreased loss*<br>• Renal disease<br>• Malignancy |
| Trans-location | *Translocation*<br>Third space loss<br>• Peritonitis<br>• Ascites<br>• Ruptured Bladder | *Translocation-greater movement of water relative to sodium*<br>Third space loss<br>• Peritonitis<br>• Ascites<br>• Ruptured bladder | *Translocation* Third space loss<br>• Peritonitis<br>• Ascites<br>• Ruptured Bladder | *Translocation*<br>• Rare | *Translocation*<br>Intracellular to extracellular<br>• Alkalemia<br>• Insulin/glucose administration<br>• Catecholamines<br>• Hypothermia | *Translocation*<br>• Uroabdomen<br>• Nonrespiratory acidosis<br>• Tissue trauma<br>• Insulin deficiency | *Translocation*<br>Third space loss<br>• Sepsis<br>• Peritonitis<br>• Pancreatitis<br>• Soft tissue trauma<br>• Chelation/ precipitation<br>• Blood product administration (citrate)<br>• Ethylene glycol toxicosis<br>• Bicarbonate therapy | *Translocation*<br>• Primary hyperparathy-roidism<br>• Bone disease<br>• Malignancy<br>• Granulomatous disease |
| Altered intake or input | *Decreased intake*<br>• Rare | *Increased intake of Na*<br>• Salt poisoning<br>• Hypertonic fluid administration | *Decreased intake*<br>• Rare | *Increased input*<br>• IV fluid therapy with excessive chloride relative to Na + (0.9% NaCl, hypertonic saline, KCl supplemented fluids | • *Decreased intake*<br>• IV fluid therapy with inadequate potassium content<br>*Increased intake of Na*<br>• Salt poisoning | *Increased intake*<br>• IV fluid therapy with excessive $K^+$ | *Decreased intake*<br>• Decreased GI absorption<br>• Hypoparathyroidism-iodiopathic or post-bilateral thy-roidectomy | *Increased intake*<br>• Dietary |

to decrease halothane MAC in dogs.[19] Although the impact of hyponatremia on other anesthetic agents has not been determined, the clinician should carefully titrate all anesthetic drugs to avoid overdose.

### Hypernatremia

Hypernatremia is defined as serum sodium concentrations >160 mEq $l^{-1}$ in dogs and 175 mEq $l^{-1}$ in cats. Hypernatremia is always associated with hyperosmolality. It is relatively rare in patients with free access to water but can be observed in the perioperative period. As with hyponatremia, patients can be hypovolemic, normovolemic, or hypervolemic depending on the primary cause of the hypernatremia. The most common causes are due to pure water losses, hypotonic fluid losses, or solute gain (Table 7.3). The hypernatremia associated with hypertonic saline or sodium bicarbonate administration is generally transient in the awake patient if unrestricted water intake is possible or if it is followed with appropriate balanced electrolyte solutions in the anesthetized patient.

Clinical signs associated with hypernatremia generally occur with serum sodium levels exceeding 170 mEq $l^{-1}$ and include anorexia, lethargy, vomiting, muscular weakness, disorientation, ataxia, seizures, coma, and death. If patients have concurrent hypovolemia or hypervolemia, they may show cardiovascular changes such as tachycardia or pulmonary edema, respectfully.

As with hyponatremia, hypernatremia should be corrected slowly over at least 48 h. If the patient is acutely hypernatremic and hypovolemic, the plasma volume deficit can be replaced with a balanced electrolyte solution over several hours followed by a slower correction of the hyperosmolality with the administration of hypotonic intravenous solutions such as 0.45% saline or 5% dextrose. In cases of chronic hypernatremia, the serum sodium concentration should be decreased by no more than 1.0 mEq $l^{-1}$ $h^{-1}$ because of the risk of neurologic complications. This can be achieved by replacement of volume deficits with relatively low sodium-containing solutions such as 0.45% saline or 5% dextrose in water. In cases of hypervolemia, administration of a loop diuretic may facilitate sodium excretion; however, if renal dysfunction is present, alternative therapies such as hemodialysis will be required.

During the anesthetic period, the clinician should continue to correct the hypernatremia as described previously. In the experimental setting, hypernatremia is associated with an increase in the MAC of inhalant anesthetics; it is possible that there will be increased inhalant anesthetic requirements.[19,20] As discussed previously, a patient's intravascular volume status will also likely affect anesthetic requirements, and anesthetic depth should be monitored and delivery of anesthetics adjusted on the basis of the individual animals assessment.

## Chloride

Chloride is the major anion in the extracellular fluid and contributes significantly to maintaining extracellular osmolality. Intracellular concentrations of chloride vary depending on the cell type; however, the intracellular concentrations of chloride are consistently considerably lower than plasma levels. As with sodium, dietary intake is the source of chloride for the body, with losses primarily occurring via the kidney and gastrointestinal tract. The regulation of plasma chloride concentrations occurs in the kidney with acid–base and sodium concentrations being the major factors that influence the reabsorption or excretion of chloride.[21]

Alterations in serum chloride may be a reflection of a primary disorder of chloride, sodium, or total body water balance. Alternatively, it may be the consequence of a compensatory response in a patient with primary changes in acid–base status (see Acid-Base Homeostasis and Alterations). For example, in a patient with a measured decrease in normal serum chloride levels and an increase in the strong ion difference with a subsequent nonrespiratory alkalosis, there could be a loss of chloride associated with vomiting secondary to pyloric obstruction. Alternatively, the patient could be hypochloremic owing to an increase in urinary excretion of chloride in response to a chronic respiratory acidosis.

Owing to the impact of total body water balance on plasma chloride, a patient's measured chloride concentration should be corrected for changes in water balance to obtain a corrected chloride concentration. The effect of abnormalities in water balance can be determined using measured sodium relative to normal sodium concentrations as a correction factor according to the following formula.

$$\text{Canine: } [Cl^-]\ \text{Corrected} = [Cl^-]\ \text{measured} \times 146/[Na^+]\ \text{measured}$$

Feline: $[Cl^-]$ Corrected = $[Cl^-]$ measured $\times 156/[Na^+]$ measured

## Hypochloremia

Hypochloremia is defined as a serum-corrected chloride concentration <107 mEq $l^{-1}$ in dogs and 117 mEq $l^{-1}$ in cats. The most common causes of corrected hypochloremia relate to excessive loss of chloride relative to sodium via the gastrointestinal or renal systems (Table 7.3).[21] Corrected hypochloremia is associated with nonrespiratory alkalosis because of an increase in the strong ion difference (see Acid-Base Homeostasis and Alterations). As mentioned previously, chronic respiratory acidosis can also result in a corrected hypochloremia as a compensatory response.

Clinical signs specifically attributed to hypochloremia have not been reported, and abnormalities in patient health status associated with corrected hypochloremia primarily result from the nonrespiratory alkalosis and concurrent electrolyte and water disorders. Treatment strategies should be aimed at correcting the underlying cause, and supportive therapy should be directed at correcting the strong ion difference. Intravenous fluid therapy with 0.9% NaCl is the treatment of choice for the dehydrated hypochloremic patient. Serum potassium levels should be monitored and supplemental KCl added if necessary to treat hypokalemia (see Potassium). In normovolemic patients, chloride can be administered as KCl or $NH_4Cl$; however, this is rarely required in the patient with normal kidney function if the primary cause of the hypochloremia is addressed. Ideally, hypochloremia and its associated acid–base alterations are corrected before anesthesia. However, if this is not possible, therapy can be continued throughout the perianesthetic periods.

Hypochloremia with a normal corrected chloride concentration is often referred to as an artificial hypochloremia and is associated with a concurrent hyponatremia.[21] It is associated with either a gain in body water or a third space loss of both sodium and chloride. Although corrected hypochloremia is associated with a nonrespiratory alkalosis, patients with hypochloremia and a normal corrected chloride level have a tendency to have a decreased strong ion difference and, therefore, a nonrespiratory acidosis.

## Hyperchloremia

Hyperchloremia is defined as a serum chloride concentration >113 mEq $l^{-1}$ in dogs and 123 mEq $l^{-1}$ in cats. The most common causes of corrected hyperchloremia relate to excessive loss of sodium relative to chloride or an excessive gain of chloride relative to sodium (Table 7.3). Corrected hyperchloremia is associated with a nonrespiratory acidosis owing to a decrease in the strong ion difference.

As with corrected hypochloremia, there are no specific clinical signs related to corrected hyperchloremia; signs are likely a reflection of a nonrespiratory acidosis and concurrent electrolyte disorder. Removal of the underlying cause of the hyperchloremia should be attempted. If the patient is dehydrated, intravenous fluid therapy with a balanced electrolyte solution should be initiated, with sodium bicarbonate added to the fluid therapy if plasma pH is <7.2. Ideally, at a minimum, the patient's volume status should be normalized before anesthesia.

Hyperchloremia with normal corrected chloride levels is generally associated with pure water loss or hypotonic loss. As with hypochloremia, the associated acid–base changes are not consistent with those of the corrected hyperchloremia. Specifically, with hyperchloremia and normal corrected chloride levels, the patient has a tendency for alkalosis due to an increase in the strong ion difference.

# Potassium

While sodium is the major extracellular cation in the body, potassium is the major intracellular cation, with the extracellular levels representing <5% of total body potassium stores. The $Na^+$–$K^+$–ATPase pump located in the cell membrane maintains the relationship of intracellular to extracellular potassium and sodium by actively pumping sodium out of the cell and potassium into the cell. The maintenance of the relationship of intracellular to extracellular potassium is crucial to the cell's normal homeostasis, volume, and resting membrane potential. In particular, serum potassium levels heavily influence the excitability of muscle and cardiac cells, as the relative distribution of potassium across the cell membrane affects the resting membrane potential and the subsequent ease of cellular depolarization and repolarization.

Serum potassium levels are influenced by the oral intake of potassium through dietary sources, output via the urine and gastrointestinal track, as well as translocation between the intracellular to extracellular space. In nutritional studies evaluating potassium-restricted diets in humans and dogs, resting serum potassium levels correlate with total body and muscle cell potassium content, respectively.[22,23] In disease states or when the body is under stress such as extreme exercise, serum potassium levels may not correlate with total body stores of potassium, an important consideration when considering the treatment of measured abnormalities in serum potassium.

Animals on commercial diets generally have an adequate intake of potassium to maintain both total body stores and normal serum potassium levels. The major factors that influence potassium translocation between the intracellular and extracellular spaces include insulin, epinephrine, and pH. Endogenous insulin and epinephrine, acting at β2-adrenergic receptors, increase the movement of potassium into cells from the extracellular space. Glucose reduces serum potassium indirectly by stimulating insulin release. Extracellular pH can also impact the serum potassium levels acutely through cellular translocation. The degree of change in serum potassium is dependent on the specific acid–base alteration. In general, acidosis increases the movement of potassium from the intracellular to extracellular space, thereby increasing serum potassium levels. The degree of change reported is somewhat variable; however, in humans with nonrespiratory acidosis, serum potassium was reported to increase by 0.17–1.67 mEq $l^{-1}$ per 0.1 unit decrease in pH, whereas nonrespiratory alkalosis decreased serum potassium by 0.1 mEq $l^{-1}$ for each 0.1 unit increase in pH.[24] With respiratory acidosis, the reported change is also relatively small, with a 0.14 mEq $l^{-1}$ increase in serum potassium per 0.1 unit decrease in pH. In normal anesthetized dogs, the creation of respiratory alkalosis decreased serum potassium by 0.4 mEq $l^{-1}$ for each 0.1 unit increase in pH.[25]

Serum potassium levels can be dramatically changed by alterations in urinary excretion of potassium. Briefly, potassium is freely filtered at the glomerulus, with ~80–90% being reabsorbed back into the blood in the proximal tubule and ascending loop of Henle. In the distal nephron, further reabsorption or secretion of potassium occurs. It is at this location that aldosterone impacts potassium homeostasis by reducing its reabsorption. Reductions in renal blood flow can reduce urinary excretion of potassium, while changes in renal function can result in either an increase or a decrease in serum potassium levels.

In clinical patients with complex disorders, it is important to recognize all factors that influence the measured serum levels of potassium, including the intake of potassium, the relative distribution of potassium in the body, as well as its level of excretion. Alterations in serum potassium rarely happen in isolation of alterations in body fluid status, and when therapies are initiated, shifts in serum levels may occur rapidly. For example, in a patient with severe hypovolemia and hypokalemia secondary to gastrointestinal loss of fluid, further reductions in serum potassium may occur with correction of the patient's volume status despite potassium supplementation.

## Hypokalemia

Hypokalemia is defined as a serum potassium level of <3.5 mEq $l^{-1}$ in both dogs and cats. As previously mentioned, normal animals generally consume their dietary potassium requirements. In the chronically anorexic patient, however, low dietary intake can contribute to hypokalemia. Anorexic patients receiving prolonged fluid therapy with intravenous replacement solutions that have low quantities of potassium (3–5 mEq $l^{-1}$) relative to daily body metabolic needs may also develop hypokalemia. Insulin, glucose, and β2-adrenergic agonist administration can reduce potassium levels secondary to intracellular transfer of potassium. Losses of potassium via the gastrointestinal tract or kidney are relatively common causes of significant hypokalemia.[26,27] Primary kidney disease, mineralocorticoid excess, or diuretic therapy can all result in hypokalemia (Table 7.3).

Clinical signs of hypokalemia include muscle weakness and dysrhythmias, both of which occur because of a shift of the resting cell membrane potential of muscle and cardiac cells to a more hyperpolarized state. Not uncommonly, specific signs of hypokalemia are not detected on physical examination but are identified on diagnostic workup of a patient with concurrent disease. With hypokalemia, cats have more severe clinical signs associated with specific potassium concentrations compared to dogs. Muscle weakness and cardiac conduction disturbances are usually not detected until potassium

levels are <2.5 mEq $l^{-1}$. Cats may demonstrate cervical ventroflexion in addition to muscle weakness. Electrocardiographic (ECG) changes associated with hypokalemia include supraventricular and ventricular arrhythmias.[27]

Treatment of hypokalemia before anesthesia depends on the presence of clinical signs attributable to the hypokalemia, the degree of serum potassium depletion, the underlying cause of the hypokalemia, and the urgency of the situation. In general, if not emergent, it is ideal to correct or improve a patients serum potassium levels before anesthesia by the enteral vs the parenteral route owing to the relative risk of producing iatrogenic hyperkalemia. If the patient is symptomatic, or the enteral route is not feasible, potassium should be administered intravenously. It is highly recommended that if the intravenous route is chosen for supplemental potassium administration, an intravenous infusion pump be used for its administration, continuous ECG monitoring be performed, and serum potassium levels be monitored, the frequency of which is dependent on the rate of correction. In general, the rate of exogenous potassium administration via the intravenous route should not exceed 0.5 mEq $kg^{-1}$ $h^{-1}$. To avoid vascular irritation at the site of administration, concentrated potassium solutions, such as potassium chloride (2 mEq $K^+$ $ml^{-1}$) or potassium phosphate (4.36 mEq $K^+$ $ml^{-1}$), can be mixed with ongoing replacement or maintenance intravenous fluid therapy to supplement potassium administration. Thorough mixing of the fluids must be performed to ensure consistent delivery of potassium, as inconsistent mixing can lead to lethal consequences.[28] Guidelines for supplementation of maintenance intravenous fluids with potassium exist on the basis of the patient's potassium level, and calculations can be performed on an individual basis with the goal of administering up to 0.5 mEq $kg^{-1}$ $h^{-1}$.[27]

During anesthesia, it is important not to cause further decreases in serum potassium in the patient with pre-existing hypokalemia. A balanced electrolyte solution should be chosen over a potassium-free crystalloid fluid such as 0.9% sodium chloride for replacement fluid therapy. As discussed previously, further supplementation of intravenous fluids with potassium chloride can be performed if the patient is symptomatic; however, the rate of potassium administration should not exceed 0.5 mEq $kg^{-1}$ $h^{-1}$. Careful attention to fluid administration should be taken to prevent inadvertent intravenous fluid boluses that could result in excessive potassium supplementation. As in the conscious patient, when potassium is given intravenously at concentrations above normal serum plasma concentrations, it is recommended that an intravenous fluid pump be used, continuous ECG monitoring be performed, and serum potassium levels be monitored. The administrations of agents such as insulin, β-adrenergic agonists, bicarbonate, and diuretics, such as furosemide, can further reduce potassium serum levels and should be avoided in the hypokalemic patient, if possible. The management of the patient's ventilation can also impact their serum potassium level, as respiratory alkalosis will result in the intracellular movement of potassium. As such, if ventilatory support is instituted during anesthesia, arterial or end-tidal carbon dioxide levels should be monitored and maintained at normal or above normal levels unless the latter is contraindicated because of coexisting conditions. During anesthetic recovery, the impact of hypokalemia on respiratory muscle strength should be considered and the adequacy of ventilation aggressively monitored before removal of oxygen supplementation.

## Hyperkalemia

Hyperkalemia is defined as a serum potassium level >5.5 mEq $l^{-1}$ in both dogs and cats. In general, hyperkalemia is present most frequently secondary to impaired excretion or translocation of potassium from the intracellular to extracellular space. Iatrogenic hyperkalemia secondary to excessive intravenous potassium supplementation can occur in the hospitalized patient. Renal disease, urethral obstruction, hypoadrenocorticism, and drug-associated impairment of potassium excretion are a few of the more common causes of hyperkalemia in small animal patients (Table 7.3). Malignant hyperthermia is a relatively rare condition but of particular significance to anesthetists, as patients may be phenotypically normal before anesthesia but develop severe hyperkalemia acutely in the perianesthetic period.[29] In humans, horses, and swine, hemolysis is associated with hyperkalemia. Interestingly, a small fraction of dogs (Akitas and English Springer Spaniels) have erythrocytes with high potassium levels. However, hemolysis, in vivo or during sample handling, is unlikely to cause a clinically significant increase in measured serum potassium levels in these animals. Potassium levels in stored canine or

feline blood also do not typically increase significantly. Canine and feline patients with severe thrombopathies or leukocytosis can have falsely elevated potassium due to storage artifact, as platelets and leukocytes have high levels of potassium, which may contaminate a serum sample if sampling processing is not rapid.[30]

Clinical signs associated with hyperkalemia primarily relate to the musculoskeletal and cardiovascular systems. Resting membrane potential is increased and closer to the threshold potential for cellular depolarization, which initially makes cells hyperexcitable. Severity of signs is somewhat dependent on the rapidity of onset of the hyperkalemia, with chronic elevations in potassium tolerated to a greater extent than acute elevations. Muscle weakness is generally present when serum potassium levels exceed 8.0 mEq $l^{-1}$. ECG changes include high peaked or deep T waves, prolonged PR interval or QRS complex, disappearance of the P wave, AV heart block, bradycardia, atrial standstill, ectopic beats, sine wave complexes, ventricular fibrillation, or standstill.[27] The latter changes are reported on the basis of results of experimental studies in otherwise healthy animals. In this situation, ECG changes were evident with potassium levels >5.5 mEq $l^{-1}$ and progressed to fibrillation or standstill with levels >10.1 mEq $l^{-1}$. In a more recent clinical study involving 37 dogs and cats with potassium levels >5.5 mEq $l^{-1}$, 20 animals had arrhythmias and 17 had normal sinus rhythms, despite potassium levels ranging from 5.5 to >10 mEq $l^{-1}$.[31] Concurrent abnormalities including other electrolyte disturbances, hydration status, and varying levels of sympathetic stimulation likely contributed to the heterogeneity in clinical signs.

Ideally, anesthesia should be delayed until the patient can be stabilized and serum potassium levels reduced below 5.5 mEq $l^{-1}$ to minimize potential dysrhythmias and further impairment in cardiovascular performance with anesthetic drug administration, which is, unfortunately, often not feasible. ECG monitoring during treatment is highly recommended. The focus of treatment before or during anesthesia should be aimed at reducing potassium administration, decreasing myocardial sensitivity to the elevated extracellular potassium concentrations, encouraging potassium movement from the extracellular to the intracellular space, and increasing potassium excretion when whole body potassium levels are thought to be elevated. If intravenous fluids containing potassium levels (>5.0 mEq $l^{-1}$) are being administered, they should be stopped and replaced with a balanced electrolyte solution or physiologic saline. In cases of severe hyperkalemia, 0.9% saline is generally recommended over solutions that contain any potassium. In cats presenting with urethral obstruction and hyperkalemia, intravenous administration of a balanced electrolyte solution resulted in a more optimal resuscitation as assessed at 12 h compared to 0.9% saline with concurrent re-establishment of urinary output.[32] Overall, the consideration of the patient's hydration status, the severity of the hyperkalemia, acid–base status, and concurrent electrolyte abnormalities should guide fluid therapy. Frequent monitoring of electrolyte and acid–base status should be used to dictate fluid therapy choices over time.

Calcium can be administered to raise the threshold potential of cardiac cells, thereby increasing the difference between the resting and threshold membrane potentials. Calcium supplementation can be achieved with either calcium gluconate 10% (0.5–1.5 ml $kg^{-1}$) or calcium chloride 10% (0.2–0.5 ml $kg^{-1}$) administered over 5–10 min. Intravenous administration of insulin (0.5 U $kg^{-1}$ of regular crystalline insulin) and glucose (0.5–1.0 g $kg^{-1}$ or 1–2 ml of 50% dextrose per kg) can also be administered to treat severe hyperkalemia. Insulin can be administered first followed immediately by glucose; they can be administered together as an infusion or separately as infusions. Irrespective of the method of administration, in addition to potassium, serum glucose levels should be monitored to avoid hyperglycemia. Correction of nonrespiratory acidosis by addressing the underlying etiology will also shift potassium intracellular and help reduce serum potassium levels. In an emergency setting, sodium bicarbonate (1–2 mEq $kg^{-1}$) can be administered to adjust pH. However, it should not be administered immediately after calcium, as it may impact the effectiveness on the myocardium of the latter. If excessive body stores of potassium are likely, diuretics such as furosemide (1–2 mg $kg^{-1}$) can be administered to facilitate potassium excretion.

Other than succinylcholine, which is not routinely used in veterinary anesthesia, there are no specific contraindications to any drugs currently used to achieve balanced anesthesia. As previously mentioned, however, hypoventilation should be avoided throughout the anesthetic period in the hyperkalemic patient. As monitoring the adequacy of ventilation is difficult

before intubation and after extubation, avoiding high doses of opioids in combination with sedatives before induction of anesthesia (i.e. premedication) and during recovery is recommended. During the anesthetic period, hypoventilation should be prevented and ventilatory support provided if necessary to ensure normocapnia.

## Calcium

The vast majority of calcium is maintained in the skeleton, wherein it is present in the relatively poorly exchangeable form, hydroxyapatite, or in the more readily available form, calcium phosphate. Although present in relatively small amounts (~1%), the remaining calcium, in both the intracellular and extracellular spaces, is critical to normal body homeostasis. Enzymatic reactions, intracellular messaging, membrane transport, muscle contraction, and nerve conduction are a few of the major activities that are dependent on normal serum calcium levels.[33,34]

Within the extracellular space, ionized calcium is the most biologically active form of calcium. However, it is also present bound to proteins or complexed to other substances such as phosphorous, bicarbonate, sulfate, citrate, or lactate. Although not biologically active, the bound and complexed forms of calcium are important, as they equilibrate with the ionized fraction and provide a readily available source of calcium when the ionized fraction is reduced.[33] Changes in the extracellular pH can shift the relationship of ionized calcium to complexed or protein bound factions, a factor that must be considered in patients with concurrent acid–base alterations. As with other electrolytes, dietary intake is the source of calcium for the body, with losses primarily occurring via the kidney and gastrointestinal tract. The skeleton can act as a source of calcium when the absorption and reabsorption of calcium from the intestine and kidney are inadequate to maintain serum calcium levels.

In the normal patient, the serum-ionized fraction of calcium is regulated primarily by parathyroid hormone, calcitriol (a metabolite of Vitamin D), and calcitonin. In response to low ionized serum calcium levels, parathyroid hormone levels increase, which increases renal tubular reabsorption of calcium and mobilization of calcium from bone and stimulates calcitriol synthesis, which subsequently increases intestinal absorption of calcium. Normal or elevated levels of serum-ionized calcium inhibits parathyroid synthesis and secretion, decreases calcitriol synthesis, and stimulates calcitonin's secretion from the thyroid gland, thus reducing the reabsorption of bone by osteoclasts. Total serum calcium measurements include the ionized, complexed, and protein-bound fractions.[33] Measurement of ionized calcium concentration is superior for the assessments of a patient's calcium status, and estimates of ionized calcium from the total calcium measurement are not recommended.[35] Several factors can influence the measurement of the ionized calcium fraction, including the type of sample (serum vs whole blood), the specific anticoagulant used, the volume of the sample relative to anticoagulant, and the analytic method used to measure calcium. Owing to the potential variability, the values should be compared to normal ranges reported for each laboratory.[33]

### Hypocalcemia

Hypocalcemia is defined as a *serum-ionized* calcium level $<1.25$ mmol $l^{-1}$ in dogs and 1.1 mmol $l^{-1}$ in cats. In terms of *total* serum calcium concentrations, levels used to define hypocalcemia are $<2.0$ mmol $l^{-1}$ in dogs and $<1.75$ mmol $l^{-1}$ in cats. Although hypoalbuminemia is one of the most common causes of hypocalcemia based on the measurement of total serum calcium, the presence of hypocalcemia based on this measurement cannot be extrapolated to ionized calcium levels (Table 7.3). When total calcium levels are below normal, ionized calcium should be measured.[35]

Mechanisms responsible for a decrease in ionized serum calcium include an increased renal loss of calcium, lack of absorption of calcium from the gastrointestinal tract, or redistribution of calcium from the ionized state to the bound or chelated state in the extracellular space. Acute and chronic renal failure, hyperphosphatemia, puerperal tetany, and pancreatitis are some of the more common causes of hypocalcemia.[33] Although less common, hypoparathyroidism can be primary or secondary after surgery. Parathyroid hormone has a very short serum half-life (3–5 min), and most dogs develop hypocalcemia early in the postoperative period (day 3–4) after bilateral parathyroidectomy or thyroid and parathyroid lobectomy.[36–38] Dogs with soft tissue trauma and both dogs and cats with sepsis have reductions in serum ionized calcium, a negative prognostic indicator

for outcome.[39–41] Massive transfusion with blood products containing citrated anticoagulants also causes hypocalcemia.[42] Although uncommon, alkalosis can increase the protein binding of calcium in the extracellular space and result in significant hypocalcemia. Ionized calcium levels also decrease in healthy dogs and cats undergoing general anesthesia and elective surgery, although values did not go below normal reference ranges and was not clinically significant.[43]

Hypocalcemia lowers the threshold potential of excitable cells, thereby facilitating membrane depolarization, an effect that is potentiated by hyperkalemia and hypomagnesemia. Rate of onset and severity of the ionized calcium deficit influence the degree of clinical signs. Clinical signs commonly reported with hypocalcemia include muscle tremors and fasciculation, facial rubbing, muscle cramping, stiff gait, seizures, and behavioral changes. Acute severe hypocalcemia can result in hypotension, dysrhythmias, and decreased myocardial contractility.[33] ECG changes include prolongation of the Q–T interval and ventricular tachycardia.[33] The severity of clinical signs associated with hypocalcemia is exacerbated by concurrent hypomagnesaemia and hyperkalemia.

In the patient with chronic hypocalcemia with no clinical signs, specific treatment for hypocalcemia may not be necessary. However, if the patient has any symptoms related to hypocalcemia or there is a potential for further reductions in calcium, therapy with calcium gluconate or calcium chloride should be initiated. Ideally, treatment would occur before anesthesia; however, a similar approach to treatment can be applied at any point during the anesthetic period if symptoms related to hypocalcemia develop. Of the two available parenteral calcium supplements, calcium gluconate is preferred over calcium chloride, as the latter will cause severe tissue irritation if injected perivascularly.[44] A treatment regime consisting of calcium gluconate (10%), 1–1.5 ml $kg^{-1}$, administered over 20–30 min followed by an infusion over 24 h containing 5–10 ml $kg^{-1}$ administered with physiologic saline or a balanced electrolyte solution is recommended for the symptomatic patient. It is advisable to monitor the ECG and arterial blood pressure during therapy. During anesthesia, alkalosis secondary to excessive ventilation or sodium bicarbonate administration should be avoided, as this will result in further reductions in ionized calcium. In patients requiring massive whole blood transfusions (>90 ml $kg^{-1}$) intraoperatively, ionized calcium should be monitored and treatment instituted if hypocalcemia develops. In the patient undergoing parathyroid or thyroid surgery in which the parathyroid glands may be disrupted, ionized calcium should be monitored postoperatively and hypocalcemia treated as mentioned previously.

## Hypercalcemia

Hypercalcemia is defined as a *serum-ionized* calcium level >1.5 mmol $l^{-1}$ in adult dogs and 1.4 mmol $l^{-1}$ in adult cats. In terms of *total* serum calcium concentrations, levels used to define hypercalcemia are values >3.0 mmol $l^{-1}$ in dogs and 2.75 mmol $l^{-1}$ in cats. Dogs and cats aged up to 2 years have ionized calcium levels that are 0.025–0.1 mmol $l^{-1}$ higher than adults.

In dogs, hypercalcemia associated with malignancy (lymphoma, anal sac adenocarcinoma), renal failure, hyperparathyroidism, or hypoadrenocortism is common, whereas idiopathic hypercalcemia, neoplasia, and renal failure are the most frequent causes of hypercalcemia in cats (Table 7.3).[33,45]

Hypercalcemia raises the resting membrane potential in excitable cells, decreasing cell excitability. At high concentrations, calcium impairs cell function and can result in cell death. Clinical signs related to hypercalcemia are primarily associated with the CNS, gastrointestinal tract, heart, and kidneys. Polydipsia, polyuria, anorexia, lethargy, weakness, vomiting, prerenal azotemia, and chronic renal failure are common. Cardiac arrhythmias, seizures, or twitching can also occur with hypercalcemia but are less common than when the patient is hypocalcemic.

The presence of clinical signs related to hypercalcemia and/or total serum calcium levels above 4 mmol $l^{-1}$ are indications to initiate aggressive treatment directed at lowering serum calcium levels. The primary treatment goal for the hypercalcemic patient is removal of the underlying cause, which frequently requires general anesthesia. In the perianesthetic period, intravenous fluid therapy should be administered with the goal of correcting volume deficits and metabolic acidosis. Unless contraindicated because of underlying cardiopulmonary disease, the rate of fluid administration should result in correction of dehydration within 4–6 h. Physiologic saline is the recommended fluid of choice in the hypercalcemic patient, as the relatively high sodium concentration facilitates calcium excretion in the urine. If the

patient has concurrent nonrespiratory acidosis, sodium bicarbonate can be added to the ongoing fluid therapy.[33] Balanced electrolyte solutions have also been shown to reduce ionized serum calcium levels, likely through volume expansion and dilution of serum calcium and can be used in place of saline when treating mild hypercalcemia. After correction of volume deficits, if the patient is still severely hypercalcemic, calciuresis can be attempted with continued aggressive fluid therapy with the addition of furosemide (2–4 mg $kg^{-1}$ IV, BID, or TID) to facilitate renal excretion of calcium. In such cases, the patient will need to be monitored for signs of volume overload and electrolytes monitored to prevent hypernatremia or hypokalemia. Glucocorticoids, including prednisolone or dexamethasone, are effective at lowering serum calcium associated with malignancy, hypervitaminosis D, cholecalciferol rodenticide toxicity, and granulomatous disease. Additional therapies that reported to offer benefit in the ongoing management of the hypercalcemic patients include drugs aimed at reducing bone reabsorption, such as calcitonin and bisphosphates.[33] During anesthesia, ventilation should be aggressively monitored and ventilation instituted when necessary to prevent respiratory acidosis.

## Acid–base homeostasis and alterations

Acid–base disturbances alter the relative concentrations of hydronium and hydroxyl concentrations in the body, with acidemia defined as a pH (negative logarithm of the hydrogen ion concentration) of arterial blood <7.35 and alkalemia as a pH > 7.45. Despite the constant generation of carbon dioxide (volatile acid) and nonvolatile acids ($H^+$) as a byproduct of oxidative metabolism, the hydrogen ion concentration in the body is maintained within a narrow range through intracellular and extracellular buffers, with by-products being excreted via the lungs ($CO_2$) or kidney ($H^+$).[46,47] The $CO_2$ partial pressure in the blood is regulated primarily by chemoreceptors in the medulla, which sense its partial pressure in cerebrospinal fluid and alter the degree of alveolar ventilation. Peripheral chemoreceptors in the aortic and carotid bodies also sense changes in hydrogen ion concentration and stimulate alveolar ventilation. The kidneys preferentially control the excretion of $Na^+$ and $Cl^-$ to influence $H^+$ and $HCO_3^-$ excretion into and reabsorption from the urine. Normal respiratory and kidney functions are essential to maintain acid–base homeostasis in the body.

There are two different methods used to describe and characterize a patient's acid–base status, the traditional and the Stewart-Fencl approach.[47–49] The former is based on the Henderson-Hasselbalch equation and relates the pH of blood to the hydrogen ion concentration and arterial partial pressure of $CO_2$ ($PaCO_2$) and classifies disturbances into respiratory and nonrespiratory disorders. The Stewart-Fencl approach provides a more thorough mechanistic approach to acid–base alterations and can explain the measured changes in a patient with complex acid–base alterations. The latter system classifies abnormalities into disorders in $PaCO_2$, strong ion difference, which is calculated as [(Na + K + Mg + Ca) − (Cl + lactate + other anions)] and the total plasma concentration of nonvolatile weak acids (primarily albumin and phosphorous), referred to as Atot. When compared to the traditional approach, the Stewart-Fencl approach requires knowledge of more variables, including electrolytes, albumin, and phosphates. The traditional approach is therefore more easily applied and remains useful particularly during the anesthetic period if its limitations are recognized. The approach to the patient in the clinical setting should be to first determine the primary disturbance, followed by assessment of the expected compensation and secondary changes to determine if more than one disturbance is present. The most common causes of primary acid–base disturbances are listed in Tables 7.4 and 7.5. The secondary changes in $PaCO_2$, pH, and $HCO_3$ in response to simple acid–base disturbances in dogs are provided in Table 7.6. Unfortunately, the anticipated changes in cats are not well characterized, but the changes observed in the dog can be used as guidelines. A review of each of the primary categories of acid–base disturbances will be followed by a step-wise approach to the assessment of a patient's acid–base status. The latter will be limited to patients with relatively common noncomplex abnormalities and normal plasma proteins and serum phosphorous levels. For a thorough review of mixed acid–base disorders, the reader is referred to several excellent reviews.[50,51]

### Respiratory acidosis

Primary respiratory acidosis results from an increase in $PaCO_2$ associated with a decrease in alveolar ventilation.

**Table 7.4** Common causes of respiratory acidosis and alkalosis in dogs and cats.[46]

| | Respiratory acidosis | Respiratory alkalosis |
|---|---|---|
| Ventilatory drive | Decreased ventilatory drive<br>• Drugs<br>• CNS disease<br>• Nonrespiratory alkalosis | Increased ventilatory drive<br>• Hypoxemia<br>• Respiratory disease<br>• Sepsis<br>• Pain<br>• Hyperthermia<br>• Nonrespiratory acidosis |
| Ability to ventilate | Decreased ability to ventilate<br>• Upper airway obstruction<br>• Neuromuscular disease<br>• Extrapulmonary disease<br>• Intrapulmonary disease | |
| $CO_2$ production | Increased $CO_2$ production<br>• Malignant hyperthermia | Decreased $CO_2$ production<br>• Pending cardiopulmonary arrest |
| Iatrogenic | • Inappropriate ventilator settings<br>• Anesthetic equipment malfunction<br>• Expired carbon dioxide absorbent | • Inappropriate ventilator settings |

**Table 7.5** Common causes of nonrespiratory acidosis and alkalosis in dogs and cats as categorized by the Traditional and Stewart-Fencl Approach.[46–48]

| Nonrespiratory acidosis | Nonrespiratory alkalosis |
|---|---|
| Increased anion gap/decreased SID[a], increased UMA[b]<br>• Lactic acidosis<br>• Diabetic ketoacidosis<br>• Toxins: salicylate, ethylene glycol<br>• Uremic acidosis (Increased $Atot^3$) | Increased SID[a], chloride deficit<br>• Vomiting<br>• Diuretics |
| Normal anion gap/decreased $SID^1$, Increased $Cl^-$<br>• Diarrhea<br>• Renal tubular acidosis<br>• Carbonic anhydrase inhibitors (acetazolamide)<br>• NaCl fluid therapy | Increased $SID^1$, Increased $Na^+$<br>• Alkali administration ($NaHCO_3$)<br>• Hyperaldosteronism<br>• Hyperadrenocorticism |
| Dilutional acidosis (decreased SID[a], decreased $Na^+$) | Decreased Atot[c]<br>• Hypoalbuminemia |

[a]SID = Strong ion difference.
[b]UMA = Unmeasured anions.
[c]Atot = Sum of nonvolatile weak acids.

**Table 7.6** Primary disturbances and expected secondary changes associated with acid–base disturbances in the dog.[46]

| Primary disturbance | pH | Secondary changes $PaCO_2$ | $HCO_3^-$ |
|---|---|---|---|
| Respiratory acidosis<br>• Acute | Decreases by 0.05 for every 10 mmHg increase in $PaCO_2$ | | Increases by 1.5 mEq $l^{-1}$ for every 10 mmHg increase in $PaCO_2$ |
| Respiratory acidosis<br>• Chronic | Decreases by 0.07 for every 10 mmHg increase in $PaCO_2$ | | Increases by 3.5 mEq $l^{-1}$ for every 10 mmHg increase in $PaCO_2$ |
| Respiratory alkalosis<br>• Acute | Increases by 0.1 for every 10 mmHg decrease in $PaCO_2$ | | Decreases by 2.5 mEq $l^{-1}$ for every 10 mmHg decrease in $PaCO_2$ |
| Respiratory alkalosis<br>• Chronic | Increases by 0.15 for every 10 mmHg decrease in $PaCO_2$ | | Decreases by 5.5 mEq $l^{-1}$ for every 10 mmHg decrease in $PaCO_2$ |
| Nonrespiratory acidosis (Decrease in SID[a], Increase in atot[b]) | | Decreases by 0.7 mmHg for each 1 mEq $l^{-1}$ decrease in $HCO_3^-$ | |
| Nonrespiratory alkalosis (increase in SID, decrease in Atot) | | Increases by 0.7 mmHg for each 1 mEq $l^{-1}$ increase in $HCO_3^-$ | |

[a]SID = Strong ion difference.
[b]Atot = Sum of nonvolatile weak acids.

The increase in $PaCO_2$ results in a decrease in pH and an increase in plasma bicarbonate secondary to increased quantities of dissolved carbonic acid. In the traditional approach to acid–base, the increase in bicarbonate that occurs secondary to increases in $PaCO_2$ is considered a compensatory response, whereas the Stewart approach identifies the compensatory response to elevations in $PaCO_2$ as an increase in urinary excretion of chloride ion, with changes in bicarbonate occurring secondarily.[48] Nonetheless, the expected changes in pH and bicarbonate as a result of elevations in $PaCO_2$ (Table 7.6) should be considered when interpreting the patient's overall acid–base status, as unexpected alterations may reflect concurrent abnormalities.

Common causes of hypoventilation and subsequent respiratory acidosis (Table 7.4) include conditions that result in a decreased ventilatory drive, a decreased ability to ventilate, an increase in carbon dioxide production, and iatrogenic causes. In the perianesthetic period, opioids, particularly pure mu-agonists, when used in combination with sedatives and most anesthetic agents, including inhalants and injectable agents, result in mild to moderate alveolar hypoventilation and respiratory acidosis.[52] Clinical signs specific to respiratory acidosis may be small relative to those related to the primary disorder resulting in hypoventilation. In particular, the patient's inspired oxygen content will dramatically alter the manifestation of respiratory acidosis, as marked hypoventilation in a patient breathing room air will result in hypoxemia and its associated signs, whereas a patient receiving oxygen supplementation (>30%) will usually not experience a reduction in oxygenation owing to hypoventilation alone. Increases in $PaCO_2$ without concurrent hypoxemia result in sympathetic nervous system stimulation, with increases in heart rate and cardiac output.[53] However, chronic respiratory acidosis without hypoxemia in the anesthetized, ventilated dog results in a decrease in heart rate and cardiac output.[54] Overall, the severity and duration of hypercapnia, as well as the specific anesthetic agents used likely influence the manifestation of elevations in $PaCO_2$ during anesthesia. The diagnosis of respiratory acidosis is by arterial blood gas analysis; in an intubated patient, end-tidal carbon dioxide levels can be used to estimate or trend the severity of hypoventilation. The method of measurement, the size of the patient, and the

breathing circuit can influence the relationship of the measured end-tidal carbon dioxide to $PaCO_2$; however, in general, end-tidal carbon dioxide is approximately 4–6 mmHg lower than $PaCO_2$ in cats and dogs.[55,56]

If primary respiratory acidosis is present before anesthesia, an intravenous catheter should be placed and supplies to secure the patient's airway and provide ventilatory support should be prepared before proceeding with sedative, analgesic, or anesthetic drug administration. When possible, the underlying cause for the hypoventilation should be discerned and removed. For example, fluid or air within the thoracic space should be removed by thoracocentesis before the induction of anesthesia. Concurrent conditions including dehydration, electrolyte abnormalities, and hypoxemia should be corrected or, at least, improved before anesthesia with intravenous fluid, electrolyte therapy, and oxygen supplementation. When feasible, monitoring of the patient's ECG, blood pressure, and hemoglobin saturation should be initiated before induction. The degree of hypercapnia is likely to increase with the induction of anesthesia and a rapid induction and tracheal intubation, with aggressive monitoring of ventilation using capnometry immediately after intubation is highly recommended. The specific degree of hypercapnia at which to institute ventilatory support has not been determined. However, during anesthesia, if pH is <7.2 or $PaCO_2$ is >60 mmHg, ventilatory support is generally recommended.[57] When pH is <7.1, cardiac contractility is decreased and hemodynamic stability may be impaired.[53] Aggressive ventilatory monitoring is indicated in patients with pre-existing respiratory acidosis both intraoperatively and during recovery from anesthesia. Oxygen supplementation and possibly prolonged ventilatory support may be required in the postanesthetic phase depending on the underlying condition.

Respiratory acidosis developing during general anesthesia with oxygen supplementation is not uncommon in healthy small animal patients, as all anesthetics produce dose-dependent respiratory depression.[52] The degree of hypoventilation is dependent on the specific anesthetic protocol used, the depth of anesthesia required, patient positioning, and the surgical intervention. Dogs and cats typically tolerate moderate increases in carbon dioxide, and ventilatory support is generally not indicated until $PaCO_2$ levels exceed 60 mmHg, assuming other acid–base and electrolyte disturbances are not present. Equipment malfunctions, expired carbon dioxide absorbent, or inappropriate ventilator settings can lead to elevations in $PaCO_2$ and should be considered, particularly when they are not consistent with the patient's perceived degree of alveolar ventilation.

## Respiratory alkalosis

Primary respiratory alkalosis occurs as a result of hyperventilation, resulting in a decrease in $PaCO_2$ and increase in pH. Plasma bicarbonate decreases secondary to the decrease in dissolved carbonic acid, and while the change in bicarbonate is explained as a compensatory change in the traditional approach, it is now understood that the kidneys compensate for respiratory alkalosis by actively reducing the excretion of chloride in the urine, with bicarbonate changes occurring secondarily (Table 7.5).

Primary respiratory alkalosis is not as common in the perioperative period as respiratory acidosis. However, it can occur secondary to an increase in ventilatory drive or a decrease in carbon dioxide production (Table 7.4). Hypoxemia, pain, exercise, and hyperthermia are more common causes of increased ventilatory drive, leading to hypocapnia and respiratory alkalosis. Iatrogenic hyperventilation in small animal patients is a common side-effect of positive pressure ventilation, which can be prevented with monitoring of end-tidal carbon dioxide levels. Acute, severe reductions in $PaCO_2$ may be indicative of a reduction in peripheral blood flow and impending cardiopulmonary arrest. There are very few clinical signs specifically related to respiratory alkalosis in the conscious patient; however, $PaCO_2$ levels <20 mmHg in the anesthetized animal reduce cerebral blood flow, myocardial perfusion, cardiac output, and systemic arterial blood pressure.[58] Treatment of respiratory alkalosis should be aimed at treating the underlying cause.

## Nonrespiratory acidosis

Primary nonrespiratory acidosis is characterized by a decrease in pH and plasma bicarbonate. In the traditional approach, etiologies of nonrespiratory acidosis are grouped into those with a normal or abnormal anion gap. The anion gap is calculated as $[(Na^+ + K^+) - (Cl^- + HCO_3^-)]$, with a normal range of 12–25 mEq $l^{-1}$ in dogs and 13–31 mEq $l^{-1}$ in cats.[46] An increase in anion gap is associated with an

increase in either endogenous or exogenous anions such as lactate, whereas an acidosis without an increase in anion gap is associated with an increase in serum chloride in proportion to the reduction in $HCO_3^-$. The latter situation is most likely to arise with diarrhea or renal failure (Table 7.5). Hypoalbuminemia results in a decrease in the anion gap, and the impact of this variable should be considered when evaluating the anion gap in the hypoproteinemic patient. In the Stewart-Fencl approach, nonrespiratory acidosis is attributed to a decrease in the strong ion difference or an increase in the total plasma concentration of nonvolatile weak acids. Most strong ion difference abnormalities result in an acidosis from an increase in $Cl^-$ or unmeasured anions or a decrease in $Na^+$. In response to a nonrespiratory acidosis, alveolar hyperventilation occurs, $PaCO_2$ decreases, and pH returns toward normal (Table 7.6).

Clinical signs of acidosis are primarily dependent on the underlying cause and the rapidity of onset of the change in pH. However, in general, a pH <7.2 is associated with a decrease in enzymatic reactions throughout the body, an impairment of normal cell functions, a reduction in myocardial contractility, cardiac output, and systemic arterial pressures and predisposes to ventricular arrhythmias.[51] Correction of nonrespiratory acidosis should ideally be performed before anesthesia by addressing the underlying cause of the disturbance, although complete correction may not be feasible without a surgical intervention. In the case of an increased anion gap associated with a lactic acidosis, fluid therapy is the cornerstone of treatment with the goal of correcting fluid deficits and improving tissue perfusion. Ketoacidosis should be corrected with intravenous fluid and insulin therapy. The addition of sodium bicarbonate to the treatment regime in the patient with lactic acidosis or ketoacidosis remains controversial; however, in the patient with uremic acidosis, fluid therapy with the addition of $NaHCO_3$ is recommended if the pH is <7.2. In the case of the patient with acidosis and a normal anion gap, fluid deficits should be corrected before anesthesia, and if the pH is <7.2, $NaHCO_3$ therapy initiated. While the traditional approach to acid–base interpretation attributes the improvement in pH with $NaHCO_3$ therapy to the $HCO3^-$ component, the current understanding is that the $Na^+$ is responsible for the improvement in the patient's status by increasing the strong ion difference, expanding the extracellular space, and increasing urine production.[48]

Major preanesthetic considerations in the patient with nonrespiratory acidosis include the impact of the underlying condition on the patient's cardiovascular status and reserve, the presence of concurrent electrolyte disturbances, the ideal intravenous fluid and its rate of administration, the need for additional treatments such as $NaHCO_3$, potential changes in the pharmacokinetics of drugs, and the need to support ventilation to prevent the development of significant increases in $PaCO_2$, which would further contribute to reductions in pH. In the hemodynamically unstable patient, an ECG and invasive blood pressure monitoring should be used to assist with the optimization of fluid and inotrope therapy. The specific anesthetic protocol chosen should be guided by the patient's cardiovascular status; the use of a technique that permits titration of drugs to effect will minimize the risk of inadvertent drug overdose. A balanced electrolyte solution is generally the fluid of choice, with the rate of administration guided by the patient's hydration status. If $NaHCO_3$ is indicated as discussed previously, it can be mixed with the replacement fluid. However, it will increase the tonicity of the fluid. If hypertonicity is contraindicated, $NaHCO_3$ can be diluted with sterile water (1.5 ml of 1 mEq $l^{-1}$ NaHCO3 with 8.5 ml of sterile water) to achieve an isotonic solution.[59] The quantity of $NaHCO_3$ to administer over the first few hours of treatment is estimated by the following formula (Equation 7.1). Blood gas analysis should be used to guide follow-up $NaHCO_3$ treatments, with the goal being to return pH to 7.2. Complete correction of pH to normal is not recommended to order to avoid iatrogenic alkalosis. To prevent a concurrent respiratory acidosis with the induction of anesthesia, the anesthetist should be prepared to support ventilation immediately after the induction of anesthesia. Ideally, the adequacy of alveolar ventilation should be monitored with intermittent arterial blood gas analysis and capnometry.

$$HCO3^-(\text{mEq}) = 0.3 \times \text{body weight (kg)} \times \text{bicarbonate deficit (mEq l}^{-1}) \quad (7.1)$$

## Nonrespiratory alkalosis

Primary nonrespiratory alkalosis is characterized by an increase in pH and plasma bicarbonate. The most common causes of nonrespiratory alkalosis in dogs and cats relate to excessive loss of chloride via the gastrointestinal tract secondary to vomiting or via the kidney due to diuretic administration (Table 7.5). In response to the alkalosis, alveolar hypoventilation occurs, $PaCO_2$ increases, and pH returns toward normal (Table 7.6). Clinical signs in patients with nonrespiratory alkalosis are primarily related to underlying conditions and associated electrolyte changes. Of particular significance is the effect of an increase in pH on serum potassium and ionized calcium, both of which decrease with the decrease in $H^+$ concentration.[24,25,33] The goal of treatment is to address the underlying cause and correct volume and chloride deficits, with concurrent monitoring of serum potassium recommended, as patients often have whole body deficits that result in hypokalemia when the pH returns toward normal. Intravenous fluid therapy with a balanced electrolyte solution or sodium chloride (0.9%) and potassium supplementation based on the individual patient is recommended. If possible, any volume deficits should be corrected before anesthesia. The choice of induction technique should be based on the individual patient's concurrent disease. Guidelines for potassium supplementation during anesthesia are provided previously.

## Step-wise approach to the assessment of acid–base status

The correct assessment of a patient's acid–base status is heavily dependent on the quality of the blood gas sample and the accuracy of the blood gas analyzer. The approach described in the following section is based on the interpretation of an arterial blood gas sample with a blood gas analyzer with the ability to report electrolytes ($Na^+$, $K^+$, $Cl^-$).

1. Evaluate the quality of the sample by assessing all of the values reported. Sample dilution or improper mixing will result in an artificial reduction in measured hemoglobin, whereas contamination with air will falsely lower $PCO_2$ and elevate $PO_2$.
2. Evaluate the pH. If pH is <7.35, the patient is academic, and if the pH is >7.45, the patient is alkalemic.
3. Consider pH and $PaCO_2$. If the direction of change is opposite, the primary disorder is respiratory in origin. If the direction of change is the same, the primary disorder is nonrespiratory in origin.
4. If the primary disorder is respiratory and the $PaCO_2$ is >45 mmHg, respiratory acidosis is present. If the primary disorder is respiratory and $PaCO_2$ is <30 mmHg, respiratory alkalosis is present. Consider if the expected change in pH and $HCO_3^-$ is appropriate for that in $PaCO_2$. If the changes are outside of anticipated range, more than one process may be present.
5. If the primary disorder is nonrespiratory, calculate the expected change in $PaCO_2$. If the change is outside of the anticipated range, more than one process may be present.
6. If the patient has a nonrespiratory acidosis, calculate the anion gap $[(Na^+ + K^+) - (Cl^- + HCO_3^-)]$ to determine most likely etiologies and the appropriate approach to treatment (Table 7.5). Consider the patient's serum phosphorous and albumin levels and their impact on the assessment of the anion gap.
7. If the patient has a nonrespiratory alkalosis, assess serum $Na^+$, $Cl^-$, and protein levels to determine the etiology of the alkalosis.

## Step-wise approach to the anesthetic management of the patient with an acid–base disorder

1. After characterization of an acid–base disorder(s), consider the underlying etiology and concurrent abnormalities.
2. Initiate measures to address abnormalities in hydration and/or electrolyte disturbances.
3. Perform a thorough assessment of the cardiovascular system, including evaluation of cardiac rhythm with an EKG and blood pressure if indicated on the basis of physical examination findings. Ensure a secure intravenous access, and attempt stabilization of hemodynamics before preanesthetic medication.
4. Assess respiratory function and effort. If compromised, consider performing therapeutic measures such as thoracocentesis with local anesthesia before induction of general anesthesia. Oxygen supplementation should be initiated in patients with reduced $PaO_2$ or $SpO_2$ levels before premedication.

5 Consider monitoring devices and support measures such as fluid therapy, positive pressure ventilation, or inotrope administration that will likely be required during the anesthetic period and prepare accordingly.
6 The specific anesthetic protocol used should be based on the individual animal's condition. A balanced anesthetic approach using an opioid analgesic for premedication, injectable anesthetic induction agents that are suitable for administration by titration such as alfaxalone, propofol, or an opioid/benzodiazepine combination, and a maintenance regime that incorporates local anesthesia and systemic analgesics to reduce general anesthetic requirements are preferable. In cases with severe respiratory acidosis, opioid premedication can be delayed until anesthetic induction and ventilator support are initiated.
7 Supportive measures including fluid, electrolyte, oxygen, and ventilatory support should be continued into the recovery until it is deemed unnecessary on the basis of the assessment of the individual patient.

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# 8 Endocrine disease

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Endocrine disease has largely been ignored in the veterinary literature up to this point with regards to its impact on anesthesia. Many would argue that this is due to the uncommon development of severe complications and the fact that many of these patients perform well despite their disease(s). This chapter presents the pathophysiology associated with five veterinary endocrinopathies and how it relates to patient management in the perianesthetic period.

## Thyroid disease

### Anatomy and physiology of the thyroid gland

The thyroid gland in dogs and cats is bilobed and sits just lateral to the trachea and medial to the common carotid arteries at the level of the thyroid cartilage.[1] Synthesis and secretion of thyroid hormones are dictated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus acts on the anterior pituitary to stimulate the release of thyrotropin-stimulating hormone (TSH). This then acts on the thyroid follicular cells to stimulate synthesis and release of triiodothyronine (T3) and thyroxine (T4) into the circulation where they act on organs throughout the body. Thyroid hormones autoregulate their release by providing negative feedback on the pituitary and hypothalamus, thereby decreasing the release of TSH and TRH, respectively.[1]

### Effects of thyroid hormones

Thyroid hormones, especially T3, work at the cellular level to elicit a broad range of biologic effects throughout the body. These effects directly influence metabolic rate, protein synthesis, and normal fetal development.[1,2] Of particular interest to the anesthesiologist are their chronotropic and inotropic effects on the heart, action on the respiratory centers of the brain to maintain sensitivity to hypercarbia and hypoxemia, and role in thermoregulation.[1,3]

### Hypothyroidism

#### Canine hypothyroidism

A deficiency of thyroid hormone through disruption of the hypothalamic-pituitary-thyroid axis results in hypothyroidism. It is a relatively common endocrinopathy in dogs with prevalence similar to that of humans, between 0.2% and 0.8%.[2,4] The etiology is primary in origin 95% of the time, with destruction via autoimmune lymphocytic thyroiditis and idiopathic atrophy being most common. It tends to affect middle age to older dogs (mean ~7 years), with English Setters, Golden Retrievers, Giant Schnauzers, Dobermans, Boxers, Shetland Sheepdogs, and Cocker Spaniels being over-represented.[1,4] No gender predisposition has been identified.

#### Feline hypothyroidism

Spontaneously occurring hypothyroidism in cats is rare.[3] It is most often encountered in cats that have been previously treated via radioiodine therapy or thyroidectomy for hyperthyroidism.[1,5] Cats develop similar clinical signs as their canine counterparts, including lethargy, weight gain, decreased grooming, and poor coat quality.[1,3]

Because it is a rare condition, many of the complications reported in humans and dogs have not been reported in cats. Cats that become hypothyroid iatrogenically, however, are shown to have an increased risk of developing azotemia and chronic

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kidney disease.[5] Those that develop azotemia also have significantly shorter survival times when compared to their euthyroid, azotemic counterparts (456 vs 728 days, respectively).[5]

## Clinical signs and symptoms

Clinical signs are varied with multiple organ systems being affected (Table 8.1).

Dermatologic abnormalities and signs associated with decreased metabolic rate are most common, presenting in 60–80% and 50% of hypothyroid dogs, respectively.[3] Although uncommon, cardiovascular and neuromuscular signs can be significant and are a source of perianesthetic morbidity.

## Clinicopathologic findings

Bloodwork changes are not pathognomonic for the disease and may not always be present. In 28–44% of dogs with hypothyroidism, a mild normocytic, normochromic, nonregenerative anemia is present.[1,4] This represents decreased erythropoiesis and bone marrow response from thyroid hormone deficiency. This anemia is rarely of concern for anesthesia but may need to be addressed in patients in whom significant blood loss is expected.[7]

The most common abnormalities seen in the biochemical profile are hypercholesterolemia and hypertriglyceridemia.[1,3] These result from impaired lipid metabolism and can be associated with atherosclerosis of blood vessels. There is a positive correlation with, and increased prevalence of, atherosclerosis in dogs diagnosed with hypothyroidism.[8] Hess et al. (2003) demonstrated that although atherosclerosis is rare in dogs (0.5% prevalence), patients who develop this disease are 51 times more likely to be hypothyroid than not.[8]

Other, less common findings include mild to moderate increases in alkaline phosphatase (ALKP), alanine transferase (ALT), aspartate aminotransferase (AST), and creatinine kinase, as well as mild hypercalcemia and hypoglycemia.[1,9,10] In contrast, cats may have a low ALKP, likely caused by decreased bone turnover.[5]

Abnormalities are not typically found in the urinalysis of hypothyroid dogs. However, it is important to evaluate renal function in the hypothyroid patient

**Table 8.1** Clinical signs and physical examination findings of hypothyroidism in dogs and cats.[1,3,4,6]

| Decreased metabolic rate | Cardiovascular | Neuromuscular |
|---|---|---|
| Lethargy[a] | Sinus bradycardia[a] | *CNS* |
| Weakness | Weak apex beat | Seizures |
| Weight gain[a] | Decreased peripheral pulses | Ataxia |
| Exercise intolerance | Diastolic hypertension | Head tilt |
| Hypothermia[a] | Decreased left ventricular pump function | Positional nyastagmus |
| Mental dullness | | Strabismus |
| Decreased appetite[a] | Low QRS voltage | Decreased facial sensation |
| *Dermatologic* | Inverted T-waves | *PNS* |
| Endocrine alopecia | Cardiac Arrhythmias | Generalized weakness |
| Dull, brittle haircoat[a] | AV block | Knuckling |
| Poor regrowth of hair[a] | Atrial fibrillation | Dragging of limbs |
| Hyperpigmentation | *Gastrointestinal* | Paraparesis |
| Poor wound healing | Constipation | Quadraparesis |
| Bruising | Diarrhea | Paralysis |
| Myxedema (puffy face)[a] | Delayed gastric emptying | Lameness |
| Decreased grooming[a] | | Exercise intolerance |
| Recurrent bacterial infections | | Muscle atrophy |
| | | Myopathy |
| | | Laryngeal paralysis (?) |
| | | Megaesophagus (?) |

[a]Clinical signs reported in cats.

Source: Adapted with permission from Reference 1.

undergoing anesthesia. Hypothyroidism is associated with decreased glomerular filtration rate (GFR) in both dogs and cats, attributed to both vasoconstriction of the afferent and efferent arterioles via impaired nitric oxide release from endothelial cells, and decreased cardiac output from a lowered metabolic rate.[5,11] The reduced GFR could be exacerbated in the perianesthetic period by hypotension and decreased renal perfusion, resulting in additional postoperative morbidity.

### Diagnosis

Diagnosis is based on the presence of clinical signs and appropriate biochemical testing. The gold standard includes determination of free thyroxine (fT4) serum levels via modified equilibrium dialysis.[1,3] Without clinical evidence of hypothyroidism, a low serum level of T4 is not diagnostic. Breed, age, certain drugs including barbiturates and corticosteroids, and the presence of chronic disease or critical illness may falsely decrease serum T4.[1,12] Accurate diagnosis often requires a thyroid panel including baseline TSH concentration, free T4, and possible autoantibody tests.[1]

### Treatment

The treatment of hypothyroidism consists of the administration of oral levothyroxine (T4). Patients are often euthyroid within 4–6 weeks of treatment at an appropriate dose.[1,12] Intravenous formulations of levothyroxine are available but are only indicated in situations of myxedema coma, a rare manifestation of severe hypothyroidism characterized by obtundation, hypothermia, hypotension, hypoventilation, bradycardia, and nonpitting edema of the face.[1,2]

### Anesthetic management

Because hypothyroidism is a common canine endocrinopathy, it is important for the anesthesiologist to be aware of the pathophysiology it causes and how it can be managed in the perianesthetic period. The presence of mild or subclinical hypothyroidism is not an absolute contraindication for anesthesia. However, it is ideal that patients be treated and rendered euthyroid before undergoing anesthesia for elective procedures.[2] Similar anesthetic practices should be used for the hypothyroid feline patient taking care to recognize the increased risk of renal morbidity when untreated.[5,13]

#### Preanesthetic physical examination

Patients with a history of hypothyroidism or where there is a high index of suspicion on the basis of clinical signs should have a thorough preanesthetic workup, including physical examination, blood work (CBC and biochemical profile), urinalysis, and recent serum T4 level. Numerous organ systems are affected by thyroid hormone deficiency, making a systematic preanesthetic physical examination especially important.

The overall body condition of the dog should be assessed, since many clinically hypothyroid patients are overweight as a result of lowered metabolic rate. Overweight or obese patients can be more difficult to manage under anesthesia.[13] Decreased thoracic compliance and compression atelectasis from increased organ weight can lead to hypoventilation and ventilation–perfusion mismatch.[7,13] This could be exacerbated by decreased sensitivity and poor response to hypercarbia and hypoxemia, as well as altered diffusion of oxygen across the alveolar capillary membrane.[2]

Careful evaluation of the cardiovascular system should be performed because hypothyroidism leads to decreased numbers and affinity of β-adrenergic receptors and a decreased catecholaminergic response.[1] Hypothyroid patients can present with bradyarrhythmias, poor peripheral pulses, and a weak apex beat from impaired myocardial contractility, decreased cardiac output, and poor peripheral perfusion.[1,3] Although this decrease in contractility may be mild in most situations, severe cases of systolic dysfunction resulting in congestive heart failure have been reported in dogs.[14]

Thoracic radiographs with or without an echocardiogram should be strongly considered in patients in whom physical examination findings suggest reduced cardiac function and are essential in patients in whom a murmur, arrhythmia, or evidence of congestive heart failure (i.e. jugular pulses, coughing, exercise intolerance) is present. In patients with arrhythmias, an electrocardiogram should be evaluated. Sinus bradycardia with decreased QRS amplitude and inverted t-waves is most common. However, first- and second-degree atrioventricular blocks, ectopic beats, and, rarely, atrial fibrillation may be identified as a result of coronary artery atherosclerosis and subsequent myocardial hypoxia.[1,3,8]

Blood pressure readings may reveal mild diastolic hypertension as a result of increased systemic vascular

resistance (SVR).[2,7,11,15] Hypertension does not usually require treatment, but the anesthetist should be aware that this could decrease circulating blood volume, and when combined with the profound response hypothyroid patients often have to anesthetic drugs, significant hypovolemia and hypotension could result.[2,7] An attempt to avoid this should be made through proper fluid loading and restoration of circulating blood volume before anesthesia.

Evaluation of the neuromuscular system is important because thyroid hormones play a vital role in axon growth and transport.[3] Peripheral neuropathies and myopathies causing generalized weakness, ataxia, and knuckling progressing to paresis and paralysis may develop in hypothyroid patients.[3,4,6] Cranial nerves may also be affected, leading to decreased facial sensation, facial nerve paralysis, and vestibular disease. Despite being mentioned in concert with hypothyroidism, a causal relationship with laryngeal paralysis and megaesophagus has not been established.[1,3] Although not common, seizures, disorientation, and circling can occur in hypothyroid dogs as a result of cerebral hypoxia originating from atherosclerosis of cerebral vessels.[3,8,16,17] In these cases further neurologic impairment could occur after anesthesia.[7]

Thyroid neoplasia is an uncommon cause of hypothyroidism in dogs; however, an examination of the cervical region should be performed. Thyroid carcinomas or squamous cell carcinomas can be large enough to cause upper airway obstruction. Affected dogs may drool, cough, have a history of voice change, or have respiratory distress.[1,12] Preparation for a difficult airway including tracheostomy setup should be performed.

### Preanesthetic period

Hypothyroid patients may have altered anesthetic drug responses. Although a true sensitivity may not exist, the combination of lowered cardiac output, decreased circulating blood volume, hepatic metabolism, and renal excretion of drugs results in more profound changes in depth and hemodynamic parameters than expected in the euthyroid patient.[2,7] Because inhalant anesthesia decreases metabolic rate, it is difficult to ascertain how hypothyroidism specifically influences minimum alveolar concentration (MAC) reduction. However, this is thought to be negligible.[18] Certainly, decreased thermoregulatory ability and cardiac output alone can significantly lower inhalant requirements in these patients.[15,18]

The untreated hypothyroid patient may respond to anesthesia with greater hemodynamic instability. It is advisable to choose anesthetic drugs that are relatively short acting and titratable to minimize negative cardiovascular effects. The phenothiazine tranquilizer, acepromazine, is long acting and causes vasodilation through antagonism of α1-adrenergic receptors.[19] In hypothyroid patients who are volume contracted and have decreased metabolic capabilities, it is best avoided. Ketamine has been promoted in human literature because of its ability to increase cardiac output and blood pressure in patients with an intact sympathetic nervous system.[2] Caution is advised in those hypothyroid patients who have arrhythmias or suspected myocardial dysfunction because increases in myocardial oxygen demand could result in greater hemodynamic instability.[1]

Decreased gastric emptying time and ileus have been documented in humans with hypothyroidism and are suspected to occur in veterinary patients as well.[1,2,7] A full stomach could result in regurgitation and aspiration of gastric contents, as well as impair ventilation. The administration of gastroprotectants and metoclopromide is recommended before anesthesia in humans and may be of use in veterinary patients as well.[2,7]

Hypothermia is a significant concern in the hypothyroid patient and results from impaired hypothalamic thermoregulation.[2] Hypothermia can be difficult to prevent and treat and, when severe, can lead to impaired coagulation, decreased inhalant MAC, impaired response to adrenergic drugs, bradycardia, and refractory hypotension.[2,7] Patient prewarming using a convective heat source for 20–30 min before anesthetic induction prevents hypothermia in healthy humans and dogs.[7,20] Although it has not been evaluated in veterinary patients with hypothyroidism, prewarming may be a viable option to prevent hypothermia.

Because they tend to have minimal effects on the cardiovascular and respiratory systems, a combination of an opioid and benzodiazepine is favorable for premedication in the hypothyroid patient. Induction using propofol allows titration to effect; however, rapid administration may lead to apnea and profound hypotension from vasodilation. Ketamine, as stated earlier, may benefit the otherwise healthy, hypothyroid

patient because it indirectly stimulates the sympathetic nervous system to help support cardiac output, heart rate, and blood pressure. Either isoflurane or sevoflurane can be used for maintaining anesthesia.

Before anesthetic induction, the patient should be preoxygenated for 5 min, as reduced functional residual capacity (FRC) from increased body weight and possible airway obstruction from swollen pharyngeal tissues could lead to rapid desaturation.[2,13] Induction and establishment of a patent airway should be rapid to avoid hypoxemia and hypoventilation, as well as aspiration of gastric contents.

### Intraoperative period

#### *Monitoring*

Standard monitoring including blood pressure, capnometry, pulse oximetry, electrocardiography (ECG), and temperature should be used. Direct or indirect methods of blood pressure monitoring can be used depending on the invasiveness of the procedure and American Society of Anesthesiologists (ASA) physical status of the patient. In patients in whom cardiovascular dysfunction is suspected, direct blood pressure monitoring is indicated.

If hypotension occurs, a systematic approach to treatment should be sought. Bolus administration of a crystalloid ($\sim$10 ml kg$^{-1}$) or colloid (i.e. hetastarch, 3–5 ml kg$^{-1}$), along with a reduction in inhalant anesthetic concentration, can help to minimize vasodilation and maintain adequate venous return to the heart. Bradyarrhythmias can be treated through anticholinergic administration, and decreased myocardial contractility may benefit from positive inotropic support.[2,13] Commonly used positive inotropes in veterinary medicine include dopamine (3–10 mcg kg$^{-1}$ min$^{-1}$) or dobutamine (1–10 mcg kg$^{-1}$ min$^{-1}$). In humans, hypothyroidism can lead to a concomitant decrease in adrenal cortical function and decreased circulating cortisol levels. If hypotension is refractory to treatment using the aforementioned methods, a physiologic dose of corticosteroids could be considered.[2]

Prevention and aggressive treatment of hypothermia with heat and moisture exchangers, warm intravenous fluid administration, circulating warm water blankets, and convective air warmers such as a Bair Hugger® should be performed. Assisted ventilation is often required because of decreased thoracic compliance and decreased sensitivity to hypercarbia and hypoxemia.[13]

#### *Locoregional anesthesia and analgesia*

Locoregional techniques are an important component of balanced anesthesia when indicated. In patients in whom a peripheral neuropathy is present, caution should be used because neurologic deficits may be exacerbated after regional anesthesia.[21] If additional clipping of hair is required for locoregional anesthesia, it is advisable to inform the owner that hair regrowth may be slow or not occur at all.[1]

### Anesthetic recovery

Monitoring should continue into the postanesthetic period. Recovery is often prolonged as a result of decreased hepatic metabolism and renal excretion of anesthetic drugs.[2,13] Esophageal suctioning before recovery may prevent aspiration of gastric contents if silent regurgitation occurred during anesthesia. Respiratory depression may lead to postoperative hypoventilation with subsequent hypoxemia. Administration of supplemental oxygen via mask, prongs, or nasal catheter should occur after extubation if hemoglobin oxygen saturation decreases to <94%.[13]

## Hyperthyroidism

### Feline hyperthyroidism

Just as thyroid hormone deficiency results in multisystem dysfunction, excessive thyroid hormone also creates a montage of effects throughout the body. Hyperthyroidism is the most common endocrinopathy in cats older than 8 years, with a mean age of 13 years.[1] The etiology is primary in origin and typically caused by multinodular adenomatous goiter or adenomatous hyperplasia similarly to humans. No secondary or tertiary causes have been identified in cats nor has a breed or gender predisposition been found.[1]

### Canine hyperthyroidism

Hyperthyroidism in dogs is uncommon. It is often the result of a functional thyroid carcinoma, which occurs only in $\sim$10% of dogs with thyroid neoplasia.[1] Affected dogs are typically older than 8 years, and more than half have distant metastases to the lung, regional lymph nodes, or liver at diagnosis.[1] Another cause of canine hyperthyroidism includes excessive levothyroxine administration to dogs being treated for hypothyroidism.[1] In dogs identified with hyperthyroidism, anesthetic precautions and preparation are similar to that of cats.

### Clinical signs and symptoms

As discussed previously, thyroid hormones influence all tissues throughout the body by increasing gene transcription.[1,22,23] Excess thyroid hormone results in an overall increase in basal metabolic rate, which increases energy needs and oxygen consumption.[1,22,24] The most common clinical signs in cats are weight loss and polyphagia.[1] Affected cats also exhibit hyperactivity and aggression and may be difficult to restrain for physical examination and blood sampling. Gastrointestinal signs of vomiting and diarrhea may be present. Diarrhea likely results from decreased ororectal transit time and malabsorption. The cause of vomiting has not been fully elucidated but may result from thyroid hormone activity on the chemoreceptor trigger zone and altered motility of the esophagus, stomach, and duodenum.[1] Because hyperthyroidism is one of many causes of "endocrine hypertension," signs associated with high blood pressure including blindness or seizures could be present.[22,24,25] Panting, tachypnea, and dyspnea may occur from hyperthermia, respiratory muscle weakness, increased metabolic oxygen requirements, and cardiac failure.[1,24]

Thyroid neoplasia in dogs can have signs attributable to a cervical space-occupying mass, including dysphagia, drooling, voice change, and varying amounts of respiratory distress.[1] Proper preparation for emergency airway management is imperative in these cases.

### Clinicopathologic findings

Analogous to hypothyroidism, there are no pathognomonic bloodwork changes associated with hyperthyroidism. The most common hematologic finding in cats is a mild increase in packed cell volume (PCV), reflective of the stimulatory effects thyroid hormones have on erythropoiesis.[1,24] Moderate increases in ALT and ALKP from a combination of increased bone turnover and decreased hepatic perfusion are seen in ~75% of hyperthyroid cats.[1] Azotemia, if encountered, should be interpreted in the context of a urinalysis to determine if it is renal or prerenal in origin. Azotemia in the presence of hyperthyroidism is of concern because the increase in GFR that accompanies hyperthyroidism should actually decrease nitrogenous waste products and creatinine levels.[1,5]

Hypernatremia, hypokalemia, and hypercalcemia can also occur.[1] Potassium should be monitored carefully, as hypokalemia can be severe and cause muscle weakness. Hypercalcemia can be paraneoplastic in dogs or reflective of increased bone turnover.[1] Elevated serum calcium when combined with a heart that is already sensitized to catecholamines can result in myocardial irritability and arrhythmia formation.[1,26]

Hypercoagulability due to increased Factor VIII occurs in humans and cats and could contribute to significant morbidity in the perianesthetic period.[1,26] Although anticoagulant therapy has been used in preparation for human surgery, its use is controversial and could result in impaired hemostasis during surgery.[1,24,26,27]

### Diagnosis

Diagnosis is usually straightforward in the face of appropriate clinical signs and an elevated T4 level. Additional diagnostics including cervical ultrasonography and scintigraphy can be used to confirm diagnosis should the T4 serum concentration not be supportive or where concurrent disease may falsely decrease thyroid hormone levels.[1]

### Treatment

There are multiple treatment options for hyperthyroidism in cats. Definitive treatments, such as thyroidectomy or radioiodine therapy, require the patient to be anesthetized or heavily sedated. Patients should be medically managed and euthyroid before anesthesia for elective procedures to avoid significant complications that can accompany uncontrolled hyperthyroidism.[2,28,29] This is performed through the administration of methimazole, or in Europe, carbimazole.[1,23,29,30] Both are thiourylenes, which inhibit the synthesis of thyroid hormones but do not influence thyroid hormones already in circulation. It is expected that cats treated via oral or transdermal routes are euthyroid, with a decrease in clinical signs after 2–4 weeks of therapy.[30] T4 levels may respond within 1 week, and so cases where there is a greater sense of urgency should be checked at that time.[1,23] Definitive treatment for functional thyroid carcinomas in dogs is thyroidectomy and requires similar medical management before anesthesia.[1]

### Anesthetic management

Anesthetic management of the hyperthyroid patient can present a myriad of complications. While mild hypothyroidism may not overtly affect anesthesia, even mild

hyperthyroidism can be of concern to the anesthetist. As with hypothyroidism, a thorough preanesthetic physical examination, considering the pathophysiology of hyperthyroidism, should be performed along with appropriate imaging and bloodwork.

Weight loss can be dramatic, and many patients present with cachexia. Although hyperthermia may be present in the awake state, the absence of body fat and the peripheral vasodilation from T3-induced relaxation of vascular smooth muscle can lead to rapid loss of core body heat in the anesthetized patient.[1,7,27] Similarly, there is equal risk of hyperthermia, as patients may respond rapidly to warming measures or could potentially develop a thyrotoxic crisis caused by excessive release of thyroid hormones.[2,24,28,31]

The cardiovascular system is greatly affected by excess thyroid hormone, necessitating a full cardiac workup before anesthesia. T3 acts directly on myocardial sodium, potassium, and calcium channels, as well as on α-myosin chains to increase contractility.[27] It also directly relaxes vascular smooth muscle, causing peripheral vasodilation. The resulting decrease in SVR causes activation of the RAAS, leading to increased plasma volume and a 50–400% increase in cardiac output.[1,27,28] In addition, the number and affinity of β-adrenergic receptors increase, leading to increased myocardial sensitivity to catecholamines. These cardiovascular changes increase the work and oxygen demand of the heart, causing progressive left ventricular hypertrophy and subsequent cardiac failure.[1,27] Thus, patients often present with tachyarrhythmias and bounding peripheral pulses. Auscultation may reveal a systolic murmur, gallop rhythm, and adventitial pulmonary sounds consistent with cardiac failure.[1,24]

Systolic hypertension is present in 17–87% of hyperthyroid cats and can also be found in dogs, necessitating blood pressure measurements in the preanesthetic evaluation.[1,22,32] Its presence can be associated with retinopathies or encephalopathies, resulting in blindness, seizures, ataxia, and altered mental status. Hypertension may require treatment before anesthesia with antihypertensive drugs, such as amlodipine. Beta-adrenergic antagonists can be effective for decreasing heart rate but are only effective in decreasing blood pressure in ~30% of affected cats.[22]

Cardiomegaly may or may not be seen on thoracic radiographs. Pleural effusion or pulmonary edema may be present if heart failure has occurred or in the rare situation of pulmonary hypertension. In dogs, radiographs may reveal metastasis that could impair oxygenation and ventilation under anesthesia.[1]

Even if cardiomegaly is not present, echocardiography should be performed if a murmur is ausculted. Thyrotoxic cardiomyopathy is present in a large number of affected cats; its severity should be quantified, and it should be treated before anesthesia. Common ECG findings include increased R-wave amplitude, sinus tachycardia, atrial fibrillation, supraventricular tachycardia, and atrial or ventricular premature contractions, all reflective of increased catecholamine sensitivity and/or myocardial hypoxia.[1,24]

### Preanesthetic period

Before surgery, a minimum database of PCV, total solids, electrolytes, and acid–base status should be performed with any aberrations identified and treated. Owners should be instructed to continue antithyroid medications the day of anesthesia because all have relatively short half-lives similar to that of humans.[7,28]

The increased metabolic rate, cardiac output, and hyperthermia caused by untreated hyperthyroidism leads to altered pharmacokinetics and pharmacodynamics of numerous anesthetic drugs. For example, in humans, hyperthyroid patients require increased fentanyl and propofol doses, and propofol clearance and volume of distribution are significantly increased.[33] Pharmacokinetics of the benzodiazepine, oxazepam, in rodents with hyperthyroidism also show increased dosing requirements to achieve effects similar to those in euthyroid rats.[34] Because of the variable drug responses and dramatic hemodynamic changes, it is best to use short-acting and reversible agents, such as opioids and benzodiazepines at standard doses, administering additional drug only if adequate sedation is not achieved.

