G.E. Cold · N. Juul *Editors*

Monitoring of Cerebral and Spinal Haemodynamics During Neurosurgery

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Preface

Make the best of it (Samuel Pepys)

Everyone interested in neuroanaesthesia talks about intracranial pressure (ICP), but in daily clinical practice nobody measures it during craniotomy. This was our view ten years ago, when Dr. Cold was asked by an international congress to make a speech with the title: Is hyperventilation mandatory during craniotomy? Panic triggered our intellectual resources and, thanks to our good friends the neurosurgeons, we soon performed the first measurement of subdural ICP. Very soon we were convinced that perioperative subdural ICP measurement not only gave important information concerning the occurrence of brain swelling after opening of dura, but also it was possible to follow the effects of ICP-reducing procedures such as hyperventilation, indomethacin, mannitol treatment and surgical decompression by drainage of ventricular fluid or cystic tumours. Moreover, we were convinced that perioperative ICP measurement combined with gas analysis from arterial and jugular venous blood would provide us with important neurophysiological information, instead of the prevailing feeling that the intracranial content is a black box until the exposure of dura. As a consequence, we introduced subdural ICP measurement and insertion of a jugular bulb catheter as routine procedures, provided resources were available, and we soon found that a database containing relevant information for interpretation of ICP data was needed.

Our database contains information from about 1,830 predominantly elective patients undergoing craniotomy. Our first publication concerning the method was published in the *British Journal of Neurosurgery* (1996), and was followed by other publications. Data from these publications are presented in this book and we acknowledge the editors for giving permission to extract data from these publications.

The studies presented in this book are prospectively collected and 8 studies were designed as controlled studies, but the majority of the comparative studies were based on data from the database. In total 16 published and 27 unpublished studies are included in this book. We are well aware that uncontrolled studies, based on collection from a database, can be criticized. Nevertheless, we argue that results from uncontrolled studies may give a hint, and stimulate the repetition of such studies in a controlled design.

As the methods of monitoring, measurement of subdural ICP and data concerning cerebral haemodynamics, and anaesthetic practice are the same, we have chosen to collect these data in a separate chapter (Chapter 2). Moreover, we have preferred the "old fashioned" way of presenting references in the text by name and year of publication, and consequently the reference lists are alphabetical.

Georg E. Cold
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Published papers concerning subdural ICP include the following:

Bundgaard H, Cold GE (2000) Studies of regional subdural pressure gradients during craniotomy. Br J Neurosurg 14:229–234

Bundgaard H, Jensen K, Cold GE et al (1996) Effects of perioperative indomethacin in intracranial pressure, cerebral blood flow, and cerebral metabolism in patients subjected to craniotomy for cerebral tumors. J Neurosurg Anesthesiol 8:273–279

Bundgaard H, Landsfeldt U, Cold GE (1997) Subdural monitoring of ICP during craniotomy: thresholds of cerebral swelling/herniation. Acta Neurochir Suppl 71:276–279

Bundgaard H, von Oettingen G, Larsen KM et al (1998) Effects of sevoflurane on intracranial pressure, cerebral blood flow and cerebral metabolism. Acta Anaesthesiol Scand 42:621–627

Bundgaard H, von Oettingen G, Jørgensen H et al (2001) Effects of dihydroergotamine on intracranial pressure, cerebral blood flow, and cerebral metabolism in patients undergoing craniotomy for brain tumors. J Neurosurg Anesthesiol 3:195–201

Cold GE, Tange M, Jensen TM et al (1996) Subdural pressure measurement during craniotomy. Correlation with tactile estimation of dural tension and brain herniation after opening of dura. Br J Neurosurg 10: 69-75

Cold GE, Bundgaard H, von Oettingen G et al (1998) ICP during anaesthesia with sevoflurane: a dose-response study. Effect of hypocapnia. Acta Neurochir Suppl 71:279–281