Drugs that promote activation of the sympathetic nervous system should be avoided, including the induction agent ketamine.[2,7,13] Indirect catecholamine release could further increase oxygen demands of the heart, leading to myocardial hypoxia and malignant arrhythmias. Likewise, anticholinergics should be avoided.[2,7,13] Acepromazine has been advocated in the past because it desensitizes the myocardium to catecholamines.[13] However, with the advent of short-acting, antihypertensive agents and concerns over rapid drops in preload associated with acepromazine, it should be

used cautiously. Thiopental was also long advocated for use in hyperthyroidism due to its ability to block peripheral conversion of T4 to T3.[7,13] However, it is currently unavailable, making propofol an acceptable alternative.[4]

Preoxygenation should be performed before anesthetic induction because of increased oxygen demand of the tissues and the increased likelihood of developing hypoxemia.[13] This allows increased time for an airway to be established before hemoglobin desaturation.

### Intraoperative period

Anesthesia can be maintained safely in the hyperthyroid patient with inhalant or injectable anesthetics (TIVA).[24,33] Although the MAC of inhalants does not increase, the required doses of injectable drugs needed to maintain an adequate anesthetic plane may be higher than expected.[13,33] Minimization of stress during anesthesia avoids excessive catecholamine release and associated cardiovascular responses.[7] A constant rate infusion of fentanyl (5–42 mcg $kg^{-1}$ $h^{-1}$) or locoregional block, if necessary, may assist in reducing the stress response and provides analgesia during anesthesia.

#### *Monitoring*

In hyperthyroid patients who require anesthesia, extensive hemodynamic monitoring should be used, including invasive blood pressure monitoring, ECG, capnometry, and pulse oximetry. Temperature monitoring is vital to detect the onset of hypothermia or hyperthermia. Because $CO_2$ production is increased from the elevated basal metabolic rate, a rebreathing circuit is advised to ensure adequate $CO_2$ removal.[7,13] Intermittent positive pressure ventilation (IPPV) may also benefit the patient, as muscle weakness can predispose them to hypoventilation, hypercapnia, and subsequent indirect stimulation of the sympathetic nervous system.[7] In extreme cases of cardiac dysfunction, central venous pressure measurement may help direct fluid therapy.[13] Intraoperative monitoring of electrolytes and glucose in prolonged procedures is advised because of the increased energy requirements and losses that can occur under anesthesia.[2]

### Thyroid storm

Thyroid storm is a life-threatening manifestation of uncontrolled hyperthyroidism documented in humans.[24,26,31] It results from the sudden release of thyroid hormones into the circulation caused by a precipitating event such as stress, anesthesia, infection, trauma, or illness.[24,31] Since there is no correlation between circulating hormone levels and the development of thyroid storm, it is difficult to ascertain which patients are at risk.[24,31] Acute thyrotoxicosis, which presents similarly, can occur in veterinary species. Clinical signs include exacerbation of those associated with hyperthyroidism, including tachyarrhythmias, hypertension, hyperthermia, congestive heart failure, and cardiac arrest (Table 8.2).[24] Treatment targets decreasing the synthesis and secretion of thyroid hormones, blocking the actions of thyroid hormones at their effector sites, providing supportive care, and eliminating the precipitating cause.[24,26,31]

As indicated earlier, methimazole is the drug of choice to decrease synthesis of thyroid hormones. However, in situations of thyroid storm, methimazole is administered in combination with an iodine compound, such as potassium iodate, to prevent preformed thyroid hormone secretion.[24] Although the immediate preanesthetic administration of methimazole to untreated hyperthyroid cats has not been investigated in terms of its effects on a thyrotoxic crisis or "thyroid storm," it appears reasonable that pretreatment may minimize

**Table 8.2** Clinical manifestations of thyroid storm.[24,25,31]

| |
|---|
| Cardiac arrhythmias[a] |
| Tachycardia |
| Gallop rhythm |
| Atrial fibrillation |
| Ventricular premature contractions |
| Hypertension[a] |
| Retinopathies |
| Sudden blindness |
| Encephalopathies |
| Tachypnea |
| Hyperthermia[a] |
| Increased $CO_2$ production[a] |
| Panting |
| Bucking ventilator[a] |
| Dyspnea |
| Pulmonary edema |
| Muscle weakness |
| Congestive heart failure |
| Cardiac arrest[a] |

[a]Manifestations observed under anesthesia.

Source: Adapted with permission from Reference 24.

severity when combined with other systemic treatments and is the current recommendation in thyrotoxic humans faced with emergent anesthesia.[2]

Tachyarrhythmias and hypertension are in part caused by increased sensitivity to catecholamines and can be combated by administration of a β-adrenergic antagonist. Under anesthesia, the most rapid-acting, titratable agent available is the selective β1-antagonist, esmolol (0.05–0.15 mg $kg^{-1}$ slow IV bolus followed by a constant rate infusion of 10–200 mcg $kg^{-1}$ $min^{-1}$).[19,24] Severe hypertension can also be treated with sodium nitroprusside or magnesium sulfate similarly to patients with pheochromocytoma.[7,19,35] Caution should be used with antihypertensive drugs, as patients with thyroid storm are already maximally vasodilated and volume depleted. Indiscriminate use could lead to rapid cardiovascular collapse.[24]

Supporting therapy should include replacement of circulating volume with crystalloids and colloids, as well as treatment of hyperthermia with active cooling methods such as ice packs.[24,26] Mechanical ventilation should be instituted to help eliminate excessive $CO_2$ produced in the pyrexic state. Cardiac failure and pulmonary edema may necessitate administration of diuretics to improve oxygenation and ventilation.[24]

#### Postanesthetic management

Monitoring should continue during recovery because thyroid storm can occur up to 48 h after anesthesia.[26] Supplemental oxygen should be available to fulfill elevated metabolic oxygen requirements and prevent hypoxemia. Frequent blood pressure monitoring and telemetry can help identify the development of thyroid storm in the immediate postoperative period. Patients undergoing surgery should receive appropriate multimodal analgesia to minimize pain and stress, as well as continued antithyroid drug administration.

## Adrenal disease

### Anatomy and physiology of the adrenal gland

Adrenal glands represent another integral component of the endocrine system, playing a vital role in fluid balance, the stress response, and sympathetic nervous system activation.[1,7] They are paired, ovoid structures lying near the cranial pole of the kidneys and are composed of a cortex and medulla. The cortex has three layers: the zona glomerulosa secretes aldosterone to stimulate sodium and water retention and the zona fasiculata and zona reticularis function together to produce cortisol and androgens. The medulla is functionally separate, producing catecholamines.[1]

### Hyperadrenocorticism (HAC; Cushing's disease)

Cortisol is normally secreted from the adrenal cortex under the regulation of the hypothalamic-anterior pituitary-adrenal axis.[1,7] The hypothalamus secretes corticotrophin-releasing hormone (CRH) to act on the anterior pituitary. It subsequently releases adrenocorticotropic hormone (ACTH) to stimulate secretion of cortisol from the adrenal cortex.[1]

#### Canine hyperadrenocorticism

Aside from hypothyroidism, hyperadrenocorticism (HAC) is the most common endocrinopathy seen in middle age to older dogs.[1,25] HAC is caused by excessive circulating glucocorticoids, namely cortisol, and can be caused by a primary functional adrenocortical tumor (AT) or be secondary to an ACTH-secreting pituitary adenoma (pituitary-dependent hyperadrenocorticism; PDH). Iatrogenic HAC from overzealous administration of glucocorticoids is also reported.[1]

Pituitary-dependent hyperadrenocorticism is cited as the cause of HAC in ~80–85% of dogs.[1,25,36] Mean age of affected dogs is ~11 years, with very little difference between PDH and AT. Common breeds include poodles, terriers, beagles, and dachshunds, with female dogs being over-represented.[1,37]

#### Feline hyperadrenocorticism

Hyperadrenocorticism is rare in cats, and etiology is most commonly pituitary in origin.[1,37] Middle-aged to older cats are primarily affected, with a median age of 10 years. No sex or breed predilection has been identified.[1,37]

#### Clinical signs

Cortisol, similarly to other endocrine hormones, has a wide scope of target organs and effects, including stimulation of hepatic gluconeogenesis, lipolysis, and protein catabolism. It can also impact erythropoesis, vascular tone, kidney function, and acts as a "safety net" in times of stress to maintain homeostasis.[6,15]

Compared to other endocrinopathies, the clinical presentation of HAC can be strikingly different between dogs and cats because cats are considerably less responsive to the effects of glucocorticoids.[37] Dogs commonly present with polyuria/polydipsia from cortisol inhibition of antidiuretic hormone (ADH) release and polyphagia, a presenting complaint not witnessed in other species.[1] Panting, pendulous abdomen, muscle weakness, and endocrine alopecia are other common clinical signs seen in canine Cushing's disease.[1,36] Clinical signs of HAC in cats tend to be more elusive and may not occur until other concurrent disease, such as diabetes mellitus, manifests.[37] Cats demonstrate muscle weakness, poor haircoat, tachypnea, and thin, fragile skin.[1,37] Rarely, both species may present with encephalopathies or retinopathies from atherosclerosis, pituitary tumor impingement, or secondary hypertension.[1,37–39]

### Clinicopathologic changes

Cortisol causes neutrophilia, monocytosis, lymphopenia, and eosinopenia.[1] This "stress leukogram" is seen commonly in dogs, whereas cats may show few hematologic changes.[37] Polycythemia can be caused by cortisol-induced erythropoiesis, increased circulating half-lives of red blood cells, or may signal the presence of a chronic hypoxic state from alveolar hypoventilation.[1]

Changes in the biochemical profile can differ between dogs and cats; however, increased ALT from hepatocyte damage and impaired hepatic perfusion, as well as hypercholesterolemia from increased lipolysis are seen in both species.[1] Both may also demonstrate mild to moderate hyperglycemia from increased gluconeogenesis and impaired insulin sensitivity.[1,37] Dogs alone see dramatic elevations in ALKP from induction of a steroid-responsive ALKP isozyme not present in other species.[1,37] Cortisol prevents ADH from binding to receptors on the renal tubules, causing diuresis and a subsequent decrease in blood urea nitrogen (BUN) in dogs.[15] This is not observed in cats due to decreased renal glucocorticoid receptors.[37]

Urinalysis is valuable in interpreting the effects of HAC. Dogs will typically have dilute urine with a SG < 1.020, whereas cats frequently maintain concentrating ability. If the urine is dilute in an affected cat, underlying renal disease should be suspected. Urinalysis may also reveal proteinuria from concurrent hypertension or infection or glycosuria from diabetes mellitus.[1,37]

Blood gas analysis may occasionally identify alveolar hypoventilation and hypoxemia from respiratory muscle weakness and organomegaly.[1,7] Hypoxemia may also be present in patients who develop pulmonary thromboembolism (PTE).[40] Excess cortisol is associated with a state of hypercoagulability and development of thromboembolic disease, as it increases production of coagulation factors II, V, VII, IX, X, and XII and decreases production of antithrombin III.[1,37]

### Diagnosis

Diagnosis of HAC is not necessarily straightforward and should only be made in light of clinical signs.[1] A multitude of tests are available; however, sensitivity is species specific, and cats and dogs differ with regards to reliable testing. In dogs, a low-dose dexmethasone suppression test is considered most diagnostic but is much less sensitive in cats.[37] A full explanation of tests and testing methods is outside the scope of this text, and the reader is directed to additional sources.[1]

### Treatment

Medical treatment of PDH usually includes administration of either mitotane (o,p'-dichlorodiphenyldichloroethane, (Lysodren®, Bristol–Myers Squibb, Princeton, NJ) or trilostane (Vetoryl®, Dechra, Overland Park, KS). Mitotane is an adrenocorticolytic drug used in dogs, which requires a loading period.[1] During this time, there is rapid destruction of adrenal cortical tissue, making patients susceptible to developing adverse effects such as vomiting, diarrhea, lethargy, and Addisonian crisis. Until this phase is over and the patient is regulated, anesthesia for elective procedures is discouraged.

Surgical options for patients with PDH include transsphenoidal hypophysectomy or bilateral adrenalectomy.[1,37,41] For patients undergoing hypophysectomy, the reader should also refer to the chapter addressing anesthesia and coexisting neurologic disease (Chapter 3). For functional AT, unilateral adrenalectomy is often curative.[42]

### Anesthetic management

Before anesthesia, a thorough physical examination, along with appropriate imaging and blood work, can pinpoint areas of concern and assist the anesthetist in preparing for anesthesia. The main actions of cortisol, as stated earlier, include gluconeogenesis, protein catabolism, and lipolysis.[1,2,7] The by-products of these

processes, when in excess, have detrimental effects on the body, with the cardiovascular system being particularly susceptible.

Hypertension from HAC occurs in ~50–86% of dogs, >80% of humans, and has been reported in cats.[1,25,38,43] A number of factors contribute to hypertension, including lipolysis-induced elevations of interleukin-6 (IL-6) and adiponectin and the development of hyperinsulinism and insulin resistance from increased gluconeogenesis.[44] Hyperinsulinism causes thickening of the vascular endothelium and increased vessel stiffness.[44] Cortisol causes vasoconstriction and increased SVR by decreasing endothelial nitric oxide, increasing levels of endothelin-1, and potentiating the vasoconstrictive effects of norepinephrine and angiotensin II.[25,43] In addition, hypercholesterolemia and hypertriglyceridemia cause the deposition of atherosclerotic plaques within the vessel walls.[8] These combined abnormalities cause hypertension and decreased perfusion of vital organs.[1,43,44]

Organomegaly, muscle weakness, and truncal obesity decrease FRC, causing compression atelectasis and preventing adequate $CO_2$ removal.[7] Hypoventilation can subsequently cause respiratory acidemia, venous admixture, and chronic hypoxemia, all of which are exacerbated under anesthesia. Pulmonary interstitial or bronchial calcium deposition may also contribute to impaired oxygenation.[1]

Increased hematocrit, slowing of blood flow, and hypercoagulability pose the threat of PTE formation, which can dramatically affect both the cardiovascular and pulmonary systems. The resultant ventilation–perfusion mismatch may trigger hypoxic pulmonary vasoconstriction, leading to increased pulmonary vascular resistance and development of right heart failure.[1,40]

Renal cortisol effects vary depending on species and the presence or absence of preexisting kidney disease. Dogs are the only species with HAC that develop polyuria and polydipsia via inhibition of ADH, leading to a subsequent elevation in GFR.[1,37,38,41] Over time, in combination with hypertension, this could result in glomerulosclerosis and renal failure.[1,37,38,41] Dogs with HAC also develop increased renal vascular resistance and decreased renal blood flow, which altogether could result in increased renal morbidity of patients.[38]

The anesthetist should also pay close attention to the patient's integument. Cats are particularly vulnerable to tearing of the skin due to decreased keratin and loss of subcutaneous tissue.[37] Restraint for catheters and blood draws should be minimal to avoid skin damage. Sedative administration before handling should be considered if fragile skin syndrome is suspected.[1,37]

### Preanesthetic period

Before anesthesia, endocrine testing, a CBC, biochemical profile, blood gas, and urinalysis should be performed. Hydration status should be determined and fluid deficits corrected before induction. Because cortisol causes vasoconstriction, patients may have a contracted blood volume, resulting in decreased venous return and profound hypotension during anesthesia. Fluids can also be used to decrease hematocrit and sludging of blood, thus reducing the risk of thromboembolism and improving perfusion of capillary beds. Before restraint for blood draws or catheter placement, blood pressures should be taken in accordance to Brown et al. (2007) and hypertension documented. The presence of hypertension may indicate a rightward shift in autoregulation of renal perfusion pressure (Figure 8.1). This necessitates maintenance of a higher mean arterial pressure during anesthesia to avoid decreased renal perfusion.[45]

Thoracic radiographs are essential in patients who present with tachypnea or coughing and may reveal neoplasia, pulmonary or bronchial mineralization, congestive heart failure, or hyperlucency associated with PTE formation.[1] Likewise, they may show no evidence of disease. This does not rule out PTE and should be interpreted in conjunction with an arterial blood gas.[40]

Because patients with HAC are at risk for hypoventilation, short-acting, reversible drugs should be used and excessive sedation avoided. Opioids and benzodiazepines are often well tolerated. Low doses of the α2-adrenergic agonist, dexmedetomidine (1 mcg $kg^{-1}$ IV or 3 mcg $kg^{-1}$ IM), can be considered in patients with HAC without evidence of concurrent cardiovascular instability. After premedication, patients should be monitored and preoxygenated because many anesthetic drugs increase muscle relaxation and exacerbate respiratory depression. In addition, increased abdominal weight lowers FRC, decreasing the time it takes for hemoglobin desaturation.[7]

### Intraoperative period

Anesthetic induction should be rapid to achieve an airway quickly and allow the anesthetist to assist

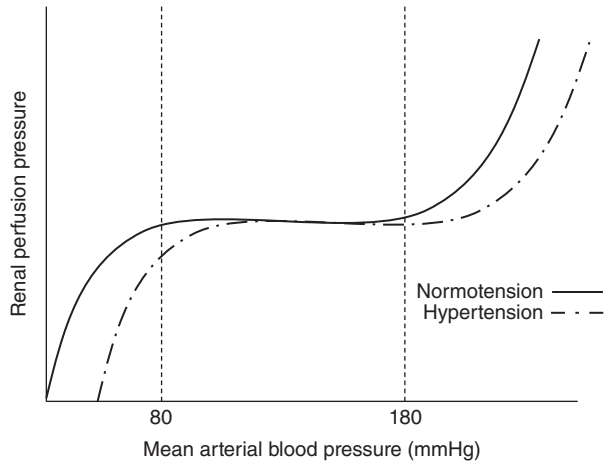


**Figure 8.1** Autoregulation of renal circulation, similarly to that of the cerebral circulation, helps to maintain steady perfusion pressure across a wide range of arterial blood pressures. In patients who are chronically hypertensive, this curve can shift to the right.[7,45] Source: Adapted with permission from Reference 7.

ventilation. The induction agent etomidate inhibits 11β-hydroxylase, the enzyme necessary to produce cortisol, causing adrenocortical suppression for up to 24–36 h.[46] Although etomidate infusion is used before anesthesia to decrease cortisol levels in humans, its benefit as a one-time induction agent in veterinary patients is unknown.[9] Because cortisol can potentiate the actions of norepinephrine, anesthetic induction using ketamine could exacerbate hypertension and tachycardia and is therefore not advised in patients with impaired cardiac function or increased oxygen demand.[25]

Intermittent positive pressure ventilation is likely indicated because inhalant anesthetics are potent respiratory depressants and decrease sensitivity and response to elevated $CO_2$ levels similarly to opioids.[13] Some patients with HAC rely on hypoxic drive for ventilation due to chronic elevations in $CO_2$.[7] Thus, when administered 100% oxygen, the drive to ventilate in these patients may disappear, making IPPV necessary.

Balanced anesthetic technique should be employed to minimize negative side effects and excessive sedation from any one drug. Multimodal analgesia using a combination of opioids and locoregional techniques may minimize the total amount of systemic drugs needed in the postoperative period and also prevent prolonged postanesthetic recumbency, a major risk factor in the development of PTE.[1]

Treatment of hypertension is often not required in the perianesthetic period. Rapid, intermittent fluctuations in blood pressure, such as those seen in hyperthyroidism or pheochromocytoma, are typically not observed; however, large pulse pressure differences can be present. Although it is debatable whether treatment with antihypertensives, such as α1-adrenergic antagonists, several days before undergoing anesthesia may be beneficial to improve circulating blood volume in those patients who have contracted volume from persistent hypertension it is this author's experience that this practice improves hemodynamic stability under anesthesia.

### *Monitoring*

Capnometry, pulse oximetry, ECG, temperature, and invasive or noninvasive blood pressure should be part of a standard monitoring protocol. When a neuromuscular blocking agent is used, train-of-four monitoring is necessary because muscle weakness can be profound. The anesthetist should pay close attention to temperature, as many of these patients are obese and at risk of hyperthermia. Arterial catheter placement for intermittent blood gas analysis allows oxygenation and ventilation to be monitored and addressed both during anesthesia, and in the recovery period, especially in patients in whom PTE formation is suspected.

Severe PTE may be identified by a rapid decrease in $ETCO_2$, hemoglobin desaturation, and cardiovascular collapse and should be confirmed with blood gas analysis.[7,40] PTE management is aimed at providing

an oxygen-rich environment and administering anticoagulant therapy.[1,7]

### Recovery

Hypoventilation is the main concern in the immediate postanesthetic period. Patients who are unable to maintain a pulse oximetry reading of >93% on room air should be administered supplemental oxygen via mask, prongs, or nasal catheter.[13] Excessive sedation should be avoided if at all possible to prevent prolonged recumbency.[1] Continued monitoring in the postanesthetic period, particularly in patients in whom PTE is suspected, is strongly advised.

## Pheochromocytoma

### Pathophysiology

Pheochromocytomas are uncommon neoplasms that arise from the chromaffin cells of the adrenal medulla.[1] Chromaffin cells are responsible for synthesis and secretion of epinephrine and norepinephrine, which in turn, act on adrenergic receptors. The adrenal medulla behaves as a sympathetic postganglionic nerve fiber and releases catecholamines under neural control to preserve homeostasis of the autonomic nervous system and during times of "fight or flight." Pheochromocytomas release catecholamines independent of neural control causing uncontrolled stimulation of adrenergic receptors, resulting in hypertension and tachyarrhythmias.[1,2]

Pheochromocytomas account for a very small percentage of all neoplasms in dogs, and only five cases have been reported in cats.[1,47,48] Other species in which pheochromocytomas have been documented include humans, horses, cattle, elephants, rhinoceros, rats, and river otters.[28,49–51] Patients are middle-age to older animals, with no sex or breed predilection.[49] Mean age of affected dogs is ~10.6 years, and affected cats have ranged in age from 7 to 22 years.[1,48]

Pheochromocytomas mainly arise from the adrenal gland(s), although an extra-adrenal origin has been reported in a dog.[1] In humans and dogs, pheochromocytomas are more commonly found on the right adrenal gland.[52] However, over a 4-year period, pheochromocytomas were primarily left sided at the author's practice (75%, n = 15; unpublished observations), suggestive of selection bias where right-sided adrenal masses may have a higher likelihood of referral to a tertiary facility and, hence, publication, due to their invasiveness and difficult removal.[52] Bilateral disease also occurs in ~10% of patients.[1]

These tumors often occur concurrently with other diseases, including other endocrinopathies such as hyperadrenocortism and diabetes mellitus.[42,52] In 1997, Barthez et al. reported that 13 of 61 (21%) dogs with adrenal tumors had both a functional AT and pheochromocytoma.[49] Likewise, one of the five documented cases in cats also had a cortisol-secreting tumor, suggesting that a diagnosis of hyperadrenocorticism is not one of exclusion for pheochromocytoma.

Approximately 25–50% of pheochromocytomas are malignant and locally invasive into nearby vasculature.[42,49] Distant metastases occur in 13–28% of cases, with the spleen, liver, lung, lymph nodes, and bone being most commonly affected.[49] When metastasis is not present, surgery is often curative, resulting in long-term survival.[42,49]

Catecholamine production by the chromaffin cells is normally 60–80% epinephrine, with the remainder being norepinephrine.[1] In humans, however, catecholamine secretion is altered in pheochromocytomas with neoplastic chromaffin cells secreting predominantly norepinephrine the majority of the time and a much smaller percentage secreting epinephrine, or in rare instances, dopamine.[1,53,54] The secretion pattern of pheochromocytomas in dogs and cats has not been fully elucidated; however, the presence of higher concentrations of normetanephrine, the metabolite of norepinephrine, vs metanephrine, the metabolite of epinephrine, may indicate that norepinephrine is the primary catecholamine in veterinary patients as well.[47,54]

### Clinical signs

Pheochromocytomas can present with any number of clinical signs, none of which is pathognomonic for the disease. Clinical signs only occur in 30–50% of patients and are related to either sympathetic nervous system activation or extensive thrombosis of associated vasculature (Table 8.3).[1,49]

Physical examination findings related to catecholamine surge may include hypertension, tachyarrhythmias, pale mucous membranes, poor femoral pulses, weakness, seizures, blindness, collapse, and sudden death (Table 8.4).[1,52,54] If the surrounding vasculature is invaded by tumor, partial occlusion of the

**Table 8.3** Clinical signs of pheochromocytoma in dogs and cats.[1,7,25,43,49,51,54,55]

| | |
|---|---|
| None | Seizures |
| Anxiety | Acute blindness |
| Pacing | Epistaxis |
| Panting | Hind limb edema |
| Dyspnea | Distended abdomen |
| Weakness | Collapse |
| Anorexia | Sudden death |
| Diarrhea | |
| Vomiting | |
| Polyuria/Polydipsia | |

Source: Adapted with permission from Feldman EC, Nelson RW. 2004. Pheochromocytoma and multiple endocrine neoplasia. In: Feldman EC, Nelson RW, editors. *Canine and Feline Endocrinology and Reproduction*. 3rd ed. pp. 444–5. St. Louis: Saunders.

**Table 8.4** Physical examination findings in dogs and cats with pheochromocytoma.[1,25,43,49,51,54,55]

| | |
|---|---|
| Unremarkable | Retinal hemorrhage |
| Hypertension | CNS signs |
| Tachycardia | Hindlimb edema |
| Arrhythmias | Abdominal pain |
| Weak femoral pulses | Ascites/fluid wave |
| Pale or hyperemic mucous membranes | |

Source: Adapted with permission from Feldman EC, Nelson RW. 2004. Pheochromocytoma and multiple endocrine neoplasia. In: Feldman EC, Nelson RW, editors. *Canine and Feline Endocrinology and Reproduction*. 3rd ed. pp. 444–5. St. Louis: Saunders.

affected vessels may cause hindlimb edema, ascites, and abdominal pain.[1] Pheochromocytomas often present with concurrent diseases including other neoplasia; the clinical signs present may be reflective of these other disease processes.

## Clinicopathologic findings

Bloodwork changes, analogous to clinical signs, tend to be mild and nondescript and may reflect those of concurrent diseases. Hematologic abnormalities include mild anemia, leukocytosis, and lymphopenia.[1] Biochemical abnormalities may include azotemia, hyperglycemia, and elevated levels of the hepatic enzymes ALT and ALKP.[1,49]

## Diagnosis

Diagnosis is difficult, as clinical signs can be vague and nonspecific. Abdominal ultrasonography, computed tomography, and magnetic resonance imaging are able to visualize larger tumors but are unable to differentiate pheochromocytomas from tumors of adrenocortical origin (Figure 8.2).[1] Diagnostic testing, therefore, has focused on quantifying catecholamine levels or their metabolites within the urine or plasma. The caveat remains that dogs and cats in hospital settings are stressed, and likely to already have elevated levels of catecholamines and metanephrines even with nonadrenal disease, resulting in false positive readings.[47] To improve test specificity, studies have focused on validating testing protocols and establishing normal ranges.[47,56] Measurement of plasma-free normetanephrine and/or plasma normetanephrine to creatinine ratios via high performance liquid chromatography is most appropriate and can be considered diagnostic if the values exceed four times the high end of the documented range for dogs.[47,54,56,57]

Other diagnostic methods include radiolabeled meta-iodobenzylguanidine (MIBG) with I-131 or I-123 or positive emissions tomography (PET) using p-[18F]flourobenzylguanidine, both of which are taken up into the neoplastic chromaffin cells and visualized.[58,59] However, these methods are expensive,

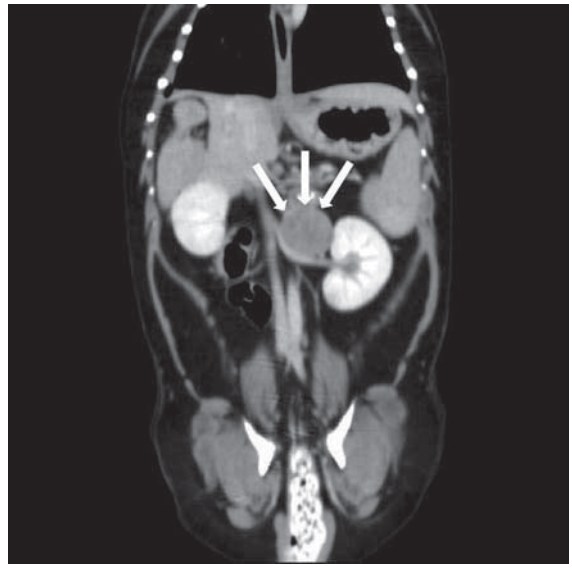

**Figure 8.2** Computed tomography image of a dog with a left-sided pheochromocytoma (arrows). Note its close association with the renal vasculature and caudal vena cava. Source: Image courtesy of Dr. C. Gendreau, The Imaging Center for Animals, Buffalo Grove, IL.

require special equipment, and are currently limited in their availability for routine veterinary use.

### Treatment

Adrenalectomy via laparoscopy or laparatomy is the treatment of choice because patients who survive the perioperative period generally have good long-term survival.[49] Tumors that are deemed nonresectable or where metastasis is already present are managed medically using α- and β-adrenergic antagonists (see the following sections).[1] Chemotherapy has been used with relatively poor results. However, the use of molecular targeted therapies such as tyrosine kinase receptor antagonists has shown promise.[60]

### Anesthetic management

There are four major anesthetic goals for pheochromocytoma resection, including adequate patient preparation, minimization of stress in the perioperative period, controlling hemodynamic instability intraoperatively until the blood supply to the tumor has been ligated, and managing the postexcisional effects of antihypertensive therapies.

#### Patient preparation

Preoperative management of patients with pheochromocytomas begins well before the scheduled surgery. Paroxysmal activation of α1-adrenergic receptors by norepinephrine results in vasoconstriction, hypertension, and reduced vascular volume.[1,52] Because catecholamines are sporadically released by the tumor, blood pressure measurements identify hypertension in <50% of canine patients.[49,55] Normal blood pressure in the presence of an adrenal tumor, therefore, does not exclude pheochromocytoma as a diagnosis nor bypass the need for preanesthetic treatment with α-adrenergic receptor antagonists. The administration of α-receptor antagonists for 1–4 weeks before anesthesia allows gradual vasodilation and re-establishment of vascular volume.[53] The use of phenoxybenzamine, a noncompetitive, nonselective α-adrenergic antagonist, began in the early 1950s and led to a significant decrease in human mortality from 40% to 60% to <6%.[52,53] Similarly, dogs pretreated with phenoxybenzamine had significantly less mortality than those that had not (13% vs 48%).[52]

Before beginning α-receptor antagonist therapy, patients should undergo an ECG for the detection of arrhythmias, an ophthalmic examination, and serial blood pressure measurements as described by the American College of Veterinary Internal Medicine consensus statement on hypertension.[43] Bloodwork, including a CBC, biochemical profile, and electrolytes, should be performed, as well as a urinalysis to look for underlying disease. Thoracic radiography to identify metastasis or other pulmonary and cardiac changes should be performed.

Patients should be started on 0.5 mg $kg^{-1}$ of phenoxybenzamine twice daily, with repeated blood pressure measurements and ECG every 3–5 days.[55] Systolic and diastolic blood pressures should be consistently <160 and 100 mm Hg, respectively, during treatment.[43] The phenoxybenzamine dose may be doubled at each blood pressure check to a maximum dose of 2 mg $kg^{-1}$ PO BID until surgery or until the patient demonstrates signs of hypotension, such as weakness, ataxia, or syncope (unpublished observations). Most patients on this regimen are adequately prepared for surgery within 10–14 days; however, some may require up to 4 weeks of therapy.

If α-adrenergic blockade has been established and the patient continues to have tachycardia or other dysrhythmias, administration of a β-adrenergic antagonist, such as atenolol may also be indicated.[53,61] The need for β-blockade in humans is decreased in patients given a selective α1-antagonist, such as doxazosin, rather than nonselective phenoxybenzamine. Since presynaptic α2-receptors are responsible for negative feedback inhibition of norepinephrine release from the nerve terminal, their blockade by phenoxybenzamine may allow continued release, thus leaving the patient susceptible to dysrhythmias.[53,62]

Before surgery, crystalloid solutions should be administered to address fluid deficits and increase perfusion. Blood pressures and ECG should be repeated, and a minimum database of PCV, total solids, electrolytes, and acid–base status should be performed.

All handling and restraint should be performed with minimal stress to the patient, as stress may trigger a catecholamine surge and lead to a pheochromocytoma crisis (Table 8.5); the most common perianesthetic triggers are anesthetic induction in itself and tumor manipulation.[1,63]

**Table 8.5** Triggers for pheochromocytoma crises.[53]

| |
|---|
| Stress |
| Anesthesia induction |
| Increased intra-abdominal pressure |
| Bladder expression |
| Abdominal insufflation |
| Histamine release |
| Morphine |
| Meperidine |
| Atracurium |
| Elevated $CO_2$ partial pressure |
| Tumor manipulation |
| Drugs causing SNS stimulation |
| Ketamine |
| Halothane |
| Ephedrine |
| Nitrous oxide |
| Metoclopramide |
| Glucagon |
| Succinylcholine |

## Preanesthetic management

Patients should be premedicated to allow easy handling and catheter placement for direct blood pressure measurement and venous access. Combinations including a pure μ-opioid agonist, such as hydromorphone or oxymorphone, and benzodiazepine are recommended, as they are short acting, titratable, and do not cause histamine release (vs morphine). Although acepromazine is an α1-receptor antagonist and could be useful in preventing hypertensive crises, caution should be used because it may exacerbate hypotension after tumor removal. Placement of an arterial catheter in the awake patient can be painful. The use of a lidocaine-prilocaine cream over the dorsal pedal artery for 30 min before placement may minimize discomfort.

After sedation, preoxygenation via face mask is advisable as long as the patient is not stressed by its administration. Since anesthetic induction can trigger a catecholamine surge, it is important to monitor invasive blood pressure and ECG through induction if possible.[53] In addition, antihypertensive and antiarrhythmic drugs should be readily available.

No ideal induction protocol has been identified for pheochromocytoma removal. Both propofol and etomidate have been used safely with various coinduction agents such as fentanyl.[42] Ketamine is avoided because it causes indirect stimulation of the sympathetic nervous system and could trigger a crisis.[53] Mask or chamber induction is not recommended due to its poor monitoring ability and undue stress to the patient. Sufficient induction agent levels should be used to ensure that intubation is smooth with minimal stimulation of the larynx.

Anesthesia can be maintained through the use of the inhalants, sevoflurane or isoflurane, or via TIVA. TIVA usually includes the administration of propofol as a constant rate infusion along with either fentanyl or remifentanil.[53,64] These agents decrease sympathetic nervous system outflow through various mechanisms, reducing catecholamine release during anesthesia.[65] Although vasodilation may be desired before tumor removal to avoid severe hypertension, it may lead to severe hypotension after excision is complete.[53,61,64,66] Inhalant anesthetic concentration can be minimized through the administration of additional agents such as opioids. When ventricular arrhythmias occur, a lidocaine constant rate infusion may be added to stabilize the myocardium.[53]

Combinations of general and locoregional anesthesia are representative of a balanced anesthetic approach. Epidural administration of opioids and local anesthetics can reduce sympathetic nervous system stimulation and subsequent catecholamine release associated with skin incision but do not affect catecholamine release associated with tumor manipulation.[53]

## Intraoperative period

### *Monitoring*

Invasive hemodynamic monitoring, particularly arterial blood pressure, is essential because rapid fluctuations can occur. The placement of a central line to measure central venous pressure can be used to assess vascular volume and direct fluid needs intraoperatively and postoperatively.[53] IPPV is often required to avoid hypoventilation, as hypercarbia can stimulate catecholamine release.[7,13] Detection and characterization of arrhythmias via ECG monitoring allow treatment with appropriate antiarrhythmics.

### *Arrhythmia/hypertension management*

Tumor manipulation frequently causes a catecholamine surge with paroxysmal hypertension and tachycardia even in patients in whom α-adrenergic blockade has been established.[63] Breakthrough hypertension and tachycardia occur from incomplete blockade with

massive catecholamine release and via release of other vasoconstrictive mediators such as neuropeptide Y.[67]

Hypertensive crises require immediate intervention. Systolic blood pressure can quickly surmount 250 mm Hg, leading to cerebral encephalopathy, stroke, retinal detachment, multiple organ failure, and cardiac arrest.[43] Treatment should be instituted as systolic blood pressure reaches 180 mm Hg, as this degree of hypertension directly correlates with target organ damage.[25,43]

Previous methods of treating hypertension have included the administration of low doses of acepromazine and increasing inhalant concentration. However, the use of rapid-onset, short-acting antihypertensive drugs has become the preferred method for maintaining hemodynamic stability. Sodium nitroprusside is a potent arteriolar and venodilator that can be administered as a constant rate infusion to control hypertension. Although its duration of action is <5 min, it can rapidly cause profound hypotension due to significant decreases in venous return.[7,53] Magnesium sulfate has also shown promise in the treatment of human pheochromocytoma crisis by reducing blood pressure through direct inhibition of catecholamine receptors, inhibition of catecholamine release from both the adrenal medulla and nerve terminal, and direct arteriolar vasodilation.[52,64,68] It has a wide therapeutic range and does not typically cause profound hypotension seen with sodium nitroprusside.[68] Clevidipine, an ultrashort-acting intravenous calcium channel antagonist, is showing promise for treatment of intraoperative hypertension in humans. It is a vasoselective arteriolar dilator that is delivered as a constant rate infusion. Because it does not cause venodilation, venous return is minimally affected, resulting in better hemodynamic stability than sodium nitroprusside.[63,68,69] Clevidipine has not been used in clinical veterinary medicine due to its high cost but may become a viable option in the future for the intraoperative management of pheochromocytoma (Table 8.6).

Supraventricular tachycardia, which may also accompany sudden release of catecholamines, is frequently treated with the selective β1-adrenergic receptor antagonist, esmolol. Esmolol has a quick onset and short duration of action and is administered as a bolus or as a constant rate infusion to decrease heart rate, myocardial contractility, and AV node conduction.[7]

The α2-adrenergic agonist, dexmedetomidine has been used to treat human pheochromocytoma crisis.[65] Its action on presynaptic α2-receptors inhibits norepinephrine release from the nerve terminal, thereby decreasing sympathetic outflow.[65] In contrast to veterinary patients, it is commonly used as an antihypertensive in humans, with transient hypertension only occurring at high doses. Although dexmedetomidine effectively reduces plasma norepinephrine concentrations by ~80% in dogs, any benefit it may offer for pheochromocytoma resection in veterinary patients has not been determined.[55]

### Emergency adrenalectomy

Although most adrenalectomies can be planned and properly prepared, some require immediate surgery due to rupture. These patients typically present in a hypovolemic state and require stabilization with fluids and/or blood products. Mortality in patients in whom α-adrenergic blockade has not been established is higher than in those with blockade due to contracted vascular volume and poor perfusion from chronic vasoconstriction.[52] Short-acting antihypertensive agents and antiarrhythmics, such as those described previously, can be used intraoperatively to minimize hemodynamic instability. Institution of β-adrenergic blockade, however, should not be instituted before α-adrenergic receptor blockade, as uninhibited, intense vasoconstriction could result.[7,53]

### Postoperative period

After ligation of the tumor blood supply, patients can become rapidly hypotensive from sudden cessation of sympathetic stimulation, adrenergic receptor down-regulation, and long-lasting effects from α and β receptor antagonists.[53,61,64,66,68] Large volume fluid resuscitation with crystalloids and/or colloids along with inotropic or vasopressor support is often necessary to increase cardiac output. The use of adrenergic agonists, such as norepinephrine and phenylephrine, may be unrewarding in this manner because of receptor down-regulation and pharmacologic adrenergic antagonism. However, vasopressin (loading dose of $0.1-0.4\ \mathrm{U\,kg^{-1}}$ followed by a constant rate infusion of $0.005-0.02\ \mathrm{U\,kg^{-1}\,min^{-1}}$), via activation of vascular V1 receptors may help by causing vasoconstriction not mediated through adrenergic mechanisms.[68] In addition, vasopressin is effective in the presence of hypoperfusion and metabolic acidosis, both of which

**Table 8.6** Antihypertensive and antiarrhythmic drugs with possible benefit in the anesthetic management of patients with pheochromocytoma [7,19,63,68,69]

| Drug Name | Mechanism of Action | Notes | Dose |
|---|---|---|---|
| Acepromazine | α receptor antagonist vasodilation | Long-acting, may exacerbate hypotension post-operatively | 0.003-0.005 mg/kg |
| Sodium Nitroprusside | Arteriolar and venodilator via nitric oxide release | Short-acting, decreases both pre- and afterload, can cause profound hypotension, cyanide metabolite | 1-10 mcg/kg/min Do not exceed 0.5 mg/kg/hr |
| Esmolol | Selective β1 antagonist, decreases HR, contractility, AV node conduction | Short-acting, metabolized by esterases, can be administered as a CRI | Bolus: 100-500 mcg/kg CRI: 10-200 mcg/kg/min |
| $MgSO_4$ | Directly inhibits catecholamine receptors and release of catecholamines from the nerve terminal, vasodilator | Wide therapeutic safety margin | Bolus: 30-50 mg/kg over 15 minutes CRI: 15-25 mg/kg/hr |
| Clevidipine | Blocks L-type $Ca^{2+}$ channels to produce selective arteriolar vasodilation | Short-acting, rapid onset, metabolized by esterases, expensive, CRI only | N/A |
| Dexmedetomidine | Activates presynaptic α2 receptors to decrease release of NE from the nerve terminal | Used as an antihypertensive in humans. Use for treatment of pheochromocytoma in veterinary species has not been evaluated | N/A |

CRI, constant rate infusion; NE, norepinephrine.

[a]No current studies evaluating effects in veterinary patients with pheochromocytoma.

may occur in the postoperative pheochromocytoma patient.[70]

Intense monitoring should continue in the post-operative period, including telemetry, central venous pressure, and direct arterial blood pressure. Although hypotension tends to occur most often, patients can continue to be hypertensive for several days and should continue to receive phenoxybenzamine until normotensive.[53,61] If significant arrhythmias are present, oxygen supplementation is advised.

## Diabetes mellitus

Diabetes mellitus results from deficient serum insulin levels or decreased sensitivity of peripheral tissues to its effects, otherwise known as "insulin resistance." It is a common pancreatic endocrinopathy of dogs and cats, with an incidence between 1 in 100 and 1 in 500, respectively.[1] Diabetes mellitus is designated as either type I, where destruction of the pancreatic β cells leads to absolute hypoinsulinemia, or type II, where a combination of impaired insulin secretion and decreased tissue insulin sensitivity leads to elevated serum glucose levels.[1]

### Canine diabetes mellitus

Type I diabetes mellitus is most commonly found in dogs and is usually caused by immune-mediated destruction of the pancreatic β cells. It affects dogs between the ages of 4 and 14 years but is most frequently diagnosed in dogs aged between 7 and 10 years. Keeshonds and female dogs are over-represented.[1]

### Feline diabetes mellitus

In contrast, 80–95% of cats with diabetes mellitus are type II diabetics, and of these, ~70% require exogenous insulin administration.[1,71] Cats are usually middle aged at presentation with a peak incidence between 10 and 13 years. Male cats are affected more frequently than female cats, and Burmese may be predisposed.[1,71]

**Table 8.7** Complications of diabetes mellitus.[8,21,73–82]

| Complication | Anesthetic concerns |
|---|---|
| Atherosclerosis | Decreased organ blood flow |
| | Ischemia |
| Hypertension | Retinal hemorrhage |
| | Hypertensive encephalopathy |
| | Impaired autoregulation of renal, cerebral, and coronary circulation |
| | Renal failure |
| Retinopathy | May be indicative of cerebral vascular impairment |
| Nephropathy | Secondary Hypertension |
| | Renal failure |
| Peripheral neuropathy | Prolonged locoregional block |
| | Prolonged or shortened neuromuscular block |
| | Increased risk of further nerve injury |
| Autonomic neuropathy | Gastroparesis |
| | Hypotension |
| | Poor vasomotor tone |
| | Respiratory depression |
| | Impaired thermoregulation |
| | Cardiac failure/arrest |

## Clinical signs and symptoms

Four classic clinical signs associated with diabetes mellitus in both cats and dogs include polyuria, polydipsia, polyphagia, and weight loss.[1,71] Clinical signs are directly related to increased serum osmolarity caused by hyperglycemia and the catabolic state from impaired glucose usage by the tissues. Other symptoms can manifest from chronic hyperglycemia, including blindness from cataract formation, and plantigrade stance in cats with diabetic neuropathy.[1,71,72]

## Clinicopathologic changes

Minimal changes are seen on the CBC but may reflect dehydration (polycythemia) or the presence of infection (leukocytosis).[1] One consistent biochemical abnormality in an uncontrolled diabetic patient is persistent hyperglycemia. Increased lipolysis causes hypercholesterolemia, hypertriglyceridemia, and higher levels of circulating fatty acids. Other changes are often reflective of complications arising from diabetes and include azotemia, elevated amylase and lipase, mild to moderate increases in ALT and ALKP, hyponatremia, and hypokalemia.[1]

Glycosuria is found as glucose levels surpass the renal tubular threshold. Osmotic diuresis from hyperglycemia decreases urine concentration, producing a specific gravity between 1.025 and 1.035.[1] Proteinuria is often present as a result of persistent hypertension and resultant glomerulopathy or urinary tract infection.[1,24] Poorly controlled diabetics may have ketonuria.[1,71]

## Diagnosis

Diabetes mellitus is confirmed with persistent fasting hyperglycemia and concurrent glycosuria. Cats can have sporadic serum glucose elevations from stress and often need serial glucose measurements or a fructosamine level to help establish the diagnosis.[1,71]

## Treatment

Treatment for most diabetic dogs and cats involves the administration of various insulin preparations, which are beyond the scope of this chapter. However, diet, activity level, treatment of concurrent diseases, and avoidance of drugs that promote insulin resistance, such as glucocorticoids, help to control diabetes mellitus.[1,71]

## Anesthetic management

In humans and dogs, anesthesia and surgery in the diabetic patient are associated with higher complication rates, mortality rates, and longer hospital stays.[28,71,73] Higher perianesthetic issues are attributed to impaired glucose homeostasis on the cardiovascular system, the

central and peripheral nervous systems, the autonomic nervous system, the kidneys, and the eyes.[1,71,72,74,75] Many of the deleterious effects are caused by damage to vascular endothelium throughout the body.[1,72,74] (Table 8.7).

Hypertension is present in ~46% of diabetic dogs and to a much lesser extent in cats and is attributed to atherosclerosis from increased lipolysis, impaired vasodilation, electrolyte abnormalities, and thickening of the vascular endothelium in response to elevated levels of the glucose by-products, sorbitol, and advanced glycosylated end-products (AGEs).[24] Hypertension subsequently increases cardiac work with eventual myocardial dysfunction and remodeling.[83] As with other forms of endocrine hypertension, blindness, renal failure, encephalopathy, stroke, and cardiac arrest are possible outcomes, and if uncontrolled, affected diabetic patients are at greater risk of hemodynamic instability under anesthesia.[24]

Since both the central and peripheral nervous systems are affected by diabetes mellitus, hyperglycemia and vascular damage can impair cerebral vasodilation in response to increasing $CO_2$ levels.[73] This, combined with atherosclerosis of the cerebral vessels, may result in decreased cerebral perfusion and ischemia. In anesthetized patients, this can be even more detrimental, as impaired autoregulation may require higher mean arterial blood pressure to maintain oxygen delivery to the brain.[7,76]

Peripheral neuropathy occurs in ~50% of diabetic humans, ~10% of diabetic cats, and more infrequently in dogs.[72,73,77] Affected patients present with hind limb weakness, ataxia, proprioceptive deficits, decreased tendon reflexes, muscle atrophy, and decreased muscle tone.[72,77] Cats, in particular, may present with a plantigrade stance and pain during distal limb manipulation from sensorimotor deficits due to vascular changes, ischemia, axonal degeneration, and demyelination.[1,72]

Autonomic neuropathy is a serious manifestation of diabetes mellitus associated with altered parasympathetic tone, leading to tachycardia, delayed gastric emptying time, orthostatic hypotension, altered respiratory responses to hypoxia, impaired thermoregulation, and cardiac failure.[73,74,76,78] Although not commonly reported in veterinary species, cardiac autonomic neuropathy has been documented in diabetic dogs.[78]

Humans with diabetes mellitus are commonly affected by diabetic nephropathy from vascular changes induced by hyperglycemia.[74] Damaged glomeruli leak protein into the urine, leading to glomerulosclerosis, decreased GFR, and eventual renal failure.[74] In veterinary patients, renal changes and proteinuria are more frequently attributed to hypertension, and care should be taken to ensure adequate renal perfusion during the perianesthetic period.[24]

## Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) causes severe hyperglycemia, dehydration, metabolic acidosis, obtundation, and cardiovascular collapse and can occur with uncontrolled disease, after severe illness, infection, or increased stress from anesthesia and surgery.[1] Proper patient stabilization includes administration of intravenous fluids, potassium supplementation, insulin, and, occasionally, sodium bicarbonate.[1]

### Preanesthetic period

Most important in the anesthetic management of diabetic patients are the goals of minimizing hyperglycemia and avoiding hypoglycemia. Anesthetic drugs and the stress of anesthesia and surgery affect blood glucose levels.[75] It is strongly recommended that newly diagnosed diabetics and those that are poorly controlled be regulated before undergoing anesthesia for elective procedures; newly diagnosed human diabetics have the highest complication rates and mortality when compared to controlled diabetics and nondiabetics.[73]

Before anesthesia, a thorough physical examination should be performed to evaluate all organ systems and assess hydration. Neurologic evaluation may suggest peripheral neuropathy, and fundoscopic examination may reveal changes in retinal vessels, suggesting hypertension.[77,79] Vascular changes in the retina are often associated with abnormalities of the cerebral vessels as well.[77] Fasting in diabetics can lead to altered insulin requirements. Owners should be advised not to administer insulin just before surgery until a blood glucose level can be checked to determine insulin needs.[1] No insulin should be given, and a 2.5–5% dextrose infusion should be started if blood glucose levels are $<100\,mg\,dl^{-1}$.[1] If blood glucose is $>300\,mg\,dl^{-1}$, half of the patient's usual insulin dose can be administered subcutaneously or an infusion of regular insulin ($0.025–0.05\,U\,kg^{-1}\,h^{-1}$) along with dextrose and potassium chloride can be started.[1,19,76] Blood glucose

levels should be checked every 30–60 min to avoid hypoglycemia and direct continued therapy.[1,75,76]

Electrolytes, acid–base status, PCV, total solids, BUN, creatinine, and lactate should also be evaluated.[75] Urine should be checked for glucose, ketones, and protein. Ketonuria is cause for concern, even if the patient is not acidotic, because hyperglycemic surges from stress could push a diabetic patient into DKA, and elective procedures should be postponed until no ketones are present.[75] Acidemia and hyperlactatemia may indicate poor tissue perfusion and hypovolemia and should be corrected before anesthesia.[7]

Osmotic diuresis leads to dehydration, loss of sodium and potassium, and decreased circulating blood volume.[2] Preoperative intravenous fluids should be administered to help prevent hemodynamic instability after anesthesia induction.[73] Because diabetic patients have increased risk of regurgitation and aspiration from delayed gastric emptying, a proton pump inhibitor, such as pantoprazole,[19] and metoclopromide are recommended.[7,73]

Decreasing surgical stress through excellent analgesia is imperative to minimize alterations in glucose. Opioids inhibit sympathetic nervous system activation and cortisol secretion and do not impair glucose homeostasis.[73,84] The administration of α2-adrenergic agonists to diabetic patients is controversial. They inhibit insulin secretion through activation of α2A-receptors on the pancreatic β cells and therefore may exacerbate hyperglycemia.[85] However, dexmedetomidine in healthy dogs does not exacerbate hyperglycemia, and is thought to be balanced by the decrease in sympathetic nervous system activity from presynaptic α2-receptor activation.[85] Thus, dexmedetomidine may benefit the diabetic patient but warrants further examination.[85]

The induction agents, propofol and etomidate, do not adversely affect glucose homeostasis and can be used in the diabetic patient.[73,84] However, ketamine indirectly stimulates the sympathetic nervous system, which could worsen hyperglycemia.[7,13] Volatile anesthetics significantly affect glucose homeostasis by inhibiting insulin release in response to hyperglycemia; however, whether this can affect outcomes of diabetic veterinary patients is not fully elucidated.[73,84]

## Intraoperative period

Anesthetic induction should be smooth and rapid, with inflation of the pilot balloon occurring while the patient is still in sternal recumbency in order to protect the airway from possible regurgitation and aspiration. Most important during the intraoperative period is monitoring blood glucose every 30–60 min for the duration of the procedure.[1] Although there is no standard as to how tight glycemic control should be in veterinary patients, an acceptable goal is to maintain blood glucose between 150 and 250 mg $dl^{-1}$. Lower glucose levels are associated with a decrease in anesthetic morbidity in humans, and it was previously recommended to keep blood glucose between 80 and 120 mg $dl^{-1}$.[76] Although these patients have decreased anesthetic complications, postoperative hypoglycemia in the intensive care unit (ICU) was higher and associated with a greater mortality rate.[76]

### Locoregional anesthesia and analgesia

Locoregional anesthesia and analgesia can be beneficial in diabetic patients, as it reduces stress and release of counter-regulatory hormones (epinephrine, glucagon, and cortisol).[75] However, its use is controversial in patients with peripheral neuropathy because of suspected reductions in nerve blood flow, increased ischemic damage in the presence of local anesthetics, and exacerbation of neurologic deficits in the postanesthetic period.[21] In rodents with diabetic peripheral neuropathy intrathecally administered local anesthetics had a prolonged duration of action but no histological spinal damage was observed.[80]

### Neuromuscular junction blockade

Vecuronium's duration of action was significantly longer in diabetic vs nondiabetic humans, possibly related to changes in the neuromuscular junction and motor nerve conduction.[81] However, the opposite was seen in diabetic dogs where its duration was significantly decreased in comparison to nondiabetic dogs. [81] Thus, it is recommended that train-of-four monitoring be used to assess return of function, considering the variable effects on muscle function blockade by these drugs.

## Complications

Diabetic patients are at risk of greater hemodynamic instability under anesthesia and may have impaired responses to anesthetic drugs.[73] Severe hypotension is more common in anesthetized diabetic dogs than

nondiabetic dogs and frequently requires colloidal and inotropic support.[82] Humans with diabetes have greater decreases in heart rate and blood pressure and incomplete responses to atropine administration under anesthesia, possibly due to autonomic dysfunction or hypovolemia from dehydration with incomplete resuscitation before anesthesia.

### Monitoring

Monitoring needs should be related to the invasiveness of the procedure and ASA physical status of the patient. Uncontrolled or unstable diabetic patients should have invasive blood pressure and central venous pressure monitoring to help assess circulating blood volume and cardiac function. Temperature, capnometry, ECG, and pulse oximetry are standard. Diabetic patients may have altered thermoregulation, putting them at greater risk for hypothermia; aggressive prevention and treatment should be pursued using circulating warm water blankets, convective heat sources, and heat and moisture exchangers.[73]

### Recovery

Glucose monitoring should continue every 30–90 min until the patient is eating. This duration can be shortened by avoiding excessive sedation in the postoperative period. It is important to recognize that the stress of surgery and release of inflammatory mediators may lead to increased insulin requirements after anesthesia.[76] Dextrose and insulin administration tailored to the needs of the patient and a multimodal approach to provide excellent analgesia can minimize stress while maintaining glucose homeostasis.[1]

## Summary

Endocrine disease adversely affects homeostasis and, as such, can impact anesthesia. Patients presenting for elective procedures should be treated beforehand and have stable disease. Although major complications resulting from these diseases are uncommon, when present, they can be significant. For those patients who are unable to be stabilized before anesthesia, a full understanding of the pathophysiology of the disease and what complications should be expected can prepare the anesthetist for the challenges they impose.

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# 9 Nutritional disease

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The World Health Organization's definition of obesity is an abnormal or excessive fat accumulation in adipose tissue to the extent that health is impaired.[1–3] An excess of adipose tissue occurs when the caloric intake surpasses the caloric expenditure.[4] Owing to the prevalence of obesity in the human population, the World Health Organization has classified obesity into simple obesity (body mass index [BMI] 30–34.9 $kg\,m^{-2}$), severe obesity (35–39.9 $kg\,m^{-2}$), morbid obesity (40–49.9 $kg\,m^{-2}$), and super morbid obesity ($\geq$40 $kg\,m^{-2}$).[5]

## Pathophysiology

Obesity is the most common medical condition in companion animals and is associated with a number of comorbidities.[2] Approximately 55% of dogs and 53% of cats in the USA are considered to be overweight or obese.[6] Worldwide, 22–40% of dogs are considered to be obese.[2] Coincident with obesity in humans comes an increase in morbidity, such as diabetes and musculoskeletal conditions.[6] The criteria for obesity are not as clear-cut in veterinary patients as with human patients, as optimal body weights have not been established for our species and varying breeds. However, it is still concluded that when a patient's weight is 15% above normal for its breed, it is "overweight," and when a patient's weight is 30% above normal, it is "obese."[2]

Risk factors for the development of obesity in veterinary patients have been identified. There is a link between certain breeds and their genetic predisposition for obesity. Cairn Terriers, West Highland White Terriers, Scottish Terriers, Shetland Sheepdogs, Basset Hounds, Cavalier King Charles Spaniels, Dachshunds, Beagles, Cocker Spaniels, and Labrador Retrievers are genetically predisposed to obesity. Likewise, particular breeds appear to be resistant to obesity, such as the sight hound group.[2] Aging is associated with an increase in the likelihood of obesity. With aging, the lean body mass decreases, resulting in a decrease in the total daily energy needs of the animal. In conjunction with a decrease in total daily energy needs, the animal's voluntary activity is typically decreased, possibly because of comorbidities of aging, such as osteoarthritis. The decrease in total daily energy needs combined with a decrease in activity can lead to weight gain if caloric intake is not decreased as well.[2]

Excessive weight can have a major impact on the overall health of the animal. In humans, morbid obesity (BMI of $\geq$40–44.9 $kg\,m^{-2}$) is associated with an increased likelihood of diabetes mellitus,[7] respiratory failure, hypertension, left ventricular hypertrophy, atherosclerosis, myocardial ischemia, and some forms of cancer compared to nonobese patients.[4] Mild to moderate hypertension is described in up to 60% of obese human patients, whereas 5–10% of obese human patients have severe hypertension. With time, hypertension can lead to left ventricular dilation, increased left ventricular wall stress, compensatory left ventricular hypertrophy, and left ventricular diastolic dysfunction.[4] An increase in body adipose tissue alters cardiopulmonary physiology, leading to an increase in cardiac output (CO), oxygen consumption, and closing capacity and a decrease in functional residual capacity (FRC). In humans, these alterations can cause the associated pathologies of hypertension, coronary artery disease,[1] and obstructive sleep apnea.[7] With morbid obesity in humans, the excessive body tissue decreases the FRC, expiratory reserve volume, and total lung capacity. The FRC decreases exponentially with increasing BMI in humans. When the FRC decreases to

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**Table 9.1** Physiologic changes associated with obesity.

| |
|---|
| Hypertension |
| Left ventricular hypertrophy |
| Restrictive pulmonary disease |
| Increased intra-abdominal pressure |
| Decreased chest wall compliance |
| Decreased lung volumes |
| Exercise intolerance |
| Increased atelectasis |
| Increased ventilation/perfusion mismatching |
| Increased volume of distribution |
| Musculoskeletal conditions |
| Increased blood volume |
| Decrease in cardiac index |

the range of the closing capacity, small airway closure takes place, leading to ventilation–perfusion mismatch, right to left shunting, and arterial hypoxemia.[3] Lastly, with increasing body weight, there is an increase in blood volume proportional to the body surface area. This increase in blood volume contributes to an increase in preload and an increase in resting CO. Ultimately, increased left heart diastolic filling and left ventricular hypertrophy can occur (Table 9.1).[1]

Adipose tissue is a major source of inflammatory mediators, and obesity is, therefore, linked to chronic low grade inflammation.[8] The chronic inflammation observed in obese humans is thought to be one of the significant links between obesity and cardiovascular disease.[8] Additional physiologic alterations associated with obesity include increases in tubular reabsorption, which initiates volume expansion of the extracellular volume. In humans, the total extracellular volume is increased; however, the circulating blood volume on a volume/weight basis is decreased.[4] Lastly, splanchnic blood flow is ~20% higher in obese compared to lean individuals. Cerebral and renal blood flow is near normal in the face of obesity.[4]

## Management of anesthesia of the obese patient

### Induction

Anesthetic induction is a demanding period regardless of the patient's BMI. With an obese patient, morbidity causes induction to be even more delicate. With induction and intubation, obese humans have a proportionately greater decrease in cardiac index (CI) than lean individuals. CI decreases 17–33% in obese patients compared to 4–11% in controls. This decrease in CI continues postoperatively in obese individuals, whereas it returns to baseline in nonobese control patients.[1,9]

The physiologic changes induced by obesity, such as the decrease in CI, can significantly affect the distribution, binding, and elimination of anesthetic drugs. The alterations in pharmacokinetics can lead to severe adverse events if dosing is based solely on the actual body weight.[4] However, systemic absorption of oral drugs does not seem to be significantly affected by obesity, although some studies report a delay in gastric emptying in the overweight patient.[4]

When evaluating the alterations of pharmacokinetics on the drug propofol, obese children require significantly less propofol for loss of lash reflex than do lean children; obese children are given a lower dose of propofol on the basis of actual body weight than their nonobese peers.[10] Clearance of propofol appears to be linearly related to lean body weight rather than to total body weight.[5] It is recommended that the dose of propofol for both induction and maintenance of anesthesia should be based on actual body weight in obese individuals analogous to their lean counterparts.[4] In obese humans, both the volume of distribution and the clearance of propofol were significantly correlated to total body water. Therefore, there is a concurrent increase in the volume of distribution, as well as clearance, with the elimination half-life being similar in obese and lean patients. There were no signs of propofol accumulation or prolonged duration of action when propofol was administered on actual body weight in obese humans.[4] Propofol should be administered on total body weight even in obese patients (Table 9.2).

**Table 9.2** Drug dosing in the obese patient.

| | |
|---|---|
| Propofol | Actual body weight |
| Thiopental | Lean body weight |
| Midazolam | Actual body weight |
| Diazepam | Actual body weight |
| Opioids | Dependent on lipophilic nature of drug |
| Highly lipophilic | Lean body weight |
| Minimally lipophilic | Actual body weight |

Thiopental, however, has a significantly longer elimination half-life when administered on actual body weight in obese individuals owing to the increased volume of distribution. The dose of thiopental for induction of anesthesia of obese patients can be based on lean body mass to avoid prolongation of effects.[4]

Whether used for sedation or part of an induction protocol, the dose of benzodiazepine should be adjusted in the overweight patient. Benzodiazepines are highly lipophilic drugs and are highly affected by excess adipose tissue. With obesity comes a significant increase in volume of distribution and elimination half-life of benzodiazepines. Regardless of the benzodiazepine being used, the dose should be increased in obese patients in proportion to the total body weight owing to increases in volume of distribution and distribution in the excess fat.[4]

Despite the growing obese population, clinical studies have, thus far, unsuccessfully defined a universal size descriptor suitable for use in the obese population. For this reason, titration to clinical end points or the use of the bispectral index remains prudent.[11] Because induction agent doses are typically titrated to clinical effect, some may argue that new dosing recommendations are unnecessary for the human or veterinary populations.[5]

## Maintenance

Concern with anesthetizing an obese patient focuses on the physiologic alterations associated with excess adipose tissue as opposed to alterations in pharmacodynamics. Obesity is linked with restrictive pulmonary disease caused by increased intra-abdominal pressure and decreased chest wall compliance due to the increased weight of the chest wall,[4,12] resulting in a decrease in static and dynamic lung volumes expiratory reserve volume and total lung capacity.[13] In addition, the mass effect of intra-abdominal adipose tissue contributes to the decrease in respiratory compliance.[1] These changes are further affected by anesthesia and surgical procedures.[4] Changes in ventilation, such as a reduction in the FRC, expiratory reserve volume, and total lung capacity are frequent observations of the clinically obese.[14] The FRC exponentially decreases with increasing total body weight.[1] Under anesthesia, lean people have a decrease in FRC by 20%, whereas obese people have a 50% decrease in FRC.[1] The low FRC and expiratory reserve volume contribute to rapid desaturation with apnea (as is often seen on anesthetic induction) or hypoventilation and air trapping with poor lung function.[13] The reduced FRC causes portions of the lung to have premature airway closure and atelectasis, resulting in ventilation–perfusion mismatch.[1]

Anesthesia further complicates the respiratory pathophysiology observed in obese individuals. The reduced lung volumes and the increased ventilation–perfusion mismatching significantly increase the likelihood of hypoxemia during and after anesthesia.[4] During inhalant anesthesia, morbidly obese human patients experience more atelectasis than lean patients. In addition, the atelectasis can remain for up to 24 h after the end of anesthesia,[11] where complete resolution occurs more immediately in nonobese patients.[12] The application of 10 cm $H_2O$ of positive end-expiratory pressure (PEEP) increases oxygenation in obese human patients and is associated with better oxygenation and a longer duration of apnea before hypoxia develops.[1] This effect is related to recruitment of alveoli.[11] However, the improvement of arterial oxygenation by the addition of PEEP does so at the expense of CO and oxygen delivery.[4]

Barotrauma during ventilation is not uncommon in obese individuals.[13,15] It is postulated that perhaps clinicians overestimate the lung size of obese patients and choose tidal volume on the basis of actual body weight rather than lean body weight.[15] The mode of ventilation is highly important in obese patients. In comparing pressure-controlled ventilation to volume control ventilation, in obese human patients (BMI > 35) undergoing laparoscopic gastric banding, pressure-controlled ventilation was associated with an increase in pH, $PaO_2$, and oxygen saturation, while $PaCO_2$ was decreased. Because there is higher inspiratory flow with pressure-controlled ventilation, increases in alveolar recruitment may lead to a decrease in ventilation–perfusion mismatching.[13]

Epidural anesthesia is a common adjunct to inhalant anesthesia for maintenance of general anesthesia. Epidural anesthesia is more difficult in the obese patient for multiple reasons. Most obvious, the landmarks are more difficult to find in obese patients, making epidurals more technically difficult.[4] In obese patients, fatty infiltration of the epidural space, in addition to an increase in blood volume secondary to increased intra-abdominal pressure, may reduce the volume of

the space, making epidurals more difficult to perform and spread of the drug less predictable.[4] Despite the downsides, epidurals are extremely useful to reduce the respiratory depression and secondary complications from the respiratory depression caused by other systemic drugs.[4]

The highly lipophilic drug sufentanil has been found to have a markedly prolonged elimination half-life in obese people. The increase is relative to that in the volume of distribution and possible accumulation of drug in excess fatty tissue.[4] Dosing of highly lipophilic drugs should be altered in obese patients. Conversely, the administration of the hydrophilic drug atracurium has no difference in recovery times between obese and nonobese individuals. The lower lipid solubility of desflurane and sevoflurane makes them the volatile anesthetics of choice in obese individuals.[4]

### Postoperative care

In the postoperative period, the depressant effects of analgesic and anesthetic drugs on the respiratory system can negatively impact patient safety. The work of breathing is greatly increased postoperatively because of the increase in body mass required to move while breathing.[4] The risk of postoperative hypoxia is high in obese patients.[4] Furthermore, oxygen demand increases by up to 50% in the immediate postoperative time, requiring a significant increase in both CO and oxygen delivery to tissues. The CO needs to increase to meet the increased oxygen demand even in the face of a decreased FRC. If CO is unable to cope, the patient is much more likely to develop postoperative complications.[1] Recovery times have been found to be comparable in obese and lean humans after anesthetic procedures lasting from 2 to 4 h. Although there is a delay in recovery due to fat accumulation of lipid-soluble drugs, the reduced blood flow to adipose reduces the tissue uptake of these drugs.[4] Therefore, the blood gas solubility, rather than fat solubility, may be the leading force influencing time to recovery in morbidly obese patients.[7]

In obese patients, there is a higher rate of postoperative infection and delayed wound healing due to the effect of obesity on the immune system. Obesity impairs cell-mediated immune responses and decreases lymphocyte immune function and the natural killer cell activity.[3]

## Other nutritional concerns

In addition to obesity, cachexia is another significant nutritional concern that can impact anesthesia. Information on anesthetizing a cachexic patient can be found in Chapter 15.

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# 10 Ophthalmic disease

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Animals that present for ophthalmic surgery present several challenges to the anesthetist, including the effects of anesthetic drugs on intraocular pressure (IOP) and tear production, patient positioning, reflexes that may occur during intraoperative manipulation of the eye, the effect of topically or systemically administered ophthalmic drugs, and, in many older animals, coexisting disease. In addition, procedures that require the globe to be positioned centrally within the orbit for optimal surgical access, for example, cataract removal, require the use of neuromuscular blocking agents (NMBAs) and mechanical ventilation.

## Intraocular pressure

Intraocular pressure is a function of the relationship between aqueous humor production and its drainage, the majority of which occurs in cats and dogs via the trabecular meshwork of the anterior chamber angle.[1] This relationship can be quantified as follows:

IOP = (aqueous humor formation rate/
aqueous humor outflow rate)
+ eipsclereal venous pressure

Ocular perfusion pressure determines the blood supply to the retina and optic nerve and is defined as the difference between mean arterial blood pressure and IOP.[2] Thus, an increase in IOP can lead to a decrease in optic nerve function, leading to a potential loss of vision if not recognized and treated. A major goal when anesthetizing animals that present with pre-existing glaucoma for both ophthalmic as well as nonophthalmic surgeries is to prevent unwanted increases in IOP. It is also imperative to prevent sudden increases in IOP in patients who present with partial or imminent loss of globe integrity (e.g. descemetocele, trauma, and deep corneal ulcer) to prevent complete rupture. The physical, physiologic, and pharmacologic causes of increased IOP are presented in Table 10.1.

Physical restraint of a struggling animal may increase IOP, as will inadvertent pressure on the jugular veins, causing increased central venous pressure. Any pressure applied to the eyes via the eyelids such as digital compression or placement of a face mask causes a direct increase in IOP. Elevating the head above the rest of the body will tend to decrease IOP. Stimulation of the larynx and pharynx during endotracheal intubation transiently increases IOP. After cataract surgery, the incidence of increased IOP is high, and it is prudent to maintain intravenous access for administration of diuretics or for sedation if anterior chamber centesis is needed, to relieve high IOP.

Vomiting, straining, and coughing increase IOP temporarily. The presence of pre-existing glaucoma and the development of hypercarbia and/or hypoxemia lead to increases in IOP.[2,3]

Most anesthetic drugs directly decrease or do not change IOP; however, side effects such as vomiting (opioids and alpha-2 agonists), hypercapnia (propofol, opioids, alpha-2 agonists, and inhalants), or myoclonus (etomidate) may cause IOP to increase. Ketamine and succinyl choline have been shown to increase IOP.[4]

## Tear production

Several studies have looked at the effect of anesthetic drugs on tear production in dogs. The use of atropine

*Canine and Feline Anesthesia and Co-Existing Disease*, First Edition. Edited by Lindsey B.C. Snyder and Rebecca A. Johnson.

**Table 10.1** Factors causing an increase in IOP.

| Physical | Physiologic | Pharmacologic |
|---|---|---|
| Pressure on eyelids (e.g. face mask) | Vomiting | Succinyl choline |
| Endotracheal intubation | Pre-existing glaucoma | Ketamine |
| Excessive restraint and struggling | Coughing | Etomidate (in cases where myoclonus occurs) |
| Pressure on the jugular veins | Tenesmus | |
| Head below body | Hypoxemia | |
| Cataract surgery | Hypercapnia | |

has been correlated with a decrease in tear production.[5] General anesthesia typically decreases tear production. Herring et al. (2000) reported that tear production was decreased during and for up to 24 h after general anesthesia and that general anesthesia lasting more than 2 h had a significantly greater impact on postoperative tear production than shorter procedures.[6] Conversely, Shepard et al. (2011) demonstrated that tear production returned to normal immediately after short (1 h) and long (4 h) episodes of anesthesia when either isoflurane or desflurane was used as the sole anesthetic agent.[7] Multiple drugs (premedicants, injectable induction agents) were used in the earlier study, including atropine, which may account for the different findings. General anesthesia with sevoflurane after morphine, acepromazine, as well as after no premedication also reduced tear production during anesthesia.[8] Tear production was decreased in cats after acepromazine and xylazine sedation.[9] In cases of unilateral surgery, the unaffected eye should be protected and treated with a topical artificial tear ointment.

## Patient positioning

The head of the patient is typically distant to the anesthetist (Figure 10.1) during ophthalmic surgery, resulting in several challenges for the anesthetist. Firstly, it is not possible to assess anesthetic depth using the palpebral reflex, position of the globe within the orbit, or jaw tone. The anesthetist must rely on cardiovascular and respiratory monitoring as indicators of changes in depth of anesthesia. Secondly, the endotracheal tube, endotracheal tube connector, and patient end of the breathing system are not visible or easily accessed. This makes it more difficult to detect accidental extubation, the presence of leaks, and disconnections. Thirdly, it may not be possible to place or access monitoring equipment on the tongue (pulse oximeter), in the esophagus (temperature probe, stethoscope), or connected to the

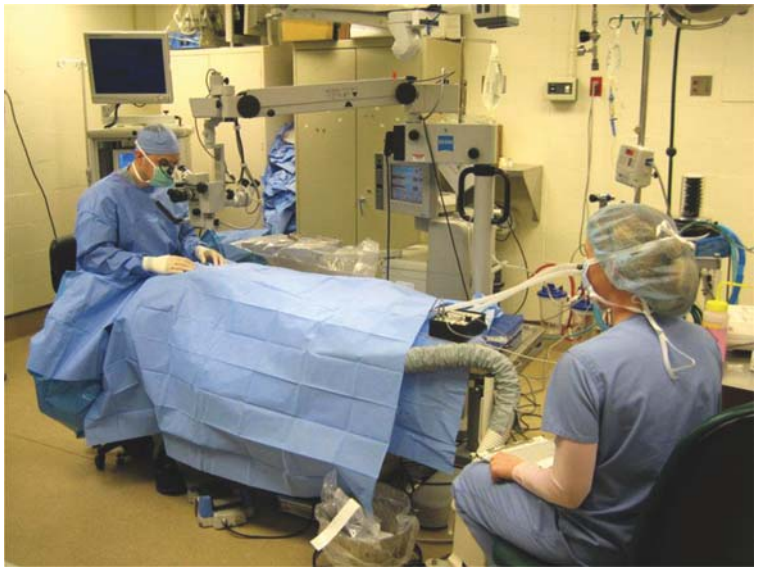


**Figure 10.1** Typical setup of an ophthalmology operating room, with the animal's head placed distant from the anesthesia machine and the anesthetist.

breathing system (capnometry). During surgery, pulse oximeter probes placed on the tongue can easily become dislodged, leading to erroneous readings. Finally, movement of the patient by the anesthetist during surgery may make it challenging for the ophthalmologist, particularly when an operating microscope is being used, as small movements will be greatly magnified in the surgeon's field of vision.

## Oculocardiac reflex

Pressure or traction on the eyeball during surgery may induce an oculocardiac reflex (OCR) via the trigeminal and vagal nerves that results in the development of dysryhthmias.[2] The most common dysrhythmia noted is bradycardia; however, ventricular ectopy and asystole may also occur. The presence of hypercarbia increases the likelihood of OCR occurring.[10] Initial management involves communicating the presence of OCR to the surgeon, who should stop manipulating the eye immediately. If the OCR persists, treatment with an anticholinergic may be necessary or commencement of cardiopulmonary resuscitation in the case of asystole.

## Ophthalmic drugs

Many patients who present for ophthalmic surgery have received ophthalmic drugs before surgery; thus, it is important to understand their potential physiologic impact before or during surgery. Systemically administered drugs are much more likely to result in side effects; however, systemic absorption of topically applied drugs can occur. It is important to recognize the potential for side effects of ophthalmic drugs administered by any route, so that when they occur they can be managed appropriately.

### Drugs used to treat glaucoma

Cholinergic agents, for example, pilocarpine, increase the rate of aqueous humor outflow. If absorbed systemically, unwanted parasympathetic effects such as bradydysrhythmia and bronchoconstriction may be seen.[1]

Topically applied adrenergic agonist drugs, for example, epinephrine and phenylephrine, may lead to systemic hypertension and tachycardia.[11] Adrenergic antagonists, for example, timolol, will have the opposite effect if absorbed, that is, bradycardia.

Inhibition of carbonic anhydrase (CA) by systemic administration of acetozolamide leads to a decrease in aqueous humor formation.[12] The CA enzyme is also present in the kidney, and its inhibition interferes with renal electrolyte exchange mechanisms, resulting in a decrease in bicarbonate reabsorption. This leads to hyperchloremia, hypokalemia, and metabolic acidosis. Topical CA inhibitors have generally superseded the use of acetozolamide, as they have minimal side effects.

The use of diuretics, for example, mannitol, may lead to an initial volume expansion, which, in patients with moderate to severe cardiovascular disease, may cause pulmonary overload and edema or congestive heart failure.[13] Ultimately, dehydration and its accompanying electrolyte and acid–base disturbances may occur.

### Topical corticosteroids

Prolonged use of corticosteroid drops may depress the adrenal cortex and possibly result in hypoadrenocorticism, thus decreasing an animal's ability to respond appropriately to the stress of anesthesia and surgery.[14] It may be necessary to administer supplementary corticosteroids before anesthesia, for example, prednisolone $1–2\,mg\,kg^{-1}$ IV (see Chapter 8).

### Drugs used to dilate the pupil

Topical atropine drops may result in tachydysrhythmias and bronchodilation if absorbed into the systemic circulation.[15]

## Coexisting disease

Patients presenting for ophthalmic surgery range in age, and older animals often have coexisting diseases of other body systems. Renal, cardiovascular, and endocrine diseases are more common in older patients and should be managed appropriately (see chapters 6, 1, and 8, respectively). The incidence of cataract formation in diabetic dogs is high, and these patients often present for anesthesia. It is important to monitor blood glucose frequently in these patients because withholding food and the unavoidable stress associated with the perioperative period (withholding food, being in the unfamiliar environment of the veterinary clinic) may lead to unexpected hyperglycemia or

hypoglycemia, and both may occur within the same anesthetic episode. The anesthetist should be prepared to treat hypoglycemia by adding dextrose to IV fluids (2.5–5% solutions are usually adequate to treat hypoglycemia). Severe hyperglycemia (blood glucose >450 mg dl$^{-1}$) can be treated with regular insulin.[16] Serial blood glucose measurement is useful to determine the current trend of blood glucose, as well as response to any treatment. Hypoglycemia is generally easier to manage than hyperglycemia, and it has been shown that inhalant anesthesia has an anti-insulin effect in rabbits.[17] Although it is not clear whether this occurs in cats and dogs, it may be prudent to delay or postpone nonemergent ophthalmic surgery in patients with a blood glucose that is >450 mg dl$^{-1}$ and rising.

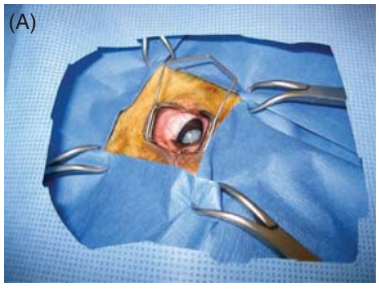
**Table 10.2** Commonly used neuromuscular blocking agents.

| Drug | Metabolism | Side effects |
|---|---|---|
| Atracurium | Up to 50% degraded by Hofmann elimination and ester hydrolysis (does not rely on hepatic metabolism) | Block may be prolonged by acidosis and hypothermia. Possibility of histamine release. |
| Cisatracurium | More than 50% eliminated by Hofmann degradation; ester hydrolysis does not occur | Block may be prolonged by acidosis and hypothermia. Does not cause histamine release. |
| Vecuronium | Hepatic (50%) and renal elimination | Cardiovascular stability. Prolonged action with renal insufficiency. |
| Rocuronium | Hepatic | Cardiovascular stability. |

## Neuromuscular blockade and ventilation

During general anesthesia, the globe of the eye rotates away from a central position (Figure 10.2A). This position is not ideal for performing intraocular and some keratoconjunctival surgeries. The use of nondepolarizing NMBAs to relax the extraocular muscles allows the eye to maintain a central position, which greatly facilitates surgery (Figure 10.2B). Nondepolarizing NMBAs exert their action on the neuromuscular junction by competitively antagonizing acetyl choline (Ach) at the post-junctional Ach receptors. Various short-acting NMBAs that have an onset of action of 1–5 min and a duration lasting up to 30 min are available for clinical use. Their pharmacologic and side effects are contrasted in Table 10.2. In addition to the details mentioned under each drug, neuromuscular blockade can be prolonged by antibiotics, hypothermia, electrolyte and acid–base disturbances, and the concurrent use of inhalational anesthetic agents.

The degree of neuromuscular blockade can be monitored using a nerve stimulator (Figure 10.3). The common fibular (peroneus) nerve running over the distal aspect of the lateral thigh is more accessible than the radial nerve during ophthalmic surgery. The most well-known technique used to determine the degree of blockade is the train-of-four. In this technique, four supramaximal stimuli are applied at 2 Hz. The twitches of the limb produced by the first stimulus (T1) and the last (T4) are compared visually or by touch by the anesthetist to provide a T4/T1 ratio. Before NMBA administration, the ratio should be 1.0. If the NMBA occupies 70% or more of the receptors, then the twitches will become weaker, or "fade," with T4 fading first, followed by T3 and T2. Return of T4 such that the T4/T1 ration is >0.7 represents clinical recovery



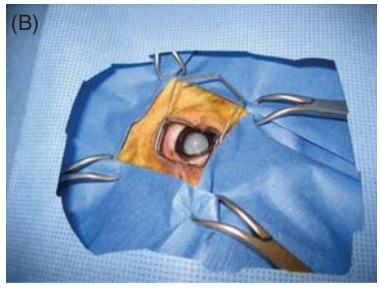




**Figure 10.2** (A) The eye before administration of a neuromuscular blocking agent (NMBA) before cataract surgery. The globe is rotated ventrally such that the sclera is prominent and the cornea partially covered by the lower eyelid. (B) The same eye after NMBA administration. The globe has returned to a more central position, with more of the cornea visible to the surgeon.

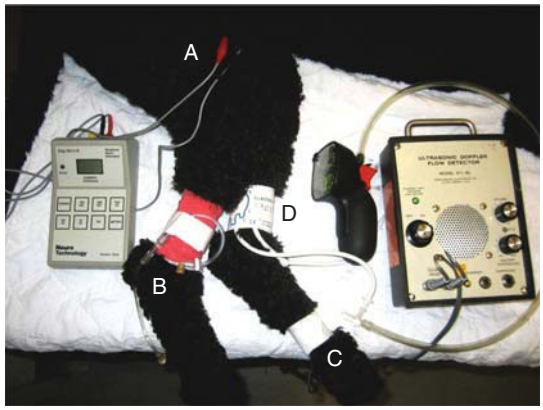



**Figure 10.3** Hind limb of a dog showing placement of crocodile clips on the skin over the common fibular (peroneal) nerve (A), intravenous catheter (B), and doppler crystal (C), and noninvasive blood pressure cuff (D).

from blockade. An alternative technique, double burst stimulation, applies 2 stimuli at 50 Hz. The ratio of the two evoked twitches is then compared in a similar manner to T4/T1.

Additional doses of NMBA may be needed for longer surgeries to maintain an optimal surgical position of the eye. Typically, the dose required to maintain neuromuscular block is one-third to one-half of the dose initially used.

The use of manual or mechanical ventilation is mandatory after the administration of NMBAs. Mechanical ventilation allows the anesthetist's hands to be free for other tasks, provides consistent tidal volume and breathing rate, and is thus preferred when neuromuscular blockade is performed. The anesthetist should be familiar with the operation of the ventilator being used, and the ventilator should be checked to ensure that it is in working order before connecting a patient to it (Figure 10.4A and B).

At the end of surgery, it is essential to determine whether residual neuromuscular blockade is present. Monitoring with a nerve stimulator and assessment of the patient's respiratory pattern are used to determine if reversal of neuromuscular blockade is required (see the previous section). Reversal of blockade with neostigmine is preceded by anticholinergic treatment to avoid bradycardia, bronchoconstriction, and diarrhea. It is possible for patients to become recurarized (the effects of paralysis return either totally or partially) even after reversal, and postoperative observation for several hours is prudent.

## Pain management

The eye has a well-developed network of sensory nerve fibers, with the cornea having abundant nociceptors that are sensitive to external injury (corneal ulcer, laceration, or foreign body). Pain from within the eye (uveitis, acute glaucoma) is most likely transmitted via stimulation of nociceptors in the ciliary body and iris.[18] Surgery of the eyelids and other periorbital tissues will also induce a pain response. As with any other surgery, analgesia for ophthalmic surgery should follow the

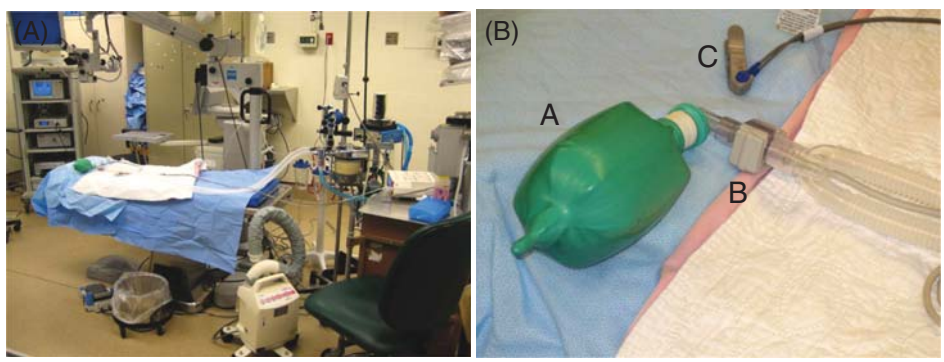



**Figure 10.4** (A and B) Before anesthesia, the ventilator should be checked to make sure it is working correctly. This is achieved by placing an anesthetic breathing bag (A) on the patient end of the anesthetic breathing circuit to act as a "lung." The ventilator can then be cycled to ensure proper function. Note also that a mainstream end-tidal $CO_2$ analyzer (B) is attached to the breathing system, and a pulse oximeter probe (C) is ready to be attached to the patient.

basic principles of pain management. The aim should be to make the patient as comfortable as possible by providing pre-emptive (administering analgesics before the start of surgery) and multimodal (using drugs that act via different receptor mechanisms) analgesia where appropriate.

### Local anesthetics

Topical local anesthesia will provide relief from keratoconjunctival pain. This class of drugs is not recommended for long-term topical pain management because of the fact that they delay healing. Their use is thus largely diagnostic. Although local anesthetic drops work rapidly, they may cause pain when administered. Intraocular local anesthetic has been investigated in dogs, with intracameral injection of preservative-free lidocaine producing no adverse effects on IOP or corneal thickness.[19] Intravenous infusion of lidocaine provided comparable analgesia to morphine infusion in dogs undergoing intraocular surgery with no side effects reported.[20] Loss of sensation to the globe and eyelids, as well as kinesis (immobility of the globe) can be achieved via retrobulbar local anesthetic administration.[21] However, owing to the possibility of severe side effects (retrobulbar hemorrhage, damage to the optic nerve, and intrathecal injection) and the ability to provide analgesia with other drug modalities, this is rarely performed. An auriculopalpebral nerve block can be performed to facilitate surgery of the upper eyelid and closely associated structures.[22] Local anesthetic is deposited subcutaneously dorsal to the zygomatic arch at its caudal one-third.

### Opioids

Topical administration of morphine 1% solution relieved pain associated with corneal ulcers in dogs, without affecting healing.[23] Systemically administered morphine decreases IOP; however, it may induce vomiting, which increases IOP. Other opioids, such as methadone, have a decreased incidence of vomiting and may be more appropriate in cases where IOP is increased. The administration of opioids can be delayed until after anesthesia has been induced. Intraoperatively, pain can be treated by IV boluses (e.g. hydromorphone) or infusions of opioids (e.g. fentanyl). Postoperative vomiting is rare in cats and dogs; however, if patients require opioids to control pain after surgery, they should be observed for vomiting and/or retching. If this occurs, opioid administration should be decreased.

### Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease inflammation by inhibiting cyclooxygenase in the arachidonic pathway, leading to inhibition of prostaglandins. Topical and systemic NSAIDs are effective at treating ocular pain and may decrease unwanted sequelae of ocular inflammation such as glaucoma. Caution should be used when administering NSAIDs to patients with renal disease, coagulopathy, hyopvolemia, hypotension, and gastrointestinal disease. Concomitant use with corticosteroids should be avoided.

## Anesthetic management

All drugs and equipment needed for the anesthetic episode should be gathered and checked before use. This includes anesthetic induction drugs, NMBAs, and reversal drugs, and monitoring equipment, including peripheral nerve stimulator and mechanical ventilator.

Drug choices in patients who are not at risk of globe rupture and have normal IOP depend on risk assessment on the basis of the patient's systemic health status and any behavioral considerations. In animals with glaucoma, ocular foreign bodies, deep corneal ulcers, or partial prolapse of the vitreus, it is essential to prevent further increases in IOP, which may lead to loss of vision or globe rupture. Drugs that may cause vomiting or retching should be avoided in these patients (opioids, alpha-2 agonists). Opioids can be administered after the patient has been anesthetized.

Animals should be gently restrained for administration of premedication and for catheter placement and induction of anesthesia. If struggling occurs or if excessive pressure around the neck (i.e. pressure on the jugular veins) is necessary, IOP will be increased. The administration of additional sedation is preferred in these cases.

Placement of an intravenous catheter in a hindlimb will give the anesthetist better access for drug administration during surgery (Figure 10.3). Fluid administration set extensions can be used to facilitate access if a catheter is placed in a forelimb; however, drugs will take longer to enter the circulation. This may be problematic

if emergency drugs need to be given. Intravenous induction of anesthesia should be performed with the goal of smoothly and rapidly intubating the animal. Intubation should not be performed under a very light plane of anesthesia, as this is more likely to result in gagging and an increase in IOP. The increase in IOP associated with intubation is short lived.

During surgery, the anesthetist must focus on changes in heart rate and blood pressure, as well as respiratory rate and pattern (if the patient is not being ventilated mechanically) as indicators of anesthetic depth. As the head is away from the anesthetist and covered with drapes, it is also important to be sure that the patient-to-breathing system connection is maintained. A deflated anesthetic breathing bag, a ventilator that cannot produce adequate peak inspiratory pressure, and a report of the smell of inhalant by the surgeon are indicators that there is a leak and intervention is required.

## Recovery

Patients should not be allowed to repeatedly gag on or make multiple attempts to cough out the endotracheal tube; the tube should be removed after the first reaction. It is essential that both eyes be protected during recovery. If both eyes have been operated on, the patient should be recovered in sternal recumbency. Emergence delirium and excitement should be treated with sedation as needed. Many animals will try to scratch at their eyes after surgery, and placement of an Elizabethan collar is often necessary to protect surgical incisions and the surface of the eye. Care must be taken not to increase IOP during restraint. It may be better to sedate a postsurgical ophthalmic patient rather than trying to perform physical restraint.

In cases where NMBAs have been administered, patients should be observed closely to ensure adequate ventilation and oxygenation. If a patient appears to be dsypneic or cyanotic, supplemental oxygen should be provided until the cause is established and treated. Oxygen delivered via facemask may be useful in situations where the patient is no longer intubated, but a facemask should not be applied to an animal's face in a way that it places undue pressure on the eyes. If the cause of the problem is not elicited, it may be necessary to reinduce anesthesia and reintubate the patient in order to maintain oxygenation.

## Postoperative care

Comorbidities aside, an intravenous catheter should remain in place for several hours in cases of cataract surgery, in animals with glaucoma, in diabetic animals, and in cases where NMBAs have been used. In glaucoma patients, and after cataract surgery, steps may need to be taken to reduce IOP, such as administering mannitol. Diabetic patients may need glucose supplementation or insulin administration until their normal routine is re-established, and following the use of NMBAs, patients may require additional reversal.

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# 11 Oral and maxillofacial disorders

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The prevalence of periodontal disease is reported to impact 30–80% of dogs and cats older than 3 years.[1–4] In addition, oral diseases have been reported among the most common diagnoses made in small animal general practices.[2] Proper control and minimization of periodontal disease potentially reduce periodontal-disease-related bacteremia[5,6] and systemic inflammatory factors (C-reactive protein)[7], both of which may serve as a risk factor for other systemic disorders. An association between periodontal disease and histologic changes in renal, hepatic, and myocardium has been proposed.[8] Aside from the potential risk for impacting organ function, which may have a direct relationship with the efficiency for metabolism and effectiveness of general anesthetic medications, chronic pain and inflammation can negatively impact an animal's quality of life and their ability to heal.

Fundamentally, periodontal disease in itself will not impact the metabolism of the premedication and induction agents used to induce general anesthesia. Chronic pain and inflammation associated with periodontal disease or other oral conditions may result in windup pain. These patients may exhibit signs of central or peripheral nervous system sensitization and may require a higher dose of premedication owing to their heightened state of sensitivity. The severity or chronicity of oral disease may also impact the effectiveness of local anesthetic drugs.

## Pain management in oral and maxillofacial patients: local and regional anesthesia

### Drug selection

There are a variety of drugs used in local and regional anesthesia for procedures involving the oral cavity. Appropriately placed regional anesthetic blocks in the oral cavity have been shown to reduce the amount of inhalant anesthetic by as much as 23%.[9] Of the sodium channel blockers used in local and regional anesthesia, the lidocaine, or amide, family of drugs is the most common. Toxic or maximum doses should always be considered when deciding how much local anesthetic to administer.

There has been a trend in anesthesia and pain management of human patients to leverage the differing mechanisms of action for various drugs to enhance or prolong the anesthetic or analgesic potential of local or regional blocks. The addition of opioids and alpha-2 agonists to a local or regional block of local anesthetic appears to demonstrate the best potential for enhancing pain relief. It has been shown that chronic nociceptive stimulation results in the upregulation of mu-opioid receptors in the peripheral nervous system. Studies in human patients have shown that by mixing an opioid with the local anesthetic, patients who undergo surgery experience an extended duration of postoperative analgesia.[10,11] Proving similar synergistic effects in veterinary patients would be challenging, and there has not been proof that the addition of opioids administered locally benefits veterinary patients who undergo oral surgery. Anecdotally, the authors of this chapter regularly use microdoses of buprenorphine (15 μg) mixed within the local anesthetic and distributed into as many regional block locations as clinically indicated and believe these patients benefit from the local opioid use. The use of alpha-adrenergic drugs combined with local anesthetics or administered as a local anesthetic also demonstrates potential benefits to patients.[12] In a literature review of alpha-2 agonists used as a local anesthetic in humans, there was pain management at the local level without evidence of hemodynamic

*Canine and Feline Anesthesia and Co-Existing Disease*, First Edition. Edited by Lindsey B.C. Snyder and Rebecca A. Johnson.

side effects from systemic absorption.[13] More chronic conditions would be expected to have the additional recruitment of peripheral mu-receptors[14] and, therefore, should benefit the most from synergy between the locally administered opioid and local anesthetics. The addition of epinephrine to local anesthetics is also a commercially available preparation proposed to improve the duration of local anesthetic activity due to (1) vasoconstrictive effects slowing tissue clearance of the local anesthetic, as well as (2) epinephrine demonstrating primary antinociceptive activity.[12]

While a longer duration of action local anesthetic may be desirable in many situations to encourage a smooth recovery and extended anesthesia of the surgery site, the presence of intraoral sutures and lack of sensation of a maxillary surgery site may result in complications with healing. In procedures, such as maxillary resections or oronasal fistula repair, excessive pressure from the tongue may be disadvantageous, and the use of longer acting local anesthetic drugs may be undesirable. Drug selection for patients undergoing a maxillectomy or oronasal fistula repair may be better served by shorter acting local anesthetic administration followed by aggressive postoperative systemically administered pain medications. Long-acting local anesthetics may result in the patient feeling sutures in oral cavity and, consequently, tongue thrusting/rubbing the surgery site, risking dehiscence of the surgical closure. In particular, in major oral surgery cases in which chronic discomfort occurs, the addition of buprenorphine to a short-acting local anesthetic may improve analgesia, although not prolonging local anesthesia.

## Doses and local anesthetic placement

The use of regional and local anesthesia in human dental patients is widely accepted as beneficial. Complications, including prolonged paresthesia or paralysis, have been reported to occur in 0.00013–0.01% of human dental patients.[15] The use of local and regional anesthesia in people permits procedures including extraction and root canal therapy to be performed on an outpatient basis. The potential regional anesthetic complication that generates the most anxiety among veterinarians is inadvertent anesthesia of the tongue. The basis for this concern is how the patient responds to the anesthetized tongue during recovery. Peripheral nerve paresthesia and subsequent self-mutilation involving the tongue of both veterinary and human patients have only been anecdotally reported.

Injection and placement of the local anesthetic medication may be accompanied by a response from the patient because of the acidic pH of the medication. In the event that there is an increase in heart rate, respiratory rate, or physical reaction by the patient, this may be loosely interpreted as confirmation that the local anesthetic has been administered in the right location. The absence of a reaction does not correlate to the local anesthetic being placed in the wrong location, as the patient may be in a deep plane of anesthesia that renders them unresponsive.

When considering needle placement and injection, some resources recommend needle bevel placement in a certain orientation when performing nerve blocks with local anesthetics. With small volumes and accurate placement, bevel direction may be less important. Placing the local anesthetic in areas over the periosteum adjacent to the foramen out of which the nerve emerges will help to distribute the anesthetic once the needle is removed and digital pressure is applied. A variety of different needle types have been used in human patients with different results. Standard short bevel needles used in veterinary patients are sufficient for placing regional blocks for dentistry and oral surgery patients. Once the needle penetrates mucosa, it should be advanced slowly to minimize the risk of nerve or vessel penetration. Unless the vessel or nerve is confined, the neurovascular structures should be displaced by the bevel rather than penetrated.[16] Some resources advocate the use of very small gauge needles. Although the physical tissue injury would be much smaller, studies in human patients looking at digital pressure on the plunger during local anesthetic administration found that anesthesiologists exerted more pressure than they thought, which translates into faster velocity and greater tissue injury with a smaller gauge needle.[16] Twenty-five to 29-g, 1–1 1/2″ needles are commonly used for local blocks in canine and feline patients undergoing oral surgery.

When performing local or regional anesthetic blocks, it is important to draw back negative pressure (aspirate) to avoid intravascular delivery. Because of the beveled orientation of the needle tip, spinning the syringe barrel 90° along the long access and reaspirating should, at some point, draw the bevel off the vessel wall and result in blood drawn into the syringe if it is in a

vessel. If blood is drawn into the syringe, advance the needle slightly forward or backward and reaspirate. If repeated attempts result in aspiration of blood, remove the needle and try positioning it again. Medication should be administered with the needle being placed on periosteum for the middle mental and caudal mandibular blocks. Even if the bevel is not directly over the nerve, by injecting on the periosteum, the local anesthetic will cover more surface area and increase the chance that the nerve will be contacted. Once the local anesthetic has been administered, the needle should be withdrawn and digital pressure applied for 1 min to provide adequate time to prevent hematoma formation. Injection should not be continued as the needle is withdrawn because inadvertent intravascular injection may result if the vessel was perforated during needle placement.

Commonly reported local anesthetics used for nerve blocks include lidocaine, bupivacaine, lidocaine/bupivacaine combinations, mepivacaine, and combinations including epinephrine. Bupivacaine and lidocaine appear to be the most frequently reported local anesthetics used in dentistry and oral surgery patients. Some variability exists regarding the reported time to onset and duration of activity of these medications; however, general expectations regarding onset of action and duration of action are illustrated in Table 11.1. Because the total maximum dose varies between bupivacaine and lidocaine, careful calculations must be made before mixing these medications.

Bupivacaine is commonly used in local and regional anesthesia for patients undergoing oral surgery because it has a longer duration of activity than lidocaine. The use of bupivacaine provides ample time to deliver oral systemic pain medications before the local anesthetic wears off. Bupivacaine's 6–10-min onset of action is considered intermediate. The duration of action may reach 4–6 h when placed in areas predominately involving soft tissue or 6–8 h when placed in a foramen.[17] Whichever drug is chosen, careful attention should be made to the dose concentration listed on the bottle, as bupivacaine is available in 0.25%, 0.5%, and 0.75% solutions.

When performing the middle mental or major palatine nerve blocks, the needle should not be threaded into the foramen. Placing the needle into either of the two foramina risks transecting or lacerating the nerve. In a study by Krug and Losey, the actual penetration of the local anesthetic medication into the middle mental foramen was questioned, as well as its clinical effectiveness.[18] Krug and Losey's study supports the fact that innervation to the teeth, oral cavity soft and hard tissues, and soft tissues of the face may be an intricate assortment of contributions from branches of multiple cranial nerves.[18] Because few measures of clinical areas of desensitization exist in veterinary patients, regional anesthetic blocks should be administered as a component of multimodal pain management, not a sole source of anesthesia and pain management.

In cases where surgical manipulation will approach midline, as in extracting the first or second incisors or biopsying near the palatal midline, consideration should be given to the potential for crossover innervation to occur.[19,20] Likewise, one should also consider the surgical manipulation associated not only with extraction, but also with closure. In addition, patients may not be adequately anesthetized by an infraorbital regional block when palatal tissues are undermined during extraction of canine or premolar teeth. In most situations, the caudal maxillary block or inferior alveolar blocks may provide more complete regional anesthesia (Table 11.2).

Intraosseous and intraligamentary anesthesia techniques have been described in the veterinary literature.[21,22] Veterinary patients commonly require multiple intraoral procedures to be performed. Rather than multiple intraligamentary or intraosseous anesthetic blocks for adequate regional anesthesia, a single regional anesthetic injection may anesthetize an entire

**Table 11.1** Local anesthetic drugs.

| Drug | Lidocaine | Bupivacaine | Mepivicaine |
|---|---|---|---|
| Time to onset | 1–2 min | 6–10 min | 1–2 min |
| Duration of activity | 1.5–2 h | 4–10 h | 2–3 h |
| Total maximum dosages | 5 mg $kg^{-1}$ (dog) 1 mg $kg^{-1}$ (cat) | 2 mg $kg^{-1}$ (dogs and cats) | |

**Table 11.2** Reasonable expectation for regional anesthesia when local anesthetic is placed correctly.

| Anesthetic block location | Anatomy covered |
|---|---|
| *Dental* | |
| Intraosseous | Tooth specific – periodontal ligament, alveolar bone, gingiva, mucosa, and pulp |
| Intraligamentary | Tooth specific – periodontal ligament, gingiva, and pulp |
| *Mandible* | |
| Caudal mandibular (inferior alveolar) | I1–M3, lower lip from the level of the caudal mental foramen forward |
| Middle mental | I1–PM2, lower lip from middle mental foramen forward |
| *Maxilla* | |
| Caudal maxillary | I1–M2, palatal mucosa, upper lip from the infraorbital canal forward |
| Infraorbital | I1–PM3, upper lip from the infraorbital canal forward |
| Major palatine | Ipsilateral palatal mucosa |

quadrant of the mouth. Local anesthetic administration using intraligamentary or intraosseous techniques may successfully anesthetize focal areas of the mouth but may require the use of specialized needles and injection ports.[21] These blocks are performed by placing the needle into the intraligamentary space in several areas around the affected tooth. This technique targets the sensory fibers of the tooth's pulp. Very small volumes of local anesthetic are used in both intraosseous and intraligamentary local anesthesia.

## Regional block placement

### Intraligamentary and intraosseous local blocks

Intraligamentary and intraosseous local anesthetic blocks provide the most focal form of local anesthesia. These techniques are not performed as commonly in veterinary medicine because they often require the use of special syringes, needles, and dosing cartridges. These local techniques used in humans are not commonly described in the veterinary literature for several reasons. Veterinary dental patients commonly have multiple locations within the oral cavity and within the same quadrant where a single regional block will provide anesthesia. Local blocks administered at the level of a specific tooth may be difficult to assess the efficacy in veterinary patients, and those techniques may be more appropriate to address pulpal innervation, whereas periodontal pocket treatment or extraction is performed more commonly in general practice. Local anesthetic administration may be less effective at providing anesthesia when soft tissue flaps are created and osteotomies are performed to facilitate tooth removal. The periodontal ligament space and root anatomy may also offer challenges, as the density of alveolar bone is greater in veterinary patients than it is in humans.[22]

Intraligamentary injections are performed by injecting 0.2 ml of local anesthetic per root at various locations around the root surface into the periodontal ligament space. A special dosing syringe is necessary, and in cases of severe periodontal disease, the pH of the inflamed environment may decrease the lipophilicity and efficacy of the anesthetic. Intraosseous anesthetic delivery requires an intraosseous delivery needle, which is inserted into the interproximal bone, and the anesthetic agent is delivered. A unique injection port remains in place for additional anesthetic delivery.[22]

### Infraorbital block

The infraorbital block is performed by administering the local anesthetic within the infraorbital canal. Signal transmission is blocked at the level of the infraorbital nerve. Ramifications in the floor of the infraorbital canal course through the alveolar bone and are responsible for innervating ipsilateral maxillary incisors, canine tooth, the first, second, and third premolar teeth, buccal mucosa, portions of the ipsilateral lip, and soft tissues of the rostral cheek (Figure 11.1). The placement of local anesthetic in this location may not reliably anesthetize the palatal mucosa, fourth premolar tooth, and may not completely anesthetize the central incisors because of crossover innervation. The volume necessary to perform this block varies from 0.1 ml in small dogs and cats up to 0.5 ml in large breed dogs.

The upper lip should be reflected dorsally and the neurovascular bundle digitally palpated. The infraorbital canal and neurovascular bundle should be palpable at the level of the distal root of the maxillary third premolar. After palpating these structures, the needle can be inserted through the mucosa and directed along the neurovascular bundle and into the canal (Figures 11.2 and 11.3). To help ensure there is no inadvertent risk to the globe, care should be taken to maintain the syringe parallel to the hard palate (Figures 11.2 and 11.3).

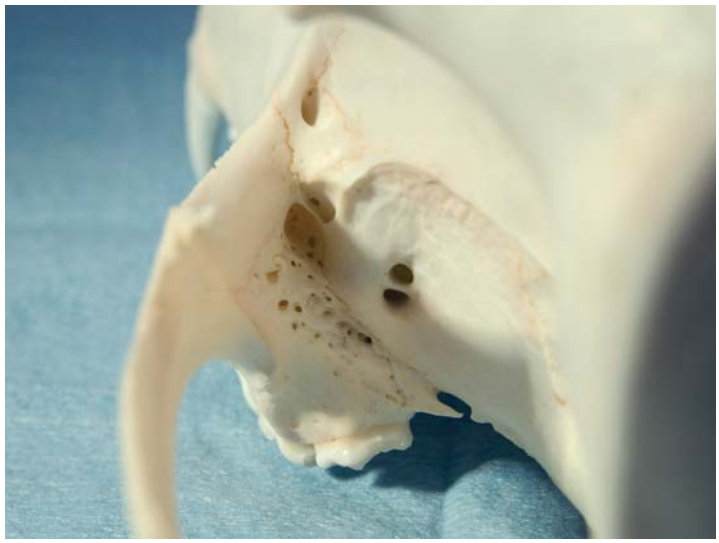

**Figure 11.1** Ramifications in the floor of the infraorbital canal provide the canals for neurovascular supply to the apices of the maxillary teeth. Placement of the infraorbital regional anesthetic block provides sodium channel blockade of the nerves at this level.

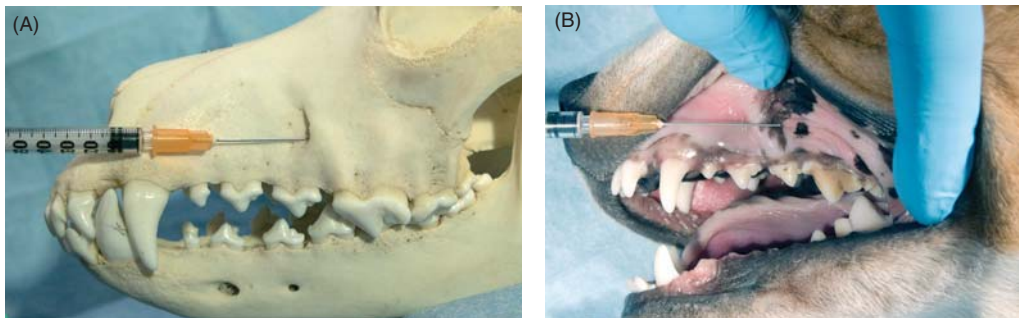


**Figure 11.2** (A and B) The infraorbital artery/vein/nerve can be palpated emerging immediately dorsal to the mesial roots of the fourth premolar and distal root of the third premolar in dogs. The vessel can be isolated through digital palpation and digitally retracted in large breed dogs. The needle bevel should pierce through mucosa several millimeters rostral to the canal opening/neurovascular bundle to permit the needle to be redirected into the canal opening. The needle should be advanced far enough to ensure intracanal placement. Note that the needle and syringe are parallel to the hard palate.

Once the needle is advanced through soft tissues to the opening of the infraorbital canal, the syringe should be aspirated and rotated along the long axis and reaspirated every 90° through a complete 360° revolution. Digital pressure should be applied for 1 min after withdrawal of the needle to prevent leakage of the local anesthetic and reduce the likelihood for development of a hematoma.

### Caudal maxillary block

Proper placement of the caudal maxillary nerve block will result in regional anesthesia of the maxillary teeth in the ipsilateral quadrant, lip, hard/soft palatal mucosa, and buccal soft tissues. By guiding the needle through the infraorbital canal and into the suborbital soft tissues, the needle tip should approximate the course of the maxillary branch of the facial nerve at the level of the sphenopalatine nerve (Figure 11.4). The local anesthetic should be administered when the needle tip has been advanced to a point immediately caudal to the last molar tooth. (Figure 11.5). Successful administration of this block in large breed dogs may require the use of a 3-inch spinal needle (Figure 11.6). Other variations to this technique have been described elsewhere.[22] By using the infraorbital canal to direct needle placement, the natural anatomy is used to guide proper placement of the local anesthetic.

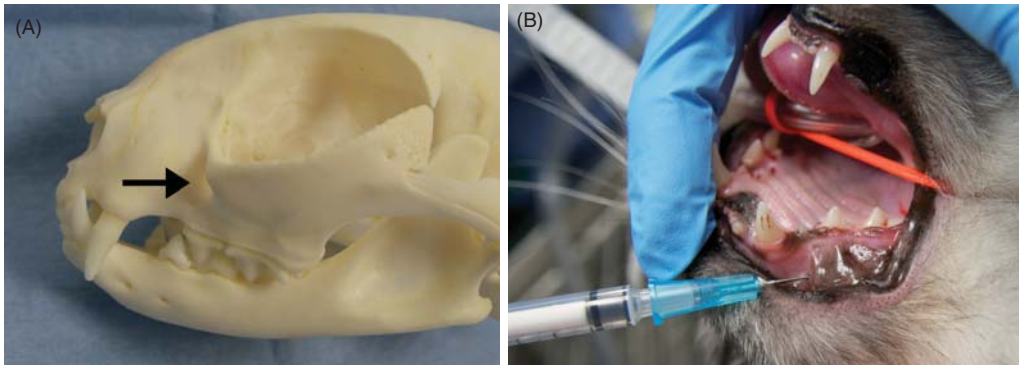


**Figure 11.3** (A) The infraorbital canal in the feline rests 4–6 mm ventral from the medial canthus of the orbital rim and apical to the maxillary third premolar. (B) Needle placement should take place immediately rostral to the third premolar to permit redirection of needle into the infraorbital canal. Care should be taken to ensure that the syringe and needle are maintained parallel to the hard palate.

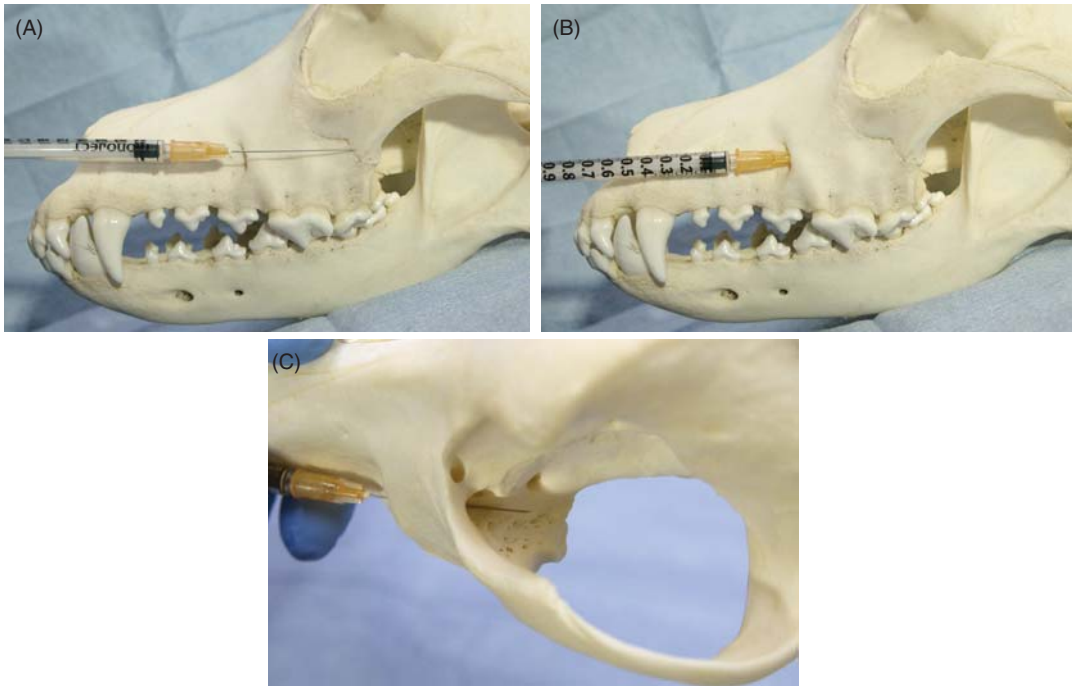


**Figure 11.4** (A) Needle length can be evaluated by laying the needle along the alveolar mucosa and palpating the caudal aspect of the maxillary bone in dogs. (B) Advancement of the needle through the infraorbital canal and maintaining the parallel position to the roof of the mouth will direct the needle bevel toward the maxillary branch of the trigeminal nerve. (C) Placing the block in this location will also block transmission of the major palatine nerve responsible for innervation of the palate.

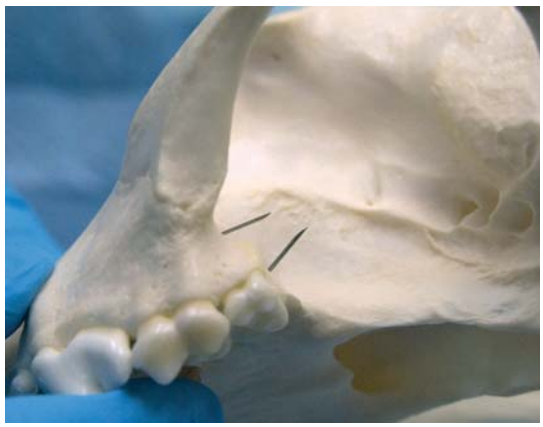

**Figure 11.5** This image demonstrates the convergent nature of the infraorbital canal and major palatine foramen by placing needles through each foramen. By advancing the local block needle caudally through the infraorbital canal, a single regional block can be placed that will anesthetize both the infraorbital branch of the maxillary nerve and the major palatine branch of the maxillary nerve. *Owing to the small size of the foramen, needles should not be advanced through the major palatine foramen.*

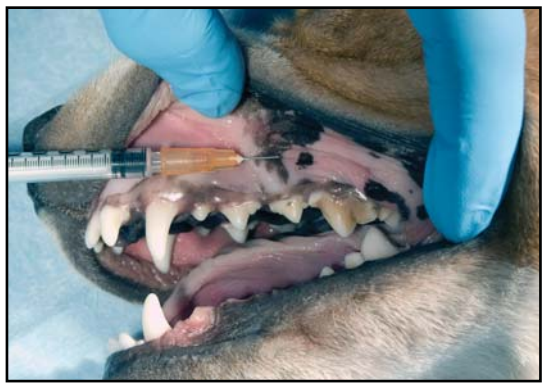

**Figure 11.6** In medium-sized and large-sized dogs, even the 1 1/2-inch needles will be inserted to approximately the hub. The caudal maxillary block is performed by threading the needle through the infraorbital canal and keeping the needle parallel with the hard palate.

Needle placement and orientation are identical to the infraorbital nerve block except that the needle is guided through the infraorbital canal. Care should be taken to maintain the needle parallel with the hard palate to reduce the risk of inadvertent globe penetration. This regional nerve block is not recommended in buphthalmic or severely enophthalmic patients, and particular attention should be paid when performing this block in brachycephalic dogs and cats (Figure 11.7).

### Major palatine block

The major palatine nerve is responsible for sensation of the palatal mucosa (Figure 11.8). This regional block may be used in conjunction with the infraorbital nerve block to provide desensitization for the extraction of the ipsilateral teeth from the incisors to the third premolar. Solely, the major palatine block may provide only complete coverage for biopsies of the palatal mucosa. In most clinical situations, performing a caudal maxillary block will desensitize the palatal mucosa, as well as the teeth and soft tissues on the ipsilateral side of the oral cavity, and the major palatine block is not needed.

The major palatine foramen rests midway between the palatal midline and the medial (palatal) aspect of the dentition because of anatomic variation. The foramen will be located somewhere rostrocaudally between the mesial aspect of the first molar tooth and mesial aspect of the fourth premolar tooth (Figure 11.9). To ensure effective delivery, the local anesthetic should be deposited closer the rostral extent of these landmarks. This will ensure that the anesthetic is delivered at the nerve as it courses rostrally. Efforts to isolate and thread the needle into the major palatine foramen should be avoided to prevent nerve injury. In addition, directing the needle at a 45° angle to the palate and penetrating the palatal mucosa 1–2 ruggal folds rostral from the desired location of local placement will help to avoid leakage of the local anesthetic immediately after withdrawal (Figure 11.10). By placing the local anesthetic against periosteum, the local anesthetic will disperse along tissue planes and improve the likelihood of effective delivery of the local anesthetic.

### Middle mental block

Ventral to the mesial root of the second premolar lies the middle mental foramen (Figure 11.11). The foramen is centered between the ventral cortex and the alveolar crest. A branch of the inferior alveolar nerve emerges through the middle mental foramen and is responsible for innervation of the ipsilateral rostral lip, mandibular incisors, and the first and second premolar teeth.

Needle placement should take place with the needle entering the rostral aspect of the labial frenum and traveling along the periosteum directed toward the mesial root of the second premolar (Figure 11.12).

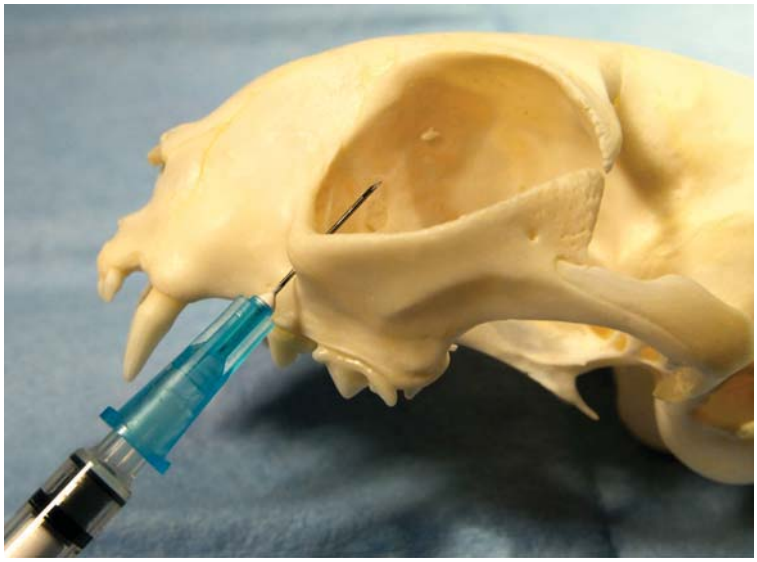

**Figure 11.7** Brachycephalic canines and feline skull shapes have a short infraorbital canal. The shortened canal minimizes the natural restriction by the canal to prevent deflection of the needle toward the globe. *Orienting the needle and syringe in this direction risks iatrogenic trauma to the globe.*

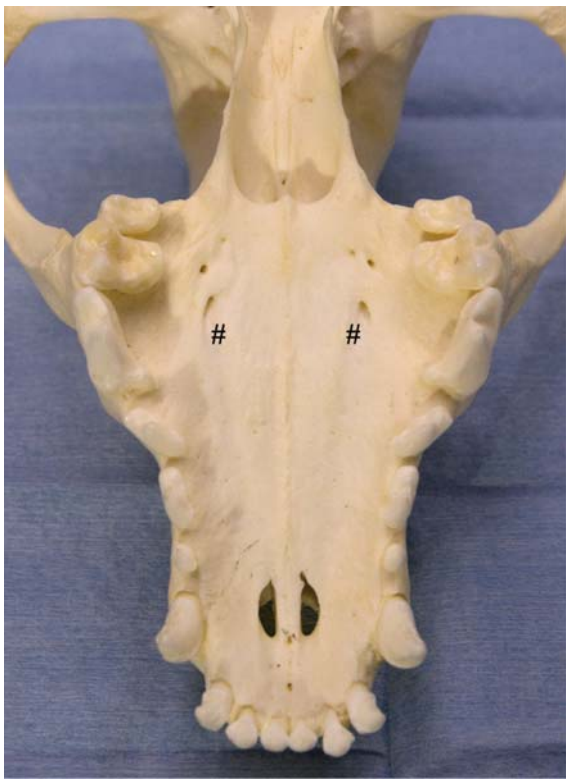


**Figure 11.8** The major palatine foramina (#). The major palatine nerve is responsible for sensation associated with the palatal mucosa.

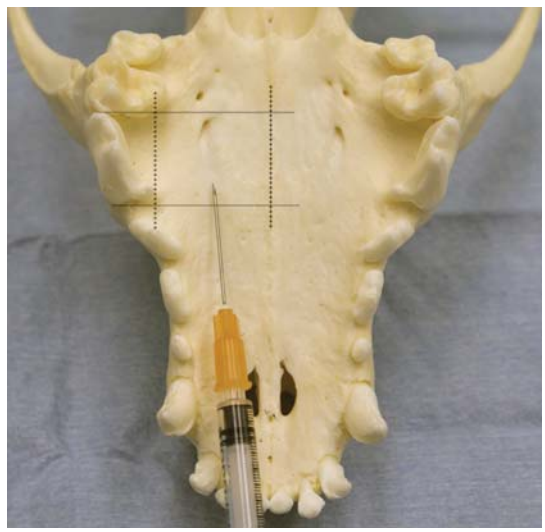

**Figure 11.9** The dashed lines represent palatal midline and the palatal edge of the fourth premolar and first molar teeth. The solid lines represent the rostral and distal most landmarks between which the major palatine foramen lies. Placement of local anesthetic should err toward the rostral edge of this area to ensure that the major palatine nerve courses through the local anesthetic.

**Figure 11.10** Needle placement for the major palatine nerve block – the needle should be placed and advanced through the palatal mucosa, with needle tip terminating at the rostral extent of the landmarks of the area where the major palatine may exist.

Directing the needle through the labial frenum allows for the placement of the needle tip along the periosteum and will aid in the retention of the local anesthetic without leakage on needle removal. The foramen may be easily palpated in larger dogs. Threading the needle into the foramen is not advised because the compact space may result in traumatic nerve damage. Unilateral placement of this local anesthetic may be insufficient to anesthetize the central incisors because of crossover innervation. Bilateral use of this technique may be necessary to adequately anesthetize the central incisors. The anesthetic volume sufficient to provide regional anesthesia ranges from 0.1 ml (cats and small dogs) to 0.3 ml (large dogs).

### Caudal mandibular block

There are two approaches for the placement of a caudal mandibular nerve block. The mandibular branch of the trigeminal nerve enters the mandibular foramen on the lingual aspect of the caudal mandible and continues in the mandibular canal as the inferior alveolar nerve. The inferior alveolar nerve is responsible for innervation of the mandibular molars, premolars, canine teeth, and incisors. The inferior alveolar nerve branches and exits the mandible at the caudal, middle, and rostral mental foramina, which are responsible for sensory information from the alveolar mucosa, gingiva, and rostral lip. The mandibular foramen is identified using several prominent landmarks. In dogs and cats, the mandibular foramen rests approximately halfway between the third mandibular molar and the angular process on the lingual side of the mandible. Palpation of the depression in the caudal mandible immediately rostral to the angular process is frequently referred to as the ventral notch of the mandible. On the lingual surface of the mandible, centered over the ventral notch is the mandibular foramen. The ventral notch may be

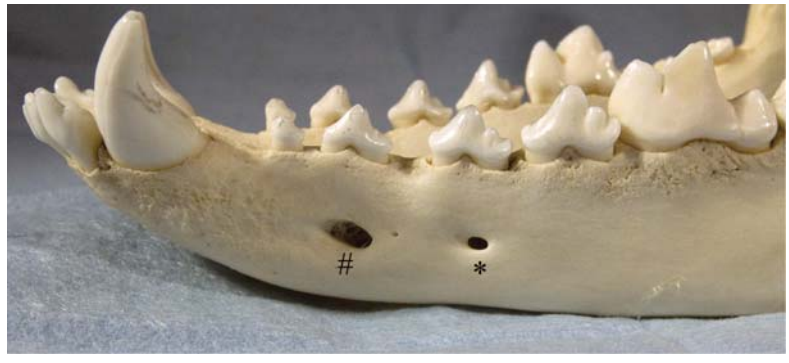


**Figure 11.11** The middle mental (#) and caudal mental (*) foramina. The middle mental foramen is more prominent, located ventral to the mesial root of the second premolar. Placing the local anesthetic at the level of the middle mental foramen will create regional anesthesia for the ipsilateral lower lip, incisors 1–3, canine tooth, and the first and second premolars.

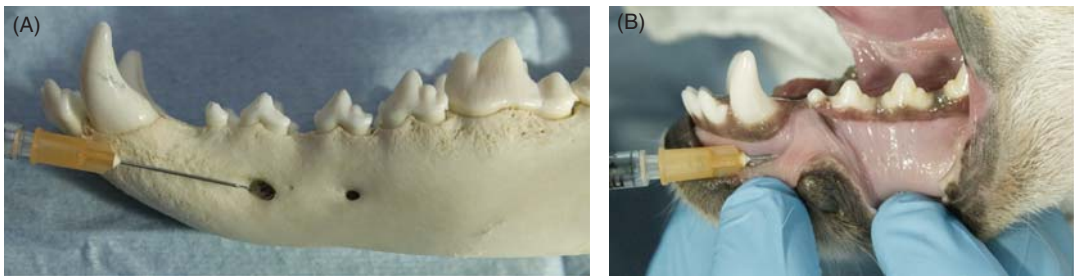


**Figure 11.12** (A and B) The middle mental foramen can be blocked by advancing the needle along the periosteum beginning with the needle penetrating mucosa immediately rostral to the labial frenum. Advancing the needle through the labial frenum will help direct the needle toward the foramen, as well as to help retain the local anesthetic along the periosteum and prevent leakage of the local anesthetic once the needle is withdrawn.

subtle and difficult to palpate in feline patients. Small amounts of local anesthetic (0.1–0.3 ml) are sufficient for regional anesthesia when placed properly.

### Intraoral approach

The angular process and last mandibular molar tooth serve as landmarks for this approach. With one hand, the lip should be retracted and the index finger placed on the angular process. Opening and closing the mouth should result in the angular process moving slightly. Incorrect placement of the index finger on the tympanic bulla will result in no movement, while placing the mandible through a range of motion. Maintaining the index finger on the angular process serves to help direct needle placement. The needle tip should be placed onto the gingiva immediately caudal and lingual to the last molar tooth. The needle should be directed along periosteum and toward the angular process. Local anesthetic should be deposited half the distance between the point of needle entry and the tip of the angular process (Figure 11.13). By maintaining the needle along periosteum, the placement of the local anesthetic along the bone will help diffusion of the local anesthetic to aid in desensitizing the mandibular nerve. Close approximation of the needle to bone also serves to reduce the likelihood of inadvertent anesthesia of the

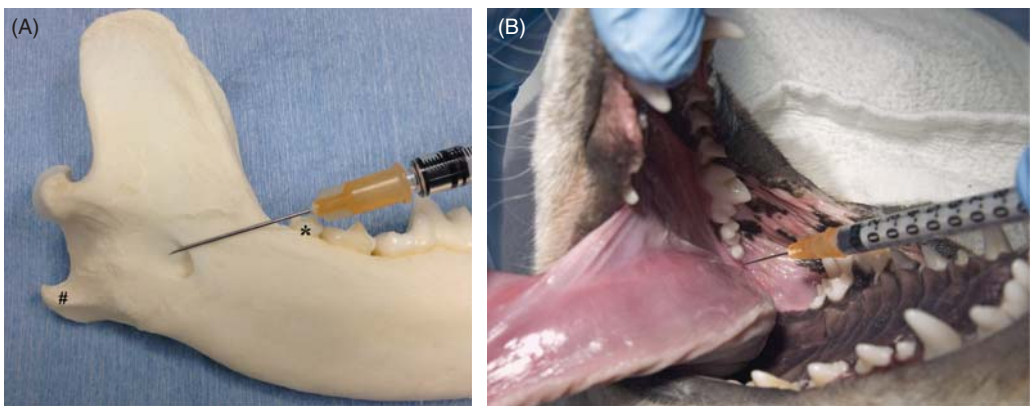


**Figure 11.13** (A) The intraoral approach to local block placement relies on the skeletal landmarks of the angular process of the mandible (#) and the mandibular third molar (*). The angular process should be palpated a finger placed on the process to provide directional support. (B) The needle is placed caudal to the last molar and immediately adjacent to the periosteum on the lingual surface. Approximately half the distance between the last molar and the angular process will be the inferior alveolar foramen. By placing the local anesthetic along periosteum and providing digital pressure afterward, the local will be dispersed over a larger area ensuring coverage of the mandibular branch of the trigeminal nerve.

lingual nerves, which may result in self-trauma of the tongue.

### Extraoral approach

The extraoral approach is dependent on the location and palpation of the ventral notch of the mandible. This approach should not be attempted if there is evidence of dermatitis or other infection in the location of needle penetration. After palpation of the ventral notch, the needle and syringe are oriented perpendicular to the ventral cortical bone. The needle should pierce the skin and contact the ventral cortical bone. Small adjustments are made reorienting the needle off the medial edge of the bone. Advancing the needle along periosteum helps to ensure that local anesthetic placement is against bone to aid in diffusion and reduce the chance that lingual nerves will be affected. The needle tip should be advanced 1/4 cm in cats and up to 1 cm in large dogs (Figure 11.14). Some references recommend digitally palpating the mandibular nerve intraorally when directing the needle extraorally. Caution should be exercised to avoid an inadvertent needle stick when practicing this technique.

## Complications and contraindications

Unpublished information suggests that local anesthetic administration may result in degeneration of the nerve associated with medication administration (J Anthony. 2010, personal communication, 11 June). Although these histologic findings are concerning, the clinical implications may be harder to measure. The long-standing benefits of local block administration in humans suggests that any frequent cellular changes may be transient or of no clinical significance.

When placing the needle through the infraorbital canal, care must be taken to avoid contacting or penetrating the globe. If the syringe and needle are oriented parallel with the hard palate, then the eye should be avoided. Retropulsion of the globe during needle placement or ophthalmic conditions such as bupthalmos may increase the risk for perforation. Care should be taken and risks considered when performing

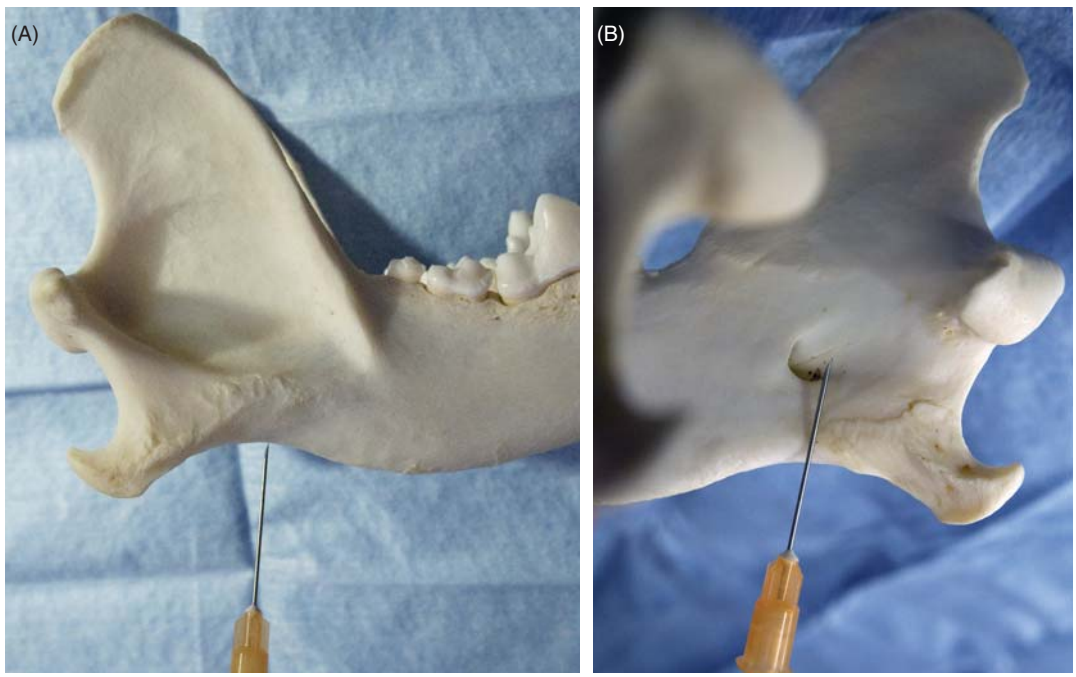


**Figure 11.14** (A) The extraoral technique for the caudal mandibular nerve block involves palpating the ventral notch of the mandible. (B) Palpating the ventral notch and placing the needle directly onto the ventral cortical bone, the needle can be "walked off" the bone (on the lingual side) and advanced 1/2 to 1 cm depending on the size of the animal. Digital pressure can be applied in the mouth after injection to help disperse the local and prevent hematoma formation.

these caudal blocks in these patients. Brachycephalic head shapes and felines should not be at increased risk for globe penetration if the needle is maintained parallel to the hard palate.

Self-trauma due to inadvertent anesthesia of the tongue is sometimes anecdotally mentioned in the veterinary literature. Close attention and deliberate anesthetic placement along the periosteum of the lingual surface of the mandible should avoid this complication. Small volumes (maximum of 0.3–0.5 ml) of anesthetic accurately placed will also reduce the likelihood of this occurrence. One author has suggested that recovery in sternal recumbency may also help reduce this occurence.[23]

Care should be taken when performing or planning regional anesthesia for the collection of tissues for histologic evaluation. Risk of tumor seeding of soft tissue or bony tumors exist if the needle is placed in the vicinity of the suspected mass. In addition, the presence of a mass may alter the local anatomy, and predictability of local block placement may be decreased. Particular consideration used when placing the needle may result in transporting tumor cells beyond the location of the mass. Whenever risk exists for potentially seeding tumor cells, other means of multimodal pain management should be considered.

## Effect of inflammation on the efficacy of local anesthetics

The most common indications for surgical intervention in the oral cavity of dogs and cats are chronic inflammatory conditions of the periodontium (periodontitis) and the endodontic system (pulpitis).

Chronic oral inflammation, such as that seen with periodontal and endodontic disease, culminates in severe infection and inflammation. As a result, local tissue pH is lowered, which diminishes the effect of local anesthetics. The acidity of the local environment decreases the lipophilicity of the anesthetic by diminishing the available nonionized base that is able to penetrate the nerve sheath, ultimately resulting in reduced efficacy of the local anesthetic.[24] In addition, inflammatory exudates can enhance nerve conduction and, thus, limit the effect of the anesthetic delivered.[24]

In order to combat the effects of inflammation on the efficacy of local anesthetics, the clinician can use techniques to improve the outcome. Firstly, the clinician should deliver the anesthetic away from the area of inflammation. Not only will this improve efficacy of the anesthetic, but also will minimize the possibility of spreading the infection to an unaffected area. Secondly, if within the safe dosage range, deliver a larger volume of anesthetic. By doing so, the clinician will effectively deliver more of the nonionized base that can diffuse through the nerve sheath and have an effect on nerve conduction.[24]

## Effect of chronicity on analgesic needs

Patients will present for oral treatment in various states of chronicity. Management of pain in acute conditions (recently fractured tooth) may be as simple as the usage of a local anesthetic immediately before treatment or, perhaps, a few days of postoperative nonsteroidal anti-inflammatory drug (NSAID). However, many patients present with chronic conditions of the oral cavity (stomatitis/gingivostomatitis, chronic pulpitis/endodontic infection, oral cancer, dental caries, TMJ disorders, and tooth resorption), which often lead to a chronic state of pain. Because the natural course of animal behavior is to mask pain, these oral conditions may be present for years before being appropriately addressed. Underappreciation and undertreatment of the pain associated with these conditions by both the owner and the treating veterinarian may confound the problem.[25] In some conditions (stomatitis/gingivostomatitis), the implementation of quality oral hygiene is crucial to successful management. In order to succeed in this endeavor, the patient must be on the precipice of being pain free. A holistic approach to pain management is important, including the use of pharmaceutics and complementary therapies (acupuncture).[25] Chronic pain leads to an alteration of the central nervous system and the way pain signals are processed (central sensitization).[25] Thus, drug therapy should be multimodal (NSAIDs, opioids, NMDA antagonists [ketamine, amantadine], combination analgesics [tramadol], anticonvulsants [gabapentin], tricyclic antidepressants, and/or steroids), and analgesic pain management should be continuous.[25] As the pain is minimized, appropriate oral hygiene can be implemented and individual drugs can be removed from the treatment regimen in a step-wise manner.

## The effect of specific oral and maxillofacial conditions on anesthetic management

### Oral and maxillofacial trauma

There are few circumstances when a maxillofacial fracture is a true emergency. Intractable bleeding (oral or nasal) would necessitate immediate anesthesia in attempt to address the bleeding or to ligate major vascular supplies such as the carotid artery. Patients with maxillofacial trauma should be closely evaluated and screened for signs of head trauma. Pupillary light reflexes, nystagmus, and aberrant cranial nerve reflex responses should increase the suspicion of head trauma. Considerations for patients sustaining head trauma can be found in Chapter 19.

Other than being extremely painful, patients with maxillofacial trauma do not pose unique anesthetic risk or considerations beyond airway management. Airway management and jaw fracture pose obvious challenges, which may be reduced with extraoral methods of intubation. Anesthetic management should proceed as for any other patient with trauma (Chapter 19).

### Oral and maxillofacial surgery

The term "oral and maxillofacial surgery" encompasses a wide range of surgery types that may include, but is not limited to, nonsurgical extraction of a single rooted tooth, repair of an oronasal fistula, and wide surgical resection of a maxillary neoplasia. The degree of intraoperative and postoperative pain will vary greatly depending on, among many things, the invasiveness of the procedure and the types of tissues that are manipulated. A nonsurgical extraction of an incisor may only cause minor discomfort that can easily be managed with an intraoperative local anesthetic, such as bupivacaine, and a postoperative NSAID. However, a more invasive procedure, such as a caudal maxillectomy, will require additional pain control measures. Potential measures to improve both intraoperative and postoperative pain in major oral surgery should be aimed at a multimodal concept and may include the following:

#### Use of a long-acting local anesthetic such as bupivacaine

Bupivacaine may have a prolonged effect up to 8 h after administration.[26] Because of the longer onset of action, proper planning will allow for administration soon after the patient is anesthetized so that it may take effect while the patient is being prepped for surgery.

#### Addition of buprenorphine to the local anesthetic

Although not evaluated in dogs or cats, multiple studies in humans have evaluated the efficacy of adding buprenorphine to bupivacaine local anesthetics. Studies show a prolonged analgesic effect of at least 28 h with a significantly lower requirement for rescue opioids due to uncontrolled pain.[11] In 75% of human patients, the addition of buprenorphine to bupivacaine provided complete analgesia that lasted 30 h beyond the duration provided by bupivacaine alone.[11] It is the authors' opinion that this technique is useful in veterinary oral surgery.

#### Redosing the local anesthetic at the end of the procedure

If a shorter acting local anesthetic such as lidocaine is used, the clinician may consider providing an additional injection at the end of the procedure to aid in postoperative pain control. If this technique is used, one must take care to avoid exceeding the maximum allowable dose.

#### Use of intraoperative and postoperative continuous rate infusions

Continuous rate infusions of opioids, such as fentanyl or morphine, with or without lidocaine and/or ketamine can be a useful technique for intraoperative and postoperative pain management. For major oral surgery cases (mandibulectomy, maxillectomy, jaw fracture repair, etc.), the authors typically use a fentanyl CRI or a CRI of morphine or fentanyl with lidocaine and ketamine (MLK/FLK).

### Airway management in oral and maxillofacial patients

There are several situations when orotracheal intubation is either impracticable or simply not possible in oral and maxillofacial patients. Several alternative techniques are available. The technique chosen depends on the peculiarities of each patient and their specific condition. However, the most common alternative technique is pharyngotomy intubation (Figure 11.15). Standard pharyngotomy intubation techniques are readily available in surgery textbooks.[27] Placement of the pharyngotomy endotracheal tube on the left side permits the placement of a pharyngostomy feeding

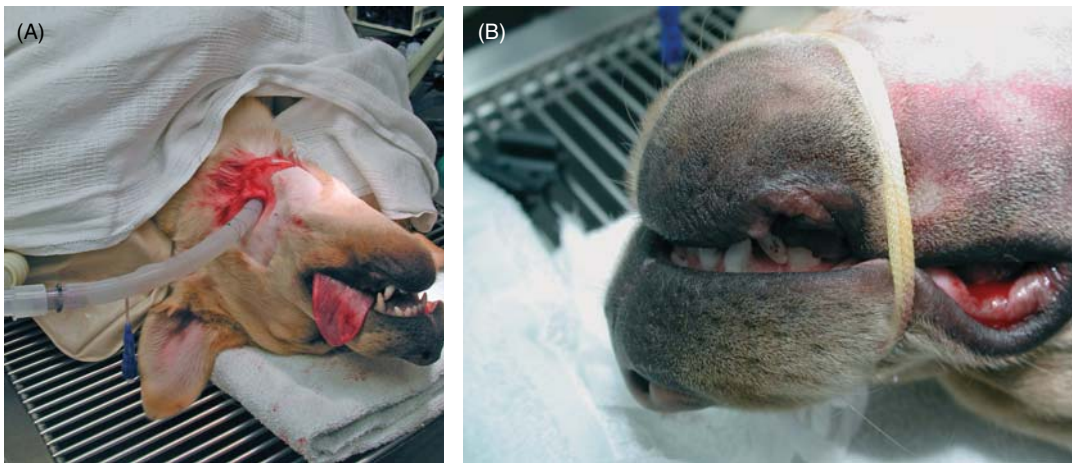


**Figure 11.15** (A) This patient sustained a caudal mandibular fracture and was maintained on inhalant with a pharyngotomy intubation placement. (B) Intubation in this manner permitted the use of a gauze muzzle to maintain this patient in normal occlusion and the fracture to be approached with an extraoral surgical approach.

tube through the same stoma before extubation if concern exists regarding the patient's willingness or ability to eat after surgery. Pharyngostomy feeding tubes may be associated with increased complications over esophagostomy feeding tubes, and so clinical decision making and surgeon's preference become important for postoperative supplemental feeding considerations.

## Oral and maxillofacial trauma

Early return to function and maintaining occlusion are fundamental principles unique to oral and maxillofacial trauma management. Often, the presence of the endotracheal tube exiting the oral cavity may obscure or interfere with evaluation of occlusion during repair. Two techniques exist to combat this challenge.

Once the patient is intubated, an identical endotracheal tube can be used to evaluate the length of the tube, and an ideal length can be established. The hose connector can be removed and the soft plastic cut and hose connector replaced. Modifications to tube length should not be so drastic that the cuffed pilot tube be disrupted. The shortened tube can be exchanged with the patient's endotracheal tube used to induce and stabilize anesthesia. The goal should be to now have a tube that has the hose connector positioned within the oral cavity. This location of the hose connector will permit intermittent disconnection from the breathing circuit to assess occlusion and ensure that the fracture repair does not result in overcorrection or undercorrection resulting in inappropriate tooth-on-tooth contact. Modifying endotracheal tube length may be safer than risking tracheal laceration or main stem bronchial intubation resulting from advancing the endotracheal tube deeper into the airway.

More practically, once the patient with maxillofacial fracture is stable under general anesthesia and a treatment plan is created that involves returning the patient to normal occlusion, converting the patient to a pharyngotomy intubation may make the repair and intraoperative evaluations of occlusion more efficient. With pharyngotomy intubation, the oral cavity is bypassed entirely and occlusion can be more closely monitored. In many situations having the oral cavity completely free and unimpinged by the endotracheal tube, it becomes quite reasonable to place the patient's mouth into the pretrauma occlusion and use gauze or other restraint to maintain the mouth in that position. Once the patient's occlusion is returned to normal, the fracture fragments should be orientated in a position that will be conducive to maintaining that normal occlusion.

Careful anesthetic consideration should be given if the selected method of fixation involves maxillomandibular fixation (MMF). When these repair techniques are used using composite or acrylic materials to bond teeth from the mandibular arcade to the maxillary arcade, a plan must be made to address how the patient will be intubated at the time of MMF removal. Once the induction agent is given, extension of the neck and use of a long

laryngoscope blade with a light source or even a rigid or flexible endoscope may be necessary to visualize the larynx to facilitate intubation. If MMF is created with reintubation considered, it may be possible to quickly cut or remove the bonding material once the induction agent has been administered, and the patient immediately intubated for further evaluation.

### Oral and maxillofacial surgery

Uninhibited access to the oral cavity is often crucial for successful major oral surgery such as maxillectomy, mandibulectomy, palatal defect repair, and glossectomy. Without having the endotracheal tube taking up valuable space in the oral cavity, surgery becomes more manageable and helps ensure a more positive outcome with fewer intraoperative complications. In this situation, a pharyngotomy intubation may be more practical.

In addition, some neoplastic lesions in the caudal oral cavity may be large enough to either significantly compromise a patient's airway or interfere with orotracheal intubation. In such circumstances, it may be necessary to perform a temporary tracheostomy until the airway can be recovered.

### Trismus

In a stricter sense, trismus is defined as an inability to open the mouth due to spastic activity of the muscles of mastication.[28] However, it is commonly used generically to describe an inability to open the mouth from any potential cause, which may include the following: masticatory myositis, craniomandibular osteopathy, tetanus, retropharyngeal abscess, retrobulbar abscess, odontogenic infection, temporomandibular apparatus dysplasia, temporomandibular apparatus trauma, temporomandibular apparatus neoplasia, salivary gland disease, and postradiation fibrosis.

These conditions share a common denominator in that the diagnostic workup for these conditions typically require general anesthesia for diagnosis and/or treatment. The degree to which a patient is affected by trismus can vary and may cause extreme difficulty intubating the patient through the oral cavity. When confronted with a patient with known trismus or a condition that could cause trismus, the anesthetist should be prepared for the implementation of tracheostomy intubation. Pharyngotomy intubation is not an option in these situations, as it requires initial orotracheal intubation while the extraoral pharyngotomy approach is made. Premedications and induction agents that can cause vomiting should be avoided.

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# 12 Hematologic disorders

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The maintenance of oxygen delivery to tissues is the principal cardiovascular goal in the management of any anesthetic episode. Oxygen delivery is the product of arterial oxygen content ($CaO_2$) and cardiac output (Q). $CaO_2$ is composed of both dissolved and hemoglobin (Hb)-bound oxygen in the blood and its calculation takes into account the arterial partial pressure of oxygen ($PaO_2$, in millimeters of mercury), the Hb concentration (in grams per deciliter blood), and saturation of arterial Hb with oxygen ($SaO_2$, in percentage). The contribution of Hb and $SaO_2$ to $CaO_2$ is much greater than that of $PaO_2$. This relationship is described by the following equation (Equation 12.1)[1]:

$$CaO_2 = \left[\frac{1.34\,\text{ml}\ O_2}{\text{g}}\text{Hb} \times [\text{Hb}] \times SaO_2\right] + [0.003\,\text{ml}\ O_2/\text{dl blood/mmHg} \times PaO_2] \quad (12.1)$$

Approximately 97% of total arterial oxygen content is bound to Hb in mammalian blood.[2] As a result, disorders in oxygen-carrying capacity, for example, anemia and dyshemoglobinemias, have a much greater impact on oxygen delivery to tissues compared to disorders of decreased dissolved oxygen stores, although low dissolved oxygen will adversely affect the Hb saturation (Table 12.1).

Table 12.1 demonstrates the effects of anemia, hypoxemia, and dyshemoglobinemia (e.g. methemoglobinemia) on arterial oxygen content and subsequent oxygen delivery. In general, mammalian arterial oxygen content is equal to 19.9 ml $O_2$ per dl blood under standard conditions (arterial partial pressure of $CO_2$ of 40 mmHg, 37°C body temperature, pH 7.4 and, [Hb] of 15 g $dl^{-1}$).[1] While severe hypoxemia (decreased $PaO_2$) causes a relatively small decrease in overall arterial oxygen content (17.2 ml $O_2$ per dl blood), severe reductions in oxygen-carrying capacity (anemia or methemoglobinemia) produce more profound reductions in $CaO_2$. Changes in cardiac output (increases in heart rate, stroke volume, or both) can compensate for low $CaO_2$ to a degree, but at critical points, tissue oxygen delivery ($DO_2$) may be compromised.

## Monitoring of oxygen content in the anesthetized patient

Arterial oxygen content may be monitored by evaluating blood gas analysis or may be estimated via oximetry and hematology tests, including packed cell volume (PCV), hematocrit (Hct), and Hb concentration. Blood gas analysis quantifies dissolved partial pressure of oxygen in arterial or venous blood ($PaO_2$, $PvO_2$) and saturation of Hb with oxygen ($SaO_2$, $SvO_2$). Patients breathing room air (~21% $O_2$) in the absence of pulmonary disease are expected to have a $PaO_2$ between 80 and 100 mmHg, $PvO_2$ of 42 ± 5 mmHg, $SaO_2$ of 98–100%, and $SvO_2$ of 75%.[3] Pulse oximetry provides a less invasive means of monitoring Hb–oxygen saturation, yielding an "SpO2" value.

The relationship between $PaO_2$ and $SaO_2$ (or $SpO_2$) is described by the oxyhemoglobin dissociation curve (Figure 12.1). In general, as $PaO_2$ increases, more oxygen is available to bind to Hb, to a maximum of 100% saturation. An $SpO_2$ value of 100% correlates with $PaO_2$ values ≥100 mmHg, whereas an $SpO_2$ of 95% correlates with a $PaO_2$ of ~80 mmHg. An $SpO_2$ value of 94% correlates with a $PaO_2$ of ~70 mmHg and is consistent with hypoxemia that merits diagnostics and treatment.

Various physiologic changes affect the affinity of Hb for oxygen and may result in a shift of the

*Canine and Feline Anesthesia and Co-Existing Disease*, First Edition. Edited by Lindsey B.C. Snyder and Rebecca A. Johnson.

**Table 12.1** Effects of anemia, hypoxemia, and methemoglobinemia on the oxygen content of arterial blood.

| Patient status | (Hb) ($g\,dl^{-1}$) | $SaO_2$ (%) | $PaO_2$ (mmHg) | $CaO_2$ (ml $O_2$ per deciliter) | $DO_2$ ($ml\,min^{-1}$) (Assuming cardiac output ~2 $l\,min^{-1}$) |
|---|---|---|---|---|---|
| Normal | 15 | 97.5 | 100 | 19.9 | 398 |
| Hypoxemia | 15 | 85 | 50 | 17.2 | 344 |
| Anemia | 7.5 | 97.5 | 100 | 10.1 | 202 |
| Methemoglobinemia (33% MetHb) | 10 | 97.5 (functional saturation) | 100 | 13.3 | 266 |

A 50% reduction in hemoglobin concentration (e.g. severe anemia) causes a more profound decrease in oxygen delivery than a 50% reduction in dissolved oxygen (severe hypoxemia). Methemoglobinemia decreases the availability of normal hemoglobin, thereby decreasing oxygen delivery to tissues. Oxygen delivery in this table is calculated on the basis of a cardiac output of 2 $l\,min^{-1}$.