Haure P, Cold GE, Hansen TM et al (2003) The ICP-lowering effect of 10° reverse Trendelenburg position during craniotomy is stable during a 10-minute period. J Neurosurg Anesthesiol 15:297–301

Jørgensen HA, Bundgaard H, Cold GE (1999) Subdural pressure measurement during posterior fossa surgery. Correlation studies of brain swelling/herniation after dural incision with measurement of subdural pressure and tactile estimation of dural tension. Br J Neurosurg 13:449–453

Olsen KS, Juul N, Cold GE (2005) Effect of alfentanil on intracranial pressure during propofol-fentanyl anesthesia for craniotomy. A randomized prospective dose-response study. Acta Anaesthesiol Scand 49:445–452

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Rasmussen M, Tankisi A, Cold GE (2004) The effects of indomethacin on intracranial pressure and cerebral haemodynamics in patients undergoing craniotomy: a randomized prospective study. Anaesthesia 59:1–8

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Rolighed Larsen JK, Haure P, Cold GE (2002) Reverse Trendelenburg position reduces intracranial pressure during craniotomy. J Neurosurg Anesthesiol 14:16–21
Stilling M, Karatasi E, Rasmussen M et al (2005) Subdural intracranial pressure, cerebral perfusion pressure, and degree of cerebral swelling in supra- and infratentorial space-occupying lesions in children. Acta Neurochir Suppl 95:133–136
Tankisi A, Cold GE (2007) Optimal reverse Trendelenburg position in patients undergoing craniotomy for cerebral tumors. J Neurosurg 106:239–244
Tankisi A, Rolighed Larsen J, Rasmussen M et al (2002) The effects of 10 degrees reverse Trendelenburg position on ICP and CPP in prone positioned patients subjected to craniotomy for occipital or cerebellar tumours. Acta Neurochir (Wien) 144:665–670
Tankisi A, Rasmussen M, Juul N et al (2006) The effects of 10° reverse Trendelenburg position (rTp) on subdural intracranial pressure and cerebral perfusion pressure in patients subjected to craniotomy for cerebral aneurysm. J Neurosurg Anesthsiol 18:11–17

Content

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Abbreviations

ARDS	Acute respiratory distress syndrome
AVD	Arteriovenous difference
$AVDO_2$	Arteriovenous oxygen difference
BIS	Bispectral index
BMI	Body mass index
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CI	Confidence interval
$CMRO_2$	Cerebral metabolic rate of oxygen
CPAP	Continuous positive airway pressure
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CT	Computed tomography
CVP	Central venous pressure
CVR	Cerebrovascular resistance
DHE	Dihydroergotamine
DPG	2,3-Dephosphoglycerate
DWI	Diffusion-weighted magnetic resonance imaging
EC_{50}	Half maximal effective concentration
EEG	Electroencephalogram
FiO_2	Fraction of inspired oxygen
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HES	Hydroxyethyl starch
ICP	Intracranial pressure
IVP	Intraventricular pressure
JBP	Jugular bulb pressure
JP	Jugular pressure
MABP	Mean arterial blood pressure
MAC	Minimal alveolar concentration
MCAO	Middle cerebral artery occlusion
MRI	Magnetic resonance imaging
NIBP	Non-invasive blood pressure

O_2Ct	Venous oxygen content
OR	Odds ratio
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
$PbrO_2$	Brain tissue oxygen tension
PEEP	Positive end-expiratory pressure
PET	Positron emission tomography
$PtiO_2$	Partial tissue oxygen tension
PVI	Pressure/volume index
PvO_2	Jugular venous oxygen tension
PVR	Peripheral vascular resistance
r	Correlation coefficient
rCBF	Regional cerebral blood flow
rCBV	Regional cerebral blood volume
rTp	Reverse Trendelenburg position
SAH	Subarachnoid haemorrhage
SATv	Jugular venous saturation
SBF	Spinal cord blood flow
SD	Standard deviation
SE	Standard error of mean
SjO_2	Jugular venous/bulb oxygen saturation
SPP	Spinal perfusion pressure
SSP	Spinal subdural pressure
TBI	Traumatic brain injury