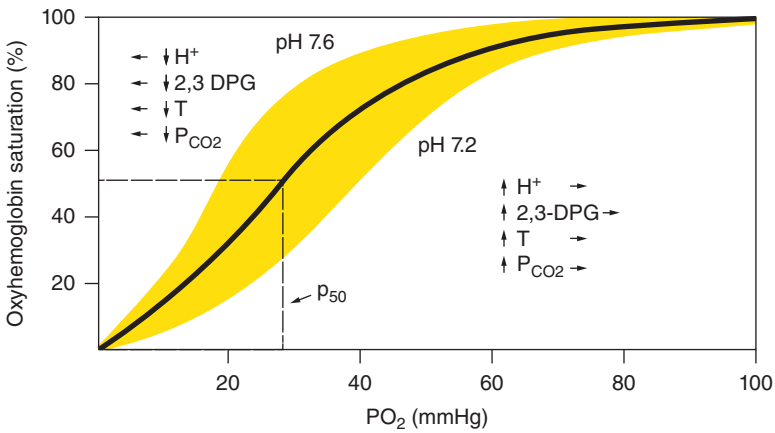


**Figure 12.1** Oxyhemoglobin dissociation curve and regulating factors. Physiologic factors that shift the curve to the left, facilitating binding of oxygen to hemoglobin include alkalemia (decreased circulating hydrogen ion concentration), decreased body temperature, decreased circulating partial pressure of $CO_2$, and decreased concentration of 2,3-diphosphoglycerate (2,3-DPG). Factors that shift the curve to the right, facilitating offloading of oxygen to the tissues are acidemia, increased 2,3-DPG concentration, increased body temperature, and increased circulating partial pressure of $CO_2$.

oxyhemoglobin curve to the right (decreased affinity, favoring offloading of oxygen to the tissues) or to the left (increased affinity, favoring onloading of oxygen to Hb). In humans, the conditions that decrease affinity of Hb for oxygen include increased partial pressure of $CO_2$, increased body temperature, increased 2,3,diphosphoglycerate (2,3 DPG) concentration within the erythrocyte, and decreased blood pH. The conditions that increase affinity of Hb for oxygen include decreased blood $CO_2$ concentration, decreased body temperature, decreased 2,3, DPG, and increased pH (Figure 12.1).

Hemoglobin structure also influences its affinity for oxygen.[4] Normal Hb must be in the reduced, ferrous ($Fe^{2+}$) state to bind oxygen. Dyshemoglobinemias include methemoglobin (MetHb) and carboxyhemoglobinemia. Methemoglobin (MetHb) is an oxidation product of Hb that forms a reversible complex with oxygen and impairs offloading of oxygen to the tissues. Causes of methemoglobinemia include congenital and acquired causes, including toxicity from acetaminophen, nitrates, benzocaine, benzyl alcohol, and prilocaine. Feline Hb appears to be more sensitive to MetHb formation than canine Hb.[5] Carboxyhemoglobin (COHb) is formed when Hb is exposed to carbon monoxide. Carbon monoxide competitively binds to Hb with an affinity more than 200-fold greater than Hb's affinity for oxygen,

and is most commonly encountered in patients who have inhaled products of combustion (e.g. house fires).[6]

Oxygen-carrying capacity may be quantified by tests including Hct, PCV, red blood cell (RBC) count, and Hb concentration. Hct is the percentage of blood composed of RBCs. Centrifugal methods yield PCV, which accurately estimates Hct. Hct can be calculated by automated cell counters; however, because many hematology analyzers are designed for human blood and most domesticated mammalian species (except for dogs) have smaller erythrocytes than humans, this method of Hct calculation has more potential for error than PCV. Calculation of Hb concentration provides the most specific indicator of oxygen-carrying capacity but may be falsely high in the presence of hemolysis, lipemia, Heinz bodies, or synthetic Hb products. When erythrocytes are normal in size and intravascular hemolysis is not significant, Hb concentrations should be approximately one-third of the Hct. For example, patients with a hemogobin concentration of 10 g per deciliter of blood are expected to have a concurrent hematocrit of approximately 30%.

Causes of anemia in companion animals can be generally classified into three categories as follows: inadequate erythrocyte production (i.e. abnormal erythropoiesis), increased consumption or destruction (e.g. hemolysis), and loss (e.g. hemorrhage; see Table 12.2). Causes of decreased erythrocyte production include systemic disease such as chronic renal failure or neoplasia with myelopthesis or can result from toxicities (e.g. estrogen). Hemolysis may be seen secondary to immune-mediated mechanisms or toxicities, and neoplasia or infection with RBC parasites (e.g. *Babesia* sp.) may also trigger hemolysis. Hemorrhage in veterinary patients may not always be obvious, and signs such as melena or elevated blood urea nitrogen (BUN) may indicate gastrointestinal bleeding and should be considered as part of the preanestheic workup. Hemorrhage may also be due to anticoagulant rodenticide toxicity, and vitamin $K_1$ therapy may be indicated before the patient undergoes any invasive procedures (see the following section). In patients presenting for anesthesia and surgery who may have indications of anemia due to any of the aforementioned causes, at minimum, a platelet count and coagulation panel are indicated to better define the patient's hemostatic ability. It is also prudent to obtain a blood type on the patient before anesthesia, to facilitate rapid transfusion if necessary during the procedure.

The chronicity of a patient's anemia may influence the management of any hemorrhage that occurs intraoperatively. With chronic anemia, Hb gradually develops an increased relative ability to carry oxygen, due to an increase in 2,3,DPG, which may compensate for a degree of the anemia-related oxygen delivery deficit.[8] As a result of this physiologic adaptation, patients with chronic anemia may tolerate small intra-anesthetic decreases in Hct without requiring RBC transfusion. Adult patients with chronic hypoxemia also develop increased 2,3-DPG levels over time, shifting their oxyhemoglobin dissociation curve to the right, which favors offloading of oxygen to their tissues.[9] Although intravenous fluid therapy may cause a dilutional drop in PCV, this does not necessarily correspond with a tissue oxygen delivery deficit (the total RBC mass has not changed); however, patients should be monitored closely for signs of impaired tissue oxygen delivery such as hyperlactatemia and tachycardia.

Hydration status should be considered in interpretation of Hct values: anemia in a dehydrated or hypovolemic patient may only reveal itself after replacement of the fluid deficit. Serum total protein, albumin, BUN, and creatinine concentrations may also be elevated in dehydrated patients, although serum protein concentrations and decreases in body weight have proven more useful than azotemia or elevated Hct as indicators of dehydration in otherwise healthy dogs.[10] Healthy horses are likewise expected to lose body weight and have elevated blood protein concentration in the face of water deprivation, with no reliable change in PCV.[11] Interpretation of PCV may be further confounded in species known to undergo splenic contraction during times of stress (e.g. horses and dogs). Azotemia should always be interpreted with respect to urine specific gravity to differentiate renal, postrenal, and prerenal (dehydration or hypovolemia) causes. Elevated BUN may also indicate gastrointestinal hemorrhage, among other differentials. Hct should always be interpreted in conjunction with historical information, physical examination, and biochemistry findings in preparation for anesthetic management of individual patients.

Caution should be exercised in the interpretation of PCV values in the midst of acute hemorrhage: due to splenic contraction, acute hemorrhage is frequently accompanied only by a decreased total protein, with a normal to increased PCV. Changes in PCV may not be

**Table 12.2** Pathophysiology of anemia.

| Pathophysiology of anemia | | | | | |
|---|---|---|---|---|---|
| **Hemorrhage** | | **Accelerated erythrocyte destruction** | | **Abnormal erythropoiesis** | |
| **Acute** | **Chronic** | **Intravascular hemolysis** | **Extravascular hemolysis** | **Reduced erythropoiesis** | **Defective erythopoiesis** |
| *GI ulcers*<br>*Hemostasis defects*<br>*Neoplasia*<br>*Thrombo-cytopenia*<br>*Trauma*<br>*Surgery* | *Disseminated intravascular coagulation (DIC)*<br>*Toxicities*<br>• Rodenticide<br>• Bracken fern<br>• Sweet clover<br>*Hemophilia A & B* | *Bacteria*<br>• *C. hemolyticum, C. novyi, C. perfringens*<br>• *E. coli*<br>*RBC parasites*<br>• *Babesia* spp.<br>*Chemicals and plants*<br>• Acetaminophen<br>• Brassica spp.<br>• Copper<br>• Onions<br>• Red Maple<br>*Immune-mediated*<br>• Hemolytic anemia (IMHA)<br>*Hypo-osmolality*<br>*Fragmentation*<br>*Hypophosphatemia*<br>*G-6-PD deficiency*<br>*GSH deficiency (sheep)*<br>*Hepatic failure (horses)*<br>*Phosphofructokinase deficiency (dogs)* | *RBC parasites*<br>• *Anaplasma* spp.<br>• *Cytauxoon* spp.<br>• *Hemobartonella (Mycoplasma)* spp.<br>*Immune-mediated*<br>• Hemolytic anemia<br>• *Ehrlichia* spp.<br>• Feline leukemia virus<br>• Hemangiosarcoma<br>• RBC parasites<br>• *Sarcocystis* spp.<br>*Intrinsic erythrocyte defects*<br>*Fragmentation*<br>• DIC<br>• Heartworm<br>• Hemangiosarcoma<br>• Vasculitis<br>*Hemophagocytic syndrome*<br>*Hypersplenism*<br>*Malignant histiocytosis* | *Anemia of chronic disorders*<br>• Chronic inflammation<br>• Neoplasia<br>*Cytotoxic bone marrow damage*<br>• Estrogen<br>• Phenylbutasone<br>• Cytotoxic cancer drugs<br>• Radiation<br>• Bracken Fern<br>*Reduced erythropoietin*<br>• Chronic renal disease<br>• *Hypoadrenocorticism*<br>• Hypothyroidism<br>• Hypoandrogenism<br>*Immune-mediated*<br>• Pure red cell aplasia<br>*Infection*<br>• Ehrlichia spp.<br>• Feline leukemia virus<br>• Feline panleukopenia virus<br>• Parvovirus<br>*Myelophthisis*<br>• Lymphocytic leukemia<br>• Metastatic neoplasia<br>• Myelofibrosis<br>• Myeloproliferative disorders | *Abnormal maturation*<br>*Disorders of heme synthesis*<br>*Disorders of nucleic acid synthesis* |

*Source:* Adapted from Brockus and Andreasen.[7]

seen until hemorrhage is severe or adequate volume resuscitation has been administered, thus uncovering the degree of blood loss. In cases of hemorrhage of <20% of the patient's blood volume, an isotonic crystalloid bolus may be given over 15 min in the amount of three times the volume of blood lost. For example, a 35-kg dog (calculated blood volume of ~3000 ml) has lost 300 ml of blood, constituting 10% of his blood volume. In order to maintain hemodynamic stability, this acute hemorrhage may be treated with 900 ml of an isotonic crystalloid solution administered over a 15-min period or titrated to specific endpoints (i.e. if hemodynamic stability is attained with a smaller volume, there is no need to give the entire calculated bolus). Following this bolus, the anesthetist may recheck the patient's PCV and other parameters to assess the dog's oxygen transport status and to gauge the potential need for a blood transfusion. Alternatively, smaller volumes

(e.g. 5 ml $kg^{-1}$) of colloid fluids (e.g. hetastarch) may be used to restore intravascular volume and may balance the adverse effects of hypoproteinemia that may occur with excessive crystalloid administration. A more generic approach to treating intraoperative hemorrhage can include IV isotonic crystalloid boluses of 20–30 ml $kg^{-1}$ and/or IV isotonic colloid boluses of 2.5–5 ml $kg^{-1}$.

## Red blood cell transfusions

The goal of RBC transfusions is to improve the oxygen-carrying capacity of the blood and, thus, the oxygen delivery to tissues in anemic patients. RBCs may be transfused in the form of fresh or stored whole blood or in prepared solutions of packed red blood cells (pRBCs). With the use of appropriate anticoagulants, pRBCs from dogs and cats may be stored refrigerated up to 35 days, although storage lesions may occur in older units. Storage lesions include a decrease in RBC deformability (due to adenosine triphosphate loss), a depletion of 2,3 DPG, and a progressive acidosis within the unit. In humans, transfusion of RBC products stored for longer periods can result in limited improvement in tissue oxygen delivery and may be implicated in the development of transfusion-related acute lung injury (TRALI).[12] No reports of TRALI have been published in the veterinary literature to date, although there is some evidence that leukoreduction of pRBC units may decrease transfusion-associated inflammation.[13] The effects of different anticoagulant storage media have been described for canine, feline, and equine RBCs.[14–16]

Red blood cell transfusion is generally indicated for anesthetized or preanesthetic patients with Hb concentrations ≤5–7 g $dl^{-1}$ (corresponding to a PCV of ~15–20%), especially if the decrease has been acute. Hb concentrations below this threshold can lead to significant decreases in oxygen delivery to tissues, and if hemorrhage occurs in these patients, the reduction in oxygen delivery may be precipitous. Hemorrhage constituting >20% of a patient's blood volume, when accompanied by clinical signs indicating a sympathetic response to hypovolemia (e.g. tachycardia and hypotension), may also justify transfusion of RBC, in addition to volume stabilization with isotonic crystalloids and colloids. Table 12.3 shows approximate blood volumes for veterinary species.

**Table 12.3** Approximate blood volumes in milliliter per kilogram for veterinary species.

| Species | Approximate blood volume (ml $kg^{-1}$) |
|---|---|
| Canine | 86 |
| Feline | 55 |
| Equine | 76 |
| Bovine | 55 |
| Mouse | 79 |

Another indicator for transfusion in anemic patients may be hyperlactatemia (blood lactate >2.0 mmol $l^{-1}$), which suggests inadequate tissue oxygen delivery. Lactic acid is produced during anaerobic glycolysis and is indicative of a situation wherein the oxygen demand of the tissues exceeds the oxygen delivered.[17] Blood lactate concentration reflects the balance of lactate production by body tissues and the liver's ability to metabolize it, which is rarely the limiting step (with the exception of significant hepatic hypoperfusion). The blood lactate should be evaluated with respect to the patient, as it may be influenced by other factors including vessel selection (central versus peripheral venous sample), struggle during venipuncture of a peripheral vein, hypoxemia, or prolonged venous occlusion during venipuncture. Hyperlactatemia may still support the decision to transfuse an anemic patient, in addition to hematology results and clinical signs indicating a sympathetic response to hypovolemia or hemorrhage (e.g. tachycardia, hypotension, and pale mucous membranes), hyperlactatemia may support the decision to transfuse an anemic patient.

Before transfusion of a patient with whole blood or pRBCs, canine and feline patients should be blood typed. If time allows, equine and ruminant species should be cross-matched for evaluation of donor compatibility (ideally this is performed before a procedure in which hemorrhage is anticipated). In general, type-specific blood transfusions in small animal patients that have not received prior blood transfusions do not require cross-matching. In emergent scenarios, DEA 1.1 negative canine blood may be used in dogs without blood typing, but the possible presence of pre-existing alloantibodies in cats makes blood typing imperative before transfusion. In patients who have received prior transfusions or for whom >3 days has elapsed since a

previous transfusion, cross-matching is recommended to decrease the chance of immunologic reactions to blood transfusion. Procedures for blood collection and cross-matching have been reviewed elsewhere.[18]

Blood product dosing is based on the volume of RBCs required to raise the recipient's PCV to a desired value. An estimated volume for administration may be obtained using the following formula (Equation 12.2):

$$\text{Volume of donor blood required (ml)} = \text{Recipient's blood volume (ml)} \times \frac{(\text{Desired PCV} - \text{Recipient PCV})}{\text{PCV of donor blood}} \quad (12.2)$$

It is generally assumed that the PCV of pRBC is 60–80%, while the donor PCV of whole blood will vary with the donor. Short hand calculations estimate a dose of 1 ml $kg^{-1}$ of pRBC or 3 ml $kg^{-1}$ of whole blood to raise the recipient PCV by 1%. A formula representing the total required volume of pRBC as 1.5 ml of pRBC × desired % PCV rise × kg BW was also recently shown to be accurate.[19] Blood is typically supplied in aliquots of 500, 250, or 125 ml, and pRBCs are usually available in units of 250 or 125 ml. If sterile tubing welders are available, these bags may also be split into smaller volumes for administration to smaller patients. Ideally, an opened bag of blood should be administered over a maximum of 4 h.

Despite compatibility testing, any recipient of a blood transfusion may develop a reaction, although acute hemolytic reactions are uncommon in dogs.[20] Identification of a transfusion reaction in an anesthetized patient can be challenging: urticaria may be hidden under surgical drapes, and changes in heart rate, blood pressure, or body temperature may be confounded by the effects of surgical stimuli, heat loss from body cavities, and anesthetic drug effects. Transfusions should be initiated at low rates, for example, 1–2 ml $kg^{-1}$ h for the first 15 min and then increased if no apparent reaction has developed. The duration of transfusion depends on the acuteness and severity of hemorrhage, although the transfusion should be complete by 4 h after initiation. Patients at greater risk for transfusion reaction may be administered intramuscular diphenhydramine, 2 mg $kg^{-1}$ body weight. Given IV, diphenhydramine may cause hypotension in the anesthetized patient, and its use is not recommended in horses. Transfusion technique significantly influences survival of RBCs in canine patients. Compared to administration by gravity flow, RBCs administered by volumetric or syringe pump may undergo more shear stress, which may cause lysis or decreased survival of the transfused cells.[21]

In emergent scenarios, blood may be given rapidly either using a pressure infusion bag or by attaching an in-line three-way stopcock and 60-ml syringe to pull blood from the unit and then rapidly infuse it into the patient. In scenarios such as these, with severe hemorrhage, the replacement of coagulation factors with fresh frozen plasma (FFP) is frequently indicated, and the plasma may be used along with crystalloid and colloid fluids to maintain intravascular volume. Fresh or stored whole blood contains both RBC and plasma components. Sequelae of massive hemorrhage in anesthetized patients include dramatically reduced drug requirement (including inhalant anesthetics), cardiovascular instability, and development of metabolic acidosis, in addition to the coagulopathy from the dilutional effects of fluid resuscitation and loss of coagulation factors. Patients administered large doses of blood products may also develop hypocalcemia (ionized calcium < 1.2 mmol $l^{-1}$) as a result of the citrate anticoagulant in blood products.[22] Hypocalcemia can precipitate cardiac arrhythmias, hypotension, and exacerbate coagulopathy. Calcium may be supplemented intravenously as follows: 5–15 mg $kg^{-1}$ of elemental calcium or 50–150 mg $kg^{-1}$ of 10% calcium gluconate over a 10–20-min period, while monitoring heart rate and rhythm via electrocardiogram. Calcium infusion should be slowed or discontinued if evidence of cardiotoxicity such as bradycardia, sudden elevation of the ST segment, or shortening of the QT interval occurs. Due to the citrate anticoagulant in blood products, the calcium must be administered through a separate or well-flushed catheter, and noncalcium-containing crystalloid fluids should be used to flush the administration set of blood cells at the end of the transfusion.

## Anesthetic considerations for patients with anemia

Anesthetic management of anemic patients should include preoxygenation, careful quantification of hemorrhage, minimization of hemodilution, and drug protocols that have a minimal influence on circulating RBC

availability. Preoxygenation for patients with decreased oxygen-carrying capacity will not greatly affect the proportion of Hb molecules bound with oxygen but will delay desaturation during anesthetic induction and may increase the oxygen transfer gradient at the level of the tissues (by increasing the amount of dissolved oxygen). In normal dogs premedicated with acepromazine and morphine and induced with propofol, 3 minutes of preoxygenation (100 $ml\,kg^{-1}min^{-1}$ of 100% oxygen) significantly delayed Hb desaturation, compared to dogs allowed to breathe room air prior to induction.[23]

Maintenance of oxygen delivery in the face of anemia depends on hemodynamic as well as metabolic compensatory mechanisms. Anemia-related decreases in $CaO_2$ stimulate a sympathetic response, which includes an increase in cardiac output (increased stroke volume or heart rate), as well as an increase in tissue oxygen extraction. These compensatory changes occur to continue fulfilling the energy substrate and oxygen requirements of aerobic metabolism. The oxygen extraction ratio, normally about 25–30%, can increase to about 60–70% before oxygen consumption ($VO_2$) is limited by oxygen delivery (Figure 12.2). Oxygen delivery in humans may remain normal in the face of Hb concentrations as low as 5 $g\,dl^{-1}$ (caused by isovolemic hemodilution) due to compensatory increases in cardiac output and oxygen extraction.[24] When oxygen delivery decreases below the point of maximal tissue oxygen extraction (the critical $DO_2$ point), tissue hypoxia ensues, and the tissues begin to use anaerobic metabolism for maintenance of cellular energy (Figure 12.2). Anaerobic metabolism can lead to a systemic lactic acidosis. Anesthetic agents that have minimal effects on cardiac output and vascular tone should be chosen for the patient with anemia, to preserve these intrinsic compensatory mechanisms as much as possible.

Anesthesia can obtund the mechanisms of compensation for anemia. Humans subjected to normovolemic hemodilution while anesthetized with a fentanyl/nitrous oxide/isoflurane in oxygen combination had much smaller increases in stroke volume (and thus cardiac index) than awake patients undergoing the same hemodilution. These anesthetized humans did show an increased oxygen extraction to compensate for the decrease in $DO_2$.[25] From the perspective of anesthetic monitoring, hemodynamic responses to inappropriate hemodilution cannot be relied on for treatment decisions. Tachycardia, for example, may not

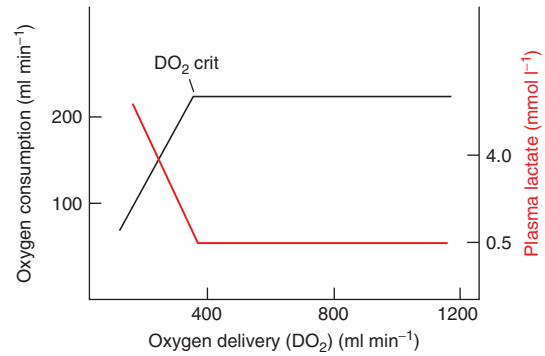


**Figure 12.2** Relationship between oxygen delivery ($DO_2$) and consumption ($VO_2$). As flow (Q) or $DO_2$ decreases, oxygen extraction increases, and $VO_2$ remains stable. When $DO_2$ decreases below the level requiring maximal tissue oxygen extraction (the critical $DO_2$ point), $VO_2$ concurrently decreases, resulting in tissue hypoxia.
Source: Adapted from Murphy et al. 2009.

occur in normovolemic patients as they approach their critical $DO_2$ point. Anemic, anesthetized patients are at greater risk of reduced tissue oxygen delivery and may have reduced capacity to activate the sympathetic compensatory mechanisms seen in conscious individuals. The anesthetist must be vigilant in monitoring vital signs, blood loss, and even serial indices of $DO_2$, such as circulating lactate, to ensure adequate $DO_2$.

Injectable and inhalant anesthetic agents may significantly decrease circulating erythrocyte mass by causing RBC sequestration in the spleen. The spleen serves as an important reservoir for RBCs, sequestering up to 40% of the RBC mass at any one time.[26] Isoflurane can decrease Hct by >30% in healthy ferrets due to splenic sequestration of RBCs.[27] Significant reductions in Hct can also occur after administration of various injectable agents; the following drugs, alone or in combination, have been shown to result in a 5–20% decrease in canine PCV: acepromazine, thiopental, propofol, and ketamine/diazepam. Combinations using thiopental and acepromazine produced greater reductions in PCV than ketamine/diazepam.[28] For this reason, acepromazine and thiopental are relatively contraindicated in anemic patients, and other drugs that may promote vasodilation and splenic engorgement (e.g. propofol) should be used sparingly.

Injectable drugs known to cause significant hemolysis should be avoided in anemic patients. Formulations of etomidate and diazepam in propylene glycol may cause

intravascular hemolysis due to hyperosmolarity.[29] The administration of both of these drugs may be indicated in some compromised patients, given the relative cardiovascular stability provided by both drugs. Dilution of etomidate solution in 0.9% saline immediately before induction will decrease the osmolarity of the solution and may help to prevent hemolysis. Anesthetists concerned about hemolysis related to diazepam may select midazolam as an alternative, as it is water soluble. Application of a multimodal approach will also reduce the total dose of drugs used and can minimize the negative side effects of each individual drug.

## Red blood cell disorders and blood viscosity

Abnormal Hct (high or low) can result in decreased oxygen delivery due to changes in blood viscosity and tissue blood flow. Hb concentration and blood viscosity for maximal relative oxygen delivery are 15 g $dl^{-1}$ and ~2 cP, respectively. Blood viscosity affects $DO_2$ by affecting the efficient movement of erythrocytes through capillaries. As blood viscosity increases, $DO_2$ decreases. Decreases in blood viscosity can also lower $DO_2$ beyond the effects of the anemia alone (Figure 12.3). The most important determinant of blood viscosity is Hct; so patients with polycythemia or anemia are especially susceptible to decreased $DO_2$. Polycythemia reduces RBC movement at the capillary level, creating a "sludging" effect, and prolongs capillary transit time. Inadequate blood viscosity, as seen in severely anemic patients, increases the likelihood of turbulent blood flow. This turbulence is recognized as physiologic cardiac murmurs in anemic patients.

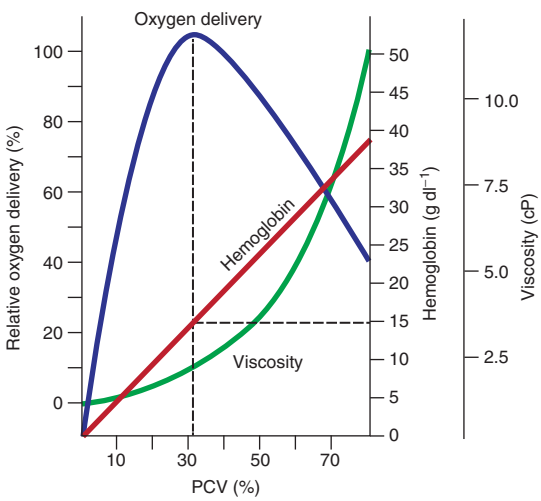


**Figure 12.3** The effects of hemoglobin concentration and blood viscosity on relative oxygen delivery. Relative oxygen delivery is maximized at a hemoglobin concentration of 15 g $dl^{-1}$ and blood viscosity of ~9 cP. From this point, decreases or increases in hemoglobin concentration and blood viscosity result in significant decreases in relative oxygen delivery.
Source: Adapted from Muir 2007.

Polycythemia or erythrocytosis describes an increased RBC number. Some canine breeds (e.g. sighthounds) may have higher erythrocyte counts than other breeds, which should be taken into consideration when interpreting Hct data.[30] Polycythemia is characterized as either absolute, denoting an increased total RBC mass, or relative polycythemia, denoting a normal RBC mass but increased Hct due to decreased plasma volume (i.e. hemoconcentration). Absolute polycythemia is further categorized into primary (polycythemia vera) and secondary polycythemia, which results from chronic hypoxia. Chronic hypoxia leading to increased release of erythropoietin and secondary proliferation of RBC lines may occur as a physiologic response to high altitudes, intracardiac right-to-left shunting, or, less commonly, severe pulmonary disease. Relative polycythemia most commonly results from loss of body fluid and subsequent hemoconcentration. Clinical signs of polycythemia are attributable to hyperviscosity and decreased microcirculatory flow. Depending on the severity of the disease, patients may be at greater risk of tissue hypoxia and thrombosis. Hyperviscosity commonly manifests as neurologic signs (seizures and collapse) secondary to compromised cerebral microcirculation.

Treatment guidelines for polycythemia depend on the pathogenesis of the disorder. Relative polycythemia should be treated with fluid therapy to replace intravascular volume, as well as directed therapy for the underlying disorder, before anesthesia. Isotonic fluid therapy should be evaluated on a case-by-case basis with regard to each patient's serum protein concentrations. For example, a combination of synthetic colloids and isotonic crystalloids may be considered for a polycythemic patient who has concurrent hypoalbuminemia, in order to minimize decreases in oncotic pressure. Intravenous fluids in cases of relative polycythemia due to hypovolemia should be

administered to achieve physiologic endpoints, and, if possible, anesthesia should be delayed until the patient has stabilized.

Therapeutic blood-letting via phlebotomy is indicated for patients with primary polycythemia, with a target Hct <55% for dogs and <50% in cats.[31] Phlebotomy may be accomplished in an awake patient or may require sedation. Sedative options can include neuroleptic combinations such as butorphanol and midazolam in dogs and ketamine with midazolam for cats. Drugs known to cause significant splenic sequestration of RBCs (e.g. acepromazine) should be avoided. Removed blood volume should be replaced with a combination of crystalloid and colloid. Alternatively, if the blood is collected into a sterile container with appropriate anticoagulant, it may be centrifuged for removal of the RBCs, so that the plasma portion may be returned to the patient.

## Disorders of hemostasis

Disorders of hemostasis encountered by the anesthetist can be generally characterized as those that predispose the animal to a hemorrhagic phenotype (hypocoagulability) and those that predispose the animal to thrombosis (hypercoagulability). There are also some disorders (e.g. disseminated intravascular coagulopathy) that form a spectrum between hypercoagulability and hypocoagulability and can present with a variable phenotype.

## Hypocoagulable disorders

### Primary hemostasis

Primary hemostasis refers to the interaction of the platelet with the vascular endothelium or subendothelium, resulting in platelet activation. The activated platelet releases a number of substances that recruit and activate additional platelets at the site of injury and also experiences a change in the distribution of membrane phospholipids.[32] The exposure of phosphatidyl serine (among others) on the platelet surface provides an anchor for assembly of the tissue factor (TF)/factor VIIa complex that will initiate secondary hemostasis, toward formation of fibrin. Disorders of primary hemostasis may be congenital or acquired and are usually problems of either platelet number or function.

#### Evaluation of primary hemostasis

A number of techniques exist to evaluate platelet function. In patients with thrombocytopenia, physical examination frequently reveals pinpoint hemorrhages (petechiae) that may be seen on the gums, the ear pinnae, the inguinal area, or on other areas without fur. Patients with thrombocytopathia who have normal platelet counts will not necessarily have petechiae.[33] Presenting complaints in patients with abnormal primary hemostasis can range from hematuria and epistaxis to oral mucosal bleeding or gastrointestinal bleeding, which may be manifest as melena.[32]

Important laboratory tests for evaluation of a patient with a primary hemostatic dysfunction include an accurate platelet count. Machine counts should be verified with a blood smear to evaluate for platelet clumping, which can result in a spurious thrombocytopenia. The simplest test of the ability of platelets to adhere to areas of endothelial damage is the buccal mucosa bleeding time (BMBT).[34] To perform the BMBT, the lip is folded up to expose the buccal mucosa and lightly secured in place with a gauze tie. Using a SimPlate® device, a standard incision (5 mm long and 1 mm deep) is made in the buccal mucosa. Once the incision is made, the area is observed (and timed) for the cessation of bleeding. If necessary, blood may be blotted using a filter paper every 30 s as long as care is taken not to disturb the fragile platelet gel forming over the incision area. The bleeding time is the time until all bleeding has ceased and is generally between 3 and 5 min in a normal animal. In cats, because the buccal mucosa is not easily accessible, a modification (oral mucosal bleeding time) is performed by placing the SimPlate above the upper canine tooth. Cats generally need to be sedated or anesthetized for this test. The BMBT will be abnormally prolonged if patients have either thrombocytopenia or thrombocytopathia.[34,35]

The PFA-100 (Dade-Behring) is a benchtop platelet function analyzer that simulates the shear stress encountered by platelets in blood flowing past a vascular defect. Using a vacuum, blood is aspirated through a small aperture coated with either collagen and adenosine diphosphate (ADP) or collagen and epinephrine. These substances will activate platelets and induce a platelet plug across the aperture. The time until the aperture is completely occluded is reported as the closure time, in seconds, with a maximum value of 300 s. The PFA-100 has been used to evaluate hemostasis in dogs and can

rapidly identify platelet defects caused by vonWillebrand's disease and nonsteroidal anti-inflammatory drugs (NSAID) administration.[36,37]

Platelet aggregometry may be performed using either whole blood or platelet-rich plasma, and it tests the ability of platelets to aggregate in response to a discrete stimulus, such as ADP or collagen. This test is performed on specialized equipment under low shear conditions and investigates how platelets respond to specific agonists or how drugs affect platelet responses.[38] Aggregometry is primarily a research tool and not readily available to most practitioners, but many studies that assess drug effects and other platelet function abnormalities report aggregometry results. Flow cytometry has also recently been used in veterinary medicine to investigate platelet function and phenotype, and information in the literature will likely expand in the coming years as the veterinary community gains more experience with this modality and as more canine or feline antibodies become available.[39]

### Disorders of primary hemostasis

Thrombocytopenia is an absolute decrease in the number of circulating platelets. Normal platelet count in dogs and cats ranges between 250 and $500 \times 10^3$ platelets per microliter. Thrombocytopenias are generally considered $<150 \times 10^3$ platelets per microliter and may be as low as $5–10 \times 10^3$ per microliter. Due to the tendency of platelets to clump if they are activated by inflammation or a traumatic blood sampling, manual verification of a low platelet count by evaluating a blood smear should be performed. At 100× power, one platelet represents $15 \times 10^3$ per microliter, so 10–15 platelets per field is considered normal. As a general rule, spontaneous bleeding does not occur at platelet counts $> 20 \times 10^3$ per microliter, although a more conservative cutoff for patients who are undergoing surgery is generally about $50 \times 10^3$ per microliter. Some breeds, notably the Cavalier King Charles Spaniel, can have a hereditary macrothrombocytopenia, where the platelets are few in number and larger than normal but without identifiable abnormalities in platelet function or hemostasis.[40]

One of the more common causes of thrombocytopenia in dogs is an immune-mediated thrombocytopenia (IMT). IMT is characterized by extremely low platelet counts ($<20 \times 10^3$ per microliter), and patients may experience spontaneous bleeding from mucosal surfaces. The cause of IMT is generally presumed to be idiopathic, although drugs (e.g. trimethoprim-sulfa) have been implicated in some cases.[41,42] Mild to moderate thrombocytopenia ($40–100 \times 10^3$ per microliter) is frequently seen in animals with diseases that induce inflammation or disseminated intravascular coagulation (DIC).[43] Some of these diseases include neoplasia, sepsis, pancreatitis, heartworm infection, or trauma with crush injury, and these patients may require emergent anesthesia and surgery for therapy of the primary cause. Infection with some of the tick-borne diseases (e.g. *Erlichia* sp. and *Borrelia* sp.) can also be associated with mild to moderate thrombocytopenia. In addition, in patients who are actively bleeding or who have experienced blood loss, a modest decrease in platelet count may be seen.

### Treatments in preparation for anesthesia

In human patients, recommendations for transfusions of platelet-containing products (platelet concentrate, platelet-rich plasma) are made in individuals with $<50 \times 10^3$ platelets per microliter who are going to undergo invasive procedures. In veterinary medicine, blood products containing platelets alone are not readily available to most practitioners. The easiest and most practical way to administer platelets to a patient before surgery is via transfusion of fresh whole blood, although the number of platelets provided will vary depending on the platelet concentration of the donor and likely will not increase the platelet count significantly. The amount of blood to transfuse may be calculated on the basis of patient RBC needs or may be empirically administered at 10–20 $ml\,kg^{-1}$ if the patient is not anemic. Despite the lack of increase in platelet count, fresh whole blood may provide enough platelets to stop ongoing bleeding and provide some hemostatic support during surgery. With appropriate attention to surgical hemostasis and transfusions as indicated, surgery can be safely performed in patients with moderate to severe thrombocytopenia.

Frozen DMSO-stabilized canine platelet concentrate is available; however, the activity of these platelets is significantly diminished compared to fresh platelets.[44] Other options that may become available in the future include lyophilized platelets, although the efficacy of these for thrombocytopenic patients undergoing surgery has not been evaluated.[38] The options for platelet transfusions in veterinary medicine have been reviewed.[45] In patients who do not need emergent surgery, vincristine (0.02 $mg\,kg^{-1}$ IV once) may be used to increase the number of circulating platelets, although

an increase in circulating platelet number may not be evident for up to 4 days.[46]

Anesthetic concerns specifically related to animals with thrombocytopenia are applicable to any patient at risk for significant hemorrhage. Animals should be handled gently, and transport during and after anesthetic induction should be carefully planned and executed to avoid iatrogenic trauma and hemorrhage. Thrombocytopenic animals may develop hematomas at the site of intramuscular injections, and these should be minimized or avoided. Animals may also develop hematomas at the site of peripheral intravenous or intra-arterial catheters; if necessary, these peripheral areas may have a pressure wrap placed to encourage hemostasis. Jugular venipuncture is contraindicated due to the inability to tamponade bleeding, and for the same reason, femoral arterial puncture is not recommended. The dorsal metatarsal site is preferred for arterial catheter placement in thrombocytopenic animals. In addition, animals are likely to bleed from disturbed mucosal areas, and catheters (e.g. intranasal and urinary), if necessary, should be placed with care, and rectal or esophageal temperature monitoring should be performed judiciously. Hemorrhage of the arytenoids or tracheal mucosa may occur from aggressive endotracheal intubation and may result in postoperative upper airway obstruction. Neuraxial analgesia and peripheral nerve block techniques are contraindicated in these patients due to the potential for catastrophic bleeding if vessel laceration occurs.

In addition to these practical aspects of patient care, the use of drugs that may impair platelet function should be avoided, and NSAIDs are contraindicated. The use of synthetic colloids (e.g. hetastarch) may be necessary for oncotic support during anesthesia; however, these drugs may also impair platelet function (see the following sections) and should be used judiciously. Transient impairment of platelet function after acepromazine administration has been described.[47] While the clinical importance in a healthy dog seems minimal, in thrombocytopenic patients, the effect, if any, may be magnified.

## Thrombocytopathias

Thrombocytopathias, or platelet dysfunction, may be caused by some systemic diseases but are more frequently seen either as an inherited trait or due to drug effects on the platelet. Clinical signs of thrombocytopathias are characterized by bleeding from mucosal surfaces. Milder forms are first diagnosed in patients who have prolonged bleeding after surgery for spay and neuter. Although patients may have cutaneous bruising, petechiae are rarely seen, as they result from an absolute decrease in platelet number. Patients usually have an adequate number of circulating platelets (although the total number may be lower if there has been hemorrhage) and a normal coagulation profile.

Platelet dysfunction has been reported in patients with significant renal failure and may result from alterations in the platelet membrane or in the platelet response to some stimuli.[35,48] Animals with hypothyroidism may have mild platelet dysfunction, but the origin of this change is unclear and of questionable clinical import.[49–51] In animals with severe uremia that require anesthesia, the same precautions listed previously for patients with thrombocytopenias are relevant. Additional anesthetic concerns for the uremic patient are discussed in chapter 6.

The most common inherited thrombocytopathia in dogs is vonWillebrand disease (vWD). vWD describes a complex of diseases associated with malformation or absence of vonWillebrand factor (vWF), necessary for tethering of activated platelets to areas of endothelial injury. Type I vWD is characterized by a lower total amount of functional vWF, although all sizes of vWF are present, and is the most common type of vWD seen in dogs, with Doberman Pinschers over-represented. The clinical severity of type I vWD depends on the quantitative degree of vWF activity present.[33] Type II vWD comprises a group of functional variants of vWF characterized by alterations in the size profile of circulating vWF (e.g. a lower amount of large molecular weight vWF).[33] Type III vWD is characterized by complete lack of circulating vWF and is the most severe clinical presentation of vWD. vWD may be diagnosed by functional assays (e.g. BMBT or PFA),[52] or the actual amount of functional vWF can be measured. The latter is reported as a percentage of activity, with normal activity between 65% and 150%. Animals affected with clinically important vWD frequently have activities of $\leq$40%.[33]

Prophylactic therapy to prevent bleeding in patients with vWD may use cryoprecipitate, which is also indicated if the patient is actively bleeding. Cryoprecipitate is made from FFP and contains a concentrated amount of vWF and coagulation factor VIII (fVIII). Cryoprecipitate is available in frozen and lyophilized forms and is usually administered at a dose of 3–5 ml kg$^{-1}$.[53]

Desmopressin acetate (DDAVP) has been used in humans and dogs with vWD and in humans with type I vWD results in a twofold–fourfold increase in circulating levels of vWF and fVIII by causing their release from endothelial cells.[54] Dogs with type I vWD showed an improvement of clinical signs (decreased mucosal bleeding time and shortened PFA closure time) and an increase in circulating vWF after DDAVP therapy.[52] The recommended dosage for DDAVP is 1 μg $kg^{-1}$, administered subcutaneously or as a subconjunctival drop. In Doberman Pinschers with an unknown vWF titer presenting for emergent surgery, the authors routinely administer DDAVP and will have transfusion products available for intraoperative and postoperative transfusion.

Other inherited platelet function defects that have been reported in veterinary species include Glanzmann thrombasthenia, reported in Great Pyrenees, Otterhounds, and a number of horses and characterized by dysfunction in the platelet fibrinogen receptor.[55] A number of dog breeds and Simmental cattle have a heritable thrombocytopathia distinguished by an intracellular signaling defect in the platelet that prevents activation of the fibrinogen binding site. Scott syndrome, a lack of platelet procoagulant activity, has been reported in German Shepherds and is characterized by an inability of platelets to support secondary hemostasis, leading to hemorrhage.[56] Frequently, these defects manifest themselves as spontaneous bleeding or as excessive bleeding after surgeries for spay or neuter or after ear crop, tail dock, or dew claw removal. Patients with these and other platelet defects who require anesthesia and surgery are at an increased risk for bleeding intraoperatively and postoperatively. Before surgery, dogs should be blood typed, and adequate plasma and RBCs should be available. The administration of PRP or platelet concentrates can also be considered for these dogs before elective surgery; if surgery is emergent and platelet products are not available, fresh whole blood remains a good option for transfusion needs during surgery, and the animals may require continued transfusion care into the postoperative period.

Many commonly used pharmaceuticals can alter platelet function and may result in impaired platelet aggregation or adhesion. NSAIDs can affect platelet aggregation by impairing the production of platelet thromboxane $A_2$ ($TXA_2$) by the cyclooxygenase (COX) enzyme. $TXA_2$ is a proaggregatory substance and helps to activate additional platelets at areas of vascular damage. It also results in vasoconstriction at the site, which may mitigate blood loss. Aspirin (ASA) is the archetypical NSAID and significantly decreases platelet aggregation to collagen in patients who are sensitive to $TXA_2$.[57] Dogs have been identified that are insensitive to the platelet effects of NSAIDs due to a presumed decreased sensitivity to $TXA_2$.[58] Feline platelets may also be relatively resistant to inhibition of $TXA_2$ release, as measured by aggregometry.[59] While ASA causes an irreversible inhibition of COX, the other commonly used veterinary NSAIDs (e.g. carprofen and meloxicam) have reversible binding and cause only a transient decrease in platelet function, if at all.[57] Because most COX in circulating platelets is presumed to be the COX-1 isoform, drugs that specifically target the COX-2 isoform (e.g. deracoxib and firocoxib) would not be expected to alter platelet function, even in sensitive dogs.[57] The use of ketoprofen has also been associated with decreases in platelet aggregation.[60] In general, there are no contraindications to the performance of local or neuraxial analgesic techniques in patients receiving NSAIDs.

Synthetic colloids are commonly used for volume support of critically ill patients in the perioperative period. These colloids (hetastarch, tetrastarch, and dextran) are usually a 6% solution in an isotonic crystalloid. Smaller molecular weight colloids (e.g. tetrastarch) are excreted more rapidly and may be amenable to a higher total daily dose. The impact of colloids on coagulation indices is well documented, and they have effects on both platelet function and clot strength that may be problematic in patients with bleeding tendencies. Hetastarches can bind to circulating vWF/fVIII complexes, resulting in increased clearance and impairing platelet adhesion to sites of vascular injury.[61] Hetastarches can also cause an increase in fibrinolysis and a weaker clot strength because they can become integrated into the clot. The effect of HES solutions on coagulation varies with the molecular composition of the product and carrier solution; products with higher molecular weights and molar substitution ratios are more likely to interfere with coagulation, due primarily to a longer duration in circulation and slower breakdown kinetics,[62,63] and products in a balanced electrolyte solution might have less effect on coagulation than those in normal saline.[64] It is generally accepted that doses up to 24 ml $kg^{-1}$ $day^{-1}$ of hetastarch (670/0.75) and up to 50 ml $kg^{-1}$ $day^{-1}$ of

tetrastarch (130/0.45) will cause minimal perturbations of platelet function and coagulation, and patients who receive more than this amount should be monitored for adverse effects. These effects may be more pronounced in patients with pre-existing defects in primary hemostasis.

Clopidogrel irreversibly inhibits platelet activation by antagonism at the ADP $P2Y_{12}$ receptor. Its use in veterinary medicine is increasing, and the pharmacokinetics and pharmacodynamics have been described in cats, dogs, and horses.[38,65,66] Few adverse events have been described in veterinary patients; however, clopidogrel does impair platelet aggregation, and the use of additional anticoagulant (e.g. heparins) or analgesic (e.g. NSAIDs) medications in these patients should be considered carefully in the context of their underlying disease. Clopidogrel is metabolized to an active metabolite by the hepatic CYP3A4/3A5 enzyme system and may affect metabolism (or be affected by metabolism) of drugs used for anesthesia that are processed in a similar manner.[38] Most notably, proton-pump inhibitor drugs (e.g. ondansetron) may affect the metabolism of clopidogrel to the active metabolite, decreasing antiplatelet effects. The anesthesiologist must consider the disease that merited initial use of antiplatelet agents, and anesthetic choices will be more dictated by this condition than by concurrent drug therapy. These drugs may, however, lead to an increase in surgical bleeding, although the literature evaluating human patients recommends that antiplatelet agents not be discontinued before anesthesia and surgery in patients with an increased risk for the development of thrombosis (e.g. patients with coronary artery disease).[67] Other authors have recommended that clopidogrel be discontinued for 5 days before surgeries where bleeding might be catastrophic (ocular surgery, neurosurgery, urological, or major vascular surgery).[68] Other publications with human patients have recommended a 7–10-day period without clopidogrel before surgery.[69] Adverse effects of neuraxial analgesia in patients receiving antiplatelet medication have been reported.[70] Each case should be evaluated individually, and if platelet function testing is available, the return of ADP sensitivity in platelets may be monitored and can help guide surgical timing, as well as the use of neuraxial techniques.

As noted previously, acepromazine may be associated with a transient decrease in platelet function, and if a clinical effect does exist, it may not be apparently unless acepromazine is coadministered with a more potent platelet antagonist, although this has not been studied. Although platelets do have $\alpha_2$-receptors, the effect of dexmedetomidine and related drugs on platelet function has not been described, although a weak agonist effect (similar to epinephrine) might be expected, at least in canine platelets. Isolated articles have described antiplatelet effects of ketamine,[71] midazolam,[72] propofol,[73] halothane, and sevoflurane,[74] but the clinical relevance is unclear. Opioid drugs, barbiturates, and etomidate appear to have little effect on aggregation of human platelets.[74]

In any animal with decreased platelet function due to disease, heritability, or drugs, the anesthetist must carefully weigh the benefits of neuraxial analgesia with the risk of bleeding. If the patient has a transient platelet dysfunction or a low platelet number due to systemic disease, a postponement of surgical procedures may be indicated if feasible until the platelet numbers can rebound or at least until appropriate transfusion products may be obtained.

## Secondary hemostasis

Secondary hemostasis refers to the aspects of coagulation that consist of the coagulation cascade, a series of serine proteases (the factors) that are sequentially activated, culminating in the formation of fibrin monomers, which are subsequently cross-linked by factor XIIIa. Although the measurement of the prothrombin time (PT) and activated partial thromboplastin time (aPTT) provides a framework for understanding the coagulation effect of the various factors in the coagulation cascade, the vast majority of coagulation *in vivo* occurs by activation of the TF pathway (extrinsic pathway), which produces a small amount of thrombin (initiation).[75] The small amount of thrombin produced by the extrinsic pathway has a strong agonist effect on the intrinsic pathway, and the majority of thrombin generated during coagulation is generated via this pathway (amplification and propagation). Initiation of coagulation requires an appropriate cell surface for the assembly of the TF-factor VII a complex, which is provided by the activated platelet, among other surfaces.[75]

### Evaluation of secondary hemostasis

Secondary hemostasis is evaluated by monitoring the formation of fibrin in blood or plasma after exposure to an activating substance. This is the basis of the activated

clotting time (ACT), the PT, aPTT, and the thrombin time (TT), which corresponds to fibrinogen concentration. The ACT is performed on whole blood added to diatomaceous earth (a strong contact activator), while the other tests are performed on citrated plasma with appropriate activators. Samples for coagulation testing should be acquired via a clean direct venipuncture and placed immediately into a plastic or siliconized glass tube containing sodium citrate (usually 3.2%) to a ratio of 1:9 citrate to blood (v:v). Some newer cage-side coagulation analyzers can analyze PT and aPTT on citrated whole blood or on native (uncitrated) whole blood. The normal values for dogs and cats will vary with the machine and technique. Prolongation of clotting times usually requires a factor to have an activity <30% of normal.

Newer viscoelastic tests of coagulation such as thromboelastography (TEG) or Sonoclot evaluate aspects of both primary and secondary hemostasis, in addition to fibrinolysis. These tests graph the change in viscosity as liquid blood forms into a clot and can describe both hypocoagulable and hypercoagulable states.[76] Numerous reports in the veterinary literature have described the evaluation of these techniques in dogs, cats, and horses, although there is currently a wide variability in techniques that make comparison across centers difficult.[77,78]

### Disorders of secondary hemostasis

Animals with ineffective secondary hemostasis may present with hypovolemic shock due to hemorrhage. Physical examination findings can include pale to white mucous membranes, tachycardia, and weak pulses. In animals without hemorrhage, physical examination will be essentially normal with regard to the underlying disease. Common sites for hemorrhage include the peritoneal cavity, pleural space, retroperitoneum, pericardium, and joints (hemarthrosis). Performing surgery on patients with significant abnormalities of secondary hemostasis can result in catastrophic hemorrhage. FFP contains all coagulation factors and is an effective way to replace clotting factors and slow or stop hemorrhage from factor deficiency. Stored plasma lacks coagulation factors V and VIII and may be less useful in the context of severe hemorrhage but does contain all of the vitamin K-dependent coagulation factors and may help to correct coagulopathies in patients with specific deficiencies (e.g. due to ingestion of anticoagulant rodenticides). Fresh whole blood also contains all coagulation factors, while stored whole blood may have experienced degradation of some factors; these products are indicated to treat anemia due to hemorrhage. In animals with hemorrhagic shock, rapid replacement of intravascular volume is indicated, and transfusion products containing RBCs (pRBC and fresh whole blood) are likely indicated.

Coagulation factor deficiencies may be congenital or acquired. Acquired factor deficiencies may result from toxicities or systemic disease. The liver is the source of circulating coagulation factors in the body, and hepatic dysfunction may result in a coagulopathy. Animals with hepatic disease, especially if undergoing invasive procedures, must have a coagulation profile performed and treatment for coagulopathy if indicated. Coagulopathies are particularly common in cats with hepatic lipidosis that frequently require anesthesia for hepatic biopsy or aspirate and placement of feeding tubes. At least part of the coagulopathy associated with hepatic lipidosis may be due to malabsorption of vitamin K, and parenteral supplementation is indicated before invasive procedures.[79] In many cats, intestinal disease contributes to the malabsorption, although cholestasis in any species may contribute to decreased absorption of vitamin K. If vitamin K therapy does not improve the coagulation profile, additional therapies (e.g. FFP) are indicated before anesthesia and surgery. Primary hepatic disease may also result from ingestion of toxins (e.g. xylitol and mushrooms) in dogs and may result in fulminant hepatic failure with coagulopathy. In addition to primary hepatic disease, systemic diseases can prolong clotting times due to factor depletion. Diseases such as sepsis, pancreatitis, neoplasia, and heartworm disease are associated with the development of the systemic inflammatory response syndrome (SIRS) and DIC. If the consumptive coagulopathy of DIC is severe, coagulation abnormalities will result from factor consumption (early DIC will just show a mild prolongation in the aPTT).[43] Anesthetic choices in these patients are driven more by the underlying disease rather than the coagulation status; however, if invasive procedures are necessary, transfusion of FFP (at least 10 $ml\,kg^{-1}$) is indicated to normalize coagulation parameters.[80] As with patients with defects of primary hemostasis, the benefits of local or neuraxial blockade should be carefully weighed with the risks of uncontrollable hemorrhage. Anesthesia for patients with hepatic disease is covered in chapter 4.

Toxins or drugs can directly affect the coagulation system. The most common toxins with these effects are the anticoagulant rodenticides. There are many generations of anticoagulant rodenticides, and newer generation formulations generally last longer than the earlier ones. Examples of first-generation rodenticides include warfarin, while brodifacoum and bromadiolone are second-generation products. Warfarin is occasionally used in clinical patients but is uncommon. Patients with acute rodenticide intoxication rarely require anesthesia; however, occasionally, anesthesia is needed to place thoracic drains for hemothorax or to remove bleeding organs from the abdomen. It is more likely (although still relatively unlikely) that a patient with rodenticide toxicosis will present for anesthesia and surgery, with the owner unaware that their coagulation function is impaired, which may result in excessive surgical and postoperative hemorrhage. In the acute scenario, if a patient is experiencing hemorrhage due to vitamin K antagonism, FFP or stored plasma is the treatment of choice, but continued treatment (and preferred treatment in the absence of hemorrhage) is administration of vitamin $K_1$ (phytonadione), orally or subcutaneously (intravenous injection may result in anaphylaxis). Depending on the degree of factor depletion, vitamin K administration will rapidly correct coagulation abnormalities in a patient without hemorrhage. Before anesthesia and surgery, at least 2–3 days of therapy (2.5–5 mg $kg^{-1}$ PO q 12–24 h) should result in normalization of coagulation times, but a repeat coagulation panel is indicated before elective procedures.

Unfractionated heparin (UFH) is a drug that can cause an acquired defect in secondary hemostasis. UFH accelerates the inactivation of coagulation factors II and X by antithrombin (AT). It is frequently used in critically ill patients who are thought to be at risk for thrombosis or thromboembolism or in those in whom anticoagulation is essential to therapy (e.g. animals receiving hemodialysis). UFH has variable pharmacodynamics that are not only dose dependent, but also unpredictable to a certain degree.[81,82] The coagulation effects of a single (250 U $kg^{-1}$) subcutaneous dose of UFH (as monitored by coagulation testing) wane 9–12 h after the dose but with more persistent coagulation effects after prolonged dosing. The maximum anticoagulant effect of a single UFH subcutaneous injection is about 4 h after the injection. UFH effect may be monitored by measuring the anti-factor Xa activity in the plasma or may be estimated by evaluating the aPTT, which prolongs with heparin therapy.[81] The anesthetist should assess the coagulation status of patients before anesthesia. In patients receiving heparin therapeutically, coagulation times are expected to be only moderately prolonged (approximately twice normal), and the danger of uncontrollable hemorrhage is not as great as in those patients with profound prolongations of coagulation times. Low molecular weight heparins (LMWH) are smaller heparin molecules that are as useful for thromboprophylaxis as UFH but which have been associated with a lower incidence of hemorrhage in humans. LMWH do not prolong any coagulation test, and so plasma levels must be measured using the anti-factor Xa activity.

In anesthesia of human patients, recommendations for neuraxial analgesia/anesthesia in individuals receiving heparin therapy during or after surgery have been made.[83,84] The recommendations include the following: avoiding neuraxial analgesia in patients with known coagulopathies, delaying surgery (and heparin administration) if the epidural puncture is traumatic, delaying the time from epidural puncture to systemic heparinization for at least 60 min, judiciously using heparin with reversal when indicated, and finally, removing epidural catheters when normal coagulation is restored (or at the nadir of heparin effect), with postoperative monitoring for signs of epidural hematoma. It has also been recommended to place indwelling epidural catheters up to 24 h before surgery in elective cases. The American College of Chest Physicians has published guidelines for perioperative management of anticoagulated patients.[69] In those patients who receive chronic vitamin K antagonist therapy (e.g. warfarin) that cannot be stopped, it is recommended to use "bridging therapy" with either UFH or LMWH for the perioperative period until dangers of hemorrhage related to surgery are over (usually 12–24 h after surgery). If vitamin K antagonist therapy can be interrupted without the need for bridging therapy, recommendations are to stop therapy ~5 days before surgery to allow normalization of coagulation times (and to verify before surgery). In human patients receiving therapy with IV UFH, recommendations are to stop this therapy 4 h before surgery, whereas if a patient is receiving subcutaneous LMWH therapy, the final dose should be 24 h before surgery (this may be different in animals, where the pharmacokinetics of these drugs does not necessarily support once-daily dosing).[85] The resumption of heparin therapy may occur at variable

intervals depending on the severity of the surgery and the relative chance of postoperative bleeding. In patients who are receiving antiplatelet therapy such as aspirin or clopidogrel, the consensus recommends stopping these drugs at least 7–10 days before surgery if possible, although in patients at high risk for thrombosis, therapy can be continued up to and through the procedure. Minor surgeries (e.g. dental prophylaxis or dermatologic procedures) generally do not require the interruption of anticoagulant therapy. For emergent surgeries on patients receiving anticoagulant or antiplatelet drugs, the availability of vitamin K or FFP is necessary for patients treated with warfarin, while UFH may be reversed with protamine (see the following section) if necessary. In patients receiving antiplatelet therapies, DDAVP (1 $\mu g\,kg^{-1}$ SC) may be given before surgery,[52] and fresh whole blood, PRP, or platelet concentrate may be helpful to prevent bleeding due to platelet inhibition. The use of activated factor VII has not been extensively described in the surgical management of anticoagulated small animals but may provide an emergent therapy for excessive surgical bleeding.[86]

Protamine is a drug that may be used to reverse the anticoagulant effects of UFH; it works by binding free heparin and allows the complex to be cleared without causing additional anticoagulation. Protamine does have an anticoagulant effect of its own, however, and may lead to anticoagulation if more drug is given than heparin is present to bind. For this reason, the dosing recommendations for protamine are scaled. The initial dose is 1 mg of protamine for every 100 U of heparin to be inactivated. This dose of protamine is decreased by half for every 30 min elapsed since the heparin administration. Protamine should be diluted in sterile 0.9% saline and administered slowly IV. Protamine is frequently used to reverse heparin effects where UFH is used in large doses, such as cardiopulmonary bypass or hemodialysis.

## Hypercoagulable states

In recent years, increased attention has been paid to diseases in veterinary medicine that may result in a hypercoagulable phenotype, indicating animals that are prone to the development of thrombosis or thromboembolism.[87] A working knowledge of these diseases and therapies is necessary for the anesthetist because it may affect case management, and animals receiving therapeutic anticoagulant therapy may experience increased bleeding during surgical procedures. Common diseases that have been associated with an increased tendency to form clots include immune-mediated hemolytic anemia (IMHA),[88] protein-losing nephropathies,[89,90] hypertrophic cardiomyopathy, sepsis, heartworm disease, and some forms of neoplasia.[91] In addition, therapy with prednisone increases TEG indices that are consistent with hypercoagulability,[92] and the natural response to both surgery and pregnancy induces a relatively hypercoagulable state. In one study of patients who developed necropsy-confirmed thromboembolism or thrombosis, the presence of a jugular vein catheter was associated with thrombosis, as was a diagnosis of hyperadrencorticism (HAC).[93] The veterinary literature is divided regarding the prevalence of a hypercoagulable presentation in patients with HAC.[94,95] DIC is associated with an initial hypercoagulable phase before the more commonly recognized hypocoagulable phase; when animals are hypercoagulable, both microthromboses and macrothromboses can occur and impair tissue oxygen delivery.

Bloodwork that may be suggestive of hypercoagulability includes TEG, as well as markers of the activation of coagulation, such as thrombin–antithrombin (TAT) complexes. A PT or aPTT that is shorter than the reference range is not necessarily associated with hypercoagulability, but other measures, such as an elevated fibrinogen concentration, are more associated with this trait. In patients with protein-losing disease (enteropathy or nephropathy), the loss of AT may predispose to hypercoagulability. AT activity can be measured in citrated plasma. In patients in whom a clot may have already formed, elevations in plasma d-dimers indicate that fibrinolysis has occurred. In patients suspected of having thrombosis, imaging of the vasculature, either using ultrasonography or CT angiography may confirm the presence of clots.

Rudolph Virchow suggested some underlying characteristics that may indicate a predisposition to thrombosis in susceptible patients.[87] These include the presence of a hypercoagulable state, occurrence of endothelial damage, and the presence of altered blood flow in the vasculature.[87] In some patients, more than one of these factors may be present. From an anesthesia standpoint, the best practice is to limit catheter placements (and thus endothelial damage) to those that are necessary

for the procedure. During anesthetic procedures, the maintenance of adequate blood pressure and tissue oxygen delivery is important, and anesthetic protocols should be chosen that minimize hemodynamic instability. If patients are suspected of thrombosis or hypercoagulability, therapy with either antiplatelet drugs or anticoagulant medications may have been instituted before anesthesia, and the precautions listed previously for these scenarios should be followed.

## Disorders of fibrinolysis

Hyperfibrinolysis in veterinary medicine is most frequently associated with DIC but has also been described as an idiosyncratic response in some sighthounds (specifically greyhounds).[96] An increase in fibrinolysis can be detected by an increased number of circulating fibrin fragments, either fibrin(ogen) degradation products (FDPs) or d-dimers. D-dimers can only be formed after fibrin cross-linking has occurred in a mature clot and so are indicative of fibrinolysis secondary to thrombosis. FDPs are less specific and can represent particles of fibrin that have broken down from clots or pieces of fibrinogen that have been broken down in circulation, without ever forming a clot. The hyperfibrinolytic aspect of DIC is not necessarily treated specifically, but transfusions of FFP can replenish fibrinogen that has been consumed. Delayed (2–3 days) postoperative bleeding in retired racing greyhounds has been reported and has been posited to be caused by hyperfibrinolysis.[97,98] It is not possible to predict which dogs will experience delayed bleeding, but it is wise to closely monitor sighthounds in the postoperative period. Drugs such as epsilon-aminocaproic acid or tranexamic acid may be useful to mitigate hyperfibrinolysis in some cases.

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# 13 Skin and musculoskeletal diseases

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This chapter presents a concise description of the pathophysiology, diagnosis, and treatment of the most relevant canine and feline skin and musculoskeletal diseases. An emphasis is given to the impact of these diseases on anesthetic management. In some instances, skin and musculoskeletal disease is presented as a secondary complication rather than the main clinical concern. Adequate preanesthetic patient assessment is essential for the successful outcome of any case.

## Burns

Skin burns are a result of secondary thermal, chemical, electrical, or radiation injury.[1,2] Patients with burns may constitute a life-threatening condition that requires intensive care and aggressive pain management. Superficial partial thickness (formerly known as first-degree) burns involve only the epidermis, and healing generally occurs within 5 days. Lesions are bright red, nonblistered, and painful. Deep partial thickness (e.g. second-degree) burns involve all epidermal layers and variable depths of the dermis. They may appear dry or blistered and moist, usually resulting in the formation of scar tissue after a prolonged healing period (Figure 13.1). Full thickness (e.g. third-degree) burns involve destruction of the entire dermis and may extend into the subcutaneous tissues. They are dry, leathery, and appear white or charred. These burns are expected to be insensate, and loss of function may result. The characterization of the severity of the injuries is warranted for appropriate treatment planning. The criterion has been adapted from the human literature and is described elsewhere.[3] Euthanasia may be advisable if lesions extend to >50% of total body surface area (TBSA).

### Metabolic derangements

After a burn injury where >20% of the patient's TBSA is affected or if the wounds are of deep partial or full thickness, a systemic inflammatory response syndrome (SIRS) may develop within minutes after the injury, resulting in cardiovascular collapse and multiorgan system failure (Figure 13.2).[4] Sepsis is another important consideration in burn patients and one of the major causes of death.[5] Wound-, respiratory-, and catheter-related infections may occur secondary to the lack of compromised integrity of the natural barriers and consequent free passage of bacteria and endotoxins through the skin, contributing to the development of multiorgan failure. Humoral- and cell-mediated immunity is altered and results in immunosuppression, which may further increase the incidence of sepsis. Some of the following are present in sepsis: fever, hypothermia (cats in general), tachycardia, bradycardia (commonly in cats), tachypnea, altered mental status, hypoglycemia or hyperglycemia, edema, leucopenia or leukocytosis, hemodynamic instability, thrombocytopenia, ileus, hypocoagulability or hypercoagulability, and hyperlactatemia, among others.[5]

Smoke inhalation injury is of particular concern and constitutes an important aspect of increased morbidity. Direct thermal damage to respiratory epithelium leads to sloughing and edema of the upper airways that, in addition to the formation of cellular casts, may obstruct the airways.[6] Systemic inflammatory response with the release of thromboxane causes pulmonary vasoconstriction, hypertension, and hypercoagulability. Carbon monoxide (CO) poisoning frequently occurs in conjunction with inhalation injury, further contributing to tissue hypoxia. CO interferes with the oxygen transport function of blood by combining with hemoglobin

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**Figure 13.1** Dorsal aspect of a dog with deep partial thickness burns.

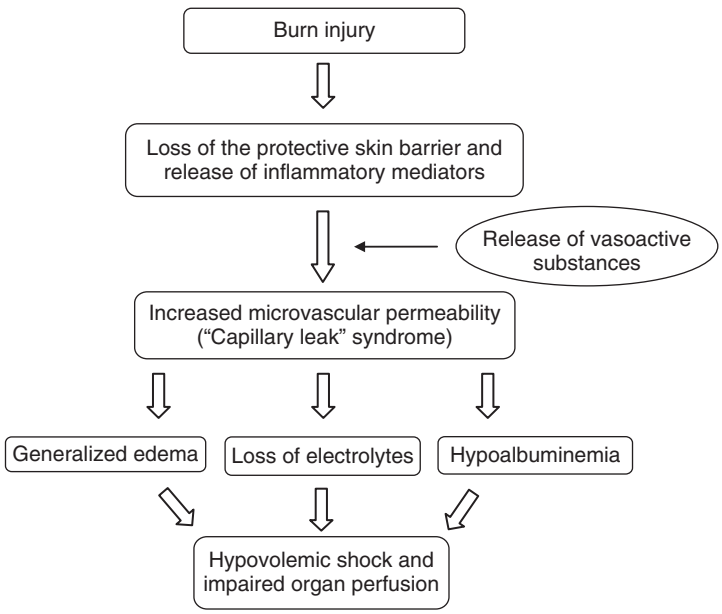


**Figure 13.2** Algorithm of burn injury.

to form carboxyhemoglobin; the latter has about 240 times the affinity of oxygen for hemoglobin.

A hypermetabolic response is typically observed until final resolution of the wounds and long after. This consists of a variety of disorders such as increased sympathetic stimulation, gluconeogenesis, protein catabolism, insulin resistance, and weight loss.

## Treatment and management of anesthesia

Emergency treatment is essential on presentation of a patient with burns. Ventilatory support should ensure that the airways are patent while minimizing the risk of hypoxemia with the administration of 100% oxygen via face mask or by flow-by. Immediately after injury, cool compresses aid in alleviating pain and stopping any ongoing burning damage due to possible high skin temperatures. Careful attention to catheter-related infection must be made. Intraosseous catheterization is an alternative if intravenous assessment is limited. Crystalloid solutions are preferred during the first 24 h of treatment because of increased microvascular permeability, which tends to ameliorate after the first 24 h. Thereafter, the addition of colloids (1–3 ml $kg^{-1}$ $h^{-1}$) for restoration of plasma volume is beneficial, especially if hypoalbuminemia is present. According to the Starling's law:

$$\text{Net filtration} = K_f[(P_{cap} - P_{if}) - (\pi_P - \pi_{if})] \qquad (13.1)$$

where, $K_f$ represents the net permeability of the capillary wall, $P$ represents the hydrostatic pressure generated by the heart ($P_{cap}$) or tissues ($P_{if}$), and $\pi$ represents the oncotic pressure generated by plasma proteins ($\pi_P$) or filtered proteins and mucopolysaccharides in the interstitium ($\pi_{if}$). Therefore, severe hypoalbuminemia as observed in burns results in a reduction of oncotic pressure, which increases the net force favoring filtration of fluid out of the capillary, leading to generalized edema. When considering colloid therapy, the newer hetastarch has lower molecular weights (130 kDa) and a molar substitution ratio of four hydroxyethyl groups (HES 130/0.4). Clinically, these compounds do not remain in plasma as long as other larger starch products (HES 450/0.7). In addition, fewer alterations in coagulation are observed when compared to other colloids (HES 200/0.5). Colloid therapy may be advantageous to the patient by reducing the inflammatory response and protecting against vascular leakage while increasing vascular volume. According to the manufacturer, maximum HES 130/0.4 has been administered at 50 ml $kg^{-1}$ $day^{-1}$ in human studies.[7]

Direct myocardial depression with hypotension can be treated with continuous rate infusion (CRI) of dopamine (7–15 μg $kg^{-1}$ $min^{-1}$ IV) or dobutamine (1–5 μg $kg^{-1}$ $min^{-1}$ IV). Electrical injury can result in variable degree of tissue injury and can be associated with ventricular fibrillation and/or noncardiogenic pulmonary edema. Electrolytes and colloid osmotic pressure measurements can be monitored frequently and used as guidelines for choosing the appropriate fluid and electrolyte replacement therapy in a long-term basis. If inhalation injury has occurred, syste mic administration of β adrenoreceptor agonists such as terbutaline or inhaled albuterol can be used to treat bronchospasm. Supplemental oxygen should be provided for as long as deemed necessary according to blood gas analysis. Nutritional support is also recommended depending on the severity and location of skin burns. Hypothermia is usually observed in patients with burns due to rapid and excessive heat loss and should be prevented and treated accordingly.

Individuals with burns are normally expected to develop excruciating pain and to have exceedingly high opioid requirements.[8] Analgesic administration is imperative, and drugs should be given in the emergency settings, especially if one considers that pain increases morbidity, the extent of protein catabolism, and delays healing. Acute neuropathic pain may be present, and multimodal analgesia must be employed. Analgesics can be administered as a CRI to maintain long-term therapeutic plasma concentrations. For example, ultrashort agonists of μ-opioid receptors such as remifentanil (2–8 μg $kg^{-1}$ $h^{-1}$) or fentanyl (1–4 μg $kg^{-1}$ $h^{-1}$) in combination with ketamine (2–10 μg $kg^{-1}$ $min^{-1}$), an N-methyl D-aspartate (NMDA) antagonist, are recommended in the treatment of central sensitization or wind-up pain. In dogs, lidocaine may also provide additional analgesia administered either using CRI (1–2 mg $kg^{-1}$ bolus followed by 25–50 μg $kg^{-1}$ $min^{-1}$ IV) or using transdermal patches. The lidocaine patch is 10 × 14 cm and contains 700 mg of lidocaine (50 mg of lidocaine per gram of adhesive patch) in an aqueous base with other inactive ingredients; this formulation of lidocaine produces analgesia without blocking all the sensory and motor inputs,[9] and it can be used in cats as well. This drug has shown to have

free radical scavenging and anti-inflammatory properties when administered systemically. Non-steroidal anti-inflammatory drug (NSAIDs) should be withheld until renal function is established. Gabapentin has been used in dogs and cats with neuropathic injury due to burns.[2] Amantadine is an NMDA antagonist for oral administration that can be given until pain persists.

General anesthesia may be required for wound management on a daily basis or for escharotomies with coverage of skin graft to attenuate postburn hypermetabolic response. Inhalant anesthetics should be reserved to cases where smoke inhalation injury is not present; sevoflurane is preferred for suppressing upper airway reactivity while being the least irritating/pungent anesthetic agent for inhalation.[10] Otherwise, total IV anesthesia with propofol (0.2–0.4 mg $kg^{-1}$ $min^{-1}$) is recommended. Ventilatory support can be provided with positive end-expiratory pressure (PEEP), but barotrauma is best avoided with the use of low peak airway pressures. Sterile endotracheal tubes (high volume, low pressure cuff) and lubricants are used for intubation of the patient to decrease the risk of secondary infection. Severe upper airway edema is treated with the early administration of a single dose of methylprednisolone. Overall, the patient should be evaluated on a case-by-case basis because shock, hyperdynamic circulation, decreased serum albumin concentration, increased $\alpha_1$ acid glycoprotein concentration, and altered receptor sensitivity alter the response to various drugs. Constant nursing contributes to the pain assessment and animal welfare. Anesthetic induction can be performed with any of the classic intravenous anesthetic agents such as propofol, alfaxalone, or ketamine-diazepam. The doses and choice of anesthetic will depend on the physical status and preoperative evaluation of the patient and the use of other drugs with anesthetic-sparing effects. Etomidate or opioid/benzodiazepine (fentanyl + midazolam) induction can be used if cardiovascular collapse is present especially in dogs. Overall, balanced anesthetic techniques are preferred; doses can be given "to effect."

## Chronic pain syndrome after feline onychectomy

Onychectomy is the removal of the third phalanx of each digit of cats.[11] The surgical procedure is aggressive, with a high incidence of postoperative complications. Owners choose to declaw their cats to prevent property damage or personal injury from scratching. The discussion of the ethical issues involved with feline onychectomy is beyond the scope of this chapter.

Laser onychectomy is considered to be the preferred surgical approach due to significantly decreased hemorrhage and postoperative complications including pain.[12] Complications after feline onychectomy can be as high as 50% and include pain, lameness, bleeding, swelling, infection, neuropathies, chronic draining tracts, and regrowth of claws.[13,14] Chronic pain syndrome after feline onychectomy is characterized by behavioral changes that may develop within the immediate postoperative period or years after the procedure. Central sensitization after severe peripheral nociceptive input results in allodynia and chronic pain. Also known as "windup," this phenomenon involves the activation of NMDA receptors. Secondary hyperalgesia is expected due to the amplification of postoperative pain.

### Clinical signs

Clinical signs include chronic lameness, decreased activity and appetite, and increased aggression. Behavioral changes include licking and chewing at the feet, walking as if on "hot coals", shaking the paws, aversion to feet being touched, spontaneous vocalizing for no apparent reason, periods of suddenly sitting still, and aggression.[15] Diagnosis of the syndrome is mostly based on clinical signs and behavioral changes after ruling out degenerative joint disease or other complications that could be surgically corrected.

### Management of anesthesia

Judicious perioperative anesthetic and analgesic management may avoid the development of chronic pain after feline declawing. Multimodal analgesia is characterized by the simultaneous use of two or more different classes of analgesics, where each class of analgesic acts at different levels of the nociceptive input pathway and have different onset and duration of action. This analgesic approach is highly advisable in managing cats undergoing declawing. In this case, dosages of each analgesic may be reduced while minimizing the incidence of side effects. Attenuation of postoperative pain usually occurs with preemptive (preventive) administration of analgesics (e.g. before the noxious event). For example, the use of opioids and local anesthetics is recommended to prevent central sensitization,

reduce intraoperative analgesic requirements, and anesthetic-induced cardiopulmonary depression due to their inhalant anesthetic-sparing effects.[16–18]

Onychectomy patients are generally young and healthy at presentation, and, therefore, minimal preoperative diagnostics are required, unless otherwise indicated. The patient's history and physical examination will guide the anesthetic plan. Premedication may include the combination of $\alpha_2$ adrenoreceptor agonists (e.g. dexmedetomidine at 5–10 μg $kg^{-1}$ IM) due to their sedative, muscle relaxant, and analgesic properties with an agonist of μ-opioid receptors (e.g. hydromorphone at 0.025–0.05 mg $kg^{-1}$ IV or IM) (Table 13.1). Preoperative administration of a NSAID has been shown to improve postoperative analgesia in cats undergoing onychectomy.[19] Induction of anesthesia is performed routinely with intravenous ketamine/diazepam (5 and 0.25 mg $kg^{-1}$, respectively), propofol (3–5 mg $kg^{-1}$), alfaxalone (2–4 mg $kg^{-1}$), or thiopental (5–8 mg $kg^{-1}$) according to the clinician's preference and health status of the animal.

In the perioperative setting and under general anesthesia, blockade of the distal branches of the radial, ulnar, median, common peroneal, and tibial nerves can be performed with bupivacaine due to its long-acting effects (Figure 13.3a and b). Local anesthetics are relatively safe when appropriate doses and techniques are used, and for this reason, toxic doses must be calculated especially in kitties. Nonflammable antiseptic is used around the local blocks sites if laser surgery is to be performed. Indeed, safety glasses must be used for protection of the eyes from any reflected beam.[11]

Buprenorphine (0.02–0.03 μg $kg^{-1}$ IV) can be administered during the recovery phase of anesthesia or in the early postoperative period when the effects of premedication are wearing off. Alternatively, hydromorphone (0.025 mg $kg^{-1}$ IV) or methadone (0.3 mg $kg^{-1}$ IV) has been used for postoperative analgesia. Buprenorphine has the advantage that it can be prescribed for "home medication". The drug is administered by owners using the buccal route. The clinician should be aware of NSAIDs label recommendations in cats, which can vary among countries. For example, in Europe, meloxicam is licensed for long-term use at 0.05 mg $kg^{-1}$ $day^{-1}$. Treatment of chronic pain after feline declawing may require off-label administration of NSAIDs, such as robenacoxib and meloxicam. These drugs may be needed for a few days at the discretion of the veterinarian, unless contraindicated.

## Treatment of chronic pain syndrome

Cats must be examined for any other source of pain when chronic pain after feline onychectomy is suspected; the feet must be evaluated for residual inflammation or underlying infection. Diagnostic imaging rules in or out remaining bony fragments, and if the syndrome is confirmed, analgesia and treatment of central sensitization are the goals of the therapy. A multimodal analgesic approach for long-term treatment with the combination of an NMDA-receptor antagonist, an opioid, and an NSAID has been proposed and is described in the following section (Table 13.1).[21] Therapy is usually constituted by "off-label" administration of analgesics with little evidence-based medicine.

**Table 13.1** Perioperative analgesic management for cats undergoing onychectomy.

| |
|---|
| Premedication: dexmedetomidine (5–10 μg $kg^{-1}$) or acepromazine (0.03–0.05 mg $kg^{-1}$) + hydromorphone (0.05–0.1 mg $kg^{-1}$) IM |
| Induction: ketamine (5 mg $kg^{-1}$) + diazepam (0.25 mg $kg^{-1}$), propofol (3–8 mg $kg^{-1}$), or alfaxalone (3–5 mg $kg^{-1}$) |
| NSAIDs: meloxicam (0.2 mg $kg^{-1}$ SC after induction; then 0.05 mg $kg^{-1}$ PO q24 h for 3 days – OFF-LABEL USE) or robenacoxib (1–2 mg/kg PO for three days) |
| Local blocks: bupivacaine 1–2 mg $kg^{-1}$ as a total dose for declawing blocks |
| Postoperative: Buprenorphine (0.02 mg $kg^{-1}$ IV 4 h after hydromorphone administration then 0.02 mg $kg^{-1}$ buccally q8 h for 2–3 days) or another dose of hydromorphone (0.025 mg $kg^{-1}$ IV) until therapy is switched to buprenorphine |
| *Treatment of feline chronic pain syndrome after onychectomy* |
| Amantadine: 3 mg $kg^{-1}$ PO q24 h for 21 days |
| Meloxicam: 0.05 mg $kg^{-1}$ PO q24 h for 4 days; then 0.025 mg $kg^{-1}$ PO q24 h for 4 days then 0.05 mg per cat PO q 24 h for 4 days, and finally 0.05 mg per cat PO q 48 h for 5 days |
| Buprenorphine: 0.01–0.02 mg $kg^{-1}$ q8 h for up to 5 days (2–3 days) |
| Gabapentin: 10–20 mg $kg^{-1}$ PO q12 h until resolution of clinical signs. Gabapentin should be tapered down over a 3-week period to avoid breakthrough pain |

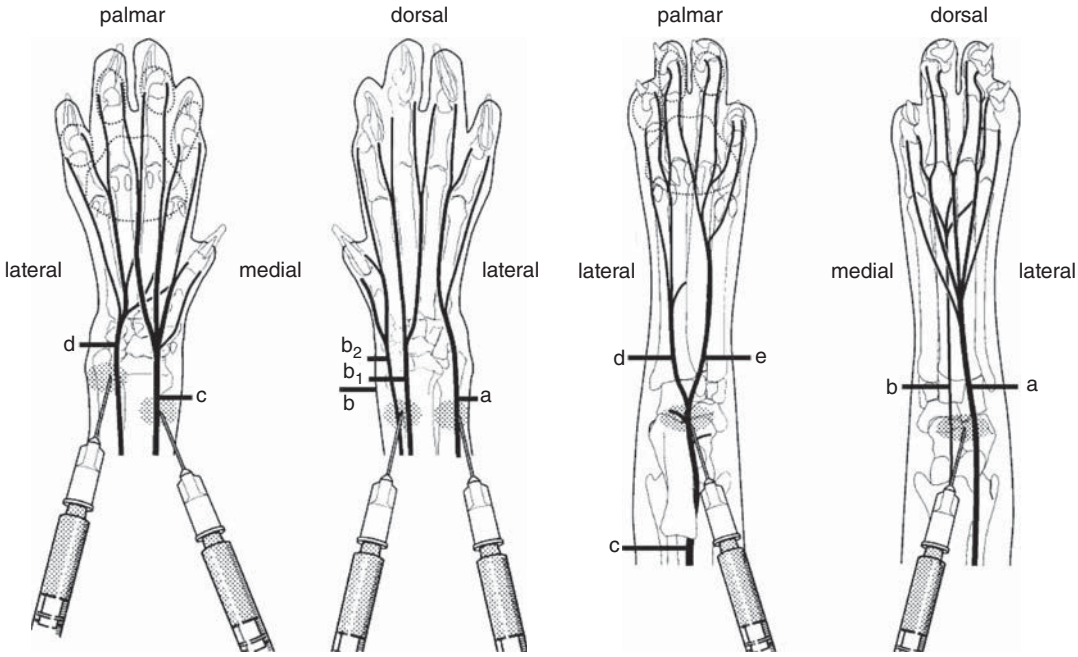


**Figure 13.3** (a) In the thoracic distal limbs, on the dorsomedial aspect and proximal to the carpal joint, the superficial branches of the radial nerve are desensitized with local anesthetics. Proximal and lateral to the accessory carpal bone, the palmar and dorsal cutaneous branches of the ulnar nerve are desensitized with local anesthetics. The median nerve is blocked proximal to the median carpal pad. Alternatively, a 4-point digital block or a ring block can be performed by injecting bupivacaine into the subcutaneous tissues distal to the carpal joints.[20] (b) In the pelvic distal limb, on the dorsomedial aspect and distal to the tarsus, the superficial branches of the common peroneal nerve are desensitized. Ventromedially and distal to the tarsal joints, the superficial branches of the tibial nerve are blocked. For these procedures, local anesthetics are administered at each site in the subcutaneous tissues using a 22G X 1-inch needle. The toxic dose of bupivacaine is always calculated.[20] Source: Adapted with permission from Reference 20.

Ketamine is a dissociative anesthetic commonly used in cats with NMDA antagonistic properties. Activation of NMDA receptors is involved with the transmission and exacerbation of nociceptive stimuli in the dorsal horn of the spinal cord, which plays a key role in neuropathic and chronic pain. Ketamine may prevent central sensitization and the development of chronic pain and is normally administered as a CRI (2–10 μg $kg^{-1}$ $min^{-1}$) during hospitalization. Amantadine (3–5 mg $kg^{-1}$ every 12 or 24 h) is also an NMDA-receptor antagonist that has been administered to cats as part of chronic pain treatment after feline onychectomy.

The analgesic therapy also involves the administration of buprenorphine. Anecdotally, a long-sustained release formulation of buprenorphine has been advocated to provide analgesia for up to 5 days in cats.[22] However, at the time of writing, there were no reports of the long-acting analgesic effects of this compound in veterinary medicine. The administration of NSAID has been recommended at a progressively decreasing dosing schedule for up to 12 days. A full biochemical profile is mandatory before NSAID therapy is initiated. The cats must be carefully observed for the development of NSAID-induced side effects. In the latter case, cessation of the NSAID administration is immediate.

Gabapentin is a calcium channel antagonist that can be used as an adjuvant in the treatment of hyperalgesia and allodynia. This drug has been widely used in the treatment of neuropathic pain in humans and rodents, although its mechanism of action is not fully elucidated. Gabapentin (10–20 mg $kg^{-1}$ every 8–12 h PO) may be useful as part of a multimodal analgesic approach in the treatment of feline onychectomy pain syndrome. Shredded paper or compressed paper pallets

should be used in the litter box until therapy has been effective.

## Diseases of the ear

The ear is a specialized extension of the integumentary system. Sedation and general anesthesia are occasionally required to perform a complete otic examination, diagnosis, and/or treatment. Ear infection or inflammation can induce neurological deficits due to close proximity of facial nerve and sympathetic innervations of the eye and ears. Otitis externa describes any inflammatory condition of the external ear canal. Clinical signs consist of head shaking, scratching, otic pain, variable accumulation of cerumen or exudates, and malodor. Otitis media may result from extension of otitis externa through the tympanic membrane, aspiration of pharyngeal contents up the auditory tube, or from hematogenous spread, neoplasia, trauma, and inflammatory polyps. However, otitis media may be a perpetuating factor for otitis externa. Otitis interna is usually an extension of otitis media or neoplasia of the middle ear. A careful neurological examination is required to locate the vestibular signs, as animals with otitis interna will present nystagmus, circling, or falling toward the side of the lesion. If there is involvement of the labyrinth, animals may become nauseated and vomit. Horner's syndrome or deficit in cranial nerves may be observed with otitis media and/or interna.[23]

### Diagnosis

Skull radiography, computed tomography (CT), and magnetic resonance imaging (MRI) are commonly indicated for evaluation of the ear. These procedures normally involve general anesthesia and are employed to evaluate the integrity of the tympanic bulla, underlying otitis media, neoplasias, polyps, foreign bodies, otitis interna, and central vestibular disease.[24] Advanced imaging helps in distinguishing the anatomic location of disease process. CT is considered superior to MRI for bony changes, whereas MRI is better for detection of soft tissue abnormalities in both dogs and cats.[25] Cytologic and culture examinations are performed to detect endoparasites/ectoparasites infection, inflammatory processes, or neoplastic lesions. Auricular tumors are more common in cats than dogs and include squamous cell carcinoma, mast cell tumor, basal cell tumor, and fibrosarcoma. General anesthesia is also performed for a complete otoscopic examination in cases of severe otitis in which thorough cleaning of the ear is necessary for therapy and diagnosis.[23]

If the tympanic membrane is intact in a dog with otitis media, a myringotomy is performed to obtain samples for culture and susceptibility testing and cytologic examination. Briefly, a spinal needle penetrates the tympanic membrane through the caudoventral aspect of the pars tensa. Suction is applied and samples collected. Ear flushing of external ear canal is usually required under the same general anesthesia episode.[24]

Brainstem auditory evoked response (BAER) is an objective test of hearing that detects the presence or absence of hearing or progression of changes in hearing. Electrodes placed on standard sites of the head record responses to an auditory stimulus generated. The waves generated are evaluated, and each wave corresponds to a special cranial nerve or portion of it or an area of the central nervous system. Since there is conduction of impulses through the brainstem, the test is also valuable for diagnosis of brainstem lesions. Sedation and anesthesia may cause changes in wave latency.[23]

### Treatment

In addition to medical therapy, surgery is commonly performed in dogs and cats for the treatment of ear diseases. Aural hematoma repair due to self-induced trauma of head shaking or scratching is an example. In this case, blood accumulates within the fractured cartilage of the pinna, and swelling is most visible on the concave aspect. Treatment of otitis externa or other underlying cause is required to avoid recurrence of aural hematoma. Surgical incision, drainage, curettage, and closure with mattress sutures provide apposition of the cartilage edges.

The two most common surgical procedures for the treatment of otitis externa are lateral ear resection and total ear canal ablation (TECA).[26] Opening the vertical ear canal with lateral ear resection in dogs improves aeration, decreases humidity, facilitates removal of cerumen or exudate, and improves the distribution of topical medication in the ear canal. TECA is the mainstay treatment of end-stage otitis and malignant otic neoplasia. The technique is always combined with bulla osteotomy to allow complete removal of all secretory epithelium and exudate associated with the external and middle ear. Severe secondary changes and proliferative disease are surgically removed with

the ear canal. Finally, a lateral bulla osteotomy of the tympanic bulla allows complete exploration of the middle ear for the removal of secretory epithelium, exudates, and/or tumor. Surgery complications include facial nerve paralysis, hemorrhage, severe pain, and hearing loss.[27] In the author's experience, secondary complications have been observed after compressive bandage placement in cats, causing obstruction of the airways with further hypoxemia, collapse, and death.

## Management of anesthesia

Health status and differentiation of ear disease between a primary or secondary disorder are important for the anesthetic management of the canine or feline patient with ear disease. Endocrinopathies can be a common cause of ear disease. Systemic glucocorticoid administration is usually the elective therapy for acute inflammation of the ear canal, chronic proliferative changes of the ear canal, and allergic otitis. Special attention should be paid to antibiotic therapy that could potentially involve drug-induced toxicity. Nephrotoxicity induced by aminoglycosides manifests clinically as nonoliguric renal failure, with a slow rise in serum creatinine and a hypoosmolar urinary output developing after several days of treatment. Systemic administration of aminoglycosides is nephrotoxic because of a small but sizable proportion of the administered dose in the proximal tubules after glomerular filtration.[28]

In case there is a ruptured eardrum, manipulation or flushing can cause material to drain through the Eustachian tube into the nasopharynx, resulting in aspiration. Therefore, a cuffed endotracheal tube is always required for these procedures.

Chronic conditions of the ear are associated with pain on palpation and may be exacerbated during the otoscopic examination. Pain on opening the mouth may be related to middle ear involvement. This is a result of inflammation, swelling, and pain within the bulla, which is located adjacent to the temporomandibular joint. The ears can be extremely sensitive and painful, and depth of anesthesia must be rapidly adjusted if head shake is observed during surgery or otoscopy. Indeed, perioperative analgesia is imperative in the management of TECA and bulla osteotomy. These surgical interventions are highly invasive and painful procedures. Opioids (e.g. morphine [0.2–0.3 mg $kg^{-1}$ in the cat or 0.5–1.0 mg $kg^{-1}$ in the dog] or hydromorphone [0.025–0.05 mg $kg^{-1}$ in the cat or 0.1–0.2 mg $kg^{-1}$ in the dog]) are recommended as part of premedication followed by an opioid CRI during the intraoperative and postoperative period. Moreover, fentanyl reduces inhalant anesthetic requirements, often resulting in less cardiopulmonary depression while providing reliable analgesia. Doses up to 42 μg $kg^{-1}$ $h^{-1}$ have produced maximum reductions in the minimum alveolar concentrations of enflurane (63%) in dogs.[29] However, lower doses of fentanyl (10–15 μg $kg^{-1}$ $h^{-1}$ IV) may be combined with lidocaine (50 μg $kg^{-1}$ $min^{-1}$ IV; in dogs only) and/or ketamine (10 μg $kg^{-1}$ $min^{-1}$ IV) as part of balanced anesthesia. Lower doses of opioids will usually prevent opioid-induced dysphoria in the anesthetic recovery. A local anesthetic block has been described in dogs undergoing TECA. Under general anesthesia, bupivacaine is injected in a line from the wing of the atlas to the caudal aspect of the vertical ear canal to block the great auricular nerve. The drug is administered between the caudodorsal aspect of the masseter muscle and rostral aspect of the vertical ear canal to desensitize the auriculotemporal nerve.[30] Another method of analgesic administration has been described with the use a local anesthetic delivery system that allows continuous delivery of local anesthetics via a fenestrated catheter (Figure 13.4).[31,32] An elastomeric bulb or syringe pump device is filled with drug to deliver

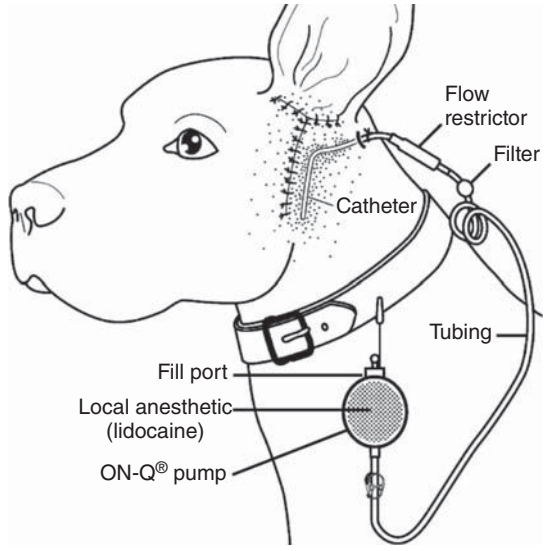


**Figure 13.4** Application of a pain booster local anesthetic infusion system in a total ear canal ablation.[32] Source: Adapted with permission from Reference 32.

a constant volume directly to the surgical site. Results of these studies suggest that there is little or no benefit in using local anesthetic blocks in dogs that underwent TECA. Despite the lack of significant differences among treated group, a benefit may exist, and failing to detect an advantage could be attributable to an inadequate dosage of the drug, technique error, inconsistent analgesia of all nerves, adequate effect of other systemic analgesics, and/or poor study design, including inappropriate methods for the recognition and evaluation of pain in animals. Multimodal analgesia with local anesthetic blocks, opioid, and anti-inflammatory drug administration is considered to be the cornerstone in the treatment of perioperative pain associated with TECA. This approach usually minimizes the development of breakthrough pain and a high incidence of opioid-induced side effects (e.g. dysphoria, respiratory depression, or drug-induced hyperalgesia).

## Laryngeal paralysis (LP)

Laryngeal paralysis (LP) is a well-recognized cause of upper respiratory stridor and dyspnea in dogs and more rarely in cats.[33] The disease is characterized by laryngeal malfunction during abduction of the arytenoid cartilages, thus creating an inspiratory partial or full upper airway obstruction. Hereditary and acquired forms have been recognized in dogs and cats.[34] The hereditary form, less frequent than the acquired form, affects young dogs of many breeds such as Bouvier, Bull Terrier, Dalmatian, Rottweiler, and Huskies. Mixed-breed dogs can be affected by both forms of the disease. The acquired form is most commonly reported in middle-aged to older dogs. Labrador Retrievers are over-represented[35,36], but other breeds such as Golden Retrievers, Afghan Hounds, Irish Setters, Standard Poodles, and Saint Bernards have been affected.[37]

Unilateral or bilateral LP can be a result of trauma or an intrathoracic or extrathoracic mass that could compress or stretch the recurrent laryngeal nerve.[33,34] In addition, neuropathy of the recurrent laryngeal nerve, myopathy of the intrinsic muscles of the larynx, as well as neuromuscular disorders such as myasthenia gravis (MG), megaesophagus, or idiophatic myositis have been associated with LP. It has been proposed that LP may actually be a manifestation of a generalized neuromuscular disorder from a peripheral neuropathy. Recent studies have demonstrated that the paralysis can be linked to esophageal dysfunction and generalized weakness,[35] as well as clinical neurological deficits, electrodiagnostic, and/or pathologic abnormalities.[36,38] In cats, LP is an uncommon cause of upper airway obstruction, and both forms have been observed. The acquired form has been reported after bilateral thyroidectomy, but no breed or sex predisposition has been identified in this species.[39]

### Clinical signs

The severity of the clinical signs is dependent on that of LP and can manifest from altered barking, gagging, coughing, and mild exercise intolerance to severe respiratory distress. Dyspnea, collapse, cyanosis, and hyperthermia may occur in the emergency setting, possibly requiring general anesthesia and ventilatory support.[34] Clinical signs are usually progressive, and patients are presented for investigation late in the course of the disease. Other clinical signs include concurrent pelvic limb weakness with bilateral cranial tibial muscle atrophy, generalized weakness, and neurological deficits.

### Diagnosis

Physical examination and laboratory findings may be unremarkable. Inspiratory stridor or increased lung sounds cranially may be noted during thoracic auscultation. The most commonly used method for diagnosing LP is laryngoscopy (Figure 13.5). The procedure is performed via examination of the laryngeal function under a light depth of general anesthesia. Failure of one or both of the arytenoid cartilages to abduct during inspiration may confirm the diagnosis.

### Treatment

The treatment of LP ultimately involves surgical management. Several interventions are described, but unilateral or bilateral arytenoid cartilage lateralization has become the surgical treatment of choice in dogs due to a lower complication rate compared to other techniques.[37] Successful medical management has been described in cats with mild clinical signs.

### Management of anesthesia

A thorough physical examination and auscultation along with thoracic radiography are recommended for the investigation of megaesophagus and aspiration

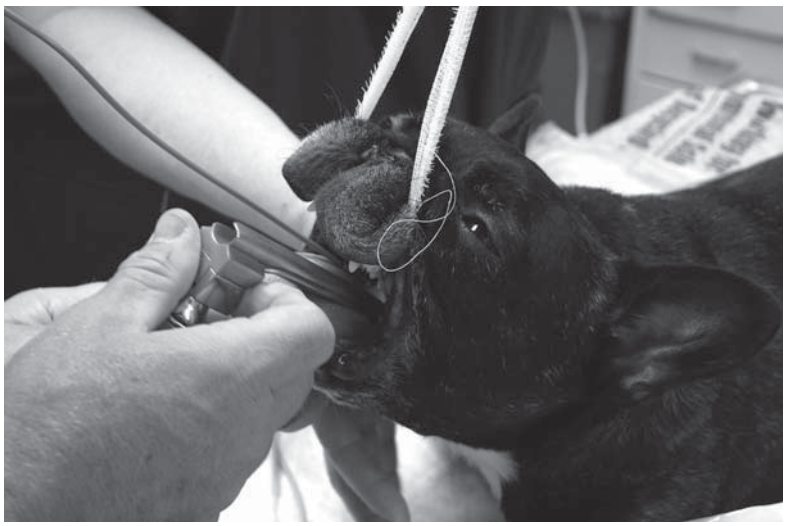

**Figure 13.5** Laryngoscopy is the preferred method for the diagnosis of laryngeal paralysis. The procedure is performed via examination of the laryngeal function under a light depth of general anesthesia. Oxygen insufflation should be provided while general anesthetics are given to effect. Source: Courtesy of Dr. G. Giannotti.

pneumonia. In addition, preoperative preparation includes determination of the severity and degree of laryngeal dysfunction. Other systemic abnormalities should also be corrected when possible. During the evaluation and before anesthesia, the patient should be handled quietly and carefully to avoid stress or fear-induced tachypnea with subsequent increased work of breathing.

Emergency medical treatment may be required in animals presenting with acute respiratory distress. Partial or total airway obstruction may be exacerbated by stress, excitement, pain, fear, and swelling of the arytenoids cartilage. Partial airway obstruction with increased inspiratory effort and work of breathing may cause increased negative pressure, leading to pulmonary edema. Resistance to breathing is dictated by Hagen–Poiseuille's law and can be severely increased during partial airway obstruction (Figure 13.6). Oxygen therapy is then required to prevent or treat hypoxemia. Stress-induced hyperthermia can be treated with ice packing, alcohol, or cold water bath and the administration of acepromazine (ACE). This drug causes a decrease in respiratory rate in dogs but no changes in $PaCO_2$, pH, or $PaO_2$. Because ACE produces mild sedation and has a relatively long duration of action, it is often used to calm anxious patients and is considered to be an appropriate choice for patients with LP. Greater

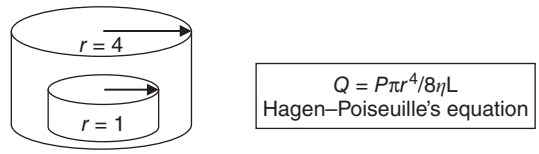


**Figure 13.6** The Hagen–Poiseuilles' law applies when flow is laminar (linear relationship of flow to pressure). Resistance is directly proportional to flow rate ($Q$) during laminar flow. The internal diameter ($r$) of the airway is the most important factor determining the resistance to gas flow. The equation shows that doubling the length (L) of the airway only doubles the airway resistance while halving the radius reduces the flow to 1/16 of its original value if the pressure ($P$) drop along the tube remains the same. The flow is proportional to the fourth power of the radius. For example, an airway has a radius of 1 and a flow of 1 ml $min^{-1}$. If the radius is increased by 4, the flow is increased to 256 ml $min^{-1}$. Changes in resistance (and therefore flow) tend to parallel changes in the work of breathing. η; viscosity of fluid. In the figure, "1" and "4" are arbitrary numbers to demonstrate what happens when there is a 4-fold increase in radius.

sedation is accomplished with the combination of ACE (0.01–0.03 mg $kg^{-1}$) and butorphanol (0.2 mg $kg^{-1}$) or buprenorphine (0.01–0.02 mg $kg^{-1}$) intravenously. Other secondary changes such as laryngeal and pulmonary edema can be addressed with the administration of corticosteroids (dexamethasone 0.2–1.0 mg $kg^{-1}$

every 12 h daily). However, steroids are usually reserved for postoperative administration when laryngeal edema and swelling, cyanosis, hypoxemia, and respiratory difficulties are observed after extubation. Tracheostomy is the last resource when other emergency treatments have failed to alleviate distress.

The use of opioids for LP examination is controversial. Opioids produce an antitussive effect through a central inhibition of the cough center that is mediated by both μ- and κ-receptor agonists.[34] Independent of their antitussive effects, opioids are known for causing dose-dependent centrally mediated respiratory depression that could be clinically relevant in patients with LP. This effect can be exacerbated by concurrent use of other respiratory depressants such as some injectable and inhalant anesthetics. Therefore, dogs and cats should be closely monitored after opioid therapy, sedation, and recovery of anesthesia; 100% oxygen should be provided. Another concern is that opioids may decrease esophageal sphincter pressure and increase the incidence of gastroesophageal reflux (GER) during anesthesia and early postoperative period. In patients with LP, postanesthesia esophagitis, regurgitation, and possible aspiration pneumonia are of great concern. There is evidence that some opioids, morphine in particular, may increase the incidence of GER during anesthesia compared to other drugs from the same class. The CRI of metoclopramide (0.01–0.02 mg $kg^{-1}$ $h^{-1}$) is commonly administered postoperatively in an attempt to increase lower esophageal sphincter tone and avoid postoperative regurgitation and aspiration.

Several clinicians do not consider arytenoid cartilage lateralization to be severely painful. Thus, clinical experience has revealed that buprenorphine, a partial agonist of μ-opioid receptors that tends to cause less respiratory depression and dysphoria than full agonists of opioid receptors (hydromorphone or morphine), may provide adequate sedation and pain management throughout surgery. A multimodal analgesic approach is beneficial with the addition of a NSAID. If profound sedation and/or respiratory depression are observed, opioids can be reversed with the administration of an opioid antagonist (naloxone or nalmefene) or an agonist-antagonist (butorphanol).[41]

Anticholinergics have been used to prevent vagal-induced bradycardia resulted from laryngeal manipulation and/or opioid administration and can be particularly useful in brachicephalic breeds. However, thick mucous can be produced, leading to increased fluid viscosity, airway obstruction, and increased work of breathing (Figure 13.6).

For laryngoscopy, a light depth of anesthesia is required in order to perform the laryngeal examination without losing the laryngeal reflex (Figure 13.5). If anesthetic depth is excessive, arytenoid motion will be depressed or absent even in healthy dogs. In this scenario, the larynx should be patiently observed continuously as the animal awakes. Dogs and cats should be preoxygenated via face mask or by flow-by, as well as throughout laryngoscopy. A tube (e.g. red rubber tube or flexible long urinary catheter) is placed close to the trachea for oxygen insufflation. The tube is connected to the oxygen line via a three-way stopcock that normally connects the anesthesia machine with the breathing system (Figure 13.7). Misdiagnosis of LP may be avoided by selecting anesthetic regimens, with the least effect on arytenoid motion. Nevertheless, there is currently no established unique protocol for the evaluation of laryngeal function in small animals.

Doxapram hydrochloride is a central nervous stimulant that increases respiratory rate and tidal volume. The drug is often given during laryngoscopy because increased intrinsic laryngeal motion may be useful for differentiating normal dogs from those with LP.[42,43] Complete airway occlusion is a risk, and endotracheal intubation may be potentially necessary with the use of doxapram. Indeed, induction and recovery phases

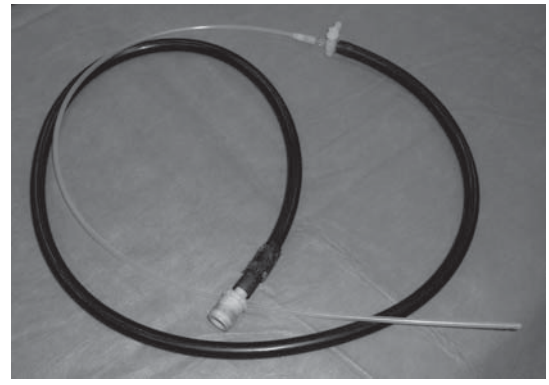

**Figure 13.7** A flexible long urinary catheter is used to provide oxygen insufflation during laryngoscopy. The distal part of the catheter is placed close to the trachea. The tube is connected to the fresh gas flow output where normally the anesthetic machine is connected to the breathing system.

of anesthesia can be critical in dogs and cats with LP. However, maintenance of anesthesia is generally uneventful when pain is controlled and the airways are secured. Standard monitoring should be adequate with the understanding that pulse oximetry is fairly useful for monitoring early hypoxemia during laryngoscopy and recovery of anesthesia. In regards to the drugs used for anesthetic induction, no significant difference was detected when thiopental, propofol, and diazepam-ketamine were compared during evaluation of laryngeal function in dogs.[44] On the contrary, arytenoid motion was significantly greater after thiopental administration when compared to propofol, ketamine-diazepam, acepromazine-thiopental, and acepromazine-propofol.[45] One should keep in mind that propofol is a potent respiratory depressant, and slow administration of small doses is advised in order to avoid apnea. In addition, ketamine has shown to cause mild decrease in respiratory rate, minute volume, and $PaO_2$. Laryngeal examination should be kept to a minimal period to avoid complications while attention is given to a rapid and smooth endotracheal intubation. Cats are prone to laryngospasm, and desensitization of the arytenoids is recommended with a few drops of lidocaine before intubation and after laryngeal examination.

Dogs and cats are generally extubated during surgery for evaluation of airway diameter after arytenoid cartilage lateralization. Small boluses of propofol (0.3–0.5 mg $kg^{-1}$) are given, and a new endotracheal tube should be available for intubation. During the recovery phase of anesthesia in dogs, it has been suggested to leave the endotracheal tube partially inflated to avoid regurgitation entering the trachea and subsequent aspiration pneumonia. Extubation is performed when coughing is observed and swallowing reflexes are returned. Sedation may be necessary aiming a stress-free recovery. ACE (0.01–0.02 mg $kg^{-1}$ IV) or dexmedetomidine (0.5 μg $kg^{-1}$ IV) can be administered after extubation or if the patient is already showing signs of agitation and/or distress. Reintubation can be performed when swelling and laryngeal edema are present. Pulmonary edema is not uncommon due to increased thoracic negative pressure and work of breathing. Furosemide (1 mg $kg^{-1}$) is administered in addition to corticosteroids, and monitoring the patient's ventilator status is of utmost important. Animals are hospitalized in the critical care setting after surgery. Postoperative complications include aspiration pneumonia, laryngeal edema, recurrence of clinical signs, and transient Horner's syndrome, among others.[36] Despite some degree of morbidity and common postoperative complications, surgery is the recommended treatment in dogs for the improvement of quality of life, especially if one considers the life-threatening nature of the disease.[37,38,46] In cats, unilateral arytenoid lateralization also appears to provide good prognosis.[39,47]

## Malignant hyperthermia

Malignant hyperthermia (MH) is defined as a pharmacogenetic clinical syndrome characterized by skeletal muscle rigidity, rapid increase in core body temperature, hypercapnia, and metabolic acidosis. MH is considered to be a clinical syndrome due to its multiple genetic and environmental points of entry.[48] This syndrome is primarily caused by a mutation in the ryanodide receptor (RYR1) gene with an autosomal dominant inheritance pattern.[49] The ryanodide receptor, or calcium-release channel, is located in the sarcoplasmic reticulum membrane of skeletal muscle and is essential to control the movement of calcium during excitation–contraction coupling process. Uncontrolled release of calcium from the sarcoplasmic reticulum into the myoplasm may cause muscle rigidity and a hypermetabolic state, with release of cations and enzymes and production of excessive heat and acids.

Malignant hyperthermia is usually triggered by halogenated volatile anesthetics (e.g. halothane, isoflurane, and sevoflurane) and depolarizing muscle relaxants (e.g. succinylcholine); stress and other ion channelopathies have also been identified as important initiating factors.[50] MH-like syndromes have been reported in various breeds of dogs, including Greyhounds, Border Collies, Cocker Spaniels, Doberman Pinschers, Pointers, and Saint Bernards. No breed disposition has been identified; the anecdotal belief that Greyhounds were genetically susceptible to MH has not been confirmed.[51] Suspected MH has been rarely described in the cat.[51]

### Clinical signs

Unlike MH in pigs, canine MH is not typically presented by lactic acidosis or an early onset of muscle rigidity but rather an increased production of carbon dioxide and oxygen consumption. Slow increases in core body

temperature are observed but lag behind carbon dioxide production and tachypnea. Ventricular premature contractions, ventricular bigeminy, fibrillation, and tachycardia have been reported in dogs and cats with MH-like syndrome.

## Diagnosis

MH episodes may occur in healthy animals without a previous history of anesthetic problems. Persistent and elevated increases in oxygen consumption and carbon dioxide concentrations despite aggressive ventilatory support should be viewed as potential positive MH cases. Other causes of hypercapnea, cardiac arrhythmias, metabolic acidosis, increased body temperature, and muscle rigidity must be ruled out. Tachypnea and tachycardia can be attributed to "light" anesthesia, which is easily addressed by proper monitoring of anesthetic depth. Hyperthermia has been observed after heat stroke or opioid administration and/or can be accidentally iatrogenic induced.

MH-like syndromes have been documented in the literature but *in vitro* muscle contracture test (IVCT) was rarely performed to confirm the diagnosis of MH. Therefore, the true incidence of MH is unknown in veterinary medicine. Suspected MH animals should be followed up with IVCT, in which a muscle sample is exposed to halothane and caffeine, and the degree of sensitivity of contractive patterns to these triggering agents is measured. However, a negative test does not exclude an MH reaction. The test is sometimes cost prohibitive, which makes the conclusive diagnostic impractical. Clinically, the use of end-tidal carbon dioxide and core body temperature monitoring are useful for early diagnosis and treatment of MH.

## Treatment and management of anesthesia

Recognition of the clinical signs and immediate elimination of known triggering factors may prevent and/or treat signs of MH (Figure 13.8). Discontinuation of inhalant anesthetics administration and depolarizing neuromuscular blocking drugs is a key component of management of MH. Decontamination of the anesthetic machine by removal of the vaporizer and the replacement of each part that might have been in contact with an inhalant anesthetic are recommended. The gas flow circuit should be flushed with fresh gas at a rate of 10 l $min^{-1}$ for a minimum of 10 min. The use of gas analyzers that monitor end-tidal inhalant anesthetics identifies any residual anesthetic in the breathing system. Even a small fraction of volatile anesthetic can trigger the syndrome in MH-susceptible patients. The carbon dioxide absorber may become hot and exhausted. Drugs considered safe for administration include barbiturates, propofol, opioids, benzodiazepines, dexmedetomidine, ketamine, droperidol, and nondepolarizing neuromuscular blocking drugs. Total intravenous anesthesia is considered if anesthesia cannot be terminated but may not prevent a MH-like syndrome to occur.[52]

Effective sedation and analgesia are important in order to minimize perioperative stress and pain, respectively, as these are considered to be triggering factors. An opioid (morphine [0.5–1 mg $kg^{-1}$] or methadone [0.5 mg $kg^{-1}$] IM) can be given with midazolam (0.2 mg $kg^{-1}$ IM), ACE (0.02–0.05 mg $kg^{-1}$ IM), or dexmedetomidine (3–5 μg $kg^{-1}$ IM). Induction of anesthesia can be accomplished with any classic IV anesthetic agent. Monitoring of end-tidal carbon dioxide is essential for the early diagnosis of a MH episode. PEEP is rapidly instituted along with invasive blood pressure and electrocardiogram monitoring. Hyperventilation and high peak airway pressure are commonly needed in an attempt to decrease carbon dioxide levels. Aggressive fluid therapy with isotonic crystalloid solutions is sometimes needed due to hypotension. In this case, Ringer's lactate with added calcium is not acceptable due to the pathogenesis of MH, and 5% dextrose in water, saline 0.9%, or balanced salt solutions are preferred. Acetate polyionic solutions are calcium-free balanced electrolyte solutions that can be infused at 60–90 ml $kg^{-1}$ $h^{-1}$ in cases of severe hypotension. However, the latter contains less sodium than plasma, which could lead to greater loss of fluid into the intracellular compartment. Acetate is metabolized rapidly throughout the body, and the alkalinizing effect is readily available. Saline 0.9% contains higher amounts of chloride than plasma and tends to decrease the strong ion difference, leading to hyperchloremic acidosis. Dextrose (5%) in water contains no electrolytes, and it is rarely indicated as the primary replacement solution. Only free water remains when dextrose is metabolized; high concentrations of glucose may be detrimental in both acute renal and cerebral injury. In any crystalloid therapy, the volume retained in the vascular space is rapidly distributed into the interstitial space, producing only a short-term

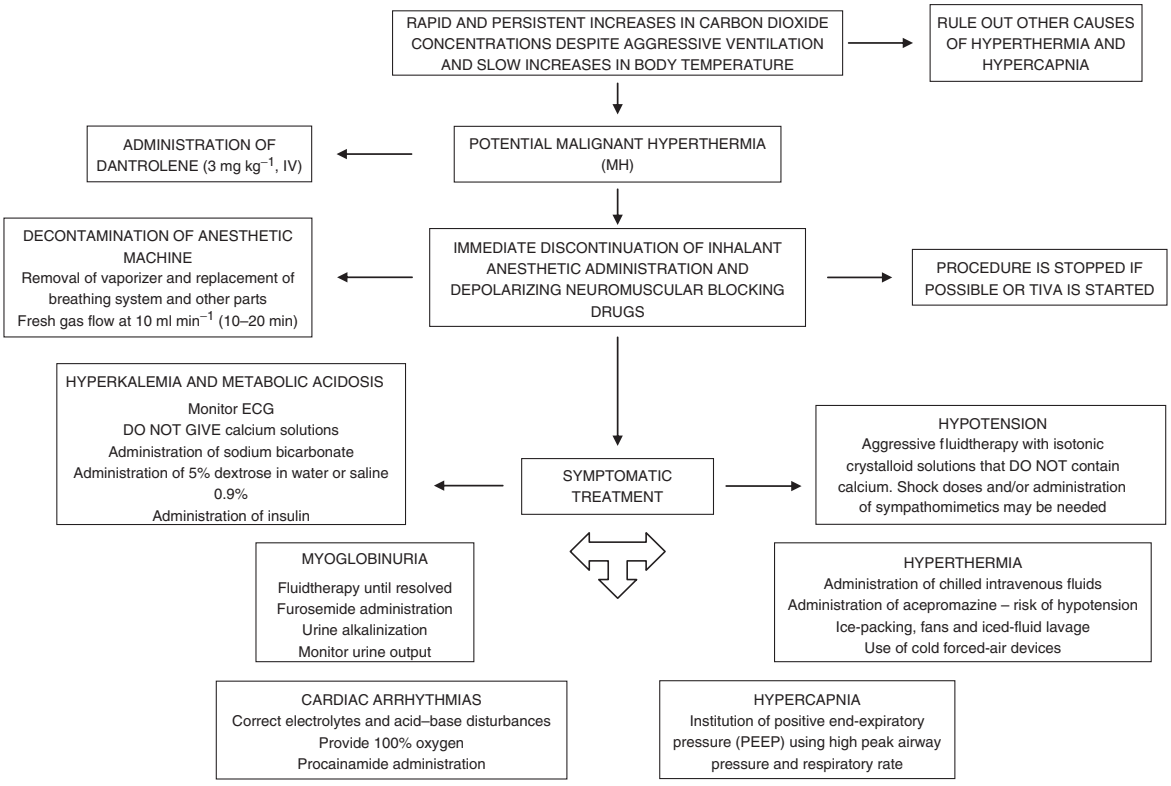


**Figure 13.8** Treatment of malignant hyperthermia.

volume expansion. However, hypertension and tachycardia may be observed due to sympathetic stimulation caused by severe hypercapnea. Fluid therapy may also be important to prevent acute renal injury associated with deposition of myoglobin in the renal tubules. The use of osmotic and loop diuretics and urine alkalinization should prevent rhabdomyolitic kidney failure. Chilled intravenous fluids are preferred to cool the patient in the presence of hyperthermia.

Cardiac arrhythmias are best treated with the administration of procainamide during episodes of MH, as lidocaine has been documented to compromise the outcome by increasing myoplasmic calcium content, leading to exacerbation of the hypermetabolic state.[53]

Most of the case reports describe cooling as part of the treatment of a MH episode. Cooling can be accomplished with ice packing, fans, and iced fluid lavage. Heating blankets and convective heaters must be turned off. Acepromazine has been used as palliative therapy for hyperthermia. The drug induces hypothermia by acting in the thermoregulatory center of the hypothalamus and blocking $\alpha_1$-adrenergic receptors, which ultimately results in peripheral vasodilation and loss of body heat.[52]

Laboratory testing may include serum electrolytes, lactate and CK measurements, and blood gas analysis. The goal is to identify acid–base disturbances (acidemia) and to monitor progression of the treatment. Hyperkalemia-induced cardiac arrhythmias are an important cause of death in these patients and should be addressed immediately. Metabolic acidosis potentiates hyperkalemia and is treated with the administration of sodium bicarbonate (1–2 mEq $kg^{-1}$, IV). Calcium solutions are contraindicated, and the prognosis may be compromised.[54] Intravenous administration of glucose combined with insulin helps driving potassium into the cells and provides an exogenous energy source with which to replace depleted cerebral metabolic substrates. A urinalysis can be useful to reveal myoglobinuria.

Dantrolene is the recommended life-saving therapeutic agent for the treatment of MH. The drug is an intracellular calcium antagonist that has skeletal muscle relaxant properties.[55] A single dose of 3 mg $kg^{-1}$ is administered immediately after the recognition of MH, but additional doses up to 10 mg $kg^{-1}$ may be needed. The drug is provided as a lyophilized power (20 mg) with mannitol, 3 g, added to improve solubility. Dantrolene should be mixed in water (60 ml) and administered via a large bore catheter to avoid venous irritation.[48] Unfortunately, because of its high cost and the low incidence of MH as an anesthesia-related complication in veterinary medicine, dantrolene is not always available in all veterinary institutions, which may lead to a high incidence of anesthetic death during the occurrence of MH cases.[54] The use of nondepolarizing neuromuscular blocking drugs has been suggested as an alternative to dantrolene because these drugs block acetylcholine from occupying binding sites at the neuromuscular junction and prevent muscle depolarization and contraction. CK elevations may be followed as a rough guide for therapy. In case of death, complete rigor mortis occurs a few minutes after the onset of cardiac arrest, and necropsy findings are usually inconclusive.

## Myasthenia gravis (MG)

Myasthenia gravis is a chronic autoimmune disorder caused by a decrease in functional nicotinic acetylcholine (Ach) receptors (AchR) at the neuromuscular junction due to their destruction or inactivation by circulating autoantibodies, typically of immunoglobulin G (IgG) class.[56] Ach is essential for muscle contraction at the neuromuscular junction. The defect in transmission resulting from AChR loss results in focal or generalized muscle weakness and exhaustion (Figure 13.9).[57] The condition is characterized by exhaustion of voluntary muscles with repetitive use or exercise followed by partial recovery or alleviation with rest. Two forms have been described as follows: congenital and acquired. The congenital form results from an inherited deficiency of Ach receptors at the postsynaptic membranes in the skeletal muscle, which is presented in puppies and kittens aged about 3–8 weeks. In this case, breeds include English Spring Spaniel, Jack Russell, and Fox terriers. On the other hand, the acquired MG is a common immune-mediated disorder that has been reported in German Shepherd, Golden and Labrador Retrievers, Chihuahuas, and Dachshunds. However, a high prevalence has been found in Akitas.[58] Abyssinians and Somali are the most common cat breeds that are predisposed to the condition with relative risk increased after 3 years of age.[59] A description of the pathogenesis, classification of MG, and treatment have been reviewed in detail elsewhere.[60]

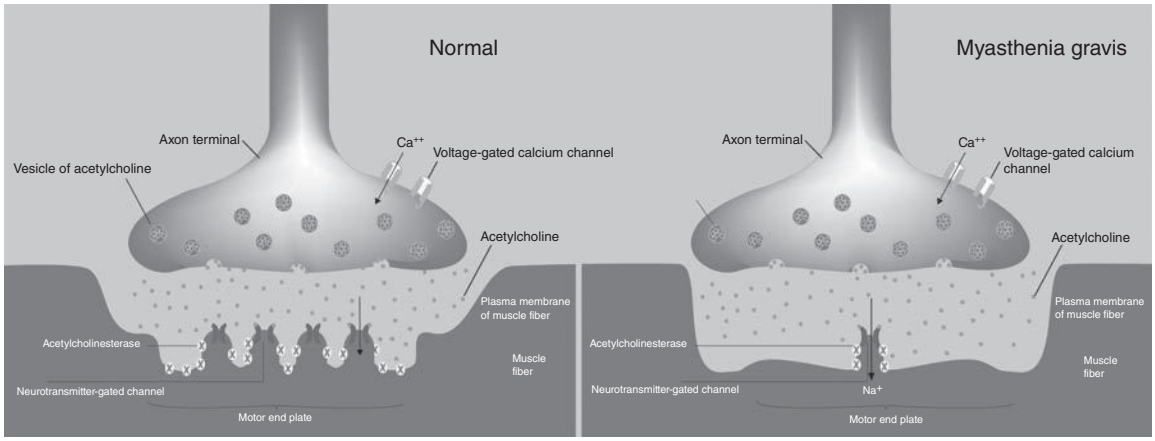


**Figure 13.9** Neuromuscular junction of a normal or myasthenic individual. Myasthenia gravis results in simplified synaptic folds, widened synaptic spaces, and less acetylcholine receptors. Source: Adapted from Drachman. 1994. Myasthenia gravis. *N Engl J Med* 330:1797–1810. Courtesy of J. Steagall.

## Clinical signs

Acquired MG has a wide spectrum of clinical presentations, which include paraneoplastic, focal, and apendicular myasthenic patients. The latter can be divided into acute fulminating or generalized MG.[61] The focal form shows facial (decreased palpebral blink), pharyngeal (decreased gag reflex), or laryngeal (vocalization changes, inspiratory stridor, and vocal fold abduction) dysfunction. Muscle weakness and fatigue in the presence of normal spinal reflexes and excessive salivation and regurgitation resulted from megaesophagus are normally observed in dogs and cats with generalized MG. Megaesophagus has been found in ~20% of cats, whereas the condition affects between 30% and 40% of dogs with acquired MG. The incidence of megaesophagus and dysphagia is usually lower in cats due to the different distribution of skeletal muscle in the esophagus between the two species.[59,62] Dysphagia, stiff and short-strided gait, muscle tremors, and/or persistent dilated pupils can be observed in both dogs and cats. Cats may be unable to retract their claws, and signs may progress to paresis, cervical ventroflexion, and weight loss.[63] These patients are at high risk of aspiration pneumonia that may lead to respiratory failure and euthanasia.[61]

## Diagnosis

The ultimate diagnosis is confirmed by the detection of serum antibodies against muscle AchR. The test is objective and quantitative and is the most reliable diagnostic technique for the diagnosis of acquired MG. Titers $\geq$ 0.3 and 0.6 nmol $l^{-1}$ are considered to be positive for MG in cats and dogs, respectively.[60] In addition, a positive response to the administration of edrophonium has been used as a diagnostic tool. The administration of an anticholinesterase drug will effectively increase the concentration of Ach in the synaptic cleft, optimizing the opportunities for successful interaction between Ach and its receptors. Most animals with MG will exhibit signs of improvement immediately after edrophonium administration, and these effects will last for ~5 min. However, the test is neither sensitive nor specific.[59] Finally, it may not be helpful in cases of focal MG in cats where the response may be unpredictable or in dogs with acute fulminating MG. In the latter, marked antibody-mediated destruction of AchR has occurred. Intercostal muscle biopsy may also be used to identify AchR antibodies at the neuromuscular junction. Electromyography may also provide definite diagnosis at a risk of aspiration during general anesthesia if megaesophagus is present. It is important to differentiate MG from other muscle disorders that cause weakness such as drug-induced MG, hyperthyroidism or hypothyroidism, and botulism, among others.[58]

## Treatment

Anticholinesterase drugs (e.g. neostigmine and pyridostigmine) are the first line of treatment for MG.

These drugs inhibit the enzyme acetylcholinesterase (true cholinesterase), which is normally responsible for the hydrolysis of Ach into choline and acetic acid and thus increase the amount of neurotransmitter available at the preganglionic sympathetic and parasympathetic nerve endings and neuromuscular junction.[57] Pyridostigmine bromide (0.2–2 mg $kg^{-1}$ PO q 8–12 h, or 0.01–0.03 mg $kg^{-1}$ $h^{-1}$ IV) has been used in dogs, and its syrup (5 mg $kg^{-1}$ PO q 12 h, diluted 1:1 with water to decrease gastric irritation) has been given to cats. The doses should be tailored to the individual needs and according to clinical response. Systemic administration of neostigmine can be given (0.01–0.04 mg $kg^{-1}$ IM q 6–8 h) to individuals with significant dysphagia and regurgitation in the emergency setting.[60] However, cholinergic crisis results from an excess of Ach at the nicotinic and muscarinic receptors due to excessive administration of an anticholinesterase drug. Corticosteroids are commonly administered if muscle weakness is not controlled by anticholinesterase drugs due to their immunosuppressant effects. Therapy is initiated with a low dose (prednisone, 0.5 mg $kg^{-1}$ $day^{-1}$) but it can be increased to immunosuppressant dosages (2–4 mg $kg^{-1}$ $day^{-1}$).

## Management of anesthesia and analgesia

Myasthenic dogs and cats may undergo general anesthesia for different surgical interventions. The placement of a gastrotomy tube might be required to provide nutritional support until regurgitation and dysphagia have resolved. A tracheal or bronchoalveolar lavage is performed if aspiration pneumonia is present. Finally, a medial sternotomy is indicated in cases of thymoma.

Perioperative considerations should include a thorough physical examination and thoracic radiographs for the assessment of megaesophagus and potential aspiration pneumonia (Figure 13.10). Other immune-mediated conditions should be identified and treated accordingly because there is usually more than one disorder involved in patients with MG. Fine-needle aspiration cytology is performed for a definite diagnosis of thymoma if a cranial mass in the mediastinum is identified. The tumor has been found in >25% of cats with MG and about 5% of dogs with the disease. Thymectomy must be considered in these cases because many animals will have a decrease in Ach antibodies titer and dramatic resolution of their signs after surgery. Anesthetic management of patients with megaesophagus is mandatory, including appropriate therapy and concerns to prevent regurgitation and aspiration pneumonia (Chapter 5).

Respiratory depression may be accentuated after administration of opioids and other intravenous anesthetics; therefore preoxygenation may be considered, and short-acting drugs may be chosen. Opioids (methadone [0.2–0.5 mg $kg^{-1}$], butorphanol [0.2–0.4 mg $kg^{-1}$, if pain is not involved], or buprenorphine [0.01–0.02 μg $kg^{-1}$, if fentanyl is not indicated intraoperatively] IV or IM) with or without midazolam (0.1–0.25 mg $kg^{-1}$ IV or IM) is recommended. Morphine, hydromorphone, and/or dexmedetomidine should be used with caution due to the risk of vomiting and further aspiration. Etomidate (1–2 mg $kg^{-1}$ IV) or alfaxalone (1–3 mg $kg^{-1}$ IV) in combination with diazepam or midazolam (0.1–0.25 mg $kg^{-1}$ IV) can be an option for the induction of anesthesia in order to minimize cardiovascular depression. Balanced anesthesia using drugs such as fentanyl, lidocaine, and/or ketamine has been reported in clinical practice in order to provide better cardiovascular stability by reducing inhalant agent requirements during anesthesia. In addition, the combination of these drugs with different pharmacologic mechanisms may provide a better analgesic protocol and even greater inhalant-sparing effect in animals undergoing surgery.

Hypotension due to compression of large intrathoracic vessels by the surgeons and the thymoma *per se* is expected and can be treated with the administration of crystalloids, colloids, and/or sympathomimetics such as dopamine (5–15 μg $kg^{-1}$ $min^{-1}$). Aggressive pain management is required for dogs and cats undergoing medial sternotomy with the use of constant rate infusion of analgesics, administration of NSAIDs if no evident contraindications, and regional anesthetic blocks (e.g. intercostal and intrapleural blocks). The epidural administration of morphine (0.1 mg $kg^{-1}$) for treatment of postoperative pain has been successfully used as an adjuvant analgesic in patients undergoing thoracotomy. Other support therapy includes prevention of hypothermia and provision of PEEP during chest opening. A detailed anesthetic management of patients with MG is described in a literature review.[63]

An important aspect of anesthetic management of patients with MG is the increased sensitivity to nondepolarizing neuromuscular blockade agents. This sensitivity

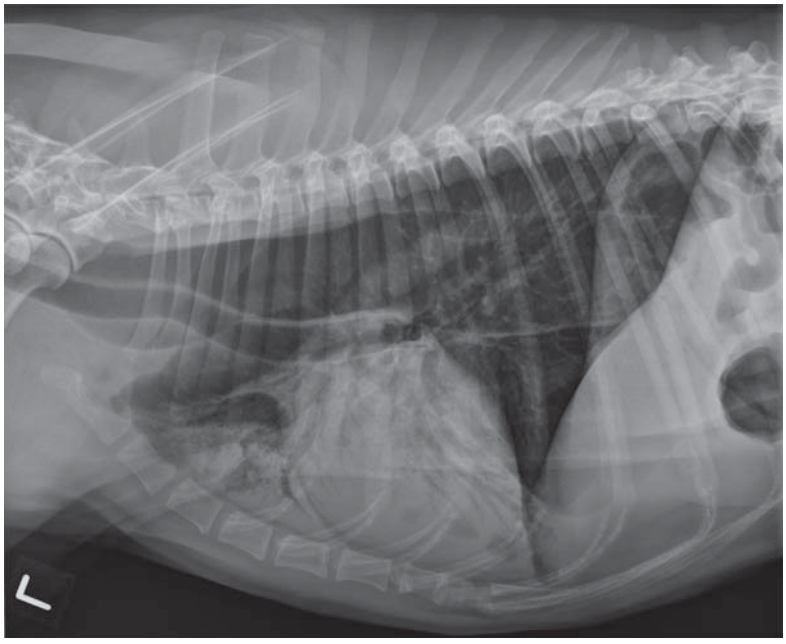

**Figure 13.10** Left lateral thoracic image of a dog with generalized megaesophagus and aspiration pneumonia, which are commonly observed in myasthenia gravis. There is generalized gas dilatation of the esophagus and a ventrally located alveolar pattern of the right cranial and middle lung lobes. Note the prominent air bronchograms that are best seen superimposed with the cardiac silhouette. Source: Courtesy of Dr. R. Drees, Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison.

is dependent on the balance between active and non-functional AchR, but these agents can produce profound skeletal muscle weakness.[56] Therefore, an initial dose should be titrated to effect, whereas close monitoring of neuromuscular blockade is accomplished using a peripheral nerve stimulator. In humans with MG, the potency of atracurium and vecuronium is increased twofold compared to the response in normal patients. Both of these drugs were reported to be administered to two myasthenic dogs undergoing thymoma removal. The doses were reduced by ~2/3 (atracurium) and 1/5 (vecuronium) of the calculated dose for normal dogs. Neuromuscular blockade was reversed with the administration of neostigmine and an anticholinergic.[64,65] Of importance, pyridostigmine inhibits the metabolism of mivacurium, and it may prolong its effect; therefore, the administration of mivacurim should be avoided in patients with MG. Animals should be monitored closely during the recovery period to ensure appropriate ventilation.

## Myopathies

General clinical signs associated with myopathies include weakness with normal proprioception, normal to decreased myotatic reflexes, voice change, stiff gait, and ventral neck flexion (most commonly in the cat). Myopathies can be of inflammatory, infectious, metabolic, or inherited origin. Decreased energy supplies can lead to abnormal muscle oxidative metabolism and resultant weakness. Endocrine disturbances such as hypothyroidism or hyperthyroidism, or hypoadrenocorticism or hyperadrenocorticism have been implicated in pathogenesis of some metabolic myopathies. Along the same lines, hypokalemia (hypokalemic myopathies) and hypocalcemia can result in severe muscle weakness and tetany, as both ions are important in the regulation of muscle ion channel and excitation–contraction coupling within the skeletal muscle. Masticatory muscle myositis (MMM) is an important type of inflammatory myositis and is discussed in Chapter 11. Other

inflammatory myopathies such as canine and feline idiopathic polymyopathies, dermatomyositis, protozoal myositis, and other inherited myopathies (hereditary Labrador retriever myopathy and myotonia) are definitely important to the well-being of the individual but of limited relevance in veterinary anesthesia and analgesia and are not discussed in depth in this chapter.

Muscle biopsy may be a relevant diagnostic tool when electrodiagnostic testing could not rule out a disease or be performed. Biopsy may reveal fiber-type grouping, group atrophy, degeneration, inflammation, or infiltration with fat and connective tissue. Myopathies generally affect fibers in a more random pattern, with muscle necrosis, regeneration, and inflammation. Infiltration with local anesthetics is considered part of the anesthetic plan, which will be ultimately determined by the health status of the individual. Depending on the behavior and physical status of the patient, small biopsies can be performed under heavy sedation with a combination of dexmedetomidine (5–10 μg $kg^{-1}$ in dogs and 10–20 μg $kg^{-1}$ in cats IM) and opioid analgesics (butorphanol 0.2 mg $kg^{-1}$ or buprenorphine 0.02 mg $kg^{-1}$ IM). Patients require vigilant monitoring using "hands-on" approach with pulse oximetry when heavy sedation is used; atipamezole (100–200 μg $kg^{-1}$ IM) can be given to reverse dexmedetomidine. More invasive biopsies that require surgical intervention are performed under general anesthesia with proper monitoring, fluidtherapy, etc. The anesthetic protocol will be decided on the basis of the age, breed, physical status of the patient, laboratory testing, imaging, etc.

## Noninfectious inflammatory joint diseases

Osteoarthritis (OA) is the most important joint disease in veterinary medicine. The other causes of noninfectious inflammatory joint diseases are relatively common in dogs but rare in cats. These disorders are described as polyarthritis syndromes mediated by immune complex formation and deposition. The syndromes include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and idiopathic and reactive polyarthritis. On radiographic evidence of joint destruction, these syndromes are classified as either erosive (RA and feline chronic progressive polyarthritis) or not. Nonerosive, noninfectious polyarthritis in which a primary cause (SLE, reactive, or RA) cannot be identified is referred to as idiopathic, immune mediated. Canine immune-mediated polyarthritis is a diagnosis of exclusion based predominantly on clinical signs, laboratorial examination including synovial fluid analysis, and failure to identify an infectious cause after culture of synovial fluid.

## Osteoarthritis

Osteoarthritis is a complex disorder of movable joints characterized by deterioration of articular cartilage, osteophyte formation and bone remodeling, pathology of periarticular tissues including synovium, subchondral bone, muscle, tendon, and ligament, and an intermittent inflammatory process of variable degree. The pathogenesis is related to joint trauma from biomechanical stress, joint injury, or abnormal loading due to neuropathy, ligamentous injury including cranial cruciate ligament deficiency, or muscle atrophy. OA pain is described as a complex interplay between structural change, biochemical alterations, peripheral and central pain processing mechanisms, and individual cognitive processing of nociception.[66]

Osteoarthritis is the most important cause of chronic pain in dogs, and the anesthetist may be consulted for questions regarding pain management of these animals. OA tends to affect older, obese, and heavy-breed dogs; however, it can be observed in young dogs as well. Radiographic signs of degenerative joint disease range from 21% to 90% of the feline population. It is clear that the condition is underdiagnosed, and the clinical relevance of OA is not known in this species.[67] Therefore, a large part of the canine and feline population undergoing general anesthesia is affected by OA. Clinical signs include change of attitude, lameness, stiff posture/gait, partial weight bearing, reluctance to move, vocalization on palpation with attempts to escape, and reduced activity. Cats are notorious for hiding signs of pain but a decrease in grooming and signs of mobility impairment and inability of jumping into counters or even into their litter box have been associated with degenerative joint disease.[68]

From the anesthetist's perspective, OA per se has limited impact on anesthetic management, and the anesthetic plan will be better chosen on a case-by-case basis where the physical status of the individual and the

presence of other concomitant diseases/drug therapies are considered. Some patients with OA develop obesity, which can increase the percentage of fat tissue over the lean mass, increasing the volume of distribution for lipophilic drugs into tissues that are not metabolically active. In these cases, doses should be reduced and/or calculated according to an estimation of lean body weight. Inflammatory and possibly neuropathic pain are of concern because cartilage damage results in elevation and stretching of richly innervated periosteum, which produces a direct stimulation of the joint capsule and bone receptors by cytokines, ligands of inflammatory origin, and physical stimulation of subchondral bone, muscle, tendons, and ligaments. Thus, osteoarthritic patients may show signs of central sensitization because of a prolonged and constant noxious stimulus input to the spinal cord produced by the degenerative process. Thereafter, some of these animals can be extremely painful during the perioperative period, and careful manipulation of joints is recommended in combination with appropriate padding.

Chronic pain management involves weight management and the administration of NSAIDs and other analgesic drugs such as tramadol, gabapentin, amantadine, and nutraceuticals, among others. For this reason, it may be observed a high incidence of side effects in the canine and feline population with OA after the administration of human analgesic products such as ibuprofen and aspirin for pain management. In addition, potential drug interactions may be appreciated. A systematic review showed that strong evidence exists for the analgesic efficacy of carprofen, firocoxib, and meloxicam in the treatment of OA but not for doxycycline, electrostimulated acupuncture, extracorporeal shockwave therapy, gold wire acupuncture, hyaluronan, pentosan polysulphate, P54FP (extract of turmeric), tiaprofenic acid, or tibial plateau leveling osteotomy in dogs.[69] The absence of evidence does not exclude the potential benefits of these therapies in the treatment of OA syndrome. New nondrug therapy modalities including physiotherapy and rehabilitation, therapeutic laser and heat, and (electro) acupuncture have been largely used in combination with analgesic administration for the treatment of OA in dogs and cats. Joint replacement surgery may be recommended when pain due to OA is persistent and disabling with significant limitation of joint function.

## Systemic lupus erythematosus

Systemic lupus erythematosus is a chronic, multisystemic, immune-mediated disease of unknown etiology; however, genetic factors are implicated in pathogenesis of the disease. In SLE, there is circulation of immune complexes that were formed by antinuclear antibody production. These complexes will induce inflammation and vasculopathies that cause organ system dysfunction (e.g. glomerulonephritis) and the resultant clinical signs.[70] Breeds affected include Spitzes, Shetland Sheepdogs, Collies, German Shepherds, Beagles, whereas reports of SLE are rare in the cat.

### Clinical signs

Systemic clinical signs will vary according to the organ involved and include intermittent fevers of unknown origin, polyarthritis, lymphadenopathy, erythematous skin lesions, hemolytic anemia with icteric mucous membranes, immune-mediated thrombocytopenia with petechiae and ecchymoses, myositis, and polyneuritis. Protein-losing nephropathy and hypoalbuminemia may result from glomerulonephritis, which can lead to ascites and peripheral edema. SLE-induced polyarthritis is the most common manifestation (70–90%) that may be confirmed by arthrocentesis. Reported clinical signs may include reluctance to walk, stiffness, lameness, joint swelling, and pain on palpation.

### Diagnosis

The determination of a CBC, platelet count, biochemistry profile, urinalysis, and urine protein/creatinine ratio is performed in order to differentiate SLE from other causes of polyarthritis.[70] Radiographic examination of the joints is important to rule out erosive polyarthritis (RA). Synovial fluid analysis after arthrocentesis will reveal increases in white blood cell count, with neutrophils representing the majority of the inflammatory cells. LE cells are rare to be found after joint taps. Bone marrow aspiration can be performed due to nonregenerative anemia, neutropenia, and/or thrombocytopenia in order to rule out multiple myeloma.[71] The presumptive diagnosis includes the LE cell test and the antinuclear antibody test (ANA). The diagnosis is suggestive for SLE when both tests are positive and the animal has two or more of the clinical signs.[72]

### Treatment

Therapy is based on symptomatic treatment of manifestations with steroids, analgesics, and immunosuppressive drugs to achieve disease remission. Prednisone treatment results in remission of the disease. Immunosuppressive doses (3–4 mg $kg^{-1}$ $day^{-1}$) may be initially used for the first 2 weeks and then decreased (1–2 mg $kg^{-1}$ $day^{-1}$) for another 2 weeks. According to the clinical response, the dose can be reduced even more (1–2 mg $kg^{-1}$ every 48 h) and tapered as needed. Synovial fluid must be re-examined routinely during therapy. Azathioprine is administered to dogs that are nonresponsive to steroid treatment; the drug can cause myelosuppression, and dogs are at an increased risk for developing pancreatitis. Chondroprotective agents may prove to be beneficial.

### Management of anesthesia and analgesia

Anesthetic management will be based on the magnitude of organ system dysfunction and the toxicity profile of drugs used for treatment of SLE (e.g. prolonged glucocorticoid therapy). Chest and abdominal radiographs may be useful to detect pleural and/or pericardial effusion, and ascites, respectively, due to hypoalbuminemia. Abrupt cessation of glucocorticoid therapy may result in Addisonian crisis, and an additional dose of steroid is given for such cases and/or during prolonged surgical interventions. However, long-term administration of corticosteroids may cause polyuria, polydipsia, hyperglycemia, and hypercholesterolemia. Table 13.2 shows the recommended guidelines for the perioperative management of SLE. Even so, the impact of SLE on provision of anesthesia has not been investigated, and the lack of evidence combined with the heterogeneity of disease manifestations makes it difficult to establish definitive anesthetic management protocols.[73] Ultimately, the anesthetic plan will be chosen on a case-by-case basis where the physical status of the individual and the presence of other concomitant diseases are considered.

In the presence of hypoalbuminemia, high protein-bound drugs should be administered cautiously and to effect (e.g. opioids, benzodiazepines, and thiopental, among others). Colloid administration is indicated for maintenance of oncotic pressure, especially for long procedures. Preoxygenation is recommended for cases of severe hemolytic anemia. Pain management is a crucial part of the treatment and should be considered as a long-term intervention. Some of these animals can be extremely painful during the perioperative period, and careful manipulation of joints is recommended. Opioids are usually administered as part of premedication, but NSAIDs are normally contraindicated due to chronic administration of corticosteroids. The use of sympathomimetics is recommended for cases where maintenance of cardiac output and blood pressure is a concern, especially when adequate renal perfusion is required.

## Rheumatoid arthritis (RA)

This condition is characterized by erosive polyarthritis and progressive joint degeneration of unknown origin. Canine RA resembles human RA where rheumatoid factors form immune complexes that are deposited in the synovium. In contrast, the pathogenesis of RA is different from feline chronic progressive polyarthritis

**Table 13.2** Key points in the perioperative management of animals with systemic lupus erythematosus.[72]

| |
|---|
| The history and physical examination should include a thorough review of disease activity and accrued organ damage. |
| A complete blood cell should be evaluated for anemia, thrombocytopenia, and leucopenia. |
| Other complementary blood work should be performed to investigate serum electrolytes, creatinine, urea, hepatic enzymes, among others. |
| Glomerulonephritis or drug-induced hepatotoxicity should be monitored. |
| Urinalysis may be important for monitoring elevated proteinuria, or the presence of red cells or white cells in the urine. |
| Thoracic radiographs are crucial to evaluate pleural and pericardial effusion. |
| Abdominal radiographs are recommended if ascites is suspected. |
| During general anesthesia, the clinician should focus on renal protective strategies with maintenance of urine output while avoiding hypoperfusion and hypotensive states. |
| Careful patient positioning is important since these animals are predisposed to pain. |
| Side effects of systemic analgesics and drug interactions must be considered in pain management. |

where an erosive process of the joint is observed because of an infectious cause. In RA, granulation tissue results in erosion of the cartilage and joint swelling and may lead the collateral ligament to rupture. Clinical signs are similar to other joint inflammatory diseases; however, radiographic features in the late stages of RA reveal periarticular osteoporosis, loss of articular cartilage, and focal irregular areas of subchondral bone destruction. Luxation is a consequence of the erosive process; destruction of the joint by an erosive process differentiates RA from other nonseptic inflammatory joint diseases. RA is considered to be a more destructive, progressive, and debilitating condition than osteoarthritis. The diagnosis is confirmed by detecting rheumatoid factor against denatured or immune complexed IgG. A titer of 1:16 or higher is considered to be positive; nevertheless, false-positives may be seen. Treatment relies on the use of immunosuppressive, analgesics, and chondroprotective drugs similarly to SLE, but the long-term erosive process is not inhibited, and response to treatment is variable. Pain and limb function may be improved after arthroplasty, joint replacement, or arthrodesis. Pain management is a crucial part of the anesthetic protocol. Multimodal analgesia and balanced anesthetic techniques can be accomplished using standard doses of opioids (morphine 0.3–0.5 mg $kg^{-1}$ IM followed by a morphine CRI 0.24 $kg^{-1}$ $h^{-1}$ IV or a fentanyl CRI 2–6 μg $kg^{-1}$ $h^{-1}$ IV), ketamine CRI (2–10 μg $kg^{-1}$ $min^{-1}$), and local anesthetic techniques (i.e. lumbosacral epidural anesthesia or sciatic/femoral nerve blocks with bupivacaine for hind limb arthodesis), in combination with long-term analgesic therapies (gabapentin 10–20 mg $kg^{-1}$ every 8–12 h PO and/or amantadine 3–5 mg $kg^{-1}$ every 12–24 h PO). NSAIDs will be contraindicated if corticosteroid therapy is administered. Premedication and induction of anesthesia will vary according to the physical status of the patient; however, overall standard monitoring and anesthetic techniques are performed.

## Reactive polyarthritis

This type of immune-mediated polyarthritis has been observed in association with chronic systemic infectious diseases, neoplasia, drug administration, or disease of the gastrointestinal tract. Therefore, arthritis is a secondary clinical manifestation of immune complex seen in association with bacterial endocarditis, pleuritis, dirofilariasis, or drug-induced polyarthritis with the use of sulfadiazine-trimethoprim and cephalexin, among others. Thus, the complete history with a full physical examination is essential for the differential diagnosis if one considers that clinical signs (cyclic fever, stiffness, and reluctance to walk) may be similar to other syndromes. Treatment should focus on eliminating the underlying cause, which can play an important role in the anesthetic management of the case (e.g. endocarditis or dirofilariasis that may cause cardiovascular depression). The anesthetic protocol will be based on a thorough physical examination and preoperative screening of patients with systemic conditions. The use of short-acting drugs that cause minimal cardiorespiratory depression is advised for premedication; opioids (morphine 0.2–0.3 mg $kg^{-1}$ or hydromorphone 0.05 mg $kg^{-1}$ IM) produce mild sedation and bradycardia in dogs, but they usually tolerate decreases in heart rate well when clinical doses are employed. Morphine may induce histamine release followed by short-lived hypotension after IV administration. Bradycardia can be reversed with anticholinergics (glycopirrolate 0.01 mg $kg^{-1}$ IV). Etomidate (1–2 mg $kg^{-1}$ IV) with or without diazepam or midazolam (0.25 mg $kg^{-1}$ IV) is used for the induction of anesthesia if cardiovascular disease is observed. Propofol (1–5 mg $kg^{-1}$ IV) or alfaxalone (1–4 mg $kg^{-1}$) may be used with cautious. Pain management should be addressed accordingly.

In summary, an understanding of the pathophysiology, diagnosis, and treatment of skin and musculoskeletal disease is important for the anesthetic management of patients with these conditions. Some of these diseases are relatively uncommon, but they may be presented as an anesthetic challenge, a secondary complication and/or a life-threatening scenario to the clinician. Emergency treatment is required with burns and MH and potentially with MG. Analgesia is normally needed as part of the anesthetic protocol if one considers that pre-existing acute or chronic pain, hyperalgesia, and/or central sensitization are commonly observed with these diseases. The anesthetic plan will be better chosen on a case-by-case basis where the physical status of the individual and the presence of other concomitant diseases/drug therapies are considered. A thorough physical examination and appreciation of the pharmacology of sedatives/analgesics and anesthetics

will facilitate the selection of drugs for premedication, induction and maintenance of anesthesia.

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# 14 Infectious disease

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Infectious diseases can impact anesthesia in several ways. The patient may have an active or latent infectious process that will affect perioperative management, or the infectious process may be the reason the patient requires surgery or may increase the risk associated with anesthesia and surgery. Any patient who undergoes surgery is susceptible to acquiring an infection at the surgical site itself. Other vulnerable areas where the body's natural defenses are breached are the respiratory tract, bloodstream, urinary tract, and gastrointestinal tract. Some infectious diseases can be transmitted to other patients or to the veterinary staff in the perioperative period. Responsible anesthetic care includes practices that decrease the acquisition and transmission of infection, as well as prevent and treat complications related to coexisting infections.

## Antibiotic resistance

The concern over antibiotic resistance is one that affects both veterinary and human patients. Antimicrobial resistance results in infections that cannot be treated effectively and efficiently and increases duration and cost of treatment. Bacteria undergo mutations at an alarmingly greater rate than other organisms. Widespread drug resistance among bacterial pathogens exists in part because there is only a limited choice of antimicrobials that target a relatively narrow range of mechanisms. Most antibiotics were developed in the 1940s and 1950s, and the mechanism of action was to impact biosynthesis of the cell wall and of DNA and proteins. Although bacteria have been continuously mutating since penicillin was discovered in 1928, only two new antibiotic chemical classes have been developed in the past 40 years: oxazolidinones and lipopeptides.[1]

Infectious diseases in human patients that have previously been eradicated, such as tuberculosis and malaria, are re-emerging, and the pathogens have developed resistance to multiple drugs, which were previously successful in treatment.

An increasing number of nosocomial infections are being caused by multidrug resistant organisms. While most of the attention has been focused on methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus pseudointermedius* (MRSP), there are an increasing number of Gram-negative pathogens responsible for serious nosocomial infections that are resistant to almost all available antibiotics. These include *Pseudomonas aeruginosa*, Acinetobacter spp., and Enterobacteriaceae.[2]

In 2003, the Infectious Diseases Society of America created the Antimicrobial Availability Task Force. This group was charged with reviewing trends in antibiotic research and development in conjunction with the rise in antibiotic resistance and then proposing different solutions to ensure the availability of effective antibiotics in the future. The group identified six especially problematic bacteria, including three Gram-negative organisms: *Acinetobacter baumannii*, extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, and *P. aeruginosa*. The other pathogens were the Gram-positive MRSA and vancomycin-resistant *Enterococcus faecium* and the filamentous fungi, Aspergillus spp.[3]

In order to minimize the development of resistance, antimicrobial use needs to be justified and appropriate. The most specific antibiotic should be selected at the correct dose and should be used for the appropriate period. The incidence of postoperative infections can be

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minimized using strict aseptic technique, minimizing surgical time, and minimizing tissue handling, especially for clean surgeries. It is therefore not necessary to use antimicrobial drugs in every surgical case to prevent infection. Likewise, all patients with indwelling catheters or undergoing invasive diagnostic procedures do not need antibiotic prophylaxis. Prophylaxis is appropriate in patients who are immunocompromised, being treated with immunosuppressive medications, or are seriously ill.[4]

Clinical practice guidelines regarding prophylactic antimicrobial use in human surgical patients have been published. An anti-infective drug should have activity against the pathogens most likely to contaminate the wound, be administered in an appropriate dosage and at a time to ensure adequate concentrations at the incision site during the period of potential contamination, be safe, and be administered for the shortest effective period to minimize adverse effects, development of resistance, and cost.[5]

## Surgical site infection

Before the use of antiseptic techniques, postoperative surgical site infections (SSIs) occurred >50% of the time. Even after the application of antisepsis to surgical practice, SSIs continued to occur in 2–5% of extra-abdominal surgeries and up to 20% of intra-abdominal surgeries.[6] Among hospitalized patients, SSIs account for 14–16% of all nosocomial infections.[7] In veterinary medicine, several studies have reported SSI rates of 3–5.8%.[8–10]

Surgical site infections are divided into superficial, deep, and organ or tissue space infections. Superficial infections involve the skin and subcutaneous tissues. Deep infections involve the fascial and muscle layers. Organ or tissue space infections involve organs or areas manipulated during surgery. Organisms implicated in SSIs are usually colonizers carried in the nose or on the skin of the patient at surgery.[11]

### Risk factors for development of SSIs

Patient-related factors increasing the risk for development of SSI include chronic illness, endocrinopathy, extremes of age, immunocompromise, corticosteroids, an American Society of Anesthesiologists' score of ≥3, prolonged preoperative hospitalization, and morbid obesity.[8,11] A veterinary study documented that animals with a concurrent endocrinopathy are 8.2 times as likely to develop an SSI.[9]

Wound-related factors associated with increased risk of SSI include excessive dead space, devitalized tissue, hematomas, contaminated wounds, and foreign material.[7,11]

Procedure-related factors associated with SSI are duration of surgery, hair removal the day before surgery, and antibiotic prophylaxis.[8] There have been many studies documenting that the risk of SSI increases with surgical time. It has been reported that with every 60 min of surgery time, open surgical wounds were twice as likely to develop infection, and infection rates doubled at 90 min.[10,12] Another study reported that for every 90 min of surgery time, there was a 2.1 greater odds of SSI.[13] Prolonged anesthesia has been reported as a predisposing factor for SSI. One veterinary study reported a 30% increase in the risk of SSI in clean wounds for each additional hour of anesthesia.[14] Anesthetic-induced perioperative hypothermia can lead to impairment of phagocytic function. In addition, prolonged anesthesia can result in hypotension or hypoxia, which may reduce perfusion and oxygenation of wound tissue with impairment of tissue regeneration.[7,15,16]

### Diagnosis

Surgical site infections typically occur within 30 days of surgery and present as poor healing with inflammation (redness, pain, heat, and swelling) at the site of surgery. Signs of systemic infection may be present such as fever, elevated white blood cell count, elevation of inflammatory markers, and poor control of blood sugar. The presence of purulent discharge at the site may indicate SSI. The definitive diagnosis is made by culturing organisms from a culture obtained aseptically.[11]

One veterinary study classified SSIs as being either infected or infected/inflamed. If purulent drainage, an abscess, or a fistula was reported; the SSI was classified as infected. An SSI was classified as infected/inflamed if it was infected or had at least three of the following signs: redness, swelling, pain, heat, serous discharge, and wound dehiscence.[8]

### Intraoperative treatment

It is well known that prophylactic antibiotics prevent postoperative wound infections, especially if the surgery involves an area with a naturally large inoculum of

bacteria such as the colon or vagina or when there is a prosthetic involved such as with joint replacement.