Chapter 1
Monitoring of Intracranial Pressure (ICP): A Review

Jens Aage Kolsen-Petersen, Bent Lob Dahl and Georg Emil Cold

Abstract

Everyone interested in neuroanaesthesia talks about intracranial pressure (ICP), but in daily clinical practice nobody measures it during craniotomy. This was the thesis that started this work more than ten years ago. A method for easy monitoring of ICP during surgery, but before opening of dura, was devised and the method was introduced in our daily clinical practice.

In this chapter indications for ICP measurement, critical levels of ICP and regional differences in ICP are described. Medical approaches to ICP control are considered, including body position, hyperventilation, hypothermia and administration of barbiturate. The effect of suctioning, positive end-expiratory pressure, sedatives and analgetics are discussed as well as the use of mannitol and hypertonic saline.

In this chapter, indication for intracranial pressure (ICP) measurement, critical levels of ICP and regional differences in ICP are described. Medical approaches to ICP control are considered, including body position, hyperventilation, hypothermia and administration of barbiturate. The effect of suctioning, positive end-expiratory pressure (PEEP), sedatives and analgesics are discussed as well as mannitol and hypertonic saline.

Lundberg (1960) introduced continuous intraventricular pressure (IVP) monitoring in the neurointensive clinic. This method, based on an intraventricular catheter connected to a pressure transducer at the level of the external auditory meatus, has remained the gold standard ever since. The main limitation of this method is the risk of infection that increases over time and is in the range 6–11% (Mayhall et al. 1984; Aucoin et al. 1986). Owing to the traumatic nature of the method, difficulties concerning the surgical procedure, especially when the cerebral ventricles are compressed, and the relatively high infection rate, other methods have been introduced. These include: epidural transducer; subdural bolt via a burr hole; subdural catheter; peroperative placement of a subdural needle; intraparenchymal transducer; lumbar spinal fluid pressure; and lumbar epidural pressure.

1.1 Normal Intracranial Pressure Values

Cerebrospinal fluid (CSF) pressure data of spinal origin are numerous. Normal pressure is generally defined as pressures below 200 mmH_2O, corresponding to 15 mmHg. In supine subjects without cerebral disorders ICP averages 11 mmHg (SD 2 mmHg, range 7–15 mmHg) (Albeck et al. 1998). In the vertical position, the ICP is approximately 10 mmHg, and does not exceed 15 mmHg (Czosnyka and Pickard 2004). Full Term infants have an ICP ranging between 2 and 6 mmHg (Dunn 2002), and during the first days after birth even sub-atmospheric ICP is common (Welch 1980). In children values between 3 and 7 mmHg are within the normal range (Dunn 2002).

1.2 Regional Differences in Intracranial Pressure

1.2.1 *Animal Studies*

It is generally believed that ICP is the same throughout the CSF spaces within the cranial cavity. Accordingly, in an experimental model of hydrocephalus in dogs, pressure gradients between ventricle, brain and subarachnoid space were not detected (Penn et al. 2005).

Pressure gradients between supra- and infratentorial compartments have been found in a pig model of epidural bleeding during expansion of a supratentorial balloon (Langfitt et al. 1964; Ganz et al. 1995). Pressure gradients within the supratentorial compartment have been studied in monkeys subjected to inflation of a balloon. It was found that pressure forces were not uniformly transmitted from an expanding mass. Even pressure decreases were observed in some brain regions (Kuchiwaki et al. 1992). Miller et al. (1987) showed evidence of temporary interhemispheric ICP gradients, ranging from 5 to 14 mmHg, in animal models of mass lesion. Supratentorial gradients of ICP have also been reported in cats and baboons after middle cerebral artery occlusion (MCAO) (Tulleken et al. 1978), and in mass lesion in the baboon (Symon et al. 1974). In a porcine model of frontal mass lesion, intraparenchymal ICP monitors were placed in the right and left hemispheres. During expansion of the mass, a pressure difference that increased as the size of the mass increased developed between intracranial regions. The regional pressures were found to vary in a consistent fashion. Right and left frontal pressures were equal. The pressure gradients through the brain were as follows: frontal pressures > temporal pressures > midbrain pressures > cerebellar pressures (Wolfla et al. 1996).