In human patients undergoing surgery, guidelines for the prevention of SSI recommend the use of preoperative and intraoperative antibiotics for all clean-contaminated procedures, for clean procedures when SSI would be a major threat for the patient, and for procedures where a prosthetic joint or any intravascular prosthetic material will be inserted.[7] The goal is to reduce intraoperative bacterial contamination below the critical level needed to induce an infection.

One veterinary study reported a significantly lower infection rate if prophylactic antibiotics were administrated and surgical duration exceeded 90 min but not for a shorter surgical time.[17] In another veterinary study, patients administered antimicrobial prophylaxis were on average 6–7 times less likely to develop SSI than those without prophylaxis.[8]

Recommendations for prophylactic perioperative antibiotic administration in human patients are as follows: for most surgical procedures, a first-generation cephalosporin such as cefazolin is effective. For surgeries in which the bowel is entered, coverage of Gram-negative organisms is important, and anaerobic coverage is appropriate if the large bowel or female genital tract is entered. The first dose should be administered within 30 min before surgical incision, and the dose should be repeated if the surgery exceeds 3 h. Antibiotic prophylaxis should usually be discontinued 24 h after the procedure. In cases of cardiac surgery, antibiotics should be administered for 48 h after the procedure.[11]

## Methicillin-resistant *Staphylococcus aureus* (MRSA)

*S. aureus* is a coagulase-positive commensal organism that colonizes the skin, mucous membranes, urogenital tract, or gastrointestinal tract of ~30% of healthy humans. Other coagulase-positive staphylococci (CPS) such as *S. pseudointermedius* may be the predominant commensal organisms in domestic animals.[18] Infection occurs when organisms are found outside their normal niche in association with tissue inflammation and pathogenic changes. Before the use of penicillin, infection with *S. aureus* resulted in high morbidity and mortality. Over time, *S. aureus* has developed resistance to penicillin and many other antibiotics. MRSA has acquired a gene that makes it resistant to methicillin and all other beta-lactam antibiotics. MRSA was first reported in 1961, after methicillin was used in human patients to treat staphylococci that were resistant to pencillin. MRSA infection is an important cause of morbidity and mortality in humans, and increasing resistance to antimicrobial therapy makes treatment challenging. MRSA has acquired a staphylococcal cassette chromosome mec (SCC mec). This SCC has a gene (mecA) that encodes for an altered penicillin-binding protein that has a lower affinity for beta-lactam antimicrobials. The result is that beta-lactam antimicrobials are ineffective. The SCC can spread between staphylococcal populations and contains insertional sequences that can allow for the incorporation of additional antimicrobial resistance markers, which account for resistance to non-beta-lactam antimicrobials.[19–21]

Asymptomatic human colonization with MRSA is more common than infection. MRSA infections have historically been nosocomial (health care associated or HA-MRSA), but there has been an increased incidence of MRSA infection in people without exposure to a health care setting (community-acquired or CA-MRSA). Infection can cause skin and soft tissue lesions, endocarditis, pneumonia, osteomyelitis, necrotizing fasciitis, or sepsis.[18] The raised, red lesions that develop at the site of a skin infection can be mistaken for spider bites. Mortality rates for sepsis (55.6%) and pneumonia (32.4%) are high.[22]

*S. aureus* readily spreads from person to person. Transmission may occur via direct contact or fomites. Domesticated animals can become colonized or infected with MRSA and may serve as a source of human infection. Dogs and cats are not natural reservoir hosts for *S. aureus*, and so infections in these species usually originate from a human.[23–25] Dogs and cats are more commonly colonized with *S. pseudintermedius* (formerly misclassified as *S. intermedius*). Methicillin-resistant *S. pseudintermedius* (MRSP or MRSI) is found in pets with and without infection. The prevalence of MRSP cultured from pets is usually <5% but it may be as high as 17%.[18] Infections of humans with MRSP is most likely secondary to exposure to colonized or infected pets and results in infections that are difficult to treat and an increased mortality risk.[26–29] MRSA or MRSP infections in pets are usually associated with pyoderma or

postoperative wound infections, but otitis, urinary tract infections, and arthropathies have also been reported.[30]

Treatment of MRSA or MRSP infection involves localized and systemic measures. Debridement and lavage of wounds and application of mupirocin, a topical antibiotic, are recommended. Systemic antibiotics should be chosen on the basis of culture and sensitivity results, and tissue penetration, therapeutic concentration, and patient comorbidites should be considered. Treatment should never include the use of beta-lactam drugs, including augmented penicillin derivatives, cephalosporins, or carbapenem drugs, as MRSA and MRSP are inherently resistant to these drugs. Fluorquinolones are not a good choice for treatment because although many MRSA seem to be susceptible *in vitro*, rapid resistance can occur *in vivo*. In humans, doxycycline is FDA approved for treatment of susceptible infections. Trimethoprim sulfonamide drugs have been used with success to treat susceptible infections, but this is not an FDA-approved use for those drugs.[18] Neither erythromycin nor clindamycin should be used because many HA-MRSA strains are resistant to erythromycin and likely have inducible resistance to clindamycin.[31] Vancomycin should not be used in animals to minimize the risk of developing resistance in humans.

Prevention of transmission of infection includes proper hand hygiene and the use of disposable gloves and gowns. An isolation protocol should be used in suspected or known cases if hospitalization is required, and contact with the pet should be limited to only those people directly involved in providing care. Draining wounds should be covered, and soiled bandage materials disposed of properly. Disinfection of equipment and surfaces should be routine protocol. Humans with known MRSA infection should not allow close contact with pets such as sharing a bed or licking of wounds. Pets with MRSA or MRSP infection should not be allowed to share a bed with humans.

## Bloodstream infection

In human patients, bloodstream infections (BSIs) are associated with the use of central venous catheters (CVCs). The mortality associated with catheter-related BSIs is as high as 10%, and mortality is usually related to endocarditis, metastatic pulmonary infection, and septic shock.[32,33] CVCs are useful for the administration of fluids, blood products, parenteral nutrition, medications, and for repeat sampling of blood and measurement of central venous pressure. They are, however, a potential biofilm surface and a port for infection directly into the bloodstream. Organisms isolated from the external surface of CVCs in humans tend to be multidrug-resistant Gram-positive and Gram-negative bacteria and fungi. Risk factors for the development of a BSI include hospitalization in the ICU, immunosuppression, neutropenia, parenteral nutrition, mechanical ventilation, multilumen catheter, catheter site, and duration of catheterization.[34] Colonization of catheters occurs extraluminally from contaminants found on the skin around the catheter insertion site or from the hands of the individual placing the catheter. Intraluminal colonization can occur due to seeding of the catheter hematogenously, infusion of a contaminated solution, or overguidewire exchange of the catheter.[35] It is imperative that strict aseptic technique is followed during preparation and placement of intravascular catheters and that proper care and maintenance are performed to reduce the risk for contamination of the hub and colonization of the catheter.

Catheter-related BSIs are diagnosed on the basis of clinical signs of infection (fever, hypotension, tachycardia, and leukocytosis), no other source of a BSI, and recovery of the suspect organism from both peripheral blood and the CVC. If a catheter-related BSI is suspected, the catheter can be removed and the tip and subcutaneous portions cultured; peripheral blood should be cultured as well. Diagnosis can be made without removing the catheter by obtaining positive blood cultures from the CVC and peripheral blood.[36]

In any patient, the catheter site should be inspected before removal for signs of discharge, swelling, redness, or pain at or below the site of insertion. In any patient who has a persistent fever of unknown origin and negative blood cultures, the catheter should be removed and the tip cultured. Appropriate antimicrobial therapy should be empirically instituted using the following guidelines: the patient is critically ill, the catheter was indwelling for >48 h, there is evidence of catheter site infection, fever (>103.5 F), systolic blood pressure <90 mm Hg, tachycardia, or leukocytosis[37] (Table 14.1).

Non-catheter-related sources for BSI include infections of the gastrointestinal, genitourinary, and respiratory tracts, skin, wounds, abdomen, and biliary

**Table 14.1** Strategies to reduce the incidence of BSI.[38–41]

| |
|---|
| Wash hands and use aseptic technique when placing and handling all catheters. |
| Prepare the skin aseptically before insertion of any catheter. |
| Central venous catheters should be placed by skilled individuals, using sterile technique. |
| The number of ports and catheter manipulations should be minimized. |
| Catheters should be secured in a way to reduce movement, and the site should be clean and protected from contamination. |
| Central venous catheters should be removed as soon as possible. |

tree. In cats with bacteremia, causes include pyothorax, GI tract disease, septic peritonitis, pyelonephritis, pneumonia, pyometra, endocarditis, osteomyelitis, and bite wounds[42] (Table 14.2).

The time course of the bacteremia should be related to the infecting organism; however, this is not always possible. Several stages of bacteremia exist and are described in the following sections (Table 14.3).

### Clinical signs

Dogs with bacteremia usually exhibit some combination of lethargy, anorexia, vomiting, diarrhea, fever, lameness, and muscle pain. Infective or immune-mediated arthritis may develop. Abdominal or lumbar pain on palpation may indicate inflammation of the kidney or spleen (septic embolization, abscess, or infarction) or diskospondylitis. Bacteremic septic patients can develop organ failure and septic shock. In dogs, the organ systems most affected and the order in which they are affected are as follows: the GI tract, liver, kidneys, and lungs. The presence of a cardiac murmur and/or arrhythmia may occur with infective endocarditis. In cats with bacteremia, anorexia, fever, and shifting leg lameness are clinical signs. Heart murmurs are present with endocarditis. The lung is the shock organ in the cat, and respiratory failure can occur early in sepsis. Serum chemistry abnormalities such as an albumin of $<2.5\,mg\,dl^{-1}$, a twofold or greater increase in alkaline phosphatase (ALP), and hypoglycemia ($<80\,mg\,dl^{-1}$) are indicative of bacteremia. Hyperbilirubinemia, bilirubinuria, and icterus can occur.[42]

## Sepsis

Sepsis is a clinical condition on a continuum, with localized inflammation on one end and severe systemic inflammatory response and multiorgan failure on the other. There is an infectious etiology that starts out localized and becomes systemic. Sepsis can be life threatening as a result of the causative organisms themselves, their toxins, and the body's own inflammatory response. Sepsis is a leading cause of postoperative morbidity. Anesthesia and surgery should be postponed until the sepsis is partially treated and

**Table 14.2** Risk factors for bacteremia in dogs and cats.[43]

| Infections diseases | Sources of infection | Causes of immunocompromise | Iatrogenic causes |
|---|---|---|---|
| Ehrlichiosis | Abcesses | Diabetes mellitus | Dental prophylaxis |
| FIV | Burns | Hepatic failure | Oral, abdominal, urogenital, or |
| FELV | Colitis | Renal failure | perianal surgery |
| Canine parvoviral enteritis | Gingivitis/stomatitis | Tumors | Invasive or protracted surgery |
| Feline panleukopenia | Pyoderma | Hematologic malignancies | Endoscopic procedures |
| | Urogenital infection | Glucocorticoids | IV catheterization |
| | Penetrating wounds | Cytotoxic drugs | Narrow spectrum or low dose |
| | Bowel injuries | Phagocytic defects | antimicrocial therapy |
| | Musculoskeletal infection | Shock | Urogenital tract manipulation |
| | | Splenectomy | |
| | | Congenital heart defects | |
| | | Advanced age | |

**Table 14.3** Stages of bacteremia.[43]

| | Time course | Likely organism | |
|---|---|---|---|
| Peracute | Several hours | Gram-positive or Gram-negative | Debilitated or immunosuppressed |
| Acute | 12–24 h | Gram-negative or staphyloccal | |
| Subacute | Weeks | Gram-positive or anaerobic | |
| Chronic | Weeks to months | Microorganisms of low toxicity (*S. intermedius*, *Brucella canis*) | Sequestration of bacteria on heart valves, in bone; abscess in liver, spleen, kidney or muscle; partial response to antimicrobial therapy |

the patient is stable. However, the source of sepsis sometimes requires urgent surgical intervention. Causes of sepsis include abscesses, endometritis, necrotizing fascitis, deep pyodermas, cellulits, prostate infections, pneumonia, peritonitis, and infected surgical sites. The most commonly involved organisms are thought to be Staphylococci, streptococci, and *Escherichia coli*.[44]

Bacterial components stimulate macrophages and neutrophils, and proinflammatory factors such as tumor necrosis factor alpha, interleukin-1, and interleukin-6 are induced. Counterregulatory host responses, interleukin-4, and interleukin-10 turn off production of the proinflammatory cytokines.[45] There is normally a balance between proinflammatory and anti-inflammatory responses. With sepsis, a systemic inflammatory response syndrome (SIRS) can occur unchecked, and the result is activation of complement, the coagulation cascade, widespread arterial vasodilation, and altered permeability at the capillary level. The clinical result ranges from multiorgan dysfunction syndrome (MODS) to death. Oftentimes, the compensatory anti-inflammatory response makes the patient more susceptible to infection from the causative and opportunistic organisms. Sepsis is associated with cardiovascular, pulmonary, renal, hepatic, and intestinal dysfunction, and hypothermia, oliguria, respiratory failure, and lactic acidosis.[44]

## Signs and symptoms

Signs are nonspecific, and the presenting complaint depends on the source of the infection. The SIRS is a defining component of sepsis and is described by the following: fever, tachycardia, tachypnea, and an inflammatory leukogram. Definitions for SIRS in dogs and cats have been published. For dogs, SIRS is diagnosed on the basis of the presence of two or more of the following criteria: body temperature <38°C or >42°C, heart rate >120 beats per minute in a calm dog, hyperventilation ($PaCO_2$ <30 mmHg), white blood cell count >18,000 $ml^{-1}$ or <5000 $ml^{-1}$ or >5% bands.[46] For cats, SIRS is diagnosed on the basis of the presence of two or more of the following criteria: body temperature <38°C or >42°C, heart rate >140 beats per minute in a calm cat, respiratory rate >20 breaths per minute or PaCO2 <28 mm Hg, white blood cell count >18,000 $ml^{-1}$ or <5000 $ml^{-1}$ or >5% bands.[46] Septic shock is defined by SIRS coupled with hypotension, lactic acidosis, and progressive organ dysfunction. Clinical findings of MODS and their implications are listed in the following section. Disseminated intravascular coagulation (DIC) and respiratory distress syndrome are terminal states (Table 14.4).

Diagnosis of sepsis is made using history, clinical signs and symptoms, and isolation of the specific causative organisms. Cultures should be submitted from blood, urine, wounds, body cavity fluid, and all suspected sources of organism growth.

Therapy for sepsis consists of removing the nidus of infection, aggressive and appropriate antimicrobial administration, goal directed fluid therapy, and treatment of cardiovascular, respiratory, renal, and hematologic disturbances. Optimization of renal function should be performed before anesthesia with appropriate fluid therapy and diuresis to maximize

**Table 14.4** Multiple organ dysfunction syndrome.

| Clinical findings | Implication |
|---|---|
| Cool extremeties, oliguria, lactic acidosis | Tissue hypoperfusion |
| Oliguria | Renal failure |
| Hyperbilirubinemia | Liver failure |
| Respiratory distress syndrome | Pulmonary compromise |
| DIC (disseminated intravascular coagulation): prolonged PT and APTT, low fibrinogen, increased fibrinogen degradation products | Failure of the coagulation system |

intravascular volume and support renal blood flow. Albumin and total protein levels should be monitored, and colloids and/or plasma should be administered to support oncotic pressure and minimize edema formation and third spacing of fluids. Packed cell volume (PCV) should be monitored, and transfusion of red blood cells may be required to maintain a minimum PCV of 25%. Patients with sepsis often are hypoglycemic, and blood glucose should be monitored and dextrose supplementation provided to maintain euglycemia.

Hemodynamic stabilization should be performed as best as possible before anesthesia, with the goals of optimizing tissue perfusion, oxygen delivery to the tissues, and cardiac output. Fluid resuscitation should be targeted to achieve a mean arterial pressure >65 mm Hg, central venous pressure of 8–12 mmHg, a normal pH without metabolic acidosis, a mixed venous oxygen saturation >70%, and adequate urine output.[47] Heart rate, pulse rate and quality, mucous membrane color, capillary refill time, respiratory rate, lung sounds, mentation, blood pressure, and an assessment of urine production should be documented before anesthesia. Thoracic radiographs should be taken to establish the status of the pulmonary system, and any abnormalities should be documented that may affect respiratory function during anesthesia and impact postoperative care. In patients with respiratory signs or evidence of pulmonary disease, an $SpO_2$ at room air should be checked and documented before anesthesia.

Acepromazine should be avoided because this drug causes irreversible vasodilation and hypotension and inhibits platelet function. Alpha-2 agonists should be avoided because they cause a decrease in cardiac output. Opioids can be used for premedication, with or without a benzodiazepene. These classes of drugs have very little impact on cardiovascular variables, and heart rate, cardiac output, and blood pressure remain stable. Etomidate should not be used in patients with sepsis because it suppresses the hypothalamic pituitary adrenal axis, and septic patients may already have adrenal insufficiency. There is concern that the adrenal insufficiency may be worsened by even a single dose of etomidate.[48] Appropriate antimicrobial drugs and doses should be administered 30 min before surgical incision and repeated every 90 min during surgery.

Isoflurane or sevoflurane can be used for the maintenance of anesthesia. A constant rate infusion (CRI) of fentanyl is anesthetic sparing, which is important because septic patients are often inappropriately vasodilated and hypotensive. Hypotension should be treated by reducing the vaporizer concentration, administering adequate crystalloids and colloids, and incorporating vasopressors such as a dopamine CRI. The addition of a positive inotrope, such as a dobutamine CRI, may be needed to treat myocardial depression. It is not uncommon for septic patients to require massive volumes of fluids under anesthesia. Adequate venous access is imperative, and direct arterial blood pressure monitoring and central venous pressure monitoring can be useful for goal directed fluid therapy. The mean arterial blood pressure should be at a minimum of 60 mm Hg to support blood flow to the brain, heart, and kidneys. Ventilation should be assisted manually or mechanically, if needed, to maintain normocapnia and adequate oxygenation. Septic patients may already have pulmonary compromise and be tachypneic and hypoxic before anesthesia. Assisted ventilation reduces inhalant requirements and ensures a stable anesthetic plane.

Epidural analgesia is contraindicated in patients with sepsis. Analgesia should be provided via a CRI of fentanyl or another opioid with a short half-life. If

additional analgesia is needed, a CRI of lidocaine or lidocaine and ketamine can be added. Lower doses of lidocaine should be used because septic patients are often vasodilated, and higher doses of lidocaine can further contribute to vasodilation and hypotension.

Postoperative care should continue to support cardiovascular, respiratory, and renal function, and adequate analgesia should be provided. It should be ascertained that the patient is ventilating adequately on its own before extubation ($ETCO_2$ between 35 and 55 mm Hg). The author recommends provision of supplemental oxygen if the $SpO_2$ on room air is <93% or the PaO2 is <80 mm Hg.

## Necrotizing fasciitis

Necrotizing fasciitis is a rapidly progressive and potentially life-threatening bacterial infection of the subcutaneous and fascial tissues. Severe and extensive local tissue damage is oftentimes accompanied by septic shock. In humans, the cause is commonly polymicrobial, but the most widely represented causative species is group A streptococcus, and it is present in 71% of all human cases.[49,50] There have not been many reports of necrotizing fasciitis in the veterinary literature, but in nine canine cases, the organism that was consistently isolated was beta-hemolytic streptococcus.[51] Group G streptococcus is a rare cause of necrotizing fasciitis in humans, but it appears to be the major cause in dogs.[52–54] Successful outcome depends on early recognition and surgical debridement.

Group G streptocooci are commensal organisms in dogs, and infection of fascial tissues may occur when the normal skin barrier is damaged. In most cases, there is a history of mild injury to the skin several days before the onset of clinical signs. In the reported canine cases of necrotizing fasciitis, the possible causes were minor dog bites, minor trauma, and skin infection.[54] In some cases, there was no history of previous trauma. People with diabetes mellitus, peripheral vascular disease, or other immunosuppressive conditions may have an increased risk of developing necrotizing fasciitis.[50,55] It is not known whether the same is true for dogs.

After the invasion of the subcutaneous space, local tissue destruction is thought to be secondary to bacterial production of exotoxins and proteinases. Necrotic tissue provides a nidus for bacterial growth and further tissue destruction. The damage initially spreads horizontally within the subcutaneous tissues and superficial fascia. With progression, the underlying muscle and overlying skin may develop ischemic necrosis as a result of bacterial toxin-induced vasoconstriction or thrombosis of vessels.[51] Systemic signs of shock including fever, tachycardia, and poor peripheral perfusion are common. Streptococcal toxic shock syndrome (STSS) is the term used to describe the rapidly progressive, hypotensive shock and multiorgan failure that can occur with severe streptococcal infection. The syndrome can occur secondary to necrotizing fasciitis or as a result of streptoccal infections of other organs. The pathogenesis of STSS is thought to involve bacterial exotoxin production, secondary cytokine release in large amounts, and subsequent shock and organ failure. Mortality in humans with necrotizing fasciitis and STSS is greatly increased.[49]

Diagnosis is based on clinical signs, surgical findings, histopathologic results, and a positive culture. However, because the disease progresses so rapidly, successful management depends on starting therapy before culture and histopathology results are available. Initial clinical signs include localized edema, erythema, and pain at the affected site with tachycardia and fever. In people, most cases involve an extremity, but the perineum and trunk are also common sites. In the cases of canine necrotizing fasciitis, 77% of the dogs had involvement of a limb. The other reported sites were the neck and ventral thorax.[54,56] The hallmark sign in people is extreme pain that does not match the appearance of the affected area. It is difficult to differentiate necrotizing fasciitis from other soft tissue infections on initial presentation because the severe fascial necrosis with the former condition is not readily apparent from the exterior. In one retrospective study, 85% of people with necrotizing fasciitis were incorrectly diagnosed as having subcutaneous abscesses or cellulits on initial presentation.[57] In human patients, computed tomography (CT) and magnetic resonance imaging (MRI) have been used to document fascial involvement and delineate the extent of tissue damage. In one previously reported case in a dog, a fistulogram was used to show extension of contrast material along the fascial planes.[56] The absence of such findings on diagnostic imaging, however, should not exclude the diagnosis of necrotizing fasciitis. Results of blood tests are often nonspecific and reflect systemic inflammation, sepsis, vasculitis, or organ dysfunction.

There may be a leukocytosis, thrombocytopenia, coagulopathy, electrolyte abnormalities, hyperglycemia, and acidosis.[58] The hallmark surgical finding in people and dogs is the ease of separation of fascia from other tissues by blunt dissection. The presence of large amounts of exudative fluid in the subcutaneous spaces of the affected area is another common finding. In order to get a definitive diagnosis, tissue for culture should be obtained from the leading edge of the affected area. Samples from the center of the wound are more likely to contain secondary invading organisms.[56] Gram staining of fine needle aspirates or impression smears may reveal chains of Gram-positive cocci. Successful treatment of necrotizing fasciitis depends on early and complete surgical debridement of necrotic tissue, and multiple surgeries are often required (Figure 14.1).

In people, surgical exploration is performed every 24–48 h, until the infection is completely removed. Amputation of a limb is sometimes needed to completely remove infected tissue. Survival is influenced by the extent of initial debridement, and so it is advisable to remove excessive tissue. The other essential components of therapy are hemodynamic support, wound care, appropriate antibiotics, analgesia, and nutritional support. Initial broad-spectrum antimicrobial therapy is recommended while waiting for culture results. In humans, the combination of penicillin, an aminoglycoside, and metronidazole or clindamycin is the most frequently suggested regime for necrotizing fasciitis.[49,50] One retrospective study in humans showed a trend toward increased survival if the therapy included clindamycin.[59] The efficacy of enrofloxacin in dogs with necrotizing fasciitis has been questioned. The theory is that the use of enrofloxacin in dogs with *Streptococcus canis* infections may contribute to the emergence of necrotizing fasciitis and STSS. Bacterial virulence may be increased because fluoroquinolones may induce bacteriophages that encode superantigen genes.[60] A broad-spectrum antibiotic regimen that includes clindamycin is recommended.

Anesthetic management for cases of necrotizing fasciitis is similar to other cases with sepsis. The extent of the necrosis and severity of the infection may not be clear. The patient should be managed analogous to a case with septic shock and should be fluid resuscitated before anesthesia. However, surgical debridement should not be postponed. Reliable venous access is essential, and blood should be crossmatched and available because of the risk of bleeding.[61] Guidelines for managing septic patients under anesthesia were previously discussed in this chapter.

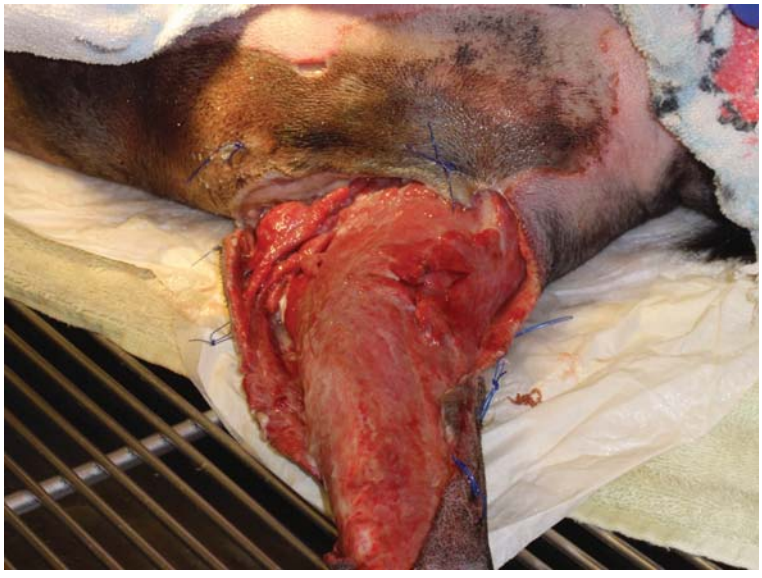

**Figure 14.1** Necrotizing fasciitis in a dog. Twenty-four hours after initial debridement. Note the new margins of the skin that needs debridement, clearly indicated by separation of the tissue and purulent discharge.

Postoperatively, these patients are at risk for developing multiorgan failure, and they should be managed in the intensive care unit with continued hemodynamic support, antimicrobial therapy, analgesia, oxygen supplementation, and nutritional support.

## Lyme disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi* and causes clinical disease in dogs. While cats can be infected, clinical disease from natural infection has not been reported in this species. Experimental infection in cats has resulted in a short-lived bacteremia with lameness, arthritis, or meningitis.[62] The primary mode of transmission is from the Ixodes tick. Wild animal reservoirs for adult ticks are deer, birds, and large mammals. Domestic hosts are humans, dogs, and cats. Clinical signs of systemic infection in dogs include fever, shifting leg lameness, anorexia, joint swelling, lymphadenomegaly, and lethargy. These signs are usually responsive to antimicrobials. Polyarthritis marked by shifting leg lameness is a common clinical sign. The arthritis is transient, but the pathologic joint changes are progressive.

Dogs with Lyme nephropathy present with renal failure and anorexia, vomiting, lethargy, dehydration, polyuria, polydipsia, and muscle wasting. Protein losing glomerulopathy has been described in naturally infected dogs. There can also be clinical signs attributable to vasculitis, thromboembolism, hypertension, uremia, and hypoproteinemia.[63]

Anesthetic management of dogs with Lyme disease should include a complete evaluation of renal function and diagnostics to document the level of hypoproteinemia and any associated clinical signs such as edema, ascites, pleural effusion, etc. Blood pressure should be measured, and hypertension should be noted. Dogs with Lyme nephropathy should be as stable as possible with regards to renal function before anesthesia and should be treated as a patient with renal dysfunction (Chapter. Anesthetic protocols should support renal function, and treatment of hypoproteinemia should be instituted if clinically indicated. Hypoproteinemia, especially hypoalbuminemia, can decrease colloid oncotic pressure, resulting in hypovolemia and hypotension under anesthesia. Further information on management of hypoproteinemia can be found elsewhere.

## Ehrlichiosis

The genus Ehrlichia is made up of Gram-negative intracellular bacteria that are transmitted by ticks and infect monocytes, macrophages, and granulocytes. Canine monocytotropic ehrlichiosis (CME) is caused by *Ehrlichia canis*, an obligate intracellular coccoid bacterium. *Ehrlichia chaffeenis* is the cause of human monocytotropic ehrlichiosis. *E. canis* is a known cause of morbidity and mortality in dogs in Asia, Europe, Africa, and the United States. The arthropod vector is the brown dog tick. Members of the family Canidae are hosts, and reservoir hosts are the domestic dog, fox, coyote, and jackal.[64]

There are three stages of infection. The acute phase may last for 7–28 days. Most dogs in the acute phase will recover with adequate treatment, whereas dogs that are not treated or those treated inappropriately may clinically recover and enter the subclinical phase. Dogs in this phase may have subnormal platelet counts, and they may be clinically healthy carriers of *E. canis* for months to years.[64] Persistently infected dogs may spontaneously recover or develop chronic disease. Chronic disease is typically associated with bone marrow hypoplasia and pancytopenia. Significantly lower platelet and leukocyte counts and lower hematocrit are linked with a high mortality risk. Severe leukopenia and anemia, prolonged activated partial thromboplastin time (aPTT), and hypokalemia are each reliable predictors of mortality with 100% probability.[65] The most common hematologic abnormality of dogs infected with *E. canis* is thrombocytopenia, and this occurs in all phases of the disease. The pathogenesis of thrombocytopenia is multifactorial. Increased platelet consumption and decreased half-life are likely secondary to immune-mediated destruction and splenic sequestration. Dogs with *E. canis* infections have antiplatelet antibodies circulating and a serum cytokine called platelet migration-inhibition factor (PMIF). PMIF is produced by lymphocytes when they are exposed to infected monocytes.[64] Thrombocytopenia is accompanied by platelet dysfunction, and this combination contributes to bleeding seen with infection.

Clinical signs of CME are multisystemic and include depression, lethargy, weight loss, anorexia, and bleeding. Clinical signs of bleeding that are frequently noticed include epistaxis and petechiae and/or ecchymoses. Lymphadenomegaly and splenomegaly may be present

in 20% and 25% of patients, respectively.[66] Ocular changes can include anterior uveitis and retinal changes. Dogs may develop changes in eye color or appearance or blindness secondary to paraproteinemia, systemic hypertension, hyphema, subretinal hemorrhage, and retinal detachment.[67] Meningitis or meningeal hemorrhage can result in seizures, stupor, acute central or peripheral vestibular dysfunction, cerebellar dysfunction, anisocoria, ataxia, intentional tremors, or hyperesthesia. Concurrent infection with other tick-borne diseases or secondary bacterial, fungal, or protozoal infections are possible in dogs with ehrlichiosis.

Diagnosis is based on travel history, living in an endemic area, tick infestation, clinical signs, hematologic abnormalities, and diagnostic tests such as serology and polymerase chain reaction. The typical hematologic abnormalities are a moderate to severe thrombocytopenia, mild anemia, and leukopenia.

Treatment of *E. canis* consists of antimicrobial agents and supportive care. Therapy should begin as early as possible, as chronically infected dogs are generally unresponsive to treatment because of multisystemic infection and myelosuppression.[64] Efficacious drugs include tetracyclines and chloramphenicol. Doxycycline 10 mg kg$^{-1}$ by mouth once a day for 28 days is recommended by the American College of Veterinary Internal Medicine's Ehrlichial Consensus Statement from 2002. Clinical improvement can usually be seen within 24 h of starting therapy in dogs in the acute or mild chronic phase. The platelet count is usually within the reference range by 10–14 days after starting treatment. Dogs can become reinfected after an effective treatment.

Supportive treatment with intravenous fluids and blood transfusions may be indicated. Anesthesia should be postponed if possible until platelet numbers and function are improving. Platelet-rich plasma may be required in an emergency situation. Desmopressin acetate (DDAVP) may be administered to treat platelet dysfunction. The dose is 1 μg kg$^{-1}$ subcutaneously 20–30 min before surgery. For elective anesthesia cases, efforts should be made to have normal platelet numbers and function and normal hematocrit before the procedure. Acepromazine should be avoided because this drug inhibits platelet function. Aspirin should not be administered in the perioperative period because this drug irreversibly inhibits platelet function. Treatment with low immunosuppressive doses of glucocorticoids (1–2 mg kg$^{-1}$ of prednisolone by mouth) for 2–7 days may be of benefit early on when the thrombocytopenia is severe.[64] Monitoring the response to treatment of ehrlichiosis is important because infection can persist for months to years. Platelet counts should be rechecked at least 1–3 months after treatment has been stopped. Further information on anesthesia of thrombocytopenic patients can be found in Chapter 12.

## Leptospirosis

Leptospirosis, a zoonotic disease with worldwide distribution, is caused by the bacterial spirochete Leptospira species. Disease in dogs is caused mainly by *Leptospira interrogans* and *Leptospira kirschneri.* Cats do seroconvert after exposure to leptospires, but clinical disease is rarely reported. Infection occurs via direct or indirect transmission. Direct transmission is by contact with infected urine, placental and venereal transfer, bite wounds, or ingestion of infected tissue. Indirect transmission, which is more common, occurs by exposure of intact mucous membranes or broken skin to urine-contaminated water, soil, bedding, and food. Leptospires do not replicate outside of the host, but they can remain viable for months in soil that has been saturated with urine. A wide range of wild and domestic animals can host leptospires, including, but not limited to, rodents, raccoons, foxes, skunks, pigs, horses, sheep, goats, dogs, cats, cows, and deer.[68] Leptospires penetrate intact mucous membranes of the mouth, nose or eyes, or abraded skin and multiply rapidly after entering the bloodstream. Organisms then spread and replicate in the kidney, spleen, liver, central nervous system, genital tract, and eyes. The host immune response is activated, and once serum antibody levels increase, the host can clear the leptospires from most organs. Organisms can remain in the kidneys and be shed in the urine for weeks to months. Damage can occur to renal, hepatic, pulmonary, vascular, cardiac, and coagulation systems. Interstitial nephritis and tubular dysfunction are thought to result from kidney swelling, decreased renal blood flow, and decreased glomerular filtration. Acute tubular necrosis can occur. Vasculitis may also contribute to renal parenchymal damage. Hepatic dysfunction can occur without major histologic changes, and the degree of icterus usually correlates with the extent of hepatic necrosis. Chronic active hepatitis has

been reported in dogs with leptospirosis. It is thought that hepatocellular injury and leptospires in the liver result in altered blood flow, fibrosis, and immune stimulation that perpetuate the chronic inflammatory response.[68] Acute pulmonary damage occurs secondary to the toxins from the organisms. Vasculitis can cause fluid exudation within the lungs. Rarely, severe and acute hemorrhage into the lungs may occur. Clinical signs can include fever, anorexia, vomiting, muscle tenderness, reluctance to move, dehydration, cardiovascular collapse, petechiae, ecchymoses, melena, epistaxis, oliguria or anuria, icterus, hematemesis, hematochezia, conjunctivitis, or uveitis.[68] Hematologic abnormalities are leukocytosis, thrombocytopenia, prolonged coagulation times, and a mild anemia. Biochemistry abnormalities are azotemia, hypoalbuminemia, hyperbilirubinemia, hyperphosphatemia, hyperglycemia, hyponatremia, hypochloremia, hypokalemia or hyperkalemia, and increases in ALP, ALT, AST, amylase, and lipase. Abnormalities on the urinalysis include specific gravity $\leq$1.029, isosthenuria or hyposthenuria, proteinuria, glucosuria, bilirubinuria, hematuria, increased granular casts, white blood cells, or an increased urine protein to creatinine ratio.[68] Thoracic radiographs may reveal a diffuse interstitial to nodular interstitial pattern or alveolar opacities. Abdominal ultrasound may show renomegaly, increased echogenicity of the renal cortices, perirenal fluid, and pylectasia.[69]

Treatment consists of supportive care with intravenous fluids, centrally acting antiemetics to treat nausea and vomiting, colloid administration to support vascular oncotic pressure, and antibiotics. Urine production should be monitored, and treatment of oliguria ($<2\,ml\,kg^{-1}\,h^{-1}$) may require the administration of mannitol, furosemide, and dopamine to cause diuresis. Persistent oliguria warrants consideration of peritoneal dialysis, hemodialysis, or continuous renal replacement therapy because acute renal dysfunction may be reversible.[70] Antibiotics should be administered as soon as leptospirosis is suspected as the cause of clinical signs because early treatment increases the chance for reversing tissue damage. Penicillin or ampicillin can be administered in the vomiting dog. Once oral medication can be tolerated, doxycycline $5\,mg\,kg^{-1}$ should be administered by mouth, every 12 h for 14 days. Concurrent administration of fluoroquinolones is not recommended because it contributes to antibiotic resistance, and efficacy has not been demonstrated.[71] Successful treatment results in gradual correction of azotemia within 10–14 days; damaged renal tissue may continue to regenerate for 4 weeks after treatment. Platelet counts usually improve within 1 week of starting treatment. Dogs treated late in the course of the disease may have permanent kidney damage.

Leptospirosis is a zoonotic disease, and precautions should be taken to avoid exposure to other animals and people caring for the patient. Gloves and a disposable gown should be worn when handling the patient to prevent contact with urine or blood. If aerosolization of urine is possible, such as when handling urinary catheters or collection systems or when cleaning, protective eyewear and a face mask should be worn.[72] An indwelling urinary catheter and collection system should be placed in order to reduce urine contamination of the environment. Leptospires are inactivated with routine disinfectants.

Anesthetic management consists of optimizing renal function and hemodynamic stability. Anesthesia should be postponed if possible until some improvement in renal function has been demonstrated. The degree of organ dysfunction should be noted, and hypovolemia, dehydration, electrolyte derangements, and acid–base disturbances should be corrected before anesthesia. Acepromazine should be avoided because of the associated vasodilation and hypotension. Opioids should be used to reduce induction drug requirements, reduce MAC, and provide analgesia. If hepatic dysfunction is present, drugs that are reversible or have a short duration of action should be used. Adequate intravenous fluids should be administered to support cardiovascular function and renal blood flow. Colloids may be required in cases with hypoalbuminemia. Guidelines for anesthetic management of renal and hepatic dysfunction can be found in Chapters 6 and 4, respectively.

## Feline immunodeficiency virus

Feline immunodeficiency virus (FIV) is a lentivirus that has many properties in common with other lentiviruses such as human immunodeficiency virus (HIV). FIV is common around the world. It is transmitted by inoculation of virus in saliva or blood, through biting or fighting wounds. Infection can be subclinical or clinical. Infection results in immunologic dysregulation, affecting neutrophils, lymphocytes, cytokine

production, immunoglobulin production, and other immune functions. Clinical stages of infection include an acute phase, a clinically asymptomatic phase, and a terminal phase (feline AIDS). Unlike HIV-infected humans, cats that are in the feline AIDS phase may recover and become asymptomatic again. Clinical signs are nonspecific and often go unnoticed in naturally infected cats. The asymptomatic phase can last weeks to years. During symptomatic phases, clinical signs reflect secondary infections, myelosuppression, neoplasia, and neurologic disease. FIV-infected cats may have respiratory disease secondary to bacterial, fungal, protozoal, or parasitic infections. Stomatitis is a common condition in FIV-infected cats and is thought to be from immune dysregulation or an immune response to chronic antigenic stimulation. Compared to noninfected cats, experimentally infected FIV cats have a higher prevalence of odontoclastic resorptive lesions.[73] Neurologic signs in FIV-infected cats can include behavioral changes, seizures, weakness, and motor abnormalities. FIV-infected cats can have ocular disease. Cats with FIV are more likely to develop lymphoma or leukemia than noninfected cats.[74] Blood work abnormalities in FIV-infected cats may include a nonregenerative anemia, leukopenia, neutropenia, thrombocytopenia, and hyperglobulinemia. Cats that are FIV positive should have an annual physical examination, complete blood count, biochemistry panel, and a urinalysis. Intensive diagnostics should be performed earlier in FIV-infected cats that are sick so that a prompt diagnosis of secondary illness can be made; this enables timely therapeutic action and a successful treatment outcome.[74]

In humans, general anesthesia causes immunosuppression that occurs within 15 min of induction and that may last for 3–11 days.[75] Although this immunosuppression may not have a clinical impact in healthy patients, HIV-infected patients may be more susceptible to postoperative infections. Likewise, FIV-positive cats may be more susceptible to complications from the immunosuppression of anesthesia. The anesthetic period should be as short as possible, and anesthetic management and practice should minimize stress and optimize analgesia. Locoregional techniques should be used whenever possible to provide preemptive analgesia and to minimize inhalant requirements. The specific anesthetic plan would depend on the systems involved. Specific anesthetic management of these system abnormalities can be found elsewhere in this book.

## Disinfecting equipment

Anesthesia equipment should be routinely cleaned and disinfected. Cases of cross contamination as a result of anesthetic equipment have been documented. Recognition of nosocomial infections from anesthetic equipment can be delayed due to a long incubation period or lack of follow-up. Patients who undergo anesthesia and surgery are at a greater risk of developing respiratory infections than those who do not. General anesthesia impairs ciliary function and mucous production, and surgery can impair the patient's ability to breathe deeply and cough, further impacting normal protective respiratory functions. A portion of anesthetized patients is already immunocompromised secondary to concurrent diseases, and this group may be unable to protect itself from environmental organisms or seemingly insignificant inoculums.[76]

Cleaning is defined as the removal of visible extraneous material from objects. Disinfection is the destruction of many, but not all, microorganisms on inanimate objects. Sterilization is the destruction of all viable forms of microorganisms.

The Centers for Disease Control and Prevention (CDC) have a classification that includes three levels of disinfection.

1. High level disinfection is a procedure that kills all organisms except bacterial spores and viruses such as Creutzfeldt-Jakob virus. These disinfectants are registered with the Environmental Protection Agency (EPA) as sterilant/disinfectants, sporicidal hospital disinfectants, or sterilants. Most high level disinfectants can result in sterilization with sufficient contact time.
2. Intermediate level disinfection kills bacteria (including *Mycobacterium tuberculosis*), some fungi, and most viruses but not bacterial spores. These disinfectants are EPA-approved hospital disinfectants that are tuberculocidal.
3. Low level disinfection kills most bacteria (not mycobacteria), some fungi, some viruses, but no spores.

**Table 14.5** Guidelines for disinfecting items related to anesthetic practice.[76]

| | | | |
|---|---|---|---|
| Critical items | Penetrate skin or mucous membranes, or come in contact with sterile areas of body | Vascular needles, catheters, regional block needles and catheters | Items must be sterile at the time of use |
| Semicritical items | Contact intact mucous membranes but do not penetrate body surfaces | Endoscopes, laryngoscope blades, reusable rectal, nasopharyngeal and esophageal temperature probes, face masks, resuscitation bags, breathing tubes and connectors, oxygen masks, esophageal stethoscopes, and tracheal and double-lumen tubes | Sterilization ideal but high level disinfection is acceptable |
| Noncritical items | Do not contact patient or touch intact skin | Stethoscopes, blood pressure cuffs and tubing, pulse oximeter sensors and cables, ECG cables, temperature monitor cables; exterior of anesthesia machine, ventilator, humidifier, scavenging system, resuscitation bags, monitor, equipment carts | Intermediate to low level disinfection |

The CDC has divided items into categories on the basis of the potential risk for infection involved in their use (Table 14.5).

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# 15 Neoplastic disease

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Cancer is a major cause of disease in animals of all ages and is the leading cause of death in older pet animals.[1] However, a precise estimate of cancer morbidity and mortality is difficult to obtain because of a number of limitations that differentiate animal from human populations. Comprehensive state-based cancer registries are available in human medicine, whereas only a few, very limited attempts have been made in veterinary medicine to create them.[1–7] The incidence rate of veterinary cancer is 0.4–2% in dogs and 0.1–0.4% in cats,[2–5] whereas cancer prevalence in a set population of veterinary patients was 4%.[7] In addition, mortality rates for veterinary cancer patients are 20–56% depending on age and breed.[1,6] Despite the fact that accurate epidemiological veterinary cancer data may still be lacking, the prevalence of cancer in pet animals continues to rise for a number of reasons but is, at least in part, related to animals living to increasingly older ages. The greater life span is the result of better preventive and therapeutic medical practices (including better nutrition and vaccination policies) and, possibly, the development of a stronger human–animal bond during the last 20 years.[1,8] As such, veterinary care for oncologic pets is currently demanded by society and veterinary professionals who are expected to provide expertise and proficiency in the clinical management of the cancer patient. A cornerstone of their medical care is the anesthetic/analgesic management during different stages of their clinical management, which ranges from diagnostic to therapeutic or palliative procedures.

## Pathophysiologic considerations

Unfortunately, cancer patients present with many pathophysiologic derangements that derive not only from the neoplasia and/or its metastases, but also from the coexisting paraneoplastic syndromes (PNSs) and the secondary effects of their therapeutic management (e.g. secondary effects of chemotherapy or radiation therapy and aggressive and invasive surgical procedures). In order to perform a safe and adequate anesthetic/analgesic management of the oncologic patient, a thorough understanding of the underlying pathophysiology is warranted.

## Paraneoplastic syndromes

Paraneoplastic syndromes include neoplasm-associated systemic alterations that occur distant to the tumor but can be directly linked to the neoplastic disease.[9] Tumors can produce and release a number of biologically active substances such as cytokines, hormones, and growth factors that lead to clinical conditions that may occasionally present a higher morbidity than the original tumor itself. PNS can be classified according to the systemic organ they target (Table 15.1).

### General manifestations

#### Cancer anorexia–cachexia syndrome

The cancer anorexia–cachexia syndrome (CACS) represents the most common paraneoplastic disorder in both human and veterinary patients. The incidence among veterinary patients is yet to be determined by appropriate clinical studies. However, Michel et al. in 2004[10] reported an estimated incidence of only 4%, which may be significantly lower than the real figure.[9] Oncologic patients frequently show weight loss and metabolic alterations associated with both adequate nutritional intake (cancer cachexia) and/or poor nutritional intake (cancer anorexia). This PNS results in alterations in carbohydrate, lipid, and protein

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**Table 15.1** Classification of most common paraneoplastic syndromes in veterinary oncology patients

| Organic system | Manifestations | |
|---|---|---|
| General manifestations | Cancer Anorexia–Cachexia Syndrome (CACS) | Fever |
| Hematological manifestations | Anemia | Erythrocytosis |
| | Leucocytosis | Thrombocytopenia |
| | Thrombocyte Hyperaggregability | Coagulation disorders |
| | Pancytopenia | Hyperproteinemia |
| Endocrine manifestations | Hypercalcemia | Hypoglycemia |
| | Syndrome of Innappropriate Secretion of Antidiuretic Hormone (SIADH) | |
| Gastrointestinal manifestations | Gastroduodenal ulceration | |
| Cutaneous manifestations | Alopecia | Cutaneous flushing |
| | Nodular dermatofibrosis | |
| Neuromuscular manifestations | Myastenia gravis | Peripheral neuropathy |
| Renal manifestations | Glomerulonephritis | |
| Miscellaneous manifestations | Hypertrophic osteopathy | |

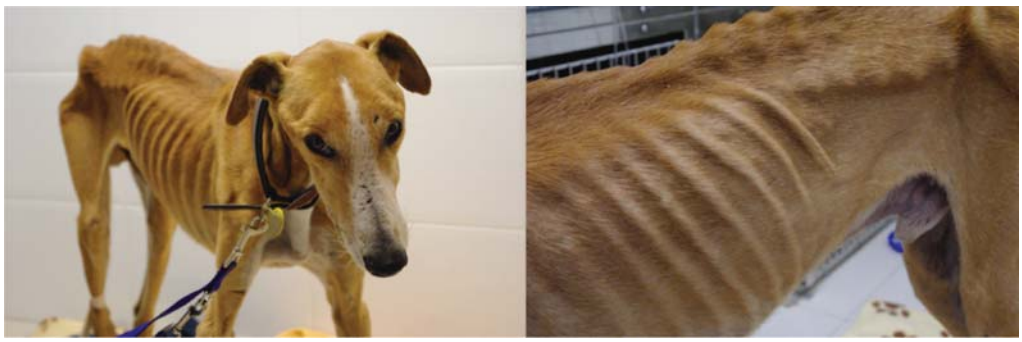

**Figure 15.1** Severe wasting in a dog because of CACS. Source: Photo courtesy of Dr. Ana Cloquell.

metabolism that, if left untreated, decrease the patients' quality of life, their survival time, and, sometimes, their chances of being suitable candidates for a more appropriate therapy.[11] Clinically, CACS is characterized by nausea, anorexia, and weight loss that ultimately lead to severe wasting owing to massive body fat depletion and a dramatic decrease in muscle protein mass (Figure 15.1).[12]

Patients may also have alterations in food perception (i.e. smell and taste), which decrease the palatability of the food they are offered.[12] The metabolic disorders associated with the CACS may occur even before weight loss is first detected, and they may often persist after the patient is successfully treated for the tumor, making weight gain challenging. The underlying pathophysiologic mechanism of the CACS is mediated by the production and release of serotonin and cytokines that lead to alterations in the resting energy expenditure, as well as in physiologic protein, fat, and carbohydrate metabolism.[12] Table 15.2 summarizes the major clinical signs associated with CACS, as well as their pathophysiologic mechanisms.

Oncologic patients with CACS require aggressive nutritional support in order to limit the adverse effects of CACS and to enhance immune system function, as well as the efficacy and tolerance of different therapeutic interventions (i.e. diets rich in omega-3 fatty acids).[13] Nasoesophageal, esophagostomy, or gastrotomy tubes

**Table 15.2** Cancer anorexia–cachexia syndrome (CACS): major clinical signs and pathophysiologic mechanisms.

| Affected system | Pathophysiologic mechanism | Clinical sign |
|---|---|---|
| Protein metabolism | Decreased protein anabolism | Muscle atrophy |
| | Increased protein catabolism | Poor body condition score |
| Carbohydrate metabolism | Altered insulin receptors | Hyperlactatemia |
| | Anaerobic glucose metabolism | |
| Lipid metabolism | Increased lipolysis | Loss of body fat |
| | Increased lipid mobilization | Poor body condition score |
| | Decreased extraction of fatty acids | |
| Resting Energy Expenditure (REE) | Abnormal glucose metabolism | Increased REE |

are also recommended in those patients who are persistently anorexic.

As a result of the aforementioned changes associated with PNS, a low fat to body mass ratio and a low muscle to body mass ratio are commonly found in these patients, and higher circulating levels of free-fraction or active drugs (e.g. barbiturates) may be present. In order to avoid overdose, prolonged, and/or rough anesthetic recoveries, careful pharmacologic choices and dosing regimens need to be applied. In addition, owing to their very low fat to body ratio, these patients may be more prone to hypothermia during the perianesthetic period. Active efforts to decrease as much heat loss as possible are warranted (i.e. insulation from cold surfaces, careful wrapping, use of heat and moisture exchange filters, and warm water blankets).

### Fever

Fever as a PNS is associated with a wide variety of tumors, and although it is very common in human patients, its incidence in veterinary medicine is unknown.[14] The pathogenesis of paraneoplastic fever is mostly due to the production and release of pyrogenic cytokines by the host immune system and/or the tumor in itself.[15] A thorough preanesthetic evaluation is warranted in order to rule out the presence of an infectious process before formulating an anesthetic plan. Severe elevations in body temperature are associated with an increased metabolic state and degree of oxygen consumption that may even exceed oxygen delivery to tissues. This situation may eventually lead to the development of a series of multiorgan dysfunctions (i.e. acute renal failure, myocardial arrhythmias, and disseminated intravascular coagulation [DIC]). If infection is ruled out and the fever is severe or life-threatening, nonsteroidal anti-inflammatory drugs (NSAIDs) should be used to inhibit the chemical mediators responsible for fever production, while still allowing for normal thermoregulation.[16] Although NSAIDs are relatively safe, they should be avoided in patients with renal disease, gastrointestinal ulceration, or bleeding disorders. Dipyrone is also an injectable NSAID, with antipyretic properties via COX-3 inhibition[17,18] not associated with the usual NSAIDs contraindications. Dipyrone may induce blood dyscrasias in human patients; however, this has not been shown in animals.[19] In addition, hyperthermia is related to an increase in inhalant minimum alveolar concentrations (MAC)[20], and anesthetic maintenance with inhalant agents may necessitate higher end-tidal inhalant concentrations.

## Hematological manifestations

### Anemia

Tumors and their metastases can alter hematopoietic cell lines after infiltration of the bone marrow, and anemia is one of the most common PNS in veterinary patients, with an incidence from 30 to 69%.[21] The most common causes are anemia of chronic disease (ACD), immune-mediated hemolytic anemia (IMHA) usually associated with hematopoietic tumors, blood loss anemia associated with paraneoplastic gastroduodenal ulceration, and microangiopathic hemolytic anemia (MAHA) most commonly associated with microvascular tumors or any type of tumor that could lead to the development of DIC.

In the case of acute or severe anemia, stabilization is desirable before general anesthesia is considered. In ACD, blood loss anemia, and MAHA, only the tumor removal can improve the condition; however, when IMHA is present, treatment with corticosteroids with or without immunosuppressive agents such as azathioprine or cyclophosphamide may significantly improve the condition before general anesthesia is undertaken.[22–26] In addition, supportive treatment with whole blood or packed red blood cell transfusion may be necessary where hypoperfusion and hypoxia are a concern. Administration of hemoglobin-based oxygen-carrying solutions (HBOCs) may also be considered if available. In addition, measures should be taken to optimize oxygenation in the anesthetized patient, such as preoxygenation before induction of general anesthesia, maintaining the $FiO_2$ of 1.0 throughout the procedure and guaranteeing optimal perfusion at all times.

**Erythrocytosis**

Polycythemia or erythrocytosis is uncommon in veterinary oncologic patients and is mainly associated with renal tumors in which an increased level of erythropoietin may be present.[27,28] Patients present with clinical signs of tissue hypoxia, polyuria, bleeding, or thrombosis that result from hyperviscosity of the blood, as well as decreased perfusion of small vessels. Stabilization via phlebotomy can be a useful temporary adjunct therapy. Serial phlebotomies of 10–20 $ml\,kg^{-1}$ of blood may be carried out until clinical symptoms have resolved or the target hematocrit is reached (usually <50% for cats and <55% in dogs). However, repeated phlebotomies may result in thrombotic complications or iron deficits, as well as concomitant aggressive fluid therapy and potential administration of plasma.[29] As a consequence, if phlebotomies are required more frequently than every 6–8 weeks, myelosuppresive therapy is advised, and hydroxyurea is considered the drug of choice.[30] Definitive treatment of PNS erythrocytosis implies the removal of the erythropoietin-producing tumor.

**Thrombocytopenia**

The incidence of thrombocytopenia in veterinary cancer patients is high, occurring in up to 58% of dogs and 20% of cats.[31–33] Clinical signs are usually not evident until the platelet count decreases below 30,000 $\mu l^{-1}$. Definitive treatment requires removal of the stimulating tumor.

Anesthetic management of PNS thrombocytopenia includes a thorough physical examination and hematological evaluation; platelet-rich plasma or plasma transfusions may be indicated. Fresh frozen plasma (FFP) transfusions of 10 and 15–18 $ml\,kg^{-1}$ have been reported with favorable results.[34,35] Transfusion reactions are rare and range from mild signs (i.e. pruritus, facial swelling, and rash) to more severe (i.e. anaphylactic reactions or even death). Patients being transfused should always be closely monitored. Corticosteroids (>2 $mg\,kg^{-1}$ PO daily) and immunosuppressive drugs such as azathioprine (2 $mg\,kg^{-1}$ PO daily, then 0.5–1 $mg\,kg^{-1}$ every other day) may be used if immune mediated.[36] In addition, the use of lyophilized platelets in thrombocytopenic dogs has recently been reported with favorable results.[37]

**Thrombocyte hyperaggregability**

Veterinary oncologic patients may present with hyperaggregability and thromboembolism. Pulmonary thromboemboli (PTE) usually present with unexplained sudden hypotension, tachycardia, tachypnea, hypoxemia, or bronchospasm. Arterial blood gas analysis may reveal hypoxemia, hypocapnia, and an increased alveolar–arterial oxygen gradient. A decrease in end-tidal $CO_2$ levels is also suggestive of pulmonary embolism, although not specific. Definitive diagnosis of intraoperative PTE may require selective pulmonary angiography or computed tomography with contrast angiography. However, these techniques are highly sophisticated and may not be readily available. Oxygen therapy should be instituted in a timely manner, and definitive therapy may include thrombolytic therapy (Streptokinase, 90,000 U as an intravenous (IV) infusion over 20–30 min, followed by 45,000 U as an IV infusion over 3–7 h)[38], as well as anticoagulation with heparin and warfarin therapy (low-molecular-weight heparin at 75–100 $U\,kg^{-1}$ SC every 8 h, followed by warfarin at 0.1 $mg\,kg^{-1}$ every 24 h).[39] Prophylactically, the selection of short-acting or reversible anesthetic agents is warranted in patients prone to developing PTE, as these protocols may allow early postoperative ambulation, therefore decreasing the incidence of additional thromboembolic episodes. In addition, in animals considered at risk for PTE, prophylactic anticoagulant

therapy may be instituted (low-molecular-weight heparin at 75–100 U kg$^{-1}$ SC every 8 h).[39]

### Coagulation disorders

Paraneoplastic syndrome coagulopathies may be present, especially if alterations in platelet number and functionality are also present, and DIC is the most frequent clinical abnormality.[40] Thrombocytopenia, prolongation of activated partial thromboplastin time (APTT), increased levels of fibrin degradation products (FDP and D-dimers), hypofibrinogenemia, and decreased antithrombin III (AT III) levels may be clear indicators of the presence of DIC.[41] Table 15.3 summarizes pathophysiologic mechanisms, clinical signs, and diagnostic tests along the different stages of DIC. Appropriate stabilization of this condition is warranted before the undertaking of general anesthesia.

### Hyperproteinemia

Hyperproteinemia occurs in animals with multiple myeloma, where monoclonal immunoglobulins are secreted in large quantities producing paraproteinemia.[42,43] Clinical signs associated with hyperproteinemia are associated with bleeding disorders (as a result of poor platelet aggregation and interference with coagulation factors)[44] and blood hyperviscosity (due to the protein–protein interactions of large, long molecules with high intrinsic viscosity).[43] Clinical signs of hyperviscosity result from tissue hypoxia because of the sludging of blood and include ocular disturbances, severe central nervous system (CNS) deficits, and cardiac disease or failure.[43,45] Stabilization before general anesthesia through plasmapheresis may be necessary to reduce protein concentrations.[46]

## Endocrine manifestations

### Hypercalcemia

Approximately two-thirds of dogs and one-third of cats that present with hypercalcemia are diagnosed with neoplasia.[47,48] The most common neoplasia associated with hypercalcemia of malignancy (HM) is lymphoma[49] but is also seen with mammary gland (adeno)carcinoma, parathyroid gland neoplasia, thyroid carcinoma, bone neoplasia, anal sac apocrine gland carcinoma, multiple myeloma, thymoma, squamous cell carcinoma, melanoma, and primary lung neoplasia.[50–54] Hypercalcemia occurs via bone resorption by osteoclasts and subsequent release of circulating calcium.[55] However, additional differentials include acute renal failure, hypoadrenocorticism, granulomatous disease, hypervitaminosis D, or a laboratory artifact (due to hemolysis or lipemia).[56] In addition, in case of acidemia, an increase in the free ionized fraction of calcium can occur.[9] Similarly, the relationship between calcium and

**Table 15.3** Disseminated intravascular coagulation (DIC).

| Stage | Controllednonovert DIC | Controlledovert DIC | Noncontrolledovert DIC |
|---|---|---|---|
| Pathophysiologic mechanism | Activated but compensated coagulation<br>Thrombin generation contained or balanced by inhibitors<br>Activation of platelets | Activated and uncompensated coagulation<br>Thrombin-Inhibitors overwhelmed<br>Inflammation-hemostasis feedback loop | Platelets and coagulation factors are consumed |
| Clinical signs | Microvascular thrombosis | Macrovascular thrombosis<br>Organ dysfunction | Hemorrhage |
| Diagnosis | Predisposing disease<br>Altered trend in PT<br>Altered trend in fibrinolytic products (FDP and D-dimers) | Increased PT, PTT<br>Increased FDP and D-dimers<br>Low fibrinogen | Increased PT, PTT<br>Increased FDP and D-Dimers<br>Low fibrinogen<br>Severe thrombocytopenia |

The DIC continuum as defined by the Scientific Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) on DIC[41] and modification for DIC in dogs (Wiinberg B, Jensen AL, Rojklaer R, et al. 2006. Prospective pilot study on performance and prognostic value of a new human, ISTH based scoring system for identifying nonovert disseminated intravascular coagulation in dogs [ACVIM abstract 203]. *J Vet Intern Med* 20(3):697–802).

serum albumin should be evaluated, and the following correction formula could be used (Equation 15.1):

$$\text{Adjusted calcium (mg dl}^{-1}\text{)} = [\text{Calcium (mg dl}^{-1}\text{)} - \text{Albumin (g dl}^{-1}\text{)}] + 3.5 \quad (15.1)$$

Total calcium levels >18 mg dl$^{-1}$ should be approached as a medical emergency.[57] Systemic signs include twitching, shaking, weakness, hypertension, bradycardia, depression, stupor, or even coma. Deposition of calcium salts on the renal parenchyma leads to prerenal and renal azotemia, whereas severe vasoconstriction causes a decrease in renal blood flow and glomerular filtration rate.[58] Decreased responsiveness to the antidiuretic hormone (ADH) at the distal tubule is responsible for the inability to concentrate urine. The urinary epithelium may then undergo degeneration and, eventually, necrosis.[57] Vomiting, polydipsia, and polyuria may develop and lead to progressive deterioration and dehydration of the patient. Since some of the symptomatic therapies to treat hypercalcemia could impair the ability to reach a final diagnosis or resolution of the etiology (e.g. glucocorticoids), the primary goal when managing a patient with HM should always be to elucidate and treat the underlying cause (for this reason, the use of corticosteroids in cases of hypercalcemia with undiagnosed neoplasia is strongly discouraged).[9,59,60]

General anesthesia should be performed with caution when calcium levels are significantly above the normal range (total calcium >12 mg dl$^{-1}$) because of hemodynamic and renal consequences (i.e. bradyarrhythmias, asystole and cardiac arrest, hypertension, azotemia, polyuria, and polydipsia). Complete normalization of calcium levels may not be achieved before anesthesia, as excision of the tumor will likely be the only definitive treatment in many cases. Nevertheless, treatment should be directed at promoting external loss of calcium, increasing renal excretion of calcium, and inhibiting bone reabsorption.[9] For example, in the case of mild hypercalcemia (12–15 mg dl$^{-1}$) and no clinical signs, rehydration with 0.9% saline could result in normocalcemia. With moderate hypercalcemia (15–18 mg dl$^{-1}$), rehydration and consequent diuresis with 0.9% saline and furosemide (1–4 mg kg$^{-1}$, in cats every 8–24 h IV, in dogs; 1–2 mg kg$^{-1}$ every 8–24 h IV) should be initiated to inhibit calcium reabsorption by the ascending loop of Henle. If the final diagnosis has been reached and lymphoma ruled out, prednisone (1 mg kg$^{-1}$ every 12 h PO, both dogs and cats) could be administered. In cases of refractory hypercalcemia, administration of salmon calcitonin (4–10 MRC units per kilogram every 24 h SC) and bisphosphonates such as zoledronate (0.25 mg kg$^{-1}$ IV, every 4–5 weeks) or pamidronate (1–1.5 mg kg$^{-1}$ IV in dogs and 1.5–2 mg kg$^{-1}$ IV in cats, every 2–4 weeks) should be considered.[61–63]

### Hypoglycemia

Hypoglycemia is mainly associated with insulin-producing islet cell pancreatic tumors.[64] However, it has been described in patients with leiomyoma, leiomyosarcoma, hepatoma, hepatocellular carcinoma, and hemangiosarcoma.[65] Pathophysiologic mechanisms include increased tumor usage of glucose, decreased hepatic gluconeogenesis, secretion of insulin-like growth factors I and II, or upregulation of insulin receptors[66], and the most common clinical signs include weakness, disorientation, seizures, and coma. With severe hypoglycemia, IV bolus of 50% dextrose (1 ml kg$^{-1}$ diluted 1:2–1:4 over 5 min) and an IV infusion of 2–2.5% dextrose or glucagon should be initiated.[67] However, care must be taken when treating hypoglycemia in patients with suspected insulinoma or other tumors secreting insulin-like analogs, as IV dextrose may stimulate the release of even larger amounts of insulin from the tumor, further aggravating the hypoglycemic state. Dextrose infusions should be formulated by adding the appropriate amount of 50% dextrose to an isotonic crystalloid fluid (such as Lactated Ringer, 0.9% NaCl, or plasma-lyte) and then administered at fluid therapy maintenance rate (40 ml kg$^{-1}$ day$^{-1}$). Do not administer 5% dextrose in water because the solution is hypotonic and devoid of electrolytes. Glucagon can also be administered. It should be reconstituted and diluted in 0.9% saline, resulting in a 1000 ng ml$^{-1}$ solution. It may be first administered as a 50 ng kg$^{-1}$ bolus followed by a 5–40 ng kg$^{-1}$ min$^{-1}$ continuous rate infusion (CRI). Some oncologic patients may already be receiving various treatments aimed at fighting hypoglycemia such as diazoxide (10–60 mg kg$^{-1}$ every 12 h PO, in dogs), as it increases glucose levels by enhancing epinephrine-induced glycogenolysis and inhibiting insulin release and uptake by cells.[68] Others may be receiving hydrochlorothiazide (2–4 mg BID PO, in dogs and cats) to potentiate the effects of diazoxide or somatostatin (5–20 g BID/TID PO or SQ).[9,68,69]

### Gastrointestinal manifestations

Gastroduodenal ulceration is associated with mast cell tumors (MCTs) or gastrinomas (gastrin-secreting non-islet cell pancreatic tumor).[70] Mast cell granules contain a number of biologically active substances such as histamine, heparin, and proteolytic enzymes[71] and are associated with gastric mucosal damage and ulceration owing to increased gastric acid secretion.[70–72] Oncologic patients diagnosed with MCT or gastrinoma should be treated with an Histamine-2 receptor antagonist such as famotidine (0.5–1 mg $kg^{-1}$ PO every 12 h, dogs and cats) or ranitidine (2 mg $kg^{-1}$ slow IV, every 12 h, dogs and cats) to prevent gastrointestinal complications.[70] The use of NSAIDs or corticosteroids should be avoided whenever possible because of the adverse effects on gastrointestinal mucosa.

### Cutaneous manifestiations

Paraneoplastic syndrome alopecia is usually bilaterally symmetrical and nonscaring and has been associated with pancreatic carcinomas with metastasis to the liver.[73–75] Patients with PNS alopecia are clinically anorexic, lose weight, are lethargic, and have difficulties standing or walking.[73–75] During the preanesthetic evaluation, a number of differential diagnoses should be ruled out such as hyperadrenocorticism, self-induced alopecia, or symmetrical alopecia.

### Renal manifestations

Oncologic patients may develop glomerulonephritis because of precipitation of tumor-related immune complexes on the glomeruli, as well as hypercalcemic nephropathy in those patients with hypercalcemia.[9,70] Careful evaluation of the renal function during the preanesthetic evaluation is warranted in order to stabilize an oncologic patient who may need general anesthesia for different diagnostic and therapeutic procedures.

### Neuromuscular manifestations

#### Myastenia gravis

Acquired myathenia gravis (MG) can occur in oncologic patients diagnosed with thymoma, osteosarcoma, lymphoma, and bile duct carcinoma.[76–80] Antibodies to nicotinic acetylcholine receptors are produced as a result of the tumor, and, as a consequence, failure of transmission across the neuromuscular junction occurs. Clinical signs include exercise intolerance, episodic muscular weakness, dysphagia, megaesophagus, and secondary aspiration pneumonia. Improvement of this tumor-associated disorder may be observed after surgical removal of the tumor in itself. However, the occurrence of megaesophagus is a negative prognostic factor.[76] The administration of immunosuppressive doses of prednisone (over 2 mg $kg^{-1}$ every 24 h PO, dogs and cats) may be attempted if surgical therapy is not an option. Since these patients frequently present with skeletal muscle weakness, perianesthetic concerns may include diaphragm insufficiency, requiring ventilator support and/or megaesophagus. Patients may show resistance to depolarizing neuromuscular blockers (such as succinylcholine).[81] However, acute sensitivity to the effects of nondepolarizing blockers (such as vecuronium, rocuronium, or atracurium) may also occur.[82] As a consequence, approximately one tenth of the initial dose is advised in these patients. Assessment of the neuromuscular block using a nerve stimulator with or without acceleromyography or electromyography should always be established in patients requiring neuromuscular blockade.

#### Peripheral neuropathy

Peripheral neuropathy affects both human and veterinary oncologic patients with lymphoma, multiple myeloma, primary lung neoplasia, mammary neoplasia, hemangiosarcoma, and MCTs.[83–86] The underlying pathophysiologic mechanism is due to autoantibodies targeting antigens expressed both in the tumor and the peripheral nerves.[70] Clinical signs range from weakness and progressive paraparesis to tetraparesis with lower motor neuron symptoms with or without polyneuropathy. Pain management is particularly important in these patients. Administration of gabapentin or pregabalin as adjuvant analgesics in addition to the standard pain management plan may be extremely beneficial in treating the neuropathic component of pain.

### Osseous manifestations

Hypertrophic osteopathy (HO) is characterized by progressive periosteal proliferation of new bone along the shafts of long bones of the appendicular skeleton and is commonly associated with primary lung tumors, although HO has also been described in tumors that metastasize to the lungs (Figure 15.2).[87–91]

The precise pathophysiologic mechanism is unknown; however, it is partly related to afferent neurologic stimulation through irritation of the vagal and/or

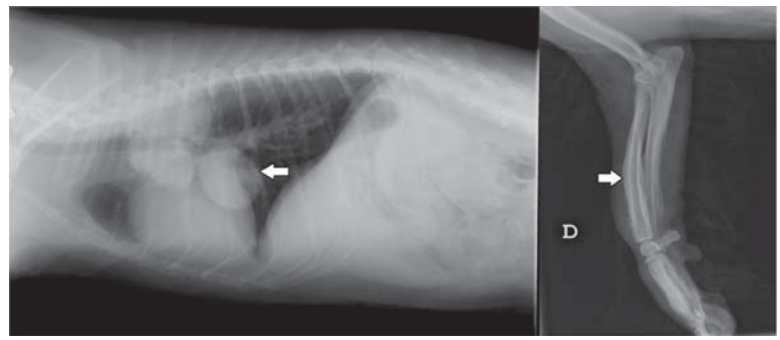


**Figure 15.2** Primary lung tumor (white arrow in A) in a patient with HO, with periosteal proliferation in the same patient (white arrow in B). Source: Photo courtesy of Dr. Sergio Monteagudo.

intercostal nerves, which subsequently enhances blood flow to the limbs.[92] Clinical signs include shifting leg lameness and reluctance to move when several limbs are affected. The extremities are usually warm and swollen, and manipulation is painful. Diagnosis is usually achieved using radiography of the affected limb, and thorough screening for the tumor responsible for the development of this PNS should be initiated in a timely manner. Management of pain associated with HO relies on the administration of NSAIDs, opioids (fentanyl transdermal patches), tramadol, and bisphosphonates.[93,94] Other treatments include vagotomy or intercostal nerve resection in order to disrupt the neurologic afferent input that causes blood flow to increase.[95] However, these therapeutic options have not been extensively studied in veterinary patients.

## Treatment

### Chemotherapy

The increased incidence and prevalence of cancer in the small animal population have led to an expansion in knowledge and availability of sophisticated treatment options for patients with cancer. Currently, most of these therapeutic options depend on complex chemotherapeutic interventions that are associated with a number of complications. Since most chemotherapy drugs exert their effects in the active phases of the cellular cycle[96], their toxic effects take place most commonly in tissues with a constant cellular turnover. As some normal tissues present a growth rate that resembles that of tumoral tissue (such as mucosa, gametes, epidermis, or hematopoietic cells)[97], chemotherapy agents will therefore affect not only tumoral tissues, but also some normal tissues. In addition, most chemotherapeutic drugs present a very narrow therapeutic margin, as their desired effect is cellular toxicity. These effects can alter the way anesthetic plans are formulated because many patient systems, including the bone marrow, gastrointestinal, dermatologic, neurologic, and urologic systems are affected; hypersensitivity reactions and acute tumor lysis syndrome (TLS) can also occur.

Myelosuppresion is commonly associated with the cytotoxic effects of chemotherapeutic agents. Anemia is rarely seen secondary to chemotherapy, as the lifespan of red cells is longer than other cells. However, certain drugs such as doxorubicin can cause recurrent bone marrow suppression and consequent exhaustion after longer periods of chemotherapy. Thrombocytopenia resulting from chemotherapeutic toxicity is rare, although rebound thrombocytosis can be observed. Neutropenia is often present after the administration of cytotoxic chemotherapeutic agents 7–21 days after treatment, especially at the nadir of the treatment.[96] Frequently, treatment is not necessary, as patients are asymptomatic and cell counts return to normal limits within a few days; however, prophylactic antibiotic therapy may be used when neutrophil counts drop below 1000 cells per microliter. Anorexia, vomiting, and cachexia are the most common side effects of chemotherapy on the gastrointestinal tract due to its cytotoxic effects. Depending on the severity of the symptoms, fluid therapy, antibiotics, and hospitalization for close observation are recommended. Hydration and volume status should be optimized before general anesthesia. Extravasation of the chemotherapeutic agents is a viable concern. Severe local tissue reactions

may lead to necrosis of the area; doxorubicin is the agent that most commonly causes the most severe reactions owing to large extravasated volumes. Clinical signs may include moist dermatitis, erythema, pruritus, pain, and, eventually, necrosis of the area within 7–10 days after extravasation, and veins should be evaluated for catheterization viability (Figure 15.3).

Local tissue reactions should be treated symptomatically by applying topical antibiotic or steroid preparations. Within 3 h of doxorubicin extravasation, dexrazoxane should be administered IV at a dose 10 times the extravasated dose and then daily for 3 days. If a vinca alkaloid is acutely extravasated, the area should be infiltrated with sterile saline ± 8.4% sodium bicarbonate and dexamethasone SP. Peripheral neuropathies are the main signs of neurotoxicity after administration of chemotherapeutic agents. These include partial paralysis, hind limb weakness, and even ileus that could lead to abdominal pain and constipation, especially if vinca alkaloids are being administered. Platinum products have been reported to cause cortical blindness. Nephrotoxicity and renal failure have also been reported secondary to cisplatin and doxorubicin administration, respectively, and stabilization of the patient may be necessary if azotemia or electrolyte derangements are present.

Acute type I hypersensitivity reactions have been reported secondary to the administration of certain chemotherapy agents such as L-asparaginase or etoposide, whereas other agents such as doxorubicin have been associated with anaphylactoid reactions because of direct stimulation of mast cell degranulation.[96] Emergency treatment should include epinephrine administration if severe vasodilation and bronchoconstriction are present, as well as fluid therapy, histamine-2 receptor antagonists (diphenhydramine), and steroids (dexamethasone) if necessary. TLS may also occur secondary to chemotherapy[98] and is associated with rapid tumor cell destruction, leading to release of intracellular ions and metabolic by-products into the extracellular environment and blood stream.[98] The most common metabolic derangements of TLS include hyperkalemia, metabolic acidosis, azotemia, and hyperphosphatemia, which could secondarily induce hypocalcemia. Clinical signs of TLS include vomiting, diarrhea, lethargy, bradyarrhythmias (secondary to hypocalcemia), and pale mucous membranes (secondary to decreased cardiac output). Initial treatment should include restoration of tissue perfusion with aggressive fluid therapy and hemodynamic stabilization, correction of electrolyte and acid–base disturbances, and renal stabilization.[98]

### Radiation therapy

Current radiation therapy is based on the use of ionizing radiation for local and regional eradication of malignant and, occasionally, benign tumors while preserving the structure and function of normal healthy tissue. The biological effect of ionizing radiation is based on its ability to cause ionization and excitation of atoms and molecules in cells that lead to the synthesis of a number of short-lived ions and unstable free radicals capable of

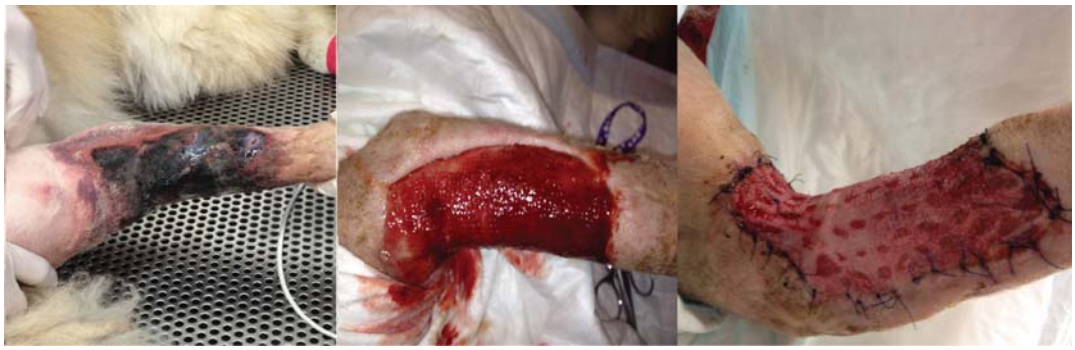


**Figure 15.3** Necrosis of forelimb in a canine patient after doxorubicin treatment (A), and surgical repair in the same patient (B and C). Source: Photo courtesy of Dr. Sanchez-Mellado.

causing molecular damage.[99] This molecular damage compromises cell survival by interaction of free radicals with cellular DNA, causing tumoral cells to enter mitosis with unrepaired DNA damage. This type of cell death is particularly relevant for tumors, as tumoral cells possess a characteristic ability to divide indefinitely. The side effects of radiation therapy on normal tissues are usually restricted to the treatment site, and they are classified chronologically into acute (during or immediately after treatment) and late effects (months to years after completion of treatment). Acute effects occur primarily from radiation-induced stem cell depletion that exceeds cell production in rapidly proliferating parenchymal tissues and usually affect mucous membranes and skin. These lesions are commonly self-limiting and resolve naturally after treatment. However, they may be temporarily painful and require supportive treatment. Late effects are considered true complications of radiation therapy and are mainly due to lesions of the vasculoconnective stroma in slowly proliferating parenchymal tissues of organs, such as lungs, heart, bone, cartilage, spinal cord, or kidneys. These lesions are not self-limited and tend to progress irreversibly to severe fibrosis, necrosis, loss of function, or even death. They are usually treated conservatively, although, occasionally, extremely severe complications may require surgical treatment.

Mucositis usually presents in the oral cavity, pharynx, and/or esophagus when tumors of the neck and head are irradiated; colitis may be present when caudal portions of the gastrointestinal system receive radiation therapy. Clinical signs include tender mouth and thickened saliva that leads to dysphagia and eventually anorexia, dehydration, and malnutrition with mucositis and severe large intestine diarrhea with colitis. Symptoms usually develop 1–2 weeks after the beginning of therapy and reach maximum development by the end of therapy, although oral mucositis should resolve 2–3 weeks after the end of therapy. Owner compliance is essential during these weeks, and interventions such as hand feeding low salt diets and detailed instruction on caloric and fluid requirements of the animal may be helpful. However, the placement of an esophagostomy/gastrostomy tube (Figure 15.4) or administration of subcutaneous fluids may be necessary in some instances to preserve the patient's hydration and nutritional status.

**Figure 15.4** Esophagostomy tube placement in a cat.

The preanesthetic evaluation should assess hydration and electrolyte status, body condition score (BCS), and the degree of oral mucositis. Oral lesions should be evaluated carefully, and special care should be taken when endotracheal intubation is performed by thoroughly lubricating the endotracheal tube (ETT), handling the laryngoscope with care, and securing the ETT in a gentle way avoiding lesion areas.

Dermatological early side effects are usually restricted to the radiation field, and their severity is dose related. They include a number of lesions such as erythema, subcutaneous fibrosis, pigmentation abnormalities, epilation, moist desquamation, and even self-mutilation of the lesion areas if care is not taken. Pain management strategies should focus on pain relief for these lesions, and every effort should be made to provide padded and careful positioning to avoid the development of decubitus ulcers. Special care should be taken to avoid burning lesions by the warming devices in those areas that have radiation side effects.

Ophthalmological consequences are dose related and vary in severity depending on the proximity of

the eyes to the radiation field. Every effort is usually made to keep the eyes out of the radiation field; however, depending on the location of the tumor, it is not always possible. Acute effects include blepharitis, blepharospasm, conjunctivitis and keratoconjunctivitis sicca (KCS), and ulceration. Care must be taken in providing an excellent lubrication of the eyes during the anesthetic period in those patients with KCS.

## Cancer pain

Pain is not just a sensation but rather an "experience" that includes both sensory-discriminative and motivational-affective components. Cancer-related pain results from one or more of the following: (i) tumor-related pain from direct invasion of different organs, bone, and nerves,[100,101], (ii) treatment-related pain after surgical intervention, chemotherapy, or radiation therapy,[102] (iii) indirect etiologies including metabolic imbalances due to PNS, vascular obstruction and by secondary infection, and/or (iv) unrelated factors associated with inactivity and deconditioning.[103] Combinations of these different etiologies result in complex pain patterns that are difficult to accurately diagnose in the veterinary cancer patient. In addition, processes related to chronification of pain such as hyperalgesia, central sensitization, synaptic remodeling, novel gene expression, and behavioral adjustment develop rapidly after persistent tissue injury, making pain management complex and challenging.[104,105]

### Pain pathophysiology

Tumor-associated pain can be either neuropathic, nociceptive, or a combination of the two. Neuropathic pain is related to central or peripheral neural tissue lesions and is characterized by aberrant somatosensory processing[101]. Nociceptive pain is associated with unhealed injury to either visceral or somatic tissues and can be dull and diffused (visceral or deep somatic) or sharp, pricking, and well localized (superficial somatic). Neuropathic pain in cancer patients is very complex, as tumor involvement of the peripheral nervous system presents many different clinical manifestations that may range from local invasion or compression of nerves to direct infiltration or perineural spread. Some of these lesions may also be associated with inflammatory changes that may lead to additional pain. The pathophysiologic mechanism underlying nerve infiltration or compression includes reparative and reactive biochemical changes that affect dendrites, soma, and axons of the entire primary afferent neuron so that it will eventually lose its neuropeptides and atrophy and degenerate.[106,107] In addition, tumors contain neovascular and inflammatory cells that sensitize or directly or indirectly (through tissue acidosis) excite the nociceptors of primary afferent neurons.[108]

Following repeated stimulation at both peripheral and central levels, *sensitization* can occur, manifesting as an enhanced response to noxious stimulation or a newly acquired responsiveness to a wider range of stimuli that includes nonnoxious stimuli. *Peripheral sensitization* occurs when nociceptors are (N-methyl-D-aspartate) sensitized. *Central sensitization* occurs when activated NMDA receptors increase excitability of secondary afferent neurons in the dorsal horn. This phenomenon is also known as "central wind-up" and has two main consequences as follows: (i) pain is more difficult to manage; larger doses and multiple drugs need to be administered, and (ii) owing to the altered interpretation of stimuli, patients perceive heightened levels of pain.

### Pain evaluation

One of the most challenging aspects of the management of the veterinary oncologic patient is related to the identification, evaluation, and quantification of pain because in veterinary patients, unlike humans, self-report is not an option. In addition, the tolerance of pain varies greatly from one individual to another, and the innate ability of animals to mask significant disease and pain on certain occasions complicates things further. Therefore, in veterinary medicine, the recognition of pain relies heavily on the interpretation of the animal's behavior by an observer, as well as the physiological responses. Although behavioral changes vary between species, a number of changes have been identified and are used in a vigorously validated animal pain scoring system for hospitalized patients called the Glasgow Composite Measure Pain Scale (GCMP). It includes the assessment of spontaneous and evoked behaviors, interactions with the animal, and clinical observations. A modified shorter version, the Short Form of the Glasgow Composite Pain Scale (Figure 15.5), was developed that should only take a few minutes to perform.[109]

Analgesia should never be withheld because of the difficulty recognizing pain in an animal. Both clinicians and technicians must be proactive in looking

**S**HORT **F**ORM OF THE **G**LASGOW **C**OMPOSITE **M**EASURE **P**AIN **S**CALE

**Dog's name** _____

**Hospital Number** _____ **Date** / / **Time**

**Surgery** Yes/No (delete as appropriate)

**Procedure or Condition** _____

*In the sections below please circle the appropriate score in each list and sum these to give the total score.*

**A. Look at dog in Kennel**

*Is the dog?*

| (i) | | (ii) | |
|---|---|---|---|
| Quiet | 0 | Ignoring any wound or painful area | 0 |
| Crying or whimpering | 1 | Looking at wound or painful area | 1 |
| Groaning | 2 | Licking wound or painful area | 2 |
| Screaming | 3 | Rubbing wound or painful area | 3 |
| | | Chewing wound or painful area | 4 |

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
*Please tick if this is the case* ☐ then proceed to **C**.

**B. Put lead on dog and lead out of the Kennel.**

*When the dog rises/walks is it?*

| (iii) | |
|---|---|
| Normal | 0 |
| Lame | 1 |
| Slow or reluctant | 2 |
| Stiff | 3 |
| It refuses to move | 4 |

**C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.**

*Does it?*

| (iv) | |
|---|---|
| Do nothing | 0 |
| Look round | 1 |
| Flinch | 2 |
| Growl or guard area | 3 |
| Snap | 4 |
| Cry | 5 |

**D. Overall**

| *Is the dog?* (v) | | *Is the dog?* (vi) | |
|---|---|---|---|
| Happy and content or happy and buncy | 0 | Comfortable | 0 |
| Quiet | 1 | Unsettled | 1 |
| Indifferent or non-responsive to surroundings | 2 | Restless | 2 |
| Nervous or anxious or fearful | 3 | Hunched or tense | 3 |
| Depressed or non-responsive to stimulation | 4 | Rigid | 4 |

**Total Score (i+ii+iii+iv+v+Vi) =** _____



**Figure 15.5** The short form composite measure pain score (CMPS-SF) can be applied quickly and reliably in a clinical setting and has been designed as a clinical decision-making tool, which was developed for dogs in acute pain. It includes 30 descriptor options within six behavioral categories, including mobility. Within each category, the descriptors are ranked numerically according to their associated pain severity, and the person carrying out the assessment chooses the descriptor within each category which best fits the dog's behavior/condition. It is important to carry out the assessment procedure as described in the questionnaire, following the protocol closely. The pain score is the sum of the rank scores. The maximum score for the six categories is 24 or 20 if mobility is impossible to assess. The total CMPS-SF score has been shown to be a useful indicator of analgesic requirement, and the recommended analgesic intervention level is 6/24 or 5/20.[109] Source: Adapted with permission from Reference 109.

for signs of pain in patients, and if in doubt, then administering analgesia and assessing response to treatment is recommended. Moreover, if a type of tumor and/or its location are considered to be painful in humans, it is appropriate to assume that it is so in animals as well. Since pain is not a static process, pain assessment should be performed before a procedure, and frequent postprocedure assessments are necessary, including home assessments. In addition, the behaviors and interactions listed in the GCMP will obviously vary with the nature and temperament of the animal.

During the past decades, many efforts have been devoted to the assessment of quality of life in human patients, and a number of methods have been developed and validated in clinical trials. However, validated and standardized criteria for measuring quality of life in animals are rare. Any assessment of the quality of life of an animal must come indirectly from a proxy informant, most commonly, the owner. In 2005, Yazbek and Fantoni[110] validated a health-related quality-of-life scale for dogs with signs of pain secondary to cancer, which can be used to evaluate the cancer management plan (Table 15.4).

## Specific pain characteristics

Tumor pain characteristics differ according to the type and stage of tumor development.[101] Osseous tumor infiltration is the most common cause of pain in oncologic patients (Figure 15.6).

The pathophysiologic pain mechanisms elicited by infiltrative bone or bone marrow tumors are associated with lesions causing periosteal elevation, release of chemical mediators that sensitize nociceptors, and increased intraosseous pressure or loss of stability. Nociceptive pain originates from nociceptors located not only in the bone in itself, but also in the bone marrow and in the periosteum.

Tumors of encapsulated organs such as kidneys, spleen, liver, or brain can enlarge the organ to several times the organ's normal size, and the organ capsule grows less rapidly than the tumor (Figure 15.7).

Pain ensues from increased intracapsular pressure, direct capsule infiltration, or from traction or pressure on the tissue suspending the organ.

Tumors and metastases in digestive and urogenital hollow organs are frequently painful (Figure 15.8).

Pain results from intestinal dilation, motility disorders, ulcerations, and blood flow impairment. Pain in

**Table 15.4** Questionnaire for evaluating health-related quality of life in dogs with signs of pain secondary to cancer.

| Questionnaire |
|---|
| **How much do you think that the disease is disturbing your dog's quality of life?** |
| Very much (0) |
| Much (1) |
| A little (2) |
| Not at all (3) |
| **Does your dog still do what it likes (eg, play or go for a walk)?** |
| No (0) |
| Rarely (1) |
| Frequently (2) |
| In a normal way (3) |
| **How is your dog's mood?** |
| Totally altered (0) |
| Some episodes of alteration (1) |
| Changed a little bit (2) |
| Normal (3) |
| **Does your dog keep its hygienic habits (ie, does your dog clean itself?)** |
| No (0) |
| Rarely (1) |
| Less than before (2) |
| Yes (3) |
| **How often do you think that your dog feels pain?** |
| All the time (0) |
| Frequently (1) |
| Rarely (2) |
| Never (3) |
| **Does your dog have an appetite?** |
| No (0) |
| Only eats when forced; will eat more of what it likes (1) |
| Little (2) |
| Normal (3) |
| **Does your dog get tired easily?** |
| Yes, always (0) |
| Frequently (1) |
| Rarely (2) |
| No (3) |
| **How is your dog sleeping?** |
| Very badly; not sleeping at all (0) |
| Badly (1) |
| Almost normally (2) |
| Normally (3) |
| **How often does your dog vomit?** |
| Always (0) |
| Frequently (1) |
| Rarely (2) |
| Never (3) |

(*continued*)

**Table 15.4** (*Continued*)

| Questionnaire |
|---|
| **How are the intestines of your dog functioning?** |
| Very Badly (0) |
| Badly (1) |
| Almost normally (2) |
| Normally (3) |
| **Is your dog able to position itself to defecate and urinate?** |
| Never (0) |
| Rarely (1) |
| Sometimes (2) |
| Urinates and defecates normally (3) |
| **How much attention is your dog giving to the family?** |
| Indifferent (0) |
| Little attention (1) |
| Increased attention; the dog is needy (2) |
| Has not changed (3) |

Scores (values in parentheses) for all 12 questions were summed to determine the health-related quality of life score. Possible scores ranged from 0 to 36.[110] Adapted with permission.

urogenital organs may be caused by arteritis, perineural tumor infiltration, or perineural inflammatory reactions.

Solid organs such as the pancreas suffer specific pain symptoms subsequent to tumor-induced necrosis that results in autodigestive pancreatitis. The autodigestion most likely results from tumorous destruction of the parenchyma, as well as from tumor infiltration and stenosis of the excretory ducts.

Tumor infiltration of soft tissues elicits pain by compressing individual nerves and plexus, as well as by affecting organs that are responsible of the patient's movement, such as tendons or muscles (Figure 15.9).

Infiltration of the interstitium and destruction of lymphatic vessels, nerves, and blood vessels prevent these organs from functioning normally.

Tumor infiltration and inflammation of serous mucosa also cause pain. Although pleural carcinomas do not usually cause pain (most likely because of the development of pleural effusion that prevents the pleurae from rubbing against each other), peritoneal carcinosis does. Pain results either from direct contact of the metastases with peripheral nerves or from the inflammatory reaction resulting from tumor-induced perforation or penetration of an abdominal hollow organ.

Peripheral nerves pain usually arises because of entrapment of individual nerves and plexus by tumor growth. However, pain can also result as tumor infiltration causes the neural cleft to widen, and infiltration of the tumor into the nerve takes place.

Blood and lymphatic vessels are invaded as malignant neoplasias begin to metastasize. Although small vessel infiltration and obstruction are rarely painful, when large veins are affected, edema and pain in the affected area of venous drainage are often present (Figure 15.10).

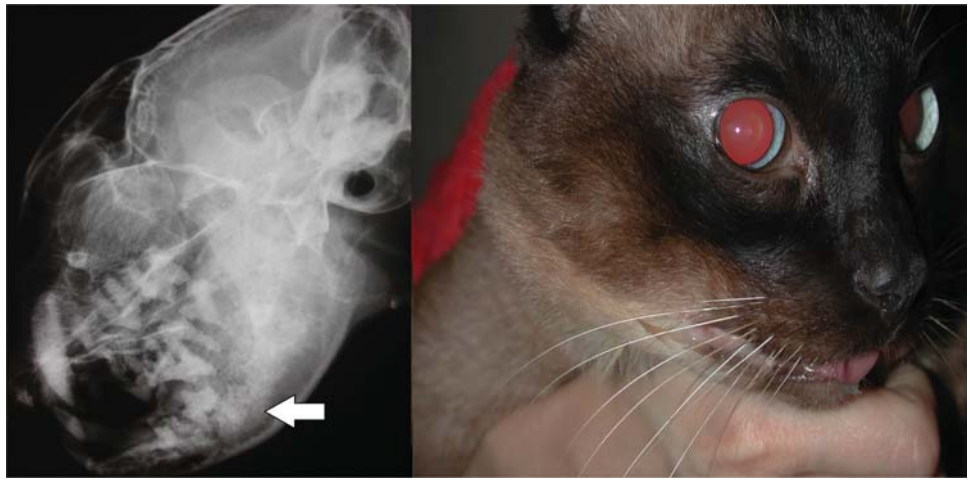

**Figure 15.6** Osteosarcoma in the mandible of a feline patient (arrow on radiograph, A). Source: Photo courtesy of Dr. Ana Ríos.

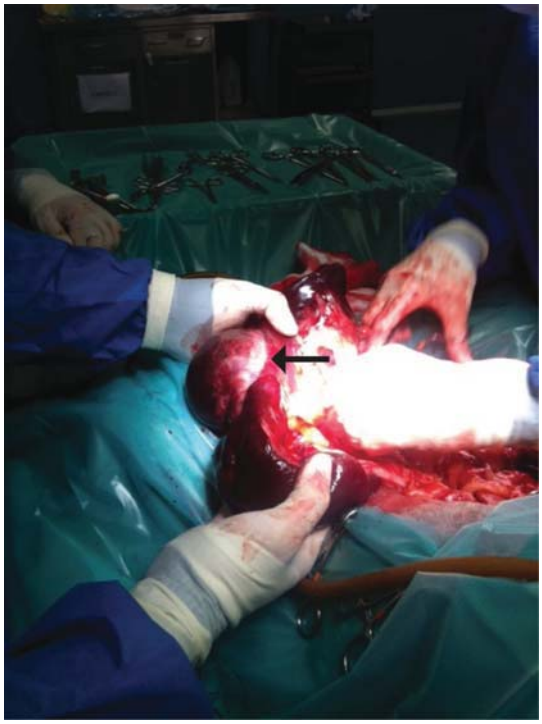

**Figure 15.7** Splenic hemangiosarcoma in a canine patient (arrow).

## Cancer pain management

Treatment of acute pain should be a priority, not only for obvious ethical reasons, but also to minimize its negative influence on postoperative morbidity and mortality (such as decreased rate of healing, hypertension, tachycardia, or ileus). Treating perioperative pain significantly reduces the tumor-promoting effects of surgery[111,112], as surgery in itself suppresses NK cell activity, which may enhance metastasis. Although drugs are the mainstay of cancer pain management, nonpharmacologic interventions are becoming increasingly popular. Overall cancer pain management therapeutic interventions may be divided into two categories as follows: pharmacologic and nonpharmacologic.

### Pharmacologic interventions

Multimodal analgesia should be used to alter more than one point along the nociceptive pathway, including nociceptive transduction, transmission to the CNS, modulation within the CNS, or perception at the cortex. This analgesic approach reduces individual drug doses, thereby reducing the potential for adverse effects. The use of pre-emptive analgesia should also

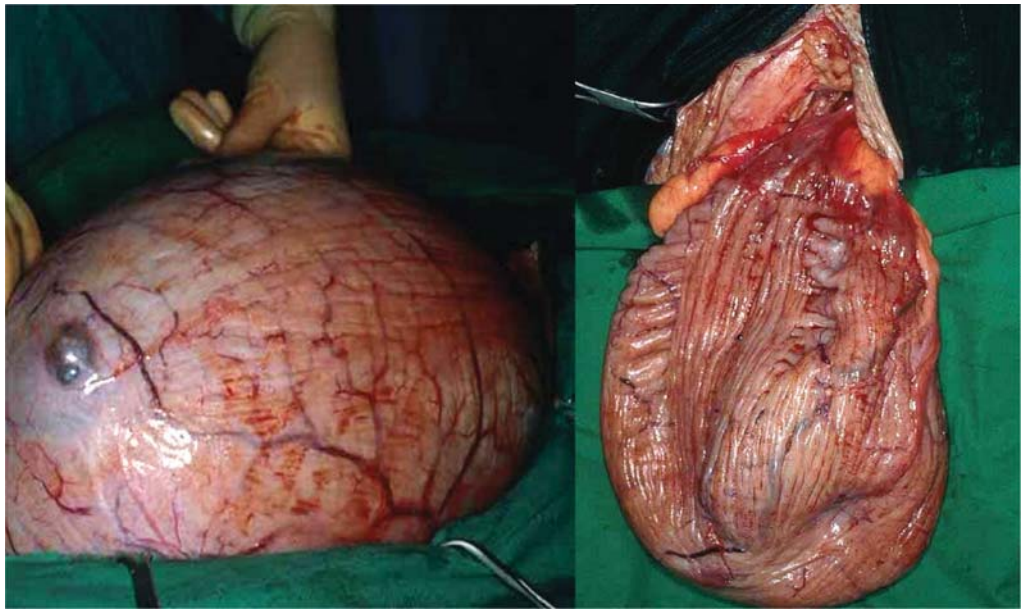

**Figure 15.8** Transitional cell carcinoma invading the entire bladder of a canine patient. Source: Photo courtesy of Dr. Hilde de Rooster and Alejandro Rubio.

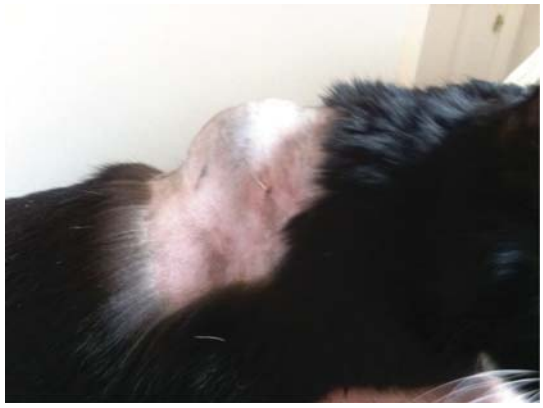

**Figure 15.9** Fibrosarcoma in the interscapular region of a feline patient.

be used to reduce central hypersensitivity or "central wind-up". In addition, providing effective multimodal and pre-emptive analgesia will not only reduce postoperative pain, but also form part of a balanced anesthesia plan that may allow significant reductions in anesthetic agent requirements. All of these interventions may ultimately lead to a smoother plane of anesthesia and optimal recovery characteristics.

The first line of analgesia should be the use of "traditional analgesics" such as opioids, NSAIDs, and local anesthetic techniques. Recently, other "adjunctive analgesics" such as NMDA antagonists, α-2 adrenergic agonists, bisphosphonates, and anticonvulsant drugs have gained popularity. The World Health Organization (WHO) has outlined a ladder or general approach to cancer pain management in humans on the basis of these drug groups: nonopioid, opioids for mild to moderate pain, opioids for moderate to severe pain, and adjuvant drugs (Figure 15.11).[113] However, there are two potential problems with the use of the WHO analgesic ladder in veterinary medicine. Firstly, there is a lack of information on which drugs are most effective on which type of cancer pain in veterinary patients. Secondly, this approach may not be appropriate for many veterinary cancer patients, as they present at an already advanced stage of disease and are already in a moderate to severe state of pain. Once pain has been allowed to become chronic, central sensitization

**Figure 15.10** Facial edema as part of superior vena cava syndrome in two canine patients. Source: Photos courtesy of Dr. Noemi del Castillo and Sonia Fernandez.

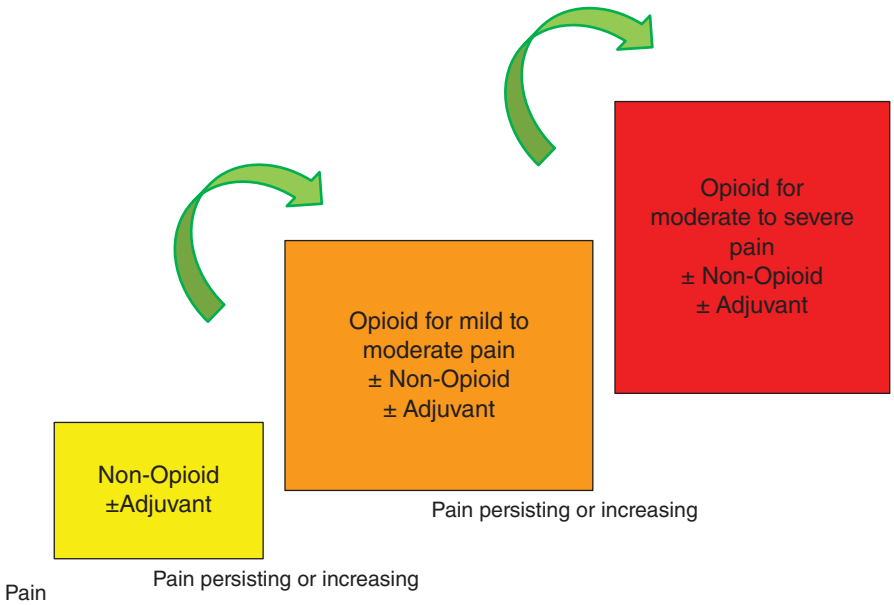


**Figure 15.11** WHO Analgesic ladder 1996.[113] Source: Adapted with permission from Reference 113.

and hyperalgesic phenomena are already taking place. In order to manage this very complex type of pain, an analgesic reverse pyramid approach may be considered, which relies on the use of multiple different classes of drugs until the intensity of pain decreases, at which point the amounts and types of drugs may be minimized.

## Opioids

Opioids such as morphine, hydromorphone, methadone, fentanyl, remifentanil, buprenorphine, or butorphanol exert their analgesic effects and their side effects through actions on the different opioid receptors (μ, δ, and κ). The most frequent side effects of opioids include dose- and drug-dependent cardiovascular depression because of a reduction in sympathetic tone (different degrees of bradycardia, although no direct systemic blood pressure or myocardial effects are commonly seen).[19] However, vasodilation from histamine release can also be observed (mainly after morphine and meperidine IV administration).[114] Dose- and drug-dependent respiratory depression, as well as panting, may be described after opioid administration. Ileus decreases gastric emptying time, and constipation may be observed, as well as short-term urinary retention. Dysphoria may occur after opioid administration. However, it is infrequent if administered to animals in pain or in combination with sedatives or tranquilizers. Finally, hypothermia and/or panting are usually observed, although cats may exhibit hyperthermia after opioid administration.

All the previously mentioned parenteral opioids may be administered by an intermittent IV or IM route.[19] However, with intermittent dosing, patients often become painful before their subsequent dose and then are extremely sedated after dosing. Alternatively, CRIs of a shorter acting, potent opioid analgesic agent can be used (e.g. fentanyl, alfentanil and remifentanil). Fentanyl administered as a CRI provides constant and reliable plasma levels that provide excellent analgesia and allow sparing of inhalant agent, therefore reducing its systemic adverse effects.[115–119] Fentanyl may also provide postoperative analgesia with constant and vigilant monitoring for respiratory depression. IV morphine is efficacious, although histamine release may limit its use in MCT.[114] Fentanyl transdermal patches provide another route of opioid administration, and analgesia can be provided for several days.[120–122] However, the degree of analgesia can be unpredictable, especially in cats, probably because of failure of patch application or inappropriate dosing, and frequent patient monitoring is essential.[123] Since plasma levels do not

reach peak values until 18–24 h after placement, additional analgesia should be provided in the immediate postoperative period. Fentanyl patches are a suitable option for patients who may need prolonged opioid administration and for those who do not tolerate oral medication. Fentanyl patches should not be prescribed when young children are in the household because potential removal and ingestion is a concern.[124,125] Finally, opioids such as morphine and fentanyl, have been administered epidurally as a means of prolonged perioperative analgesia.[126–129] With the placement of an epidural catheter, epidural opioids can be administered for days to weeks in patients suffering from peritoneal or pancreatic pain, as well as following amputations.

### Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs such as meloxicam or carprofen are used widely to treat mild to moderate pain associated with inflammation and also to reduce opioid consumption. However, they possess a much lower therapeutic index than opioids and are not reversible. NSAIDs inhibit cyclooxygenase (COX) enzymes, thereby preventing the production of prostaglandins (PG), thromboxanes, and prostacyclin from membrane phospholipids. However, the isoenzyme COX-2 is also related to the pathogenesis and progression of certain types of tumors. The synthesis of $PGE_2$ by COX-2 has been associated with the promotion of tumor genesis[130], and COX-2 overexpression inhibits apoptosis; facilitates the adhesion, increasing the invasiveness of tumor cells; increases cell growth; suppresses the immune system; and enhances angiogenesis.[131] Overexpression of COX-2 has been implicated in a number of canine carcinomas such as those affecting the bladder, kidneys, mammary tissues, intestines, squamous cell carcinoma, and some sarcomas such as osteosarcoma.[132–136] As a result, the use of selective COX-2 inhibitors is widely spread not only for their analgesic effects in patients with these types of tumors, but also for their beneficial effects on the tumor therapy.[137–149]

The most common side effects of NSAIDs include impairment of gastrointestinal protection, inhibition of platelet aggregation and vasoconstriction, and impairment of renal perfusion. Oncologic patients are at greater risk of toxic effects because of their pre-existing renal disease or the concurrent administration of nephrotoxic oncologic therapies; the use of NSAIDs is not recommended in patients, regardless of their tumor, who present gastrointestinal disorders, coagulopathies, impaired renal, and hepatic function; those who are dehydrated or hypovolemic; and, finally, those who are already receiving other NSAIDs or corticosteroids. In addition, it should be noted that cats have longer and inconsistent rates of metabolism and excretion of NSAIDs compared to other species (particularly through glucuronidation), and chronic dosing (longer than 5 days) is likely to be associated with greater risks in cats than other species and therefore should be used cautiously. Renal monitoring of the patient who is receiving NSAIDs-based therapy is warranted. The owner should be informed of the potential for toxicity, as well as instructed for monitoring of adverse events (depression, lethargy, vomiting, melena, and polyuria). Baseline blood work and urinalyses should also be performed at the beginning of therapy and repeated every 2–4 weeks, up to 1–4 months depending on the individual patient and evolution of the case.

### Local anesthetics

Local anesthesia is the only effective way of providing complete analgesia, as the main mechanism of action is via blockage of sodium channels. Perineural administration completely blocks transmission of nociception, thereby minimizing central sensitization for the duration of block. Local anesthetics can be used by topical application, local infiltration, IV and intrapleural administration, body cavity instillation, wound soaker catheters, transdermal patches, and epidural/extradural catheters. Neurologic side effects are biphasic, first shown as excitatory signs (tremors, visual disturbances, and, eventually, seizures) and then as signs of neurologic depression (coma and apnea). Cardiovascular side effects include direct myocardial depression from blockade of cardiac sodium channels.

The use of topical local anesthetics as a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA) cream has been suggested to minimize pain and discomfort during venipuncture.[150] Local anesthetics may be deposited directly over selected nerves before transection during surgical procedures. Ring blocks around the distal end of affected limbs or around a mass that needs to be excised may also be performed through infiltration of tissues. Ideally, the infiltration should be performed before surgery; however, splash blocks can also be employed while closing surgical wounds,

applying the local anesthetic at various levels during wound closure. Finally, administration of the local anesthetic adjacent to the wound during closure has been shown to reduce pain postoperatively and opioid requirements after laparotomy.[151]

Wound diffusion catheters (also known as wound soaker catheters) may be used to provide analgesia to large surgical wounds (e.g. amputations, tumor resection, and mastectomies; Figure 15.12). They are usually well tolerated, and if correctly placed, they may not only improve patient comfort, but also significantly decrease opioid requirements.

The incidence of wound infections or breakdown appears to be the same as in dogs where wound soaker catheters are not placed.[152] Occasionally, catheters may fail to provide analgesia for the full extent of the surgical site, and this may be due to uneven distribution of local anesthetic, incorrect placement, or blockage of the catheter. Local anesthetics may be administered every 6–8 h (1–2 mg kg$^{-1}$ bupivacaine).[152] The catheters can be removed 48 h after placement or remain in place for longer if required.

Local anesthetics may be administered interpleurally to provide analgesia after thoracotomy and to manage pain in a variety of pleural conditions. After drainage of the chest is performed, a 0.25% solution of bupivacaine (1.5 mg kg$^{-1}$) may be slowly administered through the drain (Figure 15.13).

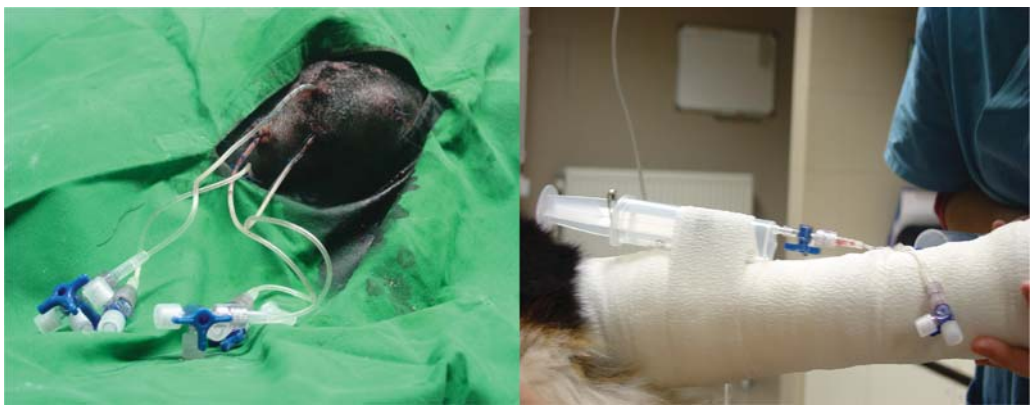

**Figure 15.12** Surgical placement of wound soaker catheter (A) with drainage and analgesic administration through the same soaker catheter (B). Source: Photo courtesy of Dr. Hilde de Rooster and Alejandro Rubio.

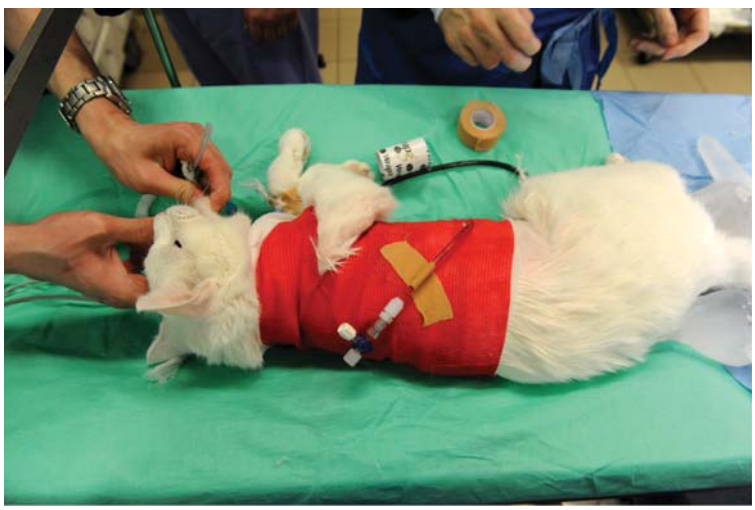

**Figure 15.13** Chest drain and interpleural administration of local anesthetic in a cat. Source: Photo courtesy of Dr. Hilde de Rooster and Alejandro Rubio.

This technique will usually provide up to 6 h of analgesia, while the pleural cavity may still be drained every hour if necessary without affecting the efficacy of analgesia.[153–158]

Local anesthetics may also be administered intraperitoneally. Carpenter et al. (2004) suggested that the combination of intraperitoneal bupivacaine administered preoperatively combined with subcutaneous wound infiltration with bupivacaine postoperatively provided improved analgesia in dogs. Sprayed and injected intraperitoneal bupivacaine relieves postoperative pain behavior and biochemical stress responses after surgery in dogs.[159,160]

Newer techniques such as IV lidocaine infusions are efficacious and safe (in dogs) while decreasing isoflurane minimum alveolar concentration MAC.[161] In addition, longer term epidural analgesia may be preferable for pain management of certain procedures and conditions (e.g. pancreatic pain, extensive hindlimb surgery, and amputations), and an epidural/extradural catheter may be placed to allow repeated administration of local anesthetics (Figure 15.14).

Drugs may be epidurally administered intermittently as a bolus or as an infusion using a syringe pump. Preservative-free morphine 0.1 mg kg$^{-1}$ may be administered every 12–24 h, whereas bupivacaine 0.06–0.12 mg kg$^{-1}$ can be administered intermittently as required. A CRI of morphine at 0.0125 mg kg$^{-1}$ h$^{-1}$ and bupivacaine 0.03 mg kg$^{-1}$ h$^{-1}$ has been reported.[162]

Lidocaine 5% patches may be applied alongside wounds that present allodynia. Studies in both dogs and cats suggest that local skin lidocaine concentrations are high, whereas plasma levels are low, suggesting that the analgesia seen after placement is most likely because of the local effect rather than a systemic effect.[163–166]

### NMDA antagonists

The use of subanesthetic doses of NMDA antagonists such as ketamine and amantadine may reduce the chances of central sensitization developing postoperatively and may also be particularly helpful for the management of pain derived from nerve damage. Side effects of this drug class include cardiovascular stimulation via sympathetic stimulation, increased salivation and respiratory tract secretions, cerebral vasodilation, and elevated systemic blood pressure that lead to significant increases in cerebral blood flow and intracranial pressure. However, at the doses used for analgesia, these effects are minimized.

#### Ketamine

Bolus administration of ketamine and low-dose ketamine infusions for adjunctive analgesia have become a common practice in the perioperative setting (e.g. hemilaminectomies for treatment of Intervertebral disc disease IVDD and amputations). A number of studies have proven the MAC-sparing properties of ketamine; however, only few studies evaluate the analgesic effects of ketamine, which suggests that ketamine decreases postoperative wound hyperalgesia, pain scores, and rescue analgesic requirements.[167–169]

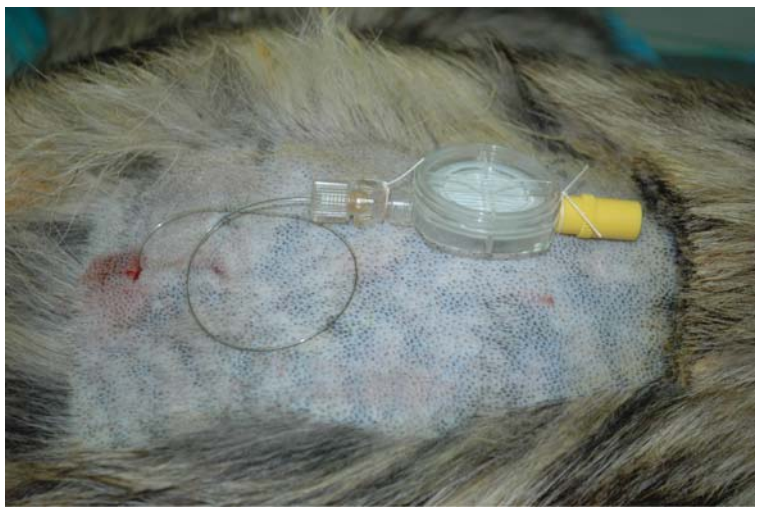

**Figure 15.14** Epidural catheter placement in a cat. Source: Photo courtesy of Dr. Veronica Vieitez.

### Amantadine

Amantadine is an antiviral drug that was originally approved to treat influenza A in people. It is also used clinically to reduce symptoms of Parkinson's disease and other drug-induced extrapyramidal syndromes. Analogous to ketamine, it is an NMDA receptor antagonist. However, it differs from ketamine in that it does not block the flow of current through open channels but stabilizes channels in the closed state. Numerous laboratory animal studies suggest that amantadine's NMDA antagonist activities may make it a useful adjunctive analgesic agent[157,170,171]; there are a limited number of controlled trials documenting its safety and efficacy in dogs and cats. It has been included in a multimodal analgesic regimen for the alleviation of refractory canine osteoarthritis pain, and dogs had activity and lameness scores.[172] Amantadine may come to play a key role in managing chronic pain in dogs in the future, and, as such, it may be an interesting therapeutic option for oncologic patients.

### $\alpha_2$-Adrenergic agonists

$\alpha_2$-Adrenergic receptor agonists such as medetomidine and dexmedetomidine are commonly used as adjunctive analgesics, although they are not considered first-line analgesics. $\alpha_2$-Adrenergic receptors and opioid receptors appear to interact, and coadministration of these two classes of drugs may achieve synergistic analgesic effects. However, the $\alpha_2$-analgesic effect is of shorter duration than the sedative effects.[173,174] They are particularly useful in patients who require anxiolysis in addition to analgesia, as microdoses are administered to patients who are cardiovascularly stable. Side effects include vasoconstriction, decreased cardiac contractility, reflex bradycardia and atrioventricular blocks, nausea and vomiting, polyuria, hyperglycemia, and increased myometrial contractility.

Continuous rate infusions may help manage pain both intraoperatively and postoperatively and are equally effective as morphine CRIs at providing postoperative analgesia, with no clinical adverse reactions.[175] In addition, the incorporation of low-dose medetomidine into an epidural protocol may achieve additive or synergistic analgesic effects when combined with standard doses of opioids or local anesthetics because of actions at spinal $\alpha_2$-receptors.[176–179] In addition to the epidural route, $\alpha_2$-agonists may be administered intra-articularly and perineurally, where they contribute to analgesia by inhibition of norepinephrine release and by enhancing peripheral nerve block intensity.

### Tramadol

Tramadol is a synthetic codeine analog that exerts weak agonist properties at all opioid receptors (particularly at μ receptors). In addition, it stimulates presynaptic serotonin release and inhibits the reuptake of serotonin and noradrenaline.[180] Its analgesic potency is one tenth that of morphine; however, recent studies comparing the effects of IV tramadol and morphine administered before ovariohysterectomy concluded that tramadol was comparable to morphine in its analgesic efficacy for this type of surgical pain.[181,182] Common side effects associated with its administration include sedation and dysphoria (especially in cats), while constipation and respiratory depression are milder than those caused by morphine. Its administration is contraindicated in patients with hepatic insufficiency and in those who are seizure prone (it decreases seizure threshold in humans). Because of its inhibitory effect on 5-hydroxytryptamine uptake, tramadol should not be administered to patients who may have received monoaminoxidase inhibitors, such as selegiline. Its main advantage is that, unlike most opioids, it is not a controlled drug, making it an excellent option for oral pain management at home once the patient is discharged.

### Anticonvulsants

Neuromodulating drugs, such as anticonvulsants, have become the mainstay of neuropathic pain treatment in human patients in the past decades. Both pregabalin and gabapentin share a similar mechanism of action by binding to the $\alpha_2\delta$ subunit of the voltage-gated calcium cannels and inhibiting the release excitatory neurotransmitters involved in pain transmission. Side effects are minimal and limited to mild ataxia and sedation.

### Gabapentin

Although widely used in human medicine,[183–185] only a few investigations have documented its effectiveness to treat chronic neuropathic pain, chronic cancer pain, chronic osteoarthritis pain, and perioperative pain in veterinary medicine.[186–190] Dosing guidelines in veterinary medicine have been largely based on human recommendations despite some key species differences in pharmacokinetics. In dogs, it is known to undergo significant hepatic metabolism to N-methyl-gabapentin

before renal elimination.[189] Gabapentin disposition has not been studied to date in cats. On the basis of anecdotal clinical experience, doses in the range of 3–10 mg kg$^{-1}$ administered orally every 8–12 h are recommended initially, and most regimens typically require significant increases to achieve the desired analgesic effect without excessive sedation.

### Pregabalin

Pregabalin was designed as the developmental successor of gabapentin in order to present a higher potency and a linear pharmacokinetic profile.[191–193] In human medicine, the analgesic efficacy of pregabalin has been extensively studied[141,194–209], and several large clinical trials substantiate its safety and efficacy.[200,203,210,211] Analgesic effects of pregabalin have not been investigated in veterinary species to date, although, at the time of publication, the only pharmacokinetic study in dogs suggests that oral administration of pregabalin at 4 mg kg$^{-1}$ every 12 h is appropriate.[193]

### Tricyclic antidepressants

Tricyclic antidepressants, such as amitriptyline, clomipramine, and imipramine, block the reuptake of norepinephrine and serotonin in the central nervous system. Their use in human medicine has been described for the treatment of neuropathic and chronic pain at doses considerably lower than those used to treat depression. Although there are no studies in the veterinary field that can support their use to this extent, clinical experience by many veterinarians substantiates their analgesic use in small animals.

### Biphosphonates

Biphosphonates such as pamidronate and zoledronate accumulate on bone surfaces and inhibit osteoclast-induced resorption, favoring bone formation. They decrease pain and potentially increase survival rates in dogs with osteosarcoma[212] and may aid in the treatment of malignant hypercalcemia and inhibition of bone metastasis.[61,213–215] They are safe and efficacious in dogs.[216–220] Currently, the recommended pamidronate protocol for dogs is 1–2 mg kg$^{-1}$ administered IV over 2 h in 250 ml of 0.9% NaCl administered every 21–28 days. There is also a number of studies investigating clinical effects of zoledronate, and they have all demonstrated significant inhibition of homeostatic osteolytic activity associated with single-dose IV administration (0.25 mg kg$^{-1}$).[221–227] Although zoledronate may possess similar bone analgesic properties as pamidronate, its use in veterinary oncology is limited because of the substantial cost associated with the drug. On the basis of these initial studies, it seems that further investigation into the efficacy of IV bisphosphonates in canine oncologic patients is clearly warranted.

### Transdermal applications

Formulation of transdermal liposomal absorptive gels, creams, and sprays containing a wide range of agents such as morphine, methadone, lidocaine, ketamine, or gabapentin and capsaicin may help to desensitize the innervation of painful areas or may allow the oral absorption of substances that may otherwise not be orally bioavailable.[228,229] Evidence supporting or denying efficacy of these treatments is lacking; however, reports of anecdotal successful use encourage their use.

## Nonpharmacologic interventions

### Analgesic radiation therapy

Fractionated radiation therapy is used to palliate pain, particularly in those patients with bone metastases.[230] Traditionally, the analgesic effects of radiation therapy were believed to derive from the elimination of tumoral cells and the reduction of tumor size. However, effects such as inhibition of prostaglandin-secreting cells, moderate bone healing and activation, and induction of transforming growth factor-beta isoforms may all account for the analgesic effects observed.[231]

### Neurolysis

Physical destruction of nerve roots or major nerve trunks in an effort to alleviate pain in limited areas of the body may be attempted. Neurolysis may be achieved by perineural, intrathecal, or epidural administration of chemical neurolytic agents, cryoneurolysis, or radiofrequency blockade. The last two techniques are the most commonly used in the United States for human patients.[232] Cryoneurolysis involves the destruction of the nerve by the application of extreme cold, whereas radiofrequency blockade requires the insertion of a small insulated electrode with a noninsulated tip near a nerve that innervates the painful area to treat. Both techniques may require a test block to guarantee that motor function is not being altered. Both provide months of analgesia to an area; however, they are not

devoid of adverse effects such as neuroma formation, neuritis of adjacent nerves, or regrowth of nerves.[233] In veterinary medicine, the fact that patients cannot verbally indicate the exact location of the painful area may lead to significant difficulties to identify motor and sympathetic from sensory function correctly.

### Surgical analgesic techniques

A number of different surgical techniques are currently being used in human medicine in an effort to alleviate pain in certain patients with specific types of tumors, particularly those involving osseous tumors and metastases affecting vertebrae. Kyphoplasty and percutaneous vertebroplasty are performed in human medicine to stabilize fractures.[234] More extreme surgical options include neuroablative techniques that can be both peripheral (neurectomy, dorsal rhizotomy, or sympathectomy) and central (myelotomy, cordotomy, or even hypophysectomy and thalamotomy).[235] Finally, technologically sophisticated surgical therapies such as gamma knife and stereotactic radiofrequency surgery will hopefully become available in veterinary medicine in the future.

### Nursing care of hospitalized patients

Pain is a complex phenomenon that not only has a physical dimension, but also includes many psychological components. It is well known that anxiety and fear may exacerbate pain and vice versa; therefore, taking care of an animal's perceived emotional needs and comfort may reduce stress and, consequently, pain levels. Patients with special needs, such as deaf and blind animals, develop greater degrees of stress because of their disabilities. Special measures are warranted to minimize extra stress. In addition, animals' perception of pain may be affected by environmental factors, therefore rendering their surrounding more familiar by the presence of a favorite toy or blanket may help decreasing stress. In the feline patient, being hospitalized in a ward of exclusive feline use has proven to be extremely helpful in reducing anxiety and fear. What is more, some animals are likely to recover better in a quiet environment, whereas others are best distracted by exposure to a more active area of the hospital. Owner visits may also be planned carefully, as some animals may benefit hugely from the time spent with their families, whereas it may be a source of anxiety and distress for others. Simple changes in the daily plan of nursing care and interventions may play a fundamental role in a comprehensive pain management plan. Venipuncture and injections are painful; therefore, planning and coordination of treatments and laboratory tests should be performed in order to minimize the total number of painful events. In fact, the establishment of patient protective policies such a "two-stick rule" (venipuncture and/or IV catheter placement should only be attempted a maximum of two times by any individual) may be an easy and effective measure. Likewise, grouping treatments in order to allow for longer periods of undisturbed rest and sleep should be considered. The possibility of dimming the lights during the night period has proven to allow animals for better rest and sleep. In addition, every effort should be made so that patients do not associate human contact with unpleasant and stressful experiences. Therefore, a "three-one rule" policy may be instituted and have each patient who is exposed to one uncomfortable situation or invasive procedure to be immediately exposed to three positive experiences such as feeding, petting, and grooming. Other simple nursing care steps may also allow the animal to feel more comfortable. For example, the bladder should be emptied at the end of surgery if possible, and if recumbency is predicted, an indwelling urinary catheter should be placed at surgery. Finally, cage preparation and maintenance are key factors in contributing to the patient comfort. Apart from obvious measures such as keeping the cage clean and dry, providing a cage of appropriate size and padding, and careful positioning of the animal to reduce pressure on painful areas, keeping in mind patient special requirements owing to other comorbidities such as arthritis is also important. Ideally, the patient's cage should be designated as a safe zone, and, as such, all procedures considered noxious should be performed in a different area (whenever safe movement and transport are possible), so that the animal feels comfortable and safe when in the cage.

## General anesthesia

Cancer is a major cause of morbidity and mortality in animals of all ages in the present day society, and veterinarians are expected to provide advanced and compassionate clinical management of oncologic patients on a daily basis. A fundamental component

of this clinical care relies on their anesthetic/analgesic management because it is often required to perform a wide range of diagnostic, therapeutic, and palliative procedures.

Preanesthetic evaluation of these patients should be thorough to rule out major complications if not corrected or stabilized in the preanesthetic period. Hematological evaluations as well as comprehensive coagulation tests are important because alterations such as neutropenia, anemia, erythrocytosis, thrombocytopenia, thrombocyte hyperaggregability, and coagulation disorders could be present in some oncologic patients. Likewise, dangerous derangements in fundamental biochemical parameters such as calcium, glucose, total proteins, or renal parameters could also be present. For this reason, a meticulous evaluation of a comprehensive biochemical analysis is also warranted. The preanesthetic evaluation should also include a detailed physical examination to assess BCS, hydration status, or the existence of oral mucositis or KCS if the patient is receiving radiation therapy. A comprehensive evaluation of thoracic radiographs (three views), abdominal ultrasound, and echocardiographs is recommended. Preanesthetic stabilization of any identified derangements is probably one of the most critical steps in the anesthetic/analgesic management of these patients. Once stabilization of life-threatening tumor- or treatment-related derangements has been achieved, any underlying pathophysiologic changes need to be individually considered, and, as a result, there is no single anesthetic protocol that can be recommended for all oncologic patients.

Premedications should include short-acting or reversible sedatives such as α2-adrenergic agonists, opioids (discussed previously), or (gamma-aminobutyric acid) GABA receptor agonists such as midazolam. Although midazolam is not a very reliable sedative in dogs and cats when administered alone, it has proven useful in older animals when combined with opioids or other sedatives. It also provides excellent muscle relaxations. However, it is its very favorable cardiovascular profile that makes it an excellent choice to obtain sedation in older or critically ill animals. Since a low fat to body mass ratio and a low muscle to body mass ratio are commonly found in patients with CACS, these patients may have higher circulating levels of free-fraction or active drugs that could result in overdose, prolonged, and/or rough recoveries. In addition, many patients with cancer require general anesthesia for short procedures on a daily basis for a period of time (such as radiation therapy sessions), and short-acting or reversible drugs are warranted. Acepromazine is frequently avoided in those patients with thrombocytopenia or coagulation disorders, as it may impair platelet aggregation[236] and has a long duration of action. In addition to the aforementioned opioids, opioids such as methadone or butorphanol may be acceptable options, as they are devoid of severe hemodynamic or gastrointestinal side effects, whereas they still provide mild to moderate sedation and analgesia. The use of butorphanol is probably not the option for the treatment of severely painful conditions, as it is an agonist/antagonist opioid whose agonist actions are exerted on κ receptors, whereas antagonist ones are exerted on μ receptors. However, the sedation obtained after butorphanol administration is probably more intense compared to pure μ agonist opioids, whereas the intensity of its cardiovascular and gastrointestinal side effects is significantly milder.

Propofol is an excellent choice for anesthetic induction because it is short-acting and has at least some extrahepatic metabolism with very little accumulation when moderate induction doses are used (2–8 $mg\,kg^{-1}$ IV). However, repeated use of propofol should be avoided in those cats that may need repeated episodes of general anesthesia, as its use has been associated with oxidative hematological lesions (characterized by increased production of Heinz bodies), as well as increased recovery times from anesthesia and anorexia.[237] Ultrashort-acting barbiturates such as thiopental could also be administered with caution. Barbiturates are highly protein bound and lipid soluble; therefore, changes in the patient's fat to body ratio and protein levels may result in increased plasma levels, predisposing to relative overdosing and prolonged recoveries. Ketamine, alfaxalone, and etomidate are also suitable options for anesthetic induction as long as there are no specific contraindications.

Any of the currently used inhalant agents (isoflurane, sevoflurane, and desflurane) may be used for anesthetic maintenance, and there are no clear advantages of one over the others. In addition, total intravenous administration (TIVA) of injectable agents such as propofol (0.3–0.7 $mg\,kg^{-1}\,min^{-1}$ IV) or alfaxalone (0.1 $mg\,kg^{-1}\,min^{-1}$ IV) can also be used depending on

disease pathophysiology and the therapeutic or diagnostic procedure to be performed. Intensive and continuous anesthetic monitoring of patients during anesthesia is necessary. As such, continuous electrocardigraphy (ECG), pulseoxyemtry ($SpO_2$), capnography ($EtCO_2$), and temperature and direct or indirect blood pressure monitoring should always be implemented. In certain patients, blood gas analysis may also be necessary in order to monitor partial pressures of $O_2$ and $CO_2$ in arterial blood. Cachectic patients may be more prone to hypothermia during the perianesthetic period; active efforts to decrease heat loss are warranted (i.e. insulation from cold surfaces, careful wrapping, use of heat and moisture exchange filters, and warm water blankets).

## Palliative care

Owners must fully understand that the word "palliation" means treatment for comfort and supportive care and not cure. Often, palliation is clearly the preferred mode of care for certain oncologic patients instead of curative treatment or euthanasia. If an oncologic patient is in the advanced or terminal stage of cancer at diagnosis, various levels of palliative care and/or hospice care (Pawspice) should be recommended as highly effective priority options.

A number of nutraceutical, nutritional, and botanical suplemental therapies can be considered as part of a palliative approach to the care of the oncologic patient. Omega fatty acids such as eicosapentaenoic and docosahexaenoic acids in the form of fish oils have been proven to be effective therapeutic options in a number of neoplasias in dogs, as well as to decrease joint inflammation.[238] Polysulphated glycosaminoglycans modulate matrix metalloproteinase activity, which is in turn related to tumor growth and connective tissue invasion.[239,240] However, many questions arise from the use of nutraceuticals, as many of them exert strong antioxidant activity, and very little evidence exists on its actions on the effectiveness of chemotherapeutic agent that may require a pro-oxidative environment.[241,242] Botanical medicines such as green tea and garlic polyphenols have proven anticarcinogenic effects in animal studies; however, other herbal supplements such as grape seed extract, avocado oils, boswelia, or rosemary seed extract neither have been studied in standardized trials nor, therefore, have been approved or controlled by the Food and Drug Administration. Of further concern is the lack of scientific data concerning dosages and dosing regimens specific for animals. In general, botanical supplements and herbal homeopathy need to be carefully considered, and owners need to be closely scrutinized on the list of botanicals administered to their animals, as some of the extracts used may lead to a number of side effects or pharmacologic drug–herb interactions. A number of herbs and their interactions with other herbs, drugs, or treatments are included in Table 15.5.

Another additional method of palliative care in the oncologic patient relies on homeopathic therapy. Strong evidence for its addition to conventional therapies to help relieve symptoms of pain and treatment side effects is lacking in veterinary medicine. However, homeopathy is in general unlikely to harm patients (minor side effects have been described, and no interactions with other drugs have been reported), unless it is wrongly used as a substitute of conventional therapy rather than as a complement. In fact, the main harm it can cause is that derived from discontinuation of conventional therapy.

Acupuncture and complementary medicine may help alleviate tension and create a sense of well-being that offsets pain. Acupuncture sessions not only can be extremely helpful to the patient with cancer, but also may bring comfort to the distressed owner. The empirical principles on which acupuncture is founded are based largely on Traditional Chinese Medicine (TCM). Acupuncture exerts neuromodulation by the insertion of thin, sterile needles into precise anatomic locations, with very minimal side effects. A few considerations need to be taken into account when performing acupuncture in patients with cancer, such as reducing the number of beads and semipermanent needles in coagulopathic or neutropenic animals and avoiding inserting needles in the proximity of the neoplastic tissue. Beneficial effects in humans include reduction of malignant pain as well as phantom limb pain, appetite stimulation, decreased nausea and constipation, and reduced toxic side effects of radiation and chemotherapy (such as gastrointestinal reactions or leukopenia) and, finally, reduction of lymphedema and surgical swelling.

It is a reality that some oncologic patients will not be treated because of owner reluctance, financial constraints, concurrent illness, or a logistical problem. However, care for the well-being of the patient should always remain the first of our concerns. Pawspice is

**Table 15.5** List of anticancer botanical compounds.

| Botanical | Indication | Interactions and adverse effects |
|---|---|---|
| Bromelai (*Ananas comosus*) | Relief of symptoms associated with cancer | Interaction with aspirin<br>Increased risk of bleeding |
| Asian Ginseng (*Panax ginseng*) | Antitumor effects<br>Immunomodulation | Interaction with insulin, oral hypoglycemic medication and warfarin |
| Cat's claw (*Uncaria tomentosa*) | Historically used to treat cancer | Inhibition of cytochrome P450 CYP3A4<br>Inhibition of platelet aggregation |
| Comfrey (*Symphytum officinale*) | Unproven antitumoral effects | Potentiation of microsomal enzyme inducers |
| Essiac tea () | Antitumor effects<br>Immunomodulation | Interaction with cytochrome P450 |
| *Ganoderma lucidum* | Anti-inflammatory effects<br>Tumor inhibition<br>Immunomodulation | Interaction with anticoagulant medications<br>Epistaxis, increased bleeding time |
| Garlic (*Allium sativum*) | Cancer prevention | Interaction with drugs with antiplatelet effects<br>Inhibition cytochrome P450<br>Induction of conjugating enzymes<br>Heinz-body anemia |
| Ginger (*Zingiber officinale*) | Anti-inflammatory effects<br>Antiemetic | Interaction with drugs with antiplatelet effects<br>Bleeding |
| Hoxsey therapy (combination of different preparations and interventions) | Unproven antitumoral effects | Some components cause a decrease in drugs absorption |
| Milk thistle | Anticarcinogenic and antiproliferative effects | Inhibition cytochrome P450<br>Diarrhea and elevation of bilirubin |
| Schisandra *(Schisandra chinensis)* | Apoptosis inducer and hepatoprotective | Inactivation of cytochrome CYP3A4 |
| Tea, green or black | Stimulation of production of immune cells | Interaction with oral codeine, theophylline and atropine<br>Interaction with cytochrome P450 and CYP1A2 |

an end-of-life hospice care program that consists of veterinarians and nursing staff helping clients to provide end-of-life care at home for their ill pet. The Pawspice option keeps the pet and owner comfortably close to their environment and satisfies the need to nest for a private farewell. One of the main goals of Pawspice is to allow more time for the client to let go of their animal with a longer, kinder, and more intimate farewell. In order to objectively assess the quality of life of animals kept under Pawspice program, an itemized scale has been designed. The Quality of Life Scale provides guidelines for the objective assessment of the Pawspice patient. This way, owners can be confident that the program is providing adequate palliative care and that their animal is well enough to justify prolonging its life. The scale includes 7 descriptors: Hurt, Hunger, Hydration, Hygiene, Happiness, Mobility, and More good days than bad (Table 15.6).

Palliative home care is founded on a number of interventions that start with evaluation and modification of the patient's environment (i.e. ramps and runs to cover slippery floors), comprehensive nutrition and adaptation to new bladder/bowel habits, and, finally, setting up a routine and schedule that will likely help the mental health and well-being of the patient. In addition, creating and following a pain diary to include notes on the Quality of Life Scale as well as regular "call back" sessions will facilitate home care. It is known that a number of psychological factors may decrease the pain threshold in people (such as insomnia, boredom, fear of worsening pain, anxiety, isolation, or frustration), and although one cannot prove that veterinary oncologic patients feel or sense similar emotions, it appears reasonable to make every effort to strive for the reduction of uncomfortable environments or to provide a steady sleep/rest schedule and diversional activities.

**Table 15.6** Quality of life scale.

| The HHHHHMM Scale |
|---|
| Hurt (0–10)<br>No Pain. Adequate pain control and breathing ability are of top concern. If the pet can't breathe, intervene. Is the pet's pain successfully managed? Is oxygen necessary? |
| Hunger (0–10)<br>No hunger. Is the pet eating enough? Does hand feeding help? Does the patient require afeeding tube? |
| Hydration (0–10)<br>Is the patient dehydrated? For patients not drinking enough, use subcutaneous fluids to supplement fluid intake. |
| Hygiene (0–10)<br>The patient should be kept brushed and cleaned, particularly after elimination. Avoid pressure sores, and keep all wounds clean. |
| Happiness (0–10)<br>Does the patient express joy and interest? Is the patient responsive to things around him (family, toys, etc)? Is the pet depressed, anxious, bored or afraid? Can the pet's bed be close to the family activities and not be isolated? |
| Mobility (0–10)<br>Can the patient get up without assistance? Does the pet need human or mechanical assistance? Does the pet feel like going for a walk? |
| More good days than bad (0–10)<br>When there are too many bad days in a row, quality of life is too compromised. The caretaker must be aware the end is near. |

A score of 5 is acceptable in each category. A total of 35 points or greater is accountable for a good Pawspice. (Adapted from Villalobos A. 2007. Canine and feline and geriatric oncology. In: Villalobos A, Kaplan L, editors. *Honoring the Human-Animal Bond.* Ames: Blackwell Publishing. Adapted with permission.

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# 16 Cesarean section and pregnancy

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Anesthetic drug selection, delivery, and monitoring techniques for dogs and cats undergoing cesarean section anesthesia are similar to those used for the nonpregnant animal. However, changes in maternal physiology and concerns for fetal viability influence drug selection, delivery, and monitoring during cesarean section anesthesia. When planning for cesarean section anesthesia, provisions should be made for neonatal resuscitation and postdelivery care. The emergent nature of many cesarean sections often results in limited availability of trained and knowledgeable staff. Puppy mortality is approximately two-thirds greater during emergent than during planned cesarean sections.[1] Maternal mortality is also significantly greater in emergent vs planned cesareans.[2] For this reason, anesthesia and delivery must be well planned before anesthetic induction. Oxygen, clean absorbent towels, a suction apparatus, and resuscitation and antagonist drugs should be available and organized before surgery.

## Maternal physiology

Pregnancy creates major maternal physiologic and anatomic adaptations associated with the increased metabolic demand imposed by the growing fetal and uterine mass.[3] Many or most of these adaptations impact anesthetic management of the periparturient, particularly those management aspects related to cardiorespiratory, gastrointestinal, and hematological systems (Table 16.1).

### Cardiorespiratory system

During pregnancy, oxygen consumption increases to meet the increased metabolic demand associated with the growing fetuses. Changes begin to occur early during pregnancy and peak during the last trimester. Cardiovascular function returns to prepartum values within 4–12 weeks postpartum in women.[4] Cardiac output increases 30–40% to meet this increased demand, and gravid uterine blood flow is 20–40 times greater than nonpregnant flow.[3] Blood flow to the mammary glands and skin also increases. The increased cardiac output is associated with a decrease in vascular tone and arterial blood pressure (10%) and an increased heart rate (55%) and stroke volume.[3] Blood volume increases up to 35% in women[3] and 23% in Beagles.[5] Accompanying this increased blood volume is an increase in red cell mass. However, plasma volume increases relatively more than red cell mass, resulting in a pregnancy-associated anemia. The magnitude of this anemia correlates with increasing fetal numbers.[6] Blood loss during normal parturition is buffered by this increased blood volume and red cell mass. Pregnancy-associated anemia will influence the use of packed cell volume as an index of dehydration.

Uterine and placental blood flow is not autoregulated (maintained constant over a wide range of perfusion pressure), and so anything that inhibits uterine arterial flow will result in decreased fetal oxygen and nutrient delivery. This includes anesthetic drugs and hemorrhage-induced hypotension. Anything causing vasoconstriction can also result in decreased uterine perfusion. Causes can include vasoactive drugs (alpha-2 agonists), excitement-induced hyperventilation and accompanying respiratory alkalosis, and pain.

In supine women, uterine blood flow is compromised as a result of accompanying aortocaval compression. Studies in dogs indicate that dorsal recumbency is not associated with a decrease in systemic blood pressure or altered arterial blood gas values.[7] These studies did not, however, investigate changes in uterine blood flow.

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**Table 16.1** Maternal physiology changes associated with pregnancy (see text for details).

| |
|---|
| Cardiovascular changes |
| Increased oxygen consumption |
| Increased cardiac output |
| Decreased vascular tone |
| Decreased arterial blood pressure |
| Increased stroke volume |
| Increased heart rate |
| Increased blood volume |
| Increased in red blood cell mass |
| Decreased packed cell volume |
| Respiratory changes |
| Increased tidal volume |
| Increased respiratory rate |
| Increased minute ventilation |
| Decreased functional residual capacity |
| Gastrointestinal changes |
| Increased intragastric pressure |
| Decreased lower esophageal sphincter pressure |
| Decreased GI motility |
| Increased gastrin production |
| Central nervous system changes |
| Increased endorphins |

Another study in pentobarbital/thiamylal anesthetized pregnant dogs determined that ligation of the inferior vena cava caudal to the renal veins did not result in diminished venous return with radiographic evidence of ample collateral venous return.[8] These studies indicate that dorsal recumbency during anesthesia does not result in hypotension in the hemodynamically normal pregnant dog.

Vasopressor and chronotropic drugs are less effective in the parturient, possibly related to a downregulation of alpha and beta adrenergic receptors and possibly increased vasodilatory prostaglandins.[3] For this reason, dehydrated or cardiovascularly compromised parturients should receive appropriate fluid therapy before anesthetic induction because anesthetic drugs are typically associated with cardiovascular depression. Blood pressure should be monitored and hypotension treated with crystalloids or colloids. Hemorrhage decreases arterial blood pressure in pregnant dogs relatively more than in nonpregnant dogs.[5] Therefore, hemorrhage and dehydration should be aggressively treated before anesthesia. Ephedrine improves blood pressure in pregnant ewes without decreasing uterine blood flow, while dopamine and dobutamine effectively improve maternal blood pressure but decrease uterine blood flow in nonanesthetized pregnant ewes.[9] The uterine blood flow decrease is dose dependent and relatively greater for dopamine than dobutamine. For this reason, ephedrine is commonly used in parturient hypotensive women. Ephedrine can be used in dogs and cats as a bolus of $0.03–0.1\,mg\,kg^{-1}$, IV and dobutamine at $2–4\,mcg\,kg^{-1}\,min^{-1}$.

Tidal volume, respiratory rate, and minute ventilation increase by 70% in women at term[3], despite the enlarged abdomen and anterior movement of the diaphragm. However, functional residual capacity (FRC) decreases, leading to decreased oxygen reserve within the lung. The decreased FRC and the increased oxygen consumption associated with pregnancy mean that long periods of apnea can more readily result in hypoxemia and hemoglobin desaturation. Because of this, preoxygenation before anesthetic induction is advisable, and apnea should be aggressively avoided during anesthesia. Maternal hyperventilation results in mild respiratory alkalosis[10] and an accompanying mild increase in $PaO_2$.

## Gastrointestinal system

The enlarged uterus increases intragastric pressure. Increased circulating progesterone decreases lower esophageal sphincter pressure and gastrointestinal (GI) motility. The increased intragastric pressure and the decreased GI motility result in a greater risk for regurgitation and aspiration during anesthesia. Concentrations of the peptide hormone gastrin, which stimulates production of stomach acid, increase in pregnant dogs[11] during anesthesia. The decreased gastric pH and regurgitation can result in a greater incidence of aspiration pneumonia and possibly esophageal inflammation. Rapid intubation with a cuffed endotracheal tube will help prevent aspiration of stomach contents. It is currently not known if a preoperative proton pump inhibitor or $H_2$ antagonist will lessen these risks.

## Central nervous system

Serum progesterone increases during pregnancy. This and possibly a pregnancy-associated endorphin increase are thought to be responsible for a 16–40% decrease in minimum alveolar concentration (MAC).[12] This decreased requirement may not be noticed during cesarean section anesthesia, as preanesthetic tranquilizers and sedatives that reduce MAC are often not used.

Inhalation anesthetics depress fetal blood pressure and minute ventilation. Therefore, high inhalant concentrations should be avoided, and local anesthetic techniques and epidurals should be considered to reduce inhalant anesthetic requirement and fetal cardiopulmonary depression.

## Drug transfer across the placenta

Little is known regarding the extent of drug passage across the placenta of dogs and cats. Most information is extrapolated from laboratory animal studies.[13] Because of species differences in placentation, extrapolation of placental drug transfer in dogs and cats from other species can be misleading. The placenta has some ability to metabolize drugs and also some carrier proteins on the maternal and fetal sides of the placenta capable of transferring drugs across the placenta. The extent of such placental metabolism and transport is unknown for dogs and cats. The safest approach is to assume that most drugs cross the placenta and affect the developing fetuses. The developing fetuses are most vulnerable to teratogenic drug effects during the first trimester, in dogs and cats, the first 20 days of gestation. Therefore, elective surgical or medical procedures requiring anesthesia should be avoided during these first 20 days of gestation.

A fundamental principle of cesarean section anesthesia is to minimize fetal concentrations of anesthetic drugs with respiratory, cardiovascular, and central nervous system (CNS) depressant properties. In addition, drugs that can be antagonized, such as opioids, are advantageous because their effects can be reversed using naloxone in puppies or kittens after delivery. Little is known of placental transfer of anesthetic drugs in dogs and cats and the respective maternal/fetal plasma concentration ratios. Studies on sheep confirm that medetomidine, propofol, ketamine, and etomidate rapidly cross the placenta to develop high fetal concentrations.

Anesthetic drugs cross the placenta by simple diffusion according to Fick's equation of diffusion[14] (Equation 16.1):

$$\frac{\Delta q}{\Delta t} = \frac{KA(C_2 - C_1)}{d} \qquad (16.1)$$

where $\Delta q/\Delta t$ represents the rate of drug transfer, and $K$ is a diffusion constant that relates to drug molecular weight, $pK_a$, lipid solubility, degree of ionization, and protein binding. $A$ is the surface area for diffusion, $C_2 - C_1$ is the drug concentration difference across the placenta, and $d$ is the membrane thickness. Properties favoring rapid placental drug transfer include drugs with a molecular weight <600 $d$, which are nonionized, highly lipid soluble, and minimally protein bound. Most anesthetic drugs have molecular weights <300 $d$ and are relatively lipid soluble. This coupled with the relatively large placental surface area means that most anesthetic drugs readily cross the placenta. Exceptions are glycopyrrolate, a relatively large polar molecule, and neuromuscular blocking drugs.

The relatively more acidic fetal blood favors ionic trapping within the fetus of weakly basic drugs when drug $pK_a$ is close to plasma pH (local anesthetics, ketamine, and opioids), possibly prolonging their action. Acidic drugs whose $pK_a$ is close to plasma pH (thiobarbiturates) more readily transfer from fetal to maternal plasma.

The ultrashort-acting drugs propofol and etomidate are extremely lipid soluble and almost completely unionized at plasma pH. Propofol a weak acid with $pK_a = 11$ rapidly and readily crosses the placenta in women achieving an umbilical vein/maternal vein ratio of 0.7–0.85 at fetal delivery.[15] The transfer of propofol in sheep is not as complete, and the fetal elimination half-life is longer than the maternal half-life in this species. This might relate to the thicker barrier for diffusion of the ovine placenta compared to that in women.[16] Regardless, propofol's relatively rapid clearance from maternal and fetal plasma makes it a suitable anesthetic induction drug. Etomidate a weak base with a $pK_a = 4.2$ achieves an umbilical venous/maternal vein plasma ratio of between 1:2 and 1:24 in women. In sheep, the transfer is not as complete, but relatively high fetal concentrations do occur.[17]

Inhalation anesthetics are highly lipid soluble and readily cross the placenta. Despite achieving concentrations associated with anesthesia in the fetuses, isoflurane, sevoflurane, and desflurane have relatively low blood:gas partition coefficients and are rapidly cleared by the newly delivered neonate if they are breathing at delivery. Excessive inhalant concentrations should be avoided to prevent neonatal apnea. Studies in women undergoing cesarean section demonstrate no difference in neonatal viability between isoflurane, sevoflurane, and desflurane,[18,19] and no difference was detected in neonatal viability in women receiving

sevoflurane compared to those receiving a spinal anesthetic. In these studies, nitrous oxide was administered to minimize the inhalant anesthetic concentrations. Methoxyflurane was the only inhalant anesthetic associated with increased canine neonatal death in a survey of anesthesia for canine cesarean section and should be avoided for cesarean section.[1] In this study, isoflurane was associated positively with puppy survival at 7 days after delivery. In another study, neonatal mortality was no different in puppies delivered during propofol/isoflurane anesthesia or epidural.[33] Sevoflurane or desflurane, because of relatively low blood:gas solubility, is useful for cesarean section anesthesia.

## Effects of opioids and NSAIDs on maternal and fetal physiology

### Opioids

Opioids include a variety of natural and synthetic products that produce analgesic effects on the basis of their combination with distinct opioid receptors. The most potent opioid analgesics activate mu-receptors and include morphine, hydromorphone, oxymorphone, fentanyl, methadone, and meperidine. Buprenorphine is classified as a partial mu-agonist. Butorphanol is a kappa-receptor agonist and mu-receptor antagonist.

Maternal administration of opioids will result in placental transfer of these drugs to the fetus according to the previously discussed Fick equation of diffusion. The extent of this transfer differs among opioids.[20] Placental transfer of buprenorphine tends to be low (<10% of placental buprenorphine reaches the fetus), while that of the highly lipid-soluble fentanyl is quite high, and fentanyl persists in the fetus long after clearing the maternal circulation.[20–22]

Significant differences in the sensitivity to opioid-induced analgesia are observed in animals during maturation compared to adults. The source of these differences is unknown. Maturity of the CNS and the blood–brain barrier, end-organ sensitivity to opioids, and solubility of different opioids have been postulated as the cause of the differences between age-related effects of mu-opioid agonists.[23] Studies have also indicated differences in side effects from adult patients, although these differences are seemingly related to those in drug metabolism and physiology between animals of different ages. The most notable example of these differences is the development of respiratory depression. Respiratory depression, although a concern in adults, is a much more important issue in neonates because even a small change in tidal volume or respiratory rate in a neonate can result in life-threatening hypoxia. While *in utero*, the lungs of the fetus are mostly nonfunctional, and the fetus is dependent on maternal circulation for normoxia and normocarbia. However, after cesarean section when the newborn is dependent on its own respiratory system for gas exchange, opioid-induced respiratory depression can lead to increased neonatal mortality.

### Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit inflammation and produce analgesia by decreasing prostaglandin synthesis by inhibition of cyclooxygenase (COX) and, in some cases, 5-lipoxygenase (LOX).[24] Prostaglandins cause vasodilation, increase vascular permeability, and sensitize pain receptors to noxious stimuli. In addition, they are responsible for regulating renal blood flow, protecting GI mucosa, and aiding platelet aggregation. COX has two clinically relevant isoforms: COX-1 and COX-2. Both are constitutively expressed in select tissues, although COX-2 is upregulated in the inflammatory cascade. Differences between NSAID effects, efficacy, and toxicity are related to COX enzymes and the inhibitory effects on pre-existing COX activities in the patient. LOX products (leukotriene B, leukotriene C, and leukotriene D) are responsible for recruitment of immune mediators and alteration of vascular permeability.[24]

Nonsteroidal anti-inflammatory drugs have minimal effects on normal cardiovascular and respiratory systems. Side effects are typically the result of COX-1 inhibition, are dose-related, and typically include GI ulceration, renal papillary necrosis, and inhibition of platelet aggregation.[24]

Nonsteroidal anti-inflammatory drugs should be used with caution in pregnant and young animals because of their reduced clearance and metabolizing organ immaturity. Fetal exposure to NSAIDs could result in significantly prolonged clearance and longer effects and side effects. NSAIDs could impact the development of organ maturation or cause significant damage to young organs.[25]

## Management of patients for cesarean section

Preanesthetic evaluation should include a thorough physical examination and evaluation of blood work (packed cell volume and total protein in healthy animals). A complete blood cell count and biochemistry panel may be helpful to evaluate overall health and especially to determine calcium and blood glucose levels in animals that have been in active labor.[26] In addition, animals undergoing sedation and/or general anesthesia should be held off food for planned cesarean sections. Pregnant animals have an increased risk of regurgitation and aspiration due to decreased lower esophageal sphincter tone and prolonged gastric emptying time.[27,28] An intravenous catheter should be placed in order to provide IV access in the case of emergency and for IV fluid administration.

Pregnant animals should be preoxygenated when possible.[29] Preoxygenation for 3 min increases the time to desaturation in healthy dogs in which propofol was administered for anesthetic induction.[30] Oxygen delivery to the placenta is an important factor influencing fetal mortality.[28] Some animals may be resistant to the placement of a facemask; therefore, preoxygenation may not be possible. In either case, it is important to intubate pregnant animals as soon as possible after anesthetic induction.

Most cesarean sections in dogs and cats are performed on unpremedicated animals because all commonly used anesthetic drugs will cross the placenta.[31] Sedatives and tranquilizers have cardiovascular and respiratory side effects for the dam and fetus that can result in increased fetal mortality. Xylazine administration was associated with fetal death, but this may have been impacted by the concurrent administration of ketamine. Ketamine, xylazine, and the combination of ketamine and xylazine should be administered with caution or avoided when possible.[1] For quiet and relatively calm parturient dogs and cats, preanesthetic sedation can be avoided to minimize cardiorespiratory depression in the newborn. If it were possible to place an IV catheter without administration of sedatives, it would be preferable to do so. Excitable and nervous animals will benefit from preanesthetic sedation. This will decrease the need for relatively high inhalant anesthetic concentrations that are often necessary in excitable animals. Fetal exposure to relatively high inhalant anesthetic concentrations results in excessive neonate respiratory depression immediately after delivery. Acepromazine is highly protein bound, and its molecular weight is relatively high compared to other sedatives. For this reason, it crosses the placenta more slowly than other anesthetic drugs. Acepromazine is not associated with increased maternal or neonatal mortality.[2] However, because it causes vasodilation, it should not be used in shocky or dehydrated parturients. A study using chlorpromazine premedication before various anesthetic combinations revealed overall puppy mortality of <4%.[32] This is less than that reported in a study of overall puppy mortality.[1] Morphine is relatively poorly lipid soluble and only 20–30% unionized at plasma pH. Therefore, it crosses the placenta less rapidly than the more lipid-soluble opioids such as fentanyl. Hydromorphone's lipid solubility is between that of morphine and fentanyl. Opioid respiratory depression can be reversed in recently delivered neonates using a drop of the opioid antagonist naloxone sublingually.

Local anesthetic techniques such as spinals and epidurals are commonly used for cesarean section in humans; their use is much less common in small animal veterinary practice. Smaller volume of local anesthetic is required during pregnancy due to the increased size of the epidural veins.[26] Lidocaine is most often used for epidurals for cesarean section due to its short onset and short duration. The administration of local anesthetics in the epidural space can result in systemic hypotension due to vasodilation.[26] Local anesthetics may also spread cranially and result in respiratory and cardiovascular depression. Local anesthetic administration in cats may result in increased severity of the previously listed effects due to cats' inherently lowered tolerance and the increased toxic effects of this drug. The advantage of epidurals and spinals is that there is minimal effect on the fetus. In one study, the respiratory rate of newborn puppies was significantly higher after epidural anesthesia in the dam compared to dams that were induced with midazolam/ketamine or propofol and maintained on enflurane.[32] While systemic local anesthetics can cross the blood placental barrier and become ionized and trapped within the fetus, lidocaine epidurals have local effects. Systemic absorption occurs over time and should not reach the placenta before removal of the fetus. The use of local anesthetic techniques requires the anesthetist to be comfortable with the technique. Patients who have received an epidural are usually

conscious during the surgical procedure. If the technique was faulty or there was uneven spread of local anesthetic within the epidural space, the patient may feel the surgery. In addition, while the caudal portion of the patient experiences motor and sensory blockade, the cranial portion does not, and the patient may move or vocalize during the procedure. The airway is also not protected, and the patient is in dorsal recumbency. Finally, the effects of the local anesthetic require time to wear off.[33] Hospital-acquired infection of the newborns is possible, and in most cases, it is preferable to send patients home as quickly as possible. Animals that have received spinals or epidurals should be monitored until motor function has returned, so their postoperative time in the hospital tends to be longer than with cesarean sections performed under general anesthesia as discussed in the following section.

Propofol is the drug of choice for anesthetic induction for cesarean section. Propofol has a short half-life, rapid hepatic and extrahepatic metabolism, and manageable respiratory and cardiovascular side effects.[33] Fetal mortality has been demonstrated to be equivalent with propofol as with mask induction using isoflurane[1,34] and without the rough induction characteristics associated with inhalant anesthetic inductions. In addition, the concentration of inhalant in dams that have experienced a mask induction has to be significantly higher than that of dams that were anesthetized using propofol for anesthetic induction. The induction of anesthesia using ketamine has been associated with decreased puppy vigor, and use of thiobarbiturates has been associated with an increased risk of no spontaneous movement of puppies at birth.[33,34]

Before intubation, care should be taken to position animals in sternal recumbency with their head above their abdomen. All pregnant animals undergoing general anesthesia should be intubated to protect their airways. If regurgitation occurs, the poll of the head should be positioned to be the highest point to protect the airway and encourage drainage out of the mouth. In the event of regurgitation, suction may be used to remove gastric contents from the back of the mouth.

The use of isoflurane for anesthetic maintenance has been associated with increased puppy survival compared to methoxyflurane.[1] While the primary route of elimination of inhalants is through ventilation, and inhalants depress ventilation, puppy survival when dams were anesthetized with isoflurane was better than with methoxyflurane.[1] It is recommended to maintain as light a plane of anesthesia as possible to minimize inhalant delivery across the placenta.[34,35]

Infiltration of local anesthetic along the line of the incision may be helpful to reduce inhalant concentrations and minimize systemic effects of inhalants.[26] Ropivacaine, a long-acting local anesthetic drug, can be used for this purpose. Some patients will even allow the anesthetist to perform this line block before the induction of general anesthesia.

Cardiovascular and respiratory parameters of the dam should be monitored during general anesthesia, consisting of heart rate, blood pressure, and hemoglobin saturation.[31] These parameters are important as indirect indices of uteroplacental perfusion. Perfusion of the uterus and placenta is pressure dependent, relying on the arterial–venous uterine blood pressure difference, and is indirectly proportional to uterine vascular resistance. It is also important to note that there is no fetal autoregulation of blood pressure. Fetal blood flow is entirely dependent on maternal cardiac output. Ventilation should be monitored using capnometry to ensure appropriate ventilation. Overventilation (low $EtCO_2$) and underventilation can both result in vasoconstriction, which may decrease blood flow to the uterus. The result of this decreased blood flow to the uterus is decreased oxygen delivery to the fetus, fetal hypoxia, and increased fetal mortality.[36] Performing a physiologic sigh (a controlled breath given by squeezing the rebreathing bag to a pressure of 15–20 cm $H_2O$) may result in enhanced surfactant flow, which results in decreased atelectasis and increased oxygenation of blood.[29]

Positioning of the animal during cesarean section requires dorsal recumbency. The structures of the canine and feline uterus are such that aortocaval compression syndrome is less of an issue in dogs and cats than in humans; fetuses generally lie lateral to the caudal vena cava and abdominal aorta. Smaller dogs, between 9 and 25 kg, are not likely to develop aortocaval compression syndrome. However, in large breed dogs, this may become a source of decreased blood flow to the uterus and hindlimbs.[7,37]

Fluid administration may be helpful to reduce dehydration in patients who have been in labor and held off food before planned cesarean section or to replace fluids lost during surgery because of either evaporation or blood loss. In addition, fluid administration may help to

maintain a patent intravenous catheter and can be used to flush-in systemic drugs during an emergency. However, only 53% of patients undergoing cesarean section received fluids in a study of perioperative management and mortality rates.[2]

Pain management of patients undergoing cesarean section is controversial. Pain tolerance in pregnant patients is increased, and there is a decreased anesthetic requirement in pregnant patients. Potential causes of the increase tolerance of pain include increased pregnanolone and pregnanadione (which have sedative effects) or increased endogenous endorphins resulting in increased pain tolerance.[28] Typical signs of pain in these patients include lack of appetite, not allowing nursing, immobility, difficulty rising, and vocalization during activity. Local anesthetic infiltrative line blocks can be helpful in the immediate postoperative period, but ropivacaine's duration of action is only ~4 h. Many veterinarians administer a dose of opioids to these patients IV or IM once the puppies have been surgically removed. Buprenorphine is often used for this purpose because it has a long duration of action and has minimal cardiovascular and respiratory side effects to the dam. However, milk transfer has not been evaluated for any of the opioids in lactating bitches or queens. Nonsteroidal anti-inflammatory drugs are also controversial. The use of NSAIDs in pregnant dogs and cats has not been evaluated, and most available NSAIDs have not been evaluated in puppies younger than 4–6 weeks.[25] Milk transfer of these drugs is also possible, although unlikely.[20]

## Management of pregnant patients for noncesarean section surgery

Anesthetic concerns for pregnant patients for noncesarean section surgery are similar to those for cesarean section patients. Surgery in pregnant patients should be avoided unless necessary due to the stress response associated with anesthesia, surgery, and hospitalization. If surgery is necessary due to traumatic injury, it is possible that the trauma itself may result in fetal loss.

Anesthetic protocols in pregnant patients for noncesarean section surgery should incorporate the recommendations and cautions made for cesarean section patients. There is little information on pharmacological treatments in veterinary medicine and the risk of such treatments to a developing fetus. In general, the fetus is at greater risk for teratogenic effects of pharmacological treatments during organogenesis (the first 20 days of pregnancy in dogs and cats).[13] Elective procedures should not be performed in this period if at all possible, to minimize stress and the effects of all drugs on the fetus.

## Fetal physiology

An understanding of fetal physiology is important, and the effects of many drugs on fetal physiology are unknown. Blood flow to the fetus occurs through the placenta.

Maternal blood via the uterine arteries crosses the placenta to the fetal circulation.[28] Blood is carried from the placenta to the fetal circulation through the umbilical vein. Approximately 50% bypasses the liver through the ductus venosus and travels to the right atrium.[38] Some of the blood from the right atrium, returning mainly from the fetal head, travels to the right ventricle while the majority of the right atrial volume shunts to the left atrium through the foramen ovale. Approximately 7% of the total cardiac output is pumped to the fetal lungs from the right ventricle, while ~60% goes through the ductus arteriosus, bypassing the lungs, and travels through the fetal circulation or to the umbilical arteries back to the placenta.[38] The blood that travels through the systemic circulation also travels to the liver. Liver metabolism in the fetus is minimal.[38] The placenta acts as a barrier similarly to the blood–brain barrier. Drugs that cross the blood–brain barrier will also cross the placenta to the fetus. The fetal environment relative to maternal is acidic, and weakly basic drugs that are relatively more ionized in a more acidic environment, such as lidocaine, can become trapped in the fetus and are inhibited from crossing through the placenta to the maternal circulation for metabolism.[31]

The first breath after birth is stimulated by fetal hypoxia and hypercarbia (due to separation from the placenta), a lowered body temperature, and an increase in sensory input from mechanical stimulation as the fetus passes through the birth canal. Inflation of the lungs causes a reduction in pulmonary vascular resistance, which decreases pressure in the right atrium, right ventricle, and the pulmonary artery.[38] Systemic vascular resistance increases due to the loss of the placental circulation, and pressure increases in the left

atrium, left ventricle, and aorta. The end result is that pressure in the left atrium is higher than the right atrium, and aortic pressure is higher than pulmonary arterial pressure. These changes reverse blood flow through the foramen ovale and ductus arteriosus, leading to their eventual closure.[38] Decreased prostaglandin concentrations are associated with constriction of the ductus.[38]

Maturity of fetal reflexes varies by species. In dogs and cats, parasympathetic innervation is mature, gag and panniculus reflexes, and pain perception is present at birth. Within 4 days, the baroreceptor reflex is present, and respiratory system innervation occurs in 2 weeks. Sympathetic innervation is mature at 11 days of age in cats and at 14 days in dogs. The cytochrome P450 system is at 85% of normal by 4 weeks, and full maturity occurs at 6 months of age.[25]

The fetus compared to an adult has a relatively higher hemoglobin concentration, and due to a leftward shift of the oxyhemoglobin dissociation curve, fetal hemoglobin remains relatively saturated with oxygen at a low $PO_2$. The P50 of fetal dog blood is 18 mmHg, while that of adult dogs is 31 mm Hg.[39] Normal fetal umbilical vein $PO_2$ is only 35 mm Hg at which hemoglobin is 80–90% saturated.[40]

## Neonatal resuscitation

Drugs and supplies for neonatal resuscitation should be available and organized before surgical delivery (Table 16.2). Weak and unresponsive neonates can result from excessive anesthetic concentrations through placental transfer. This can result in hypoxemia and hypercarbia. In addition, severe congenital anomalies that may be initially unidentifiable or progressing hypothermia can result in neonatal unresponsiveness.

Neonatal resuscitation involves the following: (1) supplying appropriate tactile stimulation, (2) improving or maintaining ventilation and oxygenation, and (3) maintaining neonatal body temperature or increasing it if hypothermic. Normally, as the fetus is expelled from the birth canal, the increased pressure on the neonate assists in stimulating the first breath and expelling fluid from the respiratory tract. This stimulation is minimized during surgical delivery. Therefore immediately after delivery and as soon as the fetal membranes are removed and the umbilicus severed, the neonate should be stimulated by vigorously drying it with an absorbent towel. Emphasis is on stimulating the perineal and abdominal areas. During this time, a suction bulb is used to clear the oral cavity of fluid. Stronger suction is not useful and can damage delicate neonatal mucosa. Although it is a common practice, there is no evidence to suggest that "swinging" newborns in an arc facilitates resuscitation. It is not necessary or recommended, as it increases the likelihood that a neonate could be dropped, thrown, or otherwise traumatized.[41]

Spontaneous breathing should be identified by observing chest wall movement and by listening for vocalization. Bradycardia signifies developing hypoxemia. If spontaneous breathing is not obvious, vigorous rubbing should be continued and manual breaths

**Table 16.2** Physical and pharmacological neonatal resuscitation.

| | | | |
|---|---|---|---|
| *Physical resuscitation* | | | |
| Vigorously dry neonates | | | |
| Clear the oral cavity of fluid using gentle suction | | | |
| Administer supplemental oxygen via facemask | | | |
| Monitor heart rate via precordial palpation | | | |
| Monitor respiratory rate Intubate if necessary | | | |
| Keep neonates warm | | | |
| *Useful drugs for resuscitation*[a] | | | |
| Drug | Dose | Route | Indication |
| Epinephrine | 0.1 mcg $kg^{-1}$ | Sublingual or via umbilical vein | Bradycardia |
| Doxapram | 1 drop | Sublingual or via umbilical vein | Respiratory stimulation |
| Naloxone | 1 drop | Sublingual or via umbilical vein | Opioid reversal |

[a]Drugs are typically administered only after physical resuscitation techniques have been unsuccessfully performed.

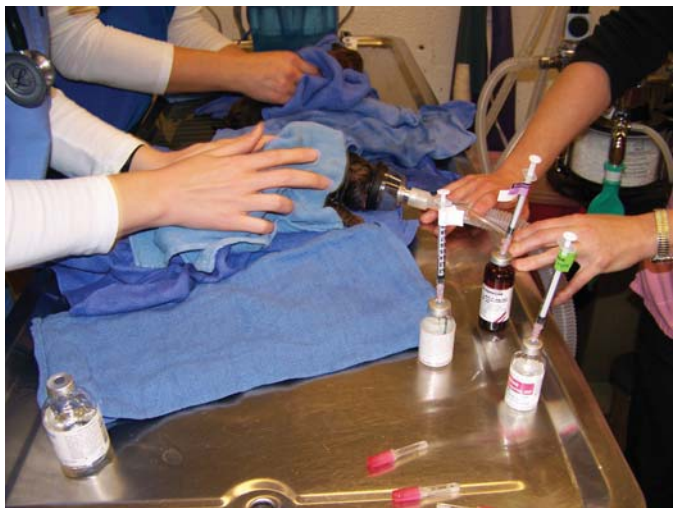

**Figure 16.1** Facemask connected to nonrebreathing anesthetic circuit to deliver 100% oxygen. Note labeled syringes with commonly used resuscitation drugs ready for sublingual administration. Also note abundance of absorbent towel for drying and rubbing neonate.

with supplemental oxygen should be administered via an endotracheal tube. Unfortunately, the neonate's small size makes endotracheal intubation difficult. The neonate's head should be extended to facilitate endotracheal intubation. A short-bladed laryngoscope is helpful to depress the tongue and identify the tiny glottis. A flexible 14-gauge or 16-gauge intravenous catheter can be modified into an endotracheal tube. The oral mucosa has high water content and is thus very fragile and easily traumatized, and so intubation must be performed carefully. Alternatively, delivery of a manual breath can be attempted by applying a tight-fitting facemask over the muzzle while extending the neonate's head and neck (Figure 16.1). Unfortunately, this often results in gas preferentially entering the stomach rather than the lungs.

The neonate's heart rate is most easily counted by palpating a precordial pulse, with thumb and fingers lightly compressing the thoracic wall. Normal newborn heart rate should be ~220 beats per minute.[42] Bradycardia indicates hypoxemia and should be treated by stimulation of breathing as described, supplemental oxygen, warming, and mechanical stimulation. Atropine to increase heart rate is ineffective because the bradycardia is not parasympathetically mediated but rather anoxia of the cardiac pacemaker/conduction system. If opioids were administered as part of the anesthetic regimen, the associated respiratory depression can be treated with naloxone, a complete opioid antagonist. It is administered sublingually (1 drop) to the neonate or through the umbilical vein. The umbilical vein is the single thin-walled structure within the umbilical stump, and the umbilical arteries are paired and thicker walled. If given through the umbilical vein, drugs should be diluted in a 0.5 ml volume to facilitate injection and absorption. Often, residual inhalant anesthetics continue to suppress neonatal ventilation. No evidence in the literature demonstrates that doxapram will successfully stimulate ventilation in the newborn. However, there is also no good evidence to indicate that it is ineffective. Doxapram can be administered as described for naloxone (1 drop sublingually or via the umbilical vein). Cardiac massage can be accomplished by side-to-side compression of the thorax using the thumb and fingers. Epinephrine (0.1 mcg $kg^{-1}$) can be administered as described for naloxone (supra vidae).

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# 17 Neonatal, pediatric, and geriatric concerns

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Neonatal, pediatric, and geriatric patients represent a clinical and therapeutic challenge for anesthesia. Although age is not a disease, it is an important independent risk factor of morbidity and mortality[1,2] and can be used as a predictor of perioperative outcome for anesthetized patients.[3,4] The odds for perioperative mortality in small animal anesthesia are age dependent. For example, a decreased risk of anesthetic mortality is observed in cats and dogs aged younger than 6 months,[3] and a significant increase is observed in older patients.[5,6] Furthermore, the odds of anesthetic-related casualties are higher in patients with coexisting diseases, which lead to poor functional organ capacity, such as pulmonary, cardiac, renal, hepatic, and endocrine diseases alone or in combination.[7] Thus, more importantly than age alone, the combination between life stage and physical status needs to be considered by the anesthesiologist while designing anesthetic protocols. This chapter reviews the common physiological and pharmacological peculiarities for the neonatal, pediatric, and geriatric patients, associated with abnormal responses to anesthetic therapies.

Defining life stages of dogs and cats and their physiological peculiarities has important clinical relevance to better understand and appreciate the possible anesthetic challenges associated with each individual. Accordingly, using the American Animal Hospital Association (AAHA) guidelines, the life stages of dogs[8] and cats[9] are classified in Tables 17.1 and 17.2.

It is important to note that defining the terms "neonatal," "pediatric," and "geriatric" is challenging in veterinary medicine. In general, the neonatal stage extends from birth to weaning, the pediatric stage ends with reproductive maturity, and the beginning of the geriatric stage depends on patient's size and breed.[8–10] Thus, the physiological status of older patients is more relevant than their chronologic age.[11,12] Consequently, geriatric patients should be subclassified into different categories on the basis of their physiological status as described in Table 17.3.[11]

## Physiological particularities in the neonatal, pediatric, and geriatric dogs and cats

### Respiratory system

The timing for each developmental stage and the degree of lung development at birth vary significantly among species.[13] For dogs and cats, the considerable development of respiratory function happens well before birth but matures in the postnatal period.[13–15] In comparison to adults, the neonatal and pediatric ribcage is more compliable, the intercostal muscles are weaker, the work and pressure required by a neonate to maintain tidal breathing are increased,[15] and the respiratory chemoreceptors are immature[15] and less sensitive to increased $CO_2$ and/or decreased $O_2$. Very young animals have higher resting respiratory rates and minute volume, greater tendencies to develop atelectasis, increased oxygen demand, and lower functional residual capacity (FRC). Altogether, these differences may lead to respiratory fatigue and hypoxemia during anesthesia. These physiological differences begin to change as the patients mature. Although the literature does not provide supportive evidence for the timing of

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**Table 17.1** Definition of canine life stages.

| Stage | Definition |
|---|---|
| Neonate | Birth to weaning (~4 weeks of life) |
| Puppy | Neonatal until reproductive maturity |
| Junior | Reproductive mature, still growing |
| Adult | Finished growing, structurally and social mature |
| Mature | From middle up to approximately the last 25% of expected lifespan (a window of time around half life expectancy for breed) |
| Senior | From maturity to life expectancy (approximately the last 25% of expected lifespan) |
| Geriatric | At life expectancy and beyond |

Source: Adapted from Bartges et al.[8]

**Table 17.2** Definition of feline life stages.

| Stage | Age |
|---|---|
| Neonate | Birth to weaning (~4 weeks of life) |
| Kitten | Neonatal to 6 months |
| Junior | 7 months to 2 years |
| Prime | 3–6 years |
| Mature | 7 –10 years |
| Senior | 11–14 years |
| Geriatric | >15 years |

Source: Adapted from Vogt et al.[9]

the full completion of alveolar development and lung maturity for dogs and cats, the maximum functional efficiency of the dog's lungs occurs at about 1 year of age.[16] Interestingly, in humans, the same level of lung maturity is not achieved until the age of 20 years.[16]

As animals age progressively, respiratory function eventually deteriorates.[17–19] Weakening of the respiratory muscles and loss of elastic tissue are commonly observed in senior and geriatric patients.[4] Together with pulmonary fibrosis,[4] these result in decreased chest wall compliance and elastic recoil of the lungs, which are subsequently associated with a decrease in the vital capacity and FRC. These physiological changes predispose patients to atelectasis when under anesthesia or during prolonged recumbency. Aged patients may also present with increased airway resistance, decreased pulmonary diffusion capacity, and decreased capillary blood volume, leading to a reduced efficiency for expiration and gas exchange impairment, which can

**Table 17.3** Sub-classification of the geriatric population.

| Classification | Definition | ASA status |
|---|---|---|
| 1 | Healthy geriatric patients – minor changes in organ function | II |
| 2 | Geriatric patients with subclinical organ dysfunction – decreased function of 1 or more organs such as the heart, liver, or kidneys | III |
| 3 | Geriatric patients with an obvious disease condition – severe clinical organ dysfunction (heart disease, endocrine disease, renal disease or neoplasia | IV, V |

Source: Adapted from Kukanich.[11]

lead to hypoxemia.[4,19] At the same time, they also have increased susceptibility to respiratory infections.[4]

For the aforementioned reasons, oxygen supplementation is recommended for neonatal, pediatric, and geriatric patients. A minimum of 3 min of preinduction oxygenation[20] via face mask, followed by supplementation during the intraoperative and postanesthetic phases (including after tracheal extubation) may prevent possible hypoxemia. During anesthesia, manual or mechanical intermittent positive pressure ventilation (IPPV) and oxygenation/ventilation monitoring are recommended (pulse oximetry, capnography, and blood gas analysis). Assisted ventilation is often recommended to maintain both normal ventilation ($PCO_2$ between 35 and 45 mmHg) and oxygenation ($PaO_2$ >60 mmHg).

## Cardiovascular system

The cardiovascular system of the neonate undergoes dramatic adjustment after birth to assume its own circulation and maintain homeostasis.[21] The neonatal circulation is often considered as a low resistance–high flow circuit because it presents with low blood pressure, low blood volume, and low systemic peripheral resistance.[21–23]

To maintain normal tissue perfusion, the neonate and pediatric patient must maintain a higher heart rate, cardiac output, plasma volume, and central venous pressure as compared to the adult.[22,23] The baroreceptors

are not fully mature until ~12 weeks of age, leading to decreased ability to vasoconstrict; thus, the heart rate is the drive for normal cardiac output. Anticholinergics are used frequently during anesthesia to maintain normal to higher heart rates and tissue perfusion. In the newborn, bradycardia is not vagally mediated and is often caused by hypoxemia.[22]

Congenital heart defects are common in veterinary medicine. In a veterinary teaching hospital setting, ~17% of dogs and 5% of cats examined during a 10-year period were diagnosed with congenital heart disease. Subaortic stenosis and patent ductus arteriosus in dogs and tricuspid valve dysplasia and ventricular septal defect in cats were among the most common congenital diseases. Cardiac disease and its anesthetic consequences are discussed in detail elsewhere in this book (see Chapter 1)[24].

For the geriatric patients, cardiopulmonary diseases are always a concern.[25] The aging process is correlated with common multifactorial intrinsic physiological changes in the cardiovascular system,[26] including decreased baroreceptor activity, circulation time, blood volume, blood pressure, and cardiac output and a limited ability to adapt to hypotension. All of these alterations lead to a reduced cardiac reserve. Most of these common changes in the geriatric heart are primary related to myocardial fibrosis, valvular fibrocalcification, and ventricular thickening with variable degrees of change.[27,28] The cardiac conduction system may also become compromised with age, leading to possible cardiac arrhythmias.[27] Therefore, drugs known as negative inotropes and arrhythmogenics should be avoided in the geriatric patient.

It has been estimated that 10% of dogs older than 5 years has mitral insufficiency, and 25% of dogs aged between 9 and 12 years has evidence of cardiac disease. The risk increases to 33% in dogs older than 13 years.[4,26] The most common cardiovascular abnormalities in dogs are as follows: valvular heart diseases, dilated cardiomyopathy, pericardial diseases, arrhythmias, and systemic hypertension.[2,26,29,30] In older cats, hypertrophic cardiomyopathy is the most common disease. These abnormalities increase the odds of morbidity and mortality in the geriatric animal. History of exercise intolerance, arrhythmias, cyanosis, abnormal pulse quality, cardiac murmurs, and/or syncope indicates a need for a more extensive preanesthetic cardiac evaluation. A complete cardiac geriatric profile includes history, physical examination, thoracic radiography, electrocardiography (ECG), blood work, and echocardiography.

During anesthesia, anesthetic-induced cardiovascular depression and hypotension[31] are the most common cardiovascular abnormalities observed in the geriatric patient. It is fundamental to ensure adequate venous return and fluid balance to minimize the risk of hypotension.[32] Due to the decreased cardiac reserve, fluid overload can lead to congestive heart failure and pulmonary edema. Therefore, fluid rate should be prescribed on the basis of individual need, hydration, and physical status. During anesthesia of geriatric patients, the authors cannot stress enough the benefits of cardiovascular monitoring to detect detrimental changes to the cardiovascular system as early as possible. Treatment should be provided on an "as-needed" basis.

## Hepatic system

In neonates, the cytochrome P-450 system is immature at birth and develops during postnatal life,[33] leading to decreased drug metabolism and prolonged drug elimination. Glucose levels are well maintained in the normal neonatal patient, although when stressed or fasted, they may become hypoglycemic because glycogen stores are relatively low, and they have low gluconeogenic ability.[34]

With advancing age, hepatic function deteriorates. During the geriatric stage, dogs and cats commonly experience decreased liver mass and hepatic blood flow secondary to reduced cardiac output, decreased microsomal enzyme activity, and generalized reduction of metabolic activity.[35] These changes are associated with hypoproteinemia, coagulopathies, hypoglycemia, and hypothermia. For all geriatric patients, liver function analysis and coagulation panel evaluation are prudent and recommended before the beginning of anesthesia or sedation, especially when highly metabolized drugs are used. Hypotension should be avoided during anesthesia of geriatric patients, as it leads to a further decrease in hepatic blood flow, exacerbating the possible ischemic hepatic damage that is already present and associated with advanced age.

## Central nervous system (CNS)

When compared to adults, reduced drug levels are required to produce effective general and local

anesthesia, as well as neuromuscular blockage due to the immature CNS and neuromuscular junctions of neonates and pediatric patients.[34,36] For that reason, a dose adjustment should be performed.

The aged patient may have compromised cognitive, sensory, motor, and autonomic functions.[37] Aging may be correlated with decreased requirements for anesthetic drugs (inhalants, benzodiazepines, opioids, and barbiturates) due to decreased brain size, loss of neurons, increased cerebrospinal fluid volume, depletion of neurotransmitters (dopamine, norepinephrine, tyrosine, and serotonin),[38–40] decreased cerebral oxygen consumption, and myelin degeneration.

The thermoregulatory center is weakened during the neonatal, pediatric, and geriatric stages. These patients are more susceptible to anesthesia-induced hypothermia.[41] Hypothermia can be associated with bradyarrhythmias, reduced minimum alveolar concentration (MAC) of inhalants, and shivering. However, shivering can increase oxygen consumption by up to 400%, and these patients can have decreased ability to thermoregulate by shivering or vasoconstriction. Once again, oxygen supplementation is recommended for these special patients.[42]

## Renal system

There is marked variation in the degree of renal maturation at birth between species.[43] In puppies, nephrogenesis is not complete until the third week of life. The canine neonatal kidney is functionally characterized by a low clearance rate, glomerular filtration, renal plasma flow, filtration fraction, depressed reabsorption of amino acids and phosphate, exaggerated proximal tubule natriuresis, and low concentrating ability.[44] In the neonatal animal, serum phosphorous concentrations are usually elevated ($\sim 9\,mg\,dl^{-1}$), and serum creatinine levels ($\sim 0.4\,mg\,dl^{-1}$) and blood urea nitrogen concentrations ($\sim 10\,mg\,dl^{-1}$) are usually lower when compared to normal health adult animals.[43]

The incidence of adult renal disease has been reported to be about 0.5–1.5% of the general population of dogs and cats.[45,46] This percentage can increase with age. The most common renal disease occurring in elderly dogs and cats is chronic kidney disease.[47] Urinary incontinence, bladder tumors, and prostate problems are also common. Decreased renal mass[48] is associated with decreased tubular size and weight and decreased glomerular numbers and filtration function.[45,49] Reabsorption of protein, water and sodium, secretion of aldosterone, secretion and reabsorption of anionic and cationic compounds, formation of vitamin D and renin, and elimination and metabolism of protein-bound compounds are all compromised.[45,49] This further influences the regulation of blood pressure, acid – base status, and erythropoietin levels, resulting in hyperphosphatemia, azotemia dehydration, and hypoproteinemia.

When general anesthesia is induced, some normally healthy patients experience a 40% reduction in renal blood flow and glomerular filtration.[41] Reduced renal blood flow is expected when reduced cardiac output is observed due to cardiovascular diseases. Consequently, the effects of anesthesia and surgery on the kidney can be exacerbated in geriatric patient with pre-existing cardiovascular or renal conditions. Factors that contribute to the susceptibility of the geriatric patient to renal failure after anesthesia and surgery should be avoided (e.g. hypoxemia, hypervolemia, hypotension, and hypercarbia).[41]

For all neonatal, pediatric, and geriatric patients, blood pressure measurements and renal function analysis (urinalysis, blood urea nitrogen (BUN), and creatinine) are recommended during the preoperative examination. During anesthesia and recovery of patients with renal failure, the author recommends close monitoring of blood pressure, cardiac and urine output, and hydration status.

## Gastrointestinal system

Increased risk of gastroesophageal reflux during anesthesia, combined with possible compromise of laryngeal and pharyngeal function may be associated with higher risk of aspiration pneumonia in geriatric patients.[50] Suctioning of the esophagus before extubation may decrease the risk of aspiration pneumonia after the extubation.

## Endocrine system

Hyperadrenocorticism, diabetes mellitus, and hypothyroidism are common conditions in the geriatric stage of dogs and cats and are discussed in Chapter 8. Older dogs may have decreased adrenal responsiveness to ACTH stimulation when compared to younger dogs. It has been suggested that corticosteroid supplementation in the preanesthetic period may be beneficial for the geriatric animal because of the possibility of adrenal

exhaustion in response to the increased stress during anesthesia and surgery.[51]

## Pharmacokinetic and pharmacodynamic considerations

When compared to pediatric or adult stages, neonatal patients have differing drug uptake, distribution, and metabolism. For example, the neonatal patient has lower albumin levels and lower albumin–drug affinity that leads to a decrease in protein binding of pharmacological agents. The blood–brain barrier is more permeable leading to a potentiation of pharmacological CNS effects. Neonates and pediatrics have a higher body water content and lower fat content than adults. This results in greater initial volume of distribution for water-soluble drugs and smaller volume of distribution for lipid-soluble drugs.[34]

The rate of induction with inhaled anesthetics in infants and children is faster when compared to adults because the rate of rise of alveolar concentration is quicker.[52] This can be explained by the larger ratio of alveolar ventilation to FRC, greater fraction of the cardiac output to vessel-rich organs, and a greater cardiac output per kilogram. Age can also significantly affect blood–gas partition coefficients, and the lower blood–gas partition coefficients in children explain, at least in part, the more rapid rise of alveolar anesthetic partial pressure in this age group.[53] Moreover, inhalant MAC in humans and animals varies with age, being greatest in the neonate and least in the elderly (the MAC of halothane in neonatal humans is 25% less than that in infants); MAC in infants is the highest of any age group.

In the elderly population, the absorption, distribution, and elimination of drugs may be compromised. Dose adjustments are sometimes needed due to decreased drug clearance from organ dysfunction, drug–drug interactions, or greater drug sensitivity.[11] The use of anesthetic drugs that produce the required pharmacological effects but with a different route of elimination that is not affected by the organ dysfunction or drug–drug interaction may eliminate or ameliorate the problem[11]. Choosing a drug with a wide safety margin is another option to minimize drug adverse effects associated with decreased drug elimination in the aged patient.[11] All drug doses should be calculated on an individual basis, taking into account the route of metabolism and excretion.[4]

## Anesthetic management of neonatal, pediatric, and geriatric patients

Anesthetic management of the neonatal, pediatric, or geriatric patient is primarily a matter of following sound principles of anesthesia as they should be applied for any veterinary patient.[54] More important than drug choice is the full understanding of the physical condition of the individual patient and attention to many details. The anesthetic protocol design should start with a deep understanding of the history of the patient with a systematic physical evaluation followed by supporting laboratory data. The anesthetist should understand the effects of anesthesia and age on the physiological reserve of the various organ systems.[54] Patients with abnormalities should be stabilized before anesthesia induction to decrease the anesthetic risks. Close monitoring of various organ systems should be performed beginning at the preinduction period and maintained until the patient regains control of vital reflexes, consciousness, body temperature, normoglycemia, and coordination.[54]

### Preanesthetic evaluation

For the neonatal patient, a systematic neurological and oral examination should be performed to access the physiological health of the patient.[36] For the pediatric patient, family history of congenital diseases is one of the most important factors to consider in the anesthetic plan. During the physical examination of pediatric patients, arterial pulses, signs of cyanosis, cardiac murmurs, respiratory abnormalities, jugular venous distention, ascites, or hepatomegaly are all signs that would lead to a possible diagnosis of congenital heart defects.[24] A complete physical examination to rule out those abnormalities is vital. Thoracic radiographs can be useful to evaluate cardiac size, great vessels, and pulmonary vasculature to confirm the possible congenital disease. Echocardiography is considered the cornerstone to establish the definitive diagnosis of a specific disease.[24]

For the geriatric patient, it is imperative that the anesthetist is aware of the comprehensive history of the geriatric cat or dog, including current medications (over-the-counter, prescription, alternative,

and supplements) and their potential impact on anesthesia.[29,55] Special attention should be given to clinical changes and signs of pain, body weight and body condition, temperature, pulse, respirations, and cardiopulmonary auscultation. In a study with geriatric dogs reported by Davies (2012), a systematic physical evaluation was able to reveal at least one previously unrecognized (by the owners) problem in 80% of the geriatric population analyzed where a mean of 7.8 problems was identified per dog.[55] Pain was one important physical abnormality commonly unrecognized by the owners of that population.[55] The AAHA senior care guideline for dogs and cats suggests careful Client Communication before anesthesia.[8]

Geriatric animals commonly have abnormalities in multiple organ systems, making laboratory blood work critical to assess anesthetic-related risks, especially in the patients receiving long-term medications for developing and/or chronic diseases.[56] The owner should be informed about possible procedural risks and benefits and a written, informed consent should be obtained.[29] For healthy-appearing senior dogs, AAHA suggests a complete blood count (CBC), complete urinalysis, and biochemical profile with electrolytes as a minimum laboratory database. For the senior and geriatric dogs and cats, T4, ECG, blood pressure, cardiac auscultation, thoracic radiographs, and echocardiogram are also recommended.[29,57]. However, on the basis of initial history, examination, and laboratory results, more specific geriatric laboratory tests may be requested to access specific organ systems.[56]

## Sedation

Sedation is not usually required for the neonatal cat or dog.[34] For the pediatric patient, mild sedation may be recommended. For this age, benzodiazepines in combination with opioids are often used (similarly to geriatric patients; see the following sections). For the geriatric patient, the recommendation for sedation will depend on patient's individual physical condition. The use of reversible, short-acting drugs is usually recommended. For example, intravenous fentanyl ($8–10\,mcg\,kg^{-1}$) together with midazolam ($0.1–0.2\,mg\,kg^{-1}$) usually sedates the sick or geriatric patient well and commonly reduces the induction agent requirements. Oftentimes, endotracheal intubation can be performed without administration of additional induction agents. Alpha-2 adrenergic receptor agonists should be avoided in neonatal and geriatric patients, as they cause significant vasoconstriction, hypertension, decreased cardiac output, and arrhythmias. Acepromazine should be avoided or used in low doses to reduce the vasodilatory effect associated with hypotension. A minimum of 3 min of preoxygenation with 100% oxygen via face mask is recommended for all neonatal, pediatric, and geriatric patients before induction and intubation. Atropine or glycopyrrolate should be administered for any neonatal and pediatric patient to support heart rate and should be available for the geriatric patients.

## Anesthesia induction and maintenance

For most neonatal patients, a mask induction with isoflurane or sevoflurane is considered simple and effective. The effects of inhaled anesthetics on blood pressure and the incidence of hypotension are similar between infants and neonates at ~1 MAC.[58] Most challenges with general anesthesia of neonatal patients are related to patient size. Intubation can be difficult; the larynx of neonatal kittens and puppies is overly fragile, and great care should be taken for an atraumatic intubation.[34] Application of regular monitoring equipment can be problematic; intravenous catheter placement can be difficult. Likewise, IPPV is generally needed in neonatal puppies because neonates tend to develop fatigue easily when increased work of breathing is required. Regular rebreathing systems are not recommended for patients <3 kg unless it is specifically made for ventilation of extremely small patients with small tidal volumes (i.e. the Hallowell Anesthesia Workstation). A nonrebreathing system, such as a modified Bain system, can also be used to reduce excess breathing resistance and to provide manual IPPV. Although neonatal anesthetic techniques are challenging, the anesthetist should try to implement them to improve the survival rate.

Young cats and dogs are frequently anesthetized for spays and neuters with a minimum number of complications.[59] Propofol and etomidate are usually considered safe in low doses for the pediatric and geriatric population.[60] Etomidate (and possibly other injectable drugs) has a higher potency in the neonatal patient, and doses should be administered on a "to effect" basis. At 10 weeks of age, the dose of etomidate became the same as the adult dose in a study on dogs.[61] Dissociative agents (i.e. ketamine and tiletamine) should be avoided in the first 2–3 weeks of life because they may be associated with higher mortality rate.[62]

Administration of warm fluids with 2.5% dextrose is often recommended.[63] Most importantly, the monitoring of temperature and blood glucose throughout the procedure should be performed and blood glucose and temperature corrected as needed. For the very small patients, fluid overload and overuse of heparinized flush through intravenous catheters should be avoided; non-heparinized solution is highly recommended as 0.9% saline is minimally expensive than and as effective as heparin in preventing phlebitis and increasing duration of patency of peripheral intravenous catheters.[64]

Hypothermia occurs more readily in pediatric patients than in adults because of the greater surface area, minimum subcutaneous fat, and reduced ability to shiver. Providing a warm environment and maintaining the animal on a heat source during presurgery, intrasurgery, and postsurgery are essential.

For the geriatric population, there is no evidence that any particular anesthetic drug is preferable for induction and/or maintenance of anesthesia.[65] On the basis of the specific pharmacological properties of some drugs, each can be considered better for a specific patient due to the specific coexisting diseases. However, drugs that heavily depend on liver metabolism and renal excretion are usually avoided or used with caution. Thus, propofol and etomidate are usually considered safe in low doses for the geriatric population.[60] Propofol causes vasodilation[60] and decreased cardiac output and is also a potent respiratory depressant. Etomidate is recommended for the geriatric patient with an unstable cardiovascular system; however, it is associated with transient suppression of adrenocortical function and should be used with care for those patients with adrenal diseases.[66]

Maintenance of anesthesia can be performed with inhaled or injectable anesthetics. Close monitoring of anesthetic level is recommended, and patients should be kept in a light plane of anesthesia if possible. Isoflurane and sevoflurane are potent vasodilator agents and can cause significant hypotension when used in high concentrations. Continuous rate infusions of fentanyl, remifentanil, lidocaine, and ketamine alone or in combination are often used to decrease the MAC of inhalant anesthetics and minimize their side effects.

Age alone is not an indication for invasive monitoring; however, diligent monitoring during the entire anesthetic period and recovery is recommended. Independent of the coexisting conditions of the geriatric patient, ECG, end-title $CO_2$, hemoglobin $O_2$ saturation, temperature, and blood pressure should be monitored. Urinary output and blood gas analysis are also recommended. Mechanical ventilation is often suggested to provide normal ventilation and minimize the physiological changes of the age in the respiratory system. Geriatric patients are often dehydrated, and careful fluid therapy is recommended. The fluid rate choice is based on hydration, cardiovascular, and electrolyte status.

## Analgesia

There are numerous lines of research suggesting that the CNS is mature enough to transduct, transmit, modulate, and perceive pain during the last trimester of pregnancy[67] (more precisely at 29 weeks of gestation for humans[68]). Therefore, analgesia for the neonatal and pediatric patient should always be discussed for any painful procedure. Although pain recognition can be difficult in the very young, studies suggest that pain and distress associated with surgery early in life can result in disturbances of eating, sleeping, and stability or the state of arousal in maturing humans;[69] it is very likely that these same effects happen in other species. Similarly, depending on the CNS status of the elderly patient, the recognition of pain can be challenging, and common sense should be applied. A painful lesion for an adult patient will very likely be painful for any other patient irrespective of their age. Along with routinely used opioids (i.e. morphine, hydromorphone, etc.), potent opioids such as fentanyl and remifentanil can be used in neonatal, pediatric, and geriatric patients; however, ventilatory monitoring needs to be implemented because they are potent respiratory depressants.[70]

Local anesthetic techniques can be used and are very effective in all ages. The dose requirements are lower for neonatal and pediatric patients than adult patients,[71] but the techniques are similar. Castrations are the most common elective surgery for the pediatric patient, and a simple intratesticular blockage with lidocaine is considered very effective and should be performed (Figure 17.1).[72,73]

## Recovery of anesthesia

In the neonate (the first 3 days after birth), genital or umbilical region stimulation induces reflex respiration[21]

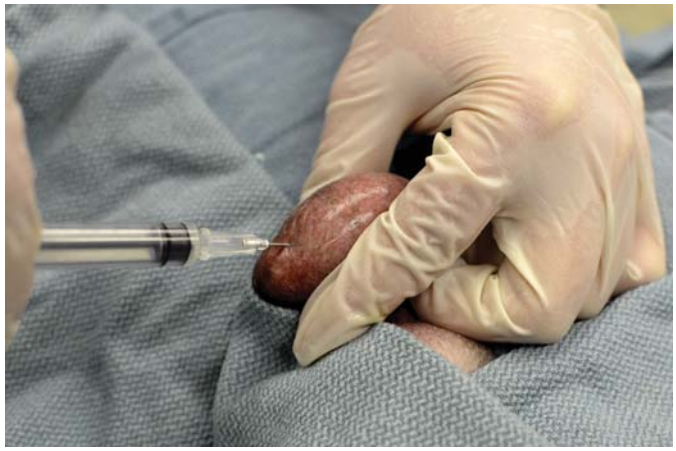

**Figure 17.1** Intratesticular block using 2% lidocaine in a young dog before surgical castration.

and can be attempted clinically to stimulate ventilation during recovery of anesthesia. Prolonged recovery, hypotension, and hypothermia are common in elderly patients. The anesthetist should be ready to provide oxygen, heat, and continuous cardiorespiratory monitoring. An open airway must be maintained via intubation until the animal is swallowing. The same basic principles that guide pain management in the general population apply to the geriatric group.[65] Providing proper nursing care for recumbent animals, including warming and turning and human touch, and compassionate verbal encouragement are recommended.[29] The AAHA senior care guidelines for dogs and cats also recommends that clients should receive postoperative directions with clear, concise, verbal, and written take-home instructions that include information about possible complications, drug effects, nursing care, nutritional management, home monitoring, and after-hours veterinary phone contact.[29]

## Conclusion

The anesthesiologist should consider age and specific coexisting diseases as a whole when designing anesthetic protocols for neonatal, pediatric, and geriatric patients. Age is a multifactorial, all-encompassing process; therefore, there is no one ideal anesthetic plan that would be recommended for all patients.[65]

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# 18 Disorders related to trauma

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In physiological terms, trauma is a combination of severe tissue injury, hemorrhage, and inflammation. Evaluation of vital signs, including level of consciousness and adequacy of airway, breathing and circulation, should be the first step of triage in severe traumatic injury patients. Initial treatment should be rapid and center on improvement of oxygen delivery. Inadequately treated pain has been repeatedly shown to increase the stress response, resulting in higher morbidity in trauma patients; effective and appropriate analgesia should also be a priority after initial stabilization. Anesthesia of trauma patients can be very challenging. Most anesthetic drugs cause some degree of cardiopulmonary depression, which can be catastrophic in patients with low cardiovascular reserve capacity. Before anesthesia, all animals should be preoxygenated and monitoring equipment connected. Anesthesia should be achieved with short-acting, reversible drugs that have minimal cardiovascular effects. In this chapter, anesthetic and analgesic options to be used in patients with severe traumatic injury are discussed.

According to the veterinary literature, trauma patients represent >13% of all referred cases.[1] Trauma is defined as transfer of energy to a living tissue, producing injury and pathology.[2] In human patients, the presence of concurrent traumatic injuries affecting multiple areas of the body can be considered severe trauma or polytrauma.[3] Recently, the term polytrauma has been better defined in humans via an Injury Severity Score (ISS). The body regions evaluated for ISS determination are the head, face, thorax, abdomen, and extremities. The severity of injury to each of the three most severely affected body regions is assigned a score on a scale from 1 to 6 (1 for minor trauma and 6 for untreatable trauma). Each score is squared, and the patient's ISS is obtained by summation of these three scores. Polytrauma is then defined as an ISS value >16, a level that has been correlated with increased mortality, morbidity, and hospitalization time.[4] Unfortunately, in veterinary medicine, there is no unanimous consensus on the definition of severe trauma nor on the classification of the severity of injury.

In physiological terms, severe trauma is a combination of severe tissue injury, hemorrhage, and inflammation. Severe trauma patients usually present with reduced vital organ reserve capacity, hypovolemic shock, tissue hypoxia, electrolyte disturbance, anaerobic metabolism, and a hypermetabolic state. Initial stabilization of the trauma patient is essential before any anesthesia. In 1989, the American College of Surgeons Trauma Committee created trauma protocols, which are also known as the ABC of trauma.[2] The main objective of the initial trauma protocol is to ensure efficient reestablishment of vital organ perfusion and to maximize oxygen delivery ($DO_2$). Cardiac output, blood hemoglobin concentration, and oxygen saturation of hemoglobin are major factors in the determination of global oxygen delivery ($DO_2$).[5,6] Initial patient evaluation should be rapid and center on provision of life support. Evaluation of vital signs, including level of consciousness and adequacy of airway, breathing and circulation, should be the first step of triage. Initial treatment of the trauma victim should make sure the *(A) airway* is patent with no signs of obstruction. After this, it is necessary to ensure the patient is *(B) breathing* with no signs of hypoxia. Most trauma patients benefit from an enriched oxygen environment (such as flow-by oxygen or a face mask). Finally, the *(C) circulation* should be assessed through

*Canine and Feline Anesthesia and Co-Existing Disease*, First Edition. Edited by Lindsey B.C. Snyder and Rebecca A. Johnson.

monitoring of the heart rate, pulse quality, blood pressure, and biochemical markers such as lactate and hematocrit.[2,7]

Venous access is imperative in trauma patients for the administration of fluids, blood products, and inotropes. Animals should have at least a large bore catheter preplaced before anesthesia induction. Animals that have a low hematocrit (<22%) or are in severe hemorrhagic shock may benefit from red blood cell (RBC) transfusion.[8] During anesthesia, the hematocrit can drop by 3–5%, making even small blood losses significant and warranting blood transfusion.[8]

After initial stabilization, imaging tools can be used to diagnose injuries such as chest contusion, pneumothorax, traumatic myocarditis, intracavity effusion, and spinal/bone fracture. In addition, before anesthesia, patients should receive a thorough physical examination, complemented by basic hemodynamic monitoring and minimum blood work.[8]

## Anesthesia in severe trauma patients

All anesthetic agents cause some degree of cardiovascular and respiratory depression. Furthermore, anesthetic drugs will blunt sympathetic drive and inhibit physiological autoregulatory mechanisms that maintain adequate blood pressure and cardiac output (CO) in trauma victims. It is, therefore, common for trauma patients to develop catastrophic cardiovascular collapse after induction of anesthesia. Anesthesia of severe trauma patients is a challenging and stressful event, best performed by experienced and well-trained personnel. Before induction of anesthesia, all animals should be preoxygenated for at least 5 min and noninvasive monitoring equipment connected.[8] In general, essential monitoring equipment consists of a capnograph, electrocardiogram (ECG), and pulse oximeter, together with noninvasive blood pressure and heart rate monitoring.[7]

Sometimes, there is a need to perform emergency procedures with little "heads up" anesthesia warning time. A prewritten checklist for the anesthesia area will ensure that all equipment is working properly and that no steps have been overlooked due to haste, allowing induction of anesthesia to proceed smoothly (Table 18.1).[9]

Total anesthesia time has been correlated with an increase in both morbidity and mortality. The anesthesia, radiology, and surgery teams should actively communicate to ensure an efficient work flow with no unnecessary time under anesthesia.[9] Preclipping/cleaning of the wound(s) and having the surgical team in sterile gowns before induction can also minimize total anesthesia time.

**Table 18.1** Checklist for anesthesia-ready area.

| **Preoperative checklist:** |
|---|
| [–] / NA: Oxygen source operational |
| [–] / NA: Anesthesia machine pressure tested |
| [–] / NA: Endotracheal tube and laryngoscope present |
| [–] / NA: Monitoring equipment operational |
| [–] / NA: Infusion pump/fluid set-up ready |
| [–] / NA: Inotropes drawn and available |
| [–] / NA: Preoperative drugs and antibiotics present |
| [–] / NA: Drug cart stocked and updated |
| [–] / NA: Crash cart stocked and updated |
| [–] / NA: Patient has IV catheter; surgical site preclipped |
| [–] / NA: Patient cross-matched and blood bank ready |

Anesthesia should be achieved with short-acting, reversible drugs that have minimal cardiovascular effects.[7] Due to the significant homeostatic changes in traumatized patients, there is no set dosage for any given anesthetic or analgesic drug. As a general rule, severe trauma patients require less anesthetic agent for equivalent effect. It is recommended to start at a fraction of the published dose (Table 18.2) and then titrate on the basis of patient response.[7] Endotracheal intubation should always be performed in anesthetized trauma patients. Maintenance of anesthesia can be obtained using inhalant anesthetics (Table 18.3), intravenous anesthetic infusion, or a combination of both.[10] Essential monitoring includes ECG, blood pressure (invasive and noninvasive), capnography, and pulse oximetry; a dedicated, trained person should be constantly evaluating the depth of anesthesia. During recovery, the patient may still require cardiopulmonary support.[11] Hemodynamic monitoring should be continued in the intensive care unit (ICU).

Trauma patients present with a vast array of physiological derangements that require specific care. For discussion, trauma patients are divided into head trauma, thoracic/abdominal trauma, and extremity orthopedic trauma.

**Table 18.2** Analgesic and sedative drug classes and comments.

| Drug class | Effects and side effects | Use in severe trauma |
|---|---|---|
| Alpha2-agonists | Reliable muscle relaxation<br>Analgesia and sedation<br>Side effects include bradycardia and vasoconstriction | Not recommended in patients who are hypovolemic, dehydrated, or in shock |
| Nonsteroid anti-inflammatory drugs (NSAIDs) | Good analgesic and anti-inflammatory properties<br>Side effects include inhibition of renal protective mechanism and gastrointestinal bleeding | Not recommended in patients who are hypovolemic, dehydrated, or in shock |
| Steroids | Good anti-inflammatory properties<br>Side effects include gastrointestinal bleeding, immunosuppression, and inhibition of renal protective mechanism | Not recommended in patients who are hypovolemic, dehydrated, or in shock |
| Phenothiazine (acepromazine) | Reliable muscle relaxation and sedation<br>No analgesic properties<br>Side effects include vasodilatation and hypotension | Not recommended in patients who are hypovolemic, dehydrated, or in shock |
| Opioids | Excellent analgesia and good sedation<br>Acts on opioid receptors<br>Side effects include bradycardia, respiratory depression, and vomiting | Excellent choice for polytrauma patients<br>Titrate drug to effect<br>Side effects are reversible with use of antagonist (naloxone) |
| Local anesthetics | Block nerve action potentials and pain recognition<br>Trivial systemic side effects at recommended doses | Regional anesthesia is an excellent alternative to provide analgesia in polytrauma patients |
| Systemic lidocaine | Decreases spontaneous action potential firing<br>Side effects include sedation, seizures, vasoconstriction, and decreased cardiac output | To be used as an intravenous infusion<br>Not recommended for use in cats |
| Benzodiazepines | Good muscle relaxation<br>Good sedation when combined with opioids<br>No analgesic properties<br>Minimal cardiovascular side effects | Good adjunctive sedative in cardiovascular unstable patients |
| NMDA receptor antagonists (ketamine) | Reduce central sensitization and "wind-up"<br>Good choice for chronic pain | Good adjunctive analgesic drug in polytrauma patient<br>To be used as an intravenous infusion |
| Tramadol | Good analgesic<br>Acts on opioid, serotonin, and adrenergic receptors | A good analgesic option; however, it requires oral administration |

## Head trauma

Cerebral perfusion pressure (CPP) is dictated by the mean arterial blood pressure (MAP) minus the intracranial pressure (ICP). Patients with head trauma have a reduced CPP due to a low MAP and increased ICP.[12] To avoid cerebral hypoperfusion (decreased CPP), it is important to avoid (or treat) hypotension. Excessive hypertension can, however, elevate ICP and also be detrimental to the CPP.[7] Initial fluid therapy of choice is hypertonic saline followed by conservative dosing of isotonic crystalloid.[13]

Anesthesia is often necessary in head trauma cases to allow diagnostic and curative procedures. General anesthesia can, however, also have therapeutic value and be helpful for patients with severe head trauma. Anesthesia reduces body metabolism, lowers the cerebral oxygen requirement, and allows for permissive hypothermia and aggressive ventilator support to be instituted. However, improper anesthesia can cause increased ICP and promote a decrease in CPP.[10]

Head trauma patients usually have reduced neurotransmitter activity, making them more sensitive to anesthetic drugs. Comatose patients can be easily intubated with the use of only mild sedatives (e.g. benzodiazepines). Once the initial neurological examination and stabilization have occurred, patients can be sedated with benzodiazepines and opioids.[10] Vomiting, retching, and gagging can cause severe elevation of

**Table 18.3** Anesthetic drugs classes and comments.

| Drug class | Effects and side effects | Use in severe trauma |
|---|---|---|
| Propofol | Good induction drug with rapid induction and fast recovery<br>Reduces intracranial pressure<br>Causes hypotension and respiratory depression | Use with care in patients who are in hypovolemic shock<br>Good option for total intravenous anesthesia (TIVA) |
| Barbiturates (thiopental) | Good induction drugs with rapid induction and fast recovery<br>Reduces intracranial pressure<br>Causes hypotension and respiratory depression | Negative cardiovascular effects are less dramatic then propofol<br>Not used for TIVA |
| Etomidate | Maintains good cardiovascular status and suppress adrenocortical function | Adrenal suppression is not a desired effect in trauma patients<br>Not indicated for use in septic shock |
| Benzodiazepines | Good muscle relaxation Good sedation when combined with opioids<br>No analgesic properties<br>Minimal cardiovascular side effects | Good adjunctive sedative in unstable cardiovascular patients |
| Dissociative (ketamine, telazol) | Good induction drugs with mild analgesic properties<br>Increase sympathetic stimulation to elevate heart rate and blood pressure<br>Can increase intracranial pressure | Good induction option for hemorrhagic and septic shock |
| Inhalant anesthetics (isoflurane, sevoflurane) | Good maintenance drugs with no analgesic properties<br>Cause dose-dependent cardiovascular depression, vasodilation, and respiratory depression | Consider use in association with sedatives to decrease inhalant concentration |

ICP. Preference should therefore be given to opioids that have a low incidence of vomiting, for example, methadone, fentanyl, buprenorphine, or butorphanol.

Induction of anesthesia can be achieved with propofol or thiopental, both of which are excellent for decreasing the cerebral oxygen requirement and reducing ICP.[7] Another advantage of these drugs is that cerebral autoregulation remains intact. This protective mechanism maintains constant cerebral blood pressure (and therefore ICP), despite significant fluctuation in systemic blood pressure (MAP from 50 to 150 mm Hg).[10] Classically, ketamine induction is contraindicated because it can cause systemic hypertension and increased cerebral oxygen consumption. Recent studies have, however, shown that low dose ketamine can have a neuroprotective effect after head trauma, probably due to its NMDA receptor antagonist effect.

Inhalant anesthetics can cause dose-dependent intracranial vasodilation, hypoventilation, and elevation of ICP. If administered at above one minimum alveolar concentration (MAC), inhalants can also promote loss of cerebral autoregulation. When this occurs, fluctuations in blood pressure generate detrimental fluctuations in cerebral blood flow (and therefore ICP). Maintenance of anesthesia for head trauma victims can be achieved with total intravenous anesthesia (TIVA). This can be accomplished through infusion of propofol in combination with a short-acting opioid such as remifentanyl or fentanyl. Infusion can be temporarily discontinued in order to conduct neurological assessment and then recommenced.

All anesthetic drugs cause some degree of hypoventilation and transient increases in carbon dioxide, which can impact cerebral vasodilation and increase ICP. After anesthesia induction, patients should be immediately intubated and intermittent positive pressure ventilation (IPPV) commenced. During anesthesia, it is preferable to maintain normocapnea ($PaCO_2$ of 30–35 mm Hg) and normoxia ($PaO_2 > 99$ mm Hg) to avoid increases in ICP.[7] Patients benefit from being mildly hypothermic

($T = 96–98°F$) throughout the procedure. A sudden reduction in heart rate accompanied by severe hypertension (Cushing's reflex) can be a sign of severely elevated ICP. Intracranial hypertension can be treated with mannitol and hypertonic saline boluses; steroid use has not been effective in reducing ICP. The use of long-acting steroids has also been reported to increase morbidity in head trauma patients and is no longer indicated.

During recovery from anesthesia, it is important to make sure the patient can properly ventilate and has a gag reflex before extubation. Postoperative analgesia can be achieved with the use of opioids. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided if the patient is hypovolemic or has recently received systemic steroids.

## Thoracic and abdominal trauma

After initial stabilization and physical examination, diagnostics should include chest radiographs and abdominal ultrasound together with assessment of blood pressure, hematocrit, blood gases, and serum biochemical profile. Most thoracic and abdominal trauma is due to blunt force or penetrating injury.[7] These patients are therefore prone to pneumothorax, diaphragmatic hernia, pulmonary contusion, and pericardial, thoracic, and/or abdominal effusion. Severe trauma patients can have a sudden decrease in circulating blood volume (hemorrhage), leading to reduced venous return and resulting in hypovolemic shock.[14] Hypovolemic shock is characterized by a decrease in CO with an increase in systemic vascular resistance (SVR).[6] If this is not corrected, factors maintaining the high SVR (vasoconstriction) will cease to be active, and the patient will progress to a hypodynamic stage.[6] Hypodynamic shock is characterized by a decrease in CO accompanied by a decrease in SVR (vasodilation) and resistance to inotropes.[15]

Initial therapy for hypovolemic shock consists of appropriate fluid therapy and use of vasopressors to ensure adequate arterial blood pressure.[16] Blood products should be available in case there are signs of low $DO_2$.[14] Attempting aggressive fluid resuscitation and aiming for supraphysiological blood pressure values may cause hemodilution and increased bleeding, resulting in increased morbidity.[7] The combination of hypertonic saline with the minimum crystalloid dose necessary to maintain MAP at ~60 mm Hg is an appropriate fluid therapy choice to treat moderate uncontrolled hemorrhage.[15] Catastrophic uncontrolled hemorrhage requires immediate and aggressive fluid therapy to maintain CO until surgical hemostasis can be performed.[13,14]

Unfortunately, the clinician is usually unable to accurately assess the volume status of the patient and predict the effects of fluid therapy.[17,18] Traditional variables used as indicators of preload to guide fluid resuscitation, such as central venous pressure (CVP), MAP, and blood lactate concentration are unable to consistently predict the hemodynamic response to a fluid challenge.[18–21] A better method is therefore needed to guide fluid therapy during anesthesia.[22] Assessment of preload through monitoring of pulse pressure variation, total end-diastolic volume, and CO or repeated cardiac echocardiogram can serve as better guides to fluid therapy but are still not commonly used in clinical cases.[21–24]

In most severe thoracic and abdominal trauma patients, anesthesia can be achieved with the use of an opioid and benzodiazepine (opioid induction) administered intravenously. Short-acting, rapid-onset opioids (such as fentanyl or remifentanyl) are preferable (Table 18.2).[10] If necessary, the administration of a low dose of ketamine should allow for endotracheal intubation (Table 18.3).[10] Maintenance of anesthesia can be achieved with an inhalant anesthetic. Due to the fact that all inhalant anesthetics produce dose-dependent hypotension, myocardial depression, and decreased CO, it is important to use the minimum amount necessary.[7,10] Infusion of ketamine, lidocaine, and/or an opioid can reduce the total amount of inhalant anesthetic necessary. When appropriate, local anesthetic blocks are an excellent option to reduce inhalant anesthetic use even further (see analgesia section).[7,25]

After surgery, the patient should be closely monitored. The first 3 h after general anesthesia is the most likely period in which anesthesia-related fatalities will occur.[26] Severe trauma patients have comorbidities that make them prone to chronic (pathologic) pain syndrome (see analgesia section). Adequate analgesia is paramount to ensure smooth recovery and decrease morbidity. NSAIDs should not be administered in the initial therapy because these patients are usually hypovolemic or have signs of organ compromise.

### Orthopedic extremity trauma

Orthopedic trauma is not usually an emergency procedure, and anesthesia can therefore be postponed until the patient is stabilized and other concomitant morbidity (such as diaphragmatic hernia or abdominal/thoracic effusion) is ruled out. Some fractures can lead to significant blood loss (e.g. fracture of the pelvis or femur), and the patient can be hypovolemic on presentation. Along with initial stabilization of the patient, care should be taken to temporarily immobilize the fractured limb(s). This procedure provides significant pain relief due to reduction of movement and dislocation of bone fragments. If spinal trauma is suspected, it is necessary to restrain and immobilize the patient with a rigid backboard to avoid any further nerve damage. The use of a radiolucent backboard will facilitate diagnosis because all diagnostic imaging procedures are preferably performed with the patient still immobilized. If dealing with an open fracture, a sterile wound dressing cover will prevent further contamination and nosocomial infection.

Once the patient is adequately stabilized and internal organ damage has been ruled out, anesthesia can be induced in a routine manner. The main concern during premedication is to decrease stress and provide good analgesia. Opioids, in association with a low dose of an alpha-2 agonist or acepromazine (Table 18.2), are a good choice for premedication.[8] Opioids provide adequate sedation, muscle relaxation, and analgesia in most animals. The use of sedatives will reduce the dose of induction and inhalant anesthetic agents required. Most short-acting intravenous induction agents are suitable for this group of patients.[10] These include propofol, thiopental, dissociative anesthetics (ketamine and tiletamine), and etomidate (Table 18.3).

Inhalant agents offer a good option for maintenance of anesthesia. Whenever possible, local anesthetic techniques such as an epidural block or brachial plexus block should be used to provide analgesia and reduce the amount of inhalant anesthetic necessary. An epidural block is a very effective way to provide analgesia and muscle relaxation in distal limbs. The most frequently used medications for epidural analgesia are local anesthetics, opioids, or combinations of these drugs.[27] NSAIDs are a good option for these patients, as long as they are normovolemic with no signs of renal or hepatic disease.

## Analgesia in severe trauma patients

After severe trauma, there is a significant amount of tissue damage, organ dysfunction, and activation of inflammatory pathways. All of these activate pain pathways. Tissue damage due to neurological traumatic injury, pulmonary contusion, soft tissue destruction, bone fractures, or vascular injury is often associated with a painful experience and may have ramifications that can last a lifetime.[25] In both veterinary and human medicine, there is still inadequate attention given to amelioration of pain. In one study of human polytrauma patients in an ICU, about 75% received inadequate analgesia and rated their pain intensity as moderate to severe.[28] It has also been found that 50% of burn patients respond poorly to analgesic treatment.[29] Furthermore, even when pain is treated in the ICU, analgesics are administered without adequate assessment of the patients' pain status. In one study, 90% of human ICU patients were treated with opioids, yet only 42% were assessed for pain.[30] Inadequately treated pain has been repeatedly shown to increase the stress response, resulting in higher morbidity.[12] As pain is a major component of trauma and has several deleterious systemic effects, early pain management is of utmost importance and should be considered a basic tenet of care of trauma patients.[31]

## Effects of pain in polytrauma patients

### Cardiovascular effects

In the severe trauma patient, a cardiovascular response is present shortly after the initial insult and is characterized by an increase in sympathetic tone, leading to an increase in peripheral vascular resistance and mean blood pressure.[32] Blood loss results in stimulation of baroreceptors, causing further increase in heart rate and SVR (vasoconstriction).[15] Acute pain exacerbates the cardiovascular response to trauma through immediate and massive release of cathecolamines.[33] This can lead to severe hypertension and undesirable tachyarrhythmias. Interestingly, persistent untreated pain has been shown to reduce the sensitivity of the arterial baroreceptors and then blunt the normal physiological tachycardic response to hypotension, further worsening the patient hemodynamics.[34]

### Neuroendocrine effects

Perhaps surprisingly, tissue damage induces release of both proinflammatory and anti-inflammatory cytokines.[35,36] Massive tissue trauma leads to an excessive inflammatory response. Cytokines and other inflammatory mediators increase the sensitivity of nociceptors in injured tissues. Severe injury and subsequent extensive inflammation results in the release of large amounts of metabolically active chemicals.[12] An overwhelming proinflammatory response leads to the clinical manifestation of systemic inflammatory response syndrome (SIRS),[7] which seems to be responsible for organ dysfunction and multiple organ failure (MOF).[37]

Pain caused by trauma is conducted to the spinal cord and then transmitted to the hypothalamus. The consequent activation of the hypothalamic centers induces the secretion of corticotrophin-releasing hormone (CRH) within minutes of the traumatic insult.[38] CRH stimulates the secretion of corticotrophin (ACTH) and enhances the production of adrenocortical hormones.[39] Pain leads to an exacerbation of the stress response and increases secretion of corticosteroids. Endogenous cortisol secretion leads to an anti-inflammatory response and immunosuppression. This overwhelming anti-inflammatory response is called compensatory anti-inflammatory response syndrome (CARS). CARS seems to be responsible for the immunosuppression that puts traumatized patients at high risk of septic complications.[40]

Long-lasting nociceptive pain also triggers activation of the N-methyl-D-aspartate (NMDA) receptors and induces acute hyperalgesia. Activation of these receptors and oversensitization of peripheral nociceptors lead to the shift from adaptive (protective) to maladaptive (pathologic) inflammatory pain.[41] Maladaptive pain is the expression of abnormal sensory processing and persists long after the tissue has healed.

In summary, untreated pain makes trauma patients more prone to SIRS, immunosuppression, sepsis, and long-lasting maladaptive pain, underscoring the need for effective and appropriate analgesia in trauma patients.

### Effects on wound healing

Studies have now investigated the relationship between pain and wound repair after routine surgery. Greater postsurgical pain is associated with delayed healing of the surgical wound.[42] Pain increases serum cortisol levels, negatively affecting wound healing.[43,44] Both the phagocytic and killing functions of leukocytes can be altered by repeated exposure to painful stimulation.[45,46] This impairs bacterial clearance, therefore resulting in a significant increase in the incidence of opportunistic infection. Pain-induced catecholamine production directly impairs keratinocyte motility and wound re-epithelialization.[47] Keratinocytes express beta2-adrenergic receptors, and activation of these has been shown to delay healing of acute surgical wounds.[48]

Trauma patients therefore appear to be highly predisposed to developing delayed and impaired wound healing if appropriate pain management is not initiated.

## Therapeutic analgesia options for trauma patients

Pain control should be an integral part of the overall treatment plan for the trauma patient. When a patient has experienced severe trauma, the clinician should assume that the condition is extremely painful and provide appropriate treatment. Analgesic treatment in trauma represents a multistage approach involving pain assessment, intervention, and repeated re-evaluation.

Some clinicians continue to work under the misconception that analgesia masks physiologic indicators of patient deterioration and delays recognition of clinical complications.[49] A meta-analysis of prospective studies performed in human polytrauma patients demonstrated the absence of adverse affects associated with the early treatment of pain and better outcomes in patients who received early analgesic intervention.[50] Observations also exist in veterinary medicine to show that analgesics do not mask the signs of patient deterioration and should not be withheld for this reason.[51]

Other important elements that influence the effects of pain in polytrauma are psychological factors such as stress, fear, and anxiety. There are now several animal studies showing the role of stress in enhancement of nociceptive responses.[52–54] The use of anxiety-reducing drugs and techniques for individuals experiencing pain has been proven to reduce the perceived severity/intensity of pain.[55] Anxiolysis could therefore represent an effective, adjunctive component of the analgesic approach to traumatized veterinary patients.

In the management of the polytrauma patient, it is also critical to consider iatrogenic pain secondary to procedures performed during daily patient care.[56] Traumatized human patients often report excruciating pain during even trivial and common procedures such as changes of body position and phlebotomy, which usually cause only minimal discomfort in healthy individuals.[57]

Injuries sustained to the abdomen, pelvis, and hind limbs benefit from epidural analgesia. The administration of epidural analgesia can lead to reduction in the overall dose of drugs necessary, together with an extended duration of analgesia and reduced systemic side effects in comparison to intravenous administration. Local anesthetic agents (bupivacaine or lidocaine) in combination with morphine are usually the drugs of choice to be administered epidurally. When local anesthetics are used epidurally, appropriate volume dosing is important to avoid excessive cranial spread and blockade of the sympathetic system. Epidural analgesia is contraindicated in patients with coagulation disorders, spinal injuries, or skin infections.[27]

Paravertebral blocks are a possible alternative to epidural analgesia and can be useful in the management of patients with thoracic trauma. A new technique in dogs and cats known as paravertebral blockade of the brachial plexus was recently developed at the Atlantic Veterinary College and was first described in 2000.[58] Due to the risk of inadvertent intravascular injection, phrenic nerve paralysis, and nerve injury, it is recommended that those performing this nerve block have adequate training and practice. In patients with rib fractures, an intercostal block is relatively simple to perform and provides effective pain management, with analgesic effects reported to last 4–6 h.

Trauma-associated pain is a complex and multifactorial symptom that requires a thoughtful approach using a variety of treatment modalities to obtain an optimal outcome. Multimodal (or balanced) analgesia represents an approach to pain management using a combination of several drugs with different mechanisms of action in order to minimize the dose of each single agent.[59] Using several drugs in combination, however, introduces a significant variable, which is generally unpredictable. This important variable is the effect of each drug on the concentration of the others at their sites of effect. Multimodal analgesics allow one to reduce drug dosage and have other benefits; however, it is therefore important to stress that the clinician should use the minimum number of drugs necessary to achieve optimal control of pain. Opioids have the advantages of being effective, titratable, reversible analgesics with minimal cardiovascular side effects. For these reasons, they constitute first-line analgesics for trauma patients. A possible initial approach to multimodal analgesia in trauma patients may therefore include an opioid and a regional block.[7] When used in combination with opioids, benzodiazepines provide adjunctive sedation with few cardiovascular side effects.[25] The decision whether to include a sedative depends on the patient's temperament.

Anesthesia of severe trauma patients is very challenging and best performed by experienced and well-trained personnel. Patients should always be stabilized before anesthesia. All anesthetic/analgesic agents promote some degree of cardiovascular impairment; there is no completely safe anesthetic protocol. All cases should be evaluated individually and protocols modified according to the disease pathophysiology and clinician's physical examination of the particular patient. Continuous patient monitoring, together with a vigilant anesthetist, is probably the best solution to reduce morbidity during surgery.

Trauma can activate several different pain pathways and should be aggressively treated. Untreated pain can cause an accentuation of the stress response, leading to development of chronic disabling pain and is associated with delayed wound healing. Multimodal analgesia and continuous patient reassessment constitute the cornerstones of pain management.

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