1.2.2 *Human Studies*

Pressure gradients between supra- and infratentorial compartments have been reported during fossa posterior surgery (Rosenwasser et al. 1989; Poon et al. 2002).

Pressure gradients, related to the underlying tumour and/or gravity, have been reported in patients with cerebral tumours (Bundgaard and Cold 2000). Significant and lasting ICP gradients (> 10 mmHg) were found between the frontal hemispheres in all patients with an acute subdural haematoma (Chambers et al. 1998). In patients with mass lesions, supratentorial pressure gradients up to 28 mmHg have been observed (Weaver et al. 1982; Marshall et al. 1986; Broaddus et al. 1989; Chambers et al. 2001), as in patients with intracerebral haematoma (Roux et al. 1984). In clinical studies of head injury, interhemispheric supratentorial pressure gradients have been demonstrated. Mindermann and Gratzl (1998) found that even in patients without space-occupying lesions, pressure difference exists, and argue that simultaneous bilateral ICP measurement may be warranted in the initial posttraumatic phase. Transient gradients that disappear with time are frequently observed, and may indicate an increase in the size of the lesion (Sahuquillo et al. 1999).

Interhemispheric pressure differences were not demonstrated in a clinical study of head injury with bilateral frontal placement of transducers (Yano et al. 1987).

1.3 Pressure/Volume Relationship

Intracranial volume is on average 900 cm^3 in men and 600 cm^3 in women in the first few months of life. By the age of 15 years, it increases up to 1,500 cm^3 in men and 1,300 cm^3 in women. The change in intracranial volume that occurs with age is not linear. Three main periods can be distinguished, each lasting approximately 5 years (0–5, 5–10 and 10–15 years), during which the growth of intracranial volume is linear (Sgouros et al. 1999).

Compliance is defined as the pressure reaction to a change in intracranial volume (DV/DP). The exponential nature of the pressure/volume curve indicates that a similar volume increment at different points of the curve results in a different pressure response. The slope of the pressure/volume curve is dependent on the compensatory mechanisms. Thus, changes in ventricular fluid volume and cerebral blood volume (CBV) influence the pressure increase obtained during volume expansion. Furthermore, the steepness of the pressure/volume curve varies under different pathological circumstances, and is also influenced by therapy with mannitol and steroids. Furthermore, compliance decreases with age and may account for some of the poor outcomes in elderly brain-injured patients (Kiening et al. 2002).

It has been stressed that different compartments exist, not only between supra- and infratentorial regions and interhemispherically, but also between ipsilateral supratentorial regions. Thus, pressure gradients occur between these compartments (see above) and the pressure/volume relationship therefore differs as well (Schaller and Graf 2005).

The pressure/volume index (PVI) is defined as the volume necessary to raise the ICP by a factor of 10 mmHg. By plotting the pressure on a logarithmic axis against volume, the otherwise exponential curve becomes linear. The slope of this curve is the pressure/volume index. In adults the pressure/volume index averages 25 ml, whereas in infants the index averages 10 ml (Shapiro and Marmarou 1989).

Recently, the Spiegelberg intracranial pressure and intracranial compliance monitor system have been tested. Good correlation of compliance was found with the CSF-bolus injection technique in experimental (Yau et al. 2000) and clinical studies (Piper et al. 1999). In a recent study of patients with severe head injury, it was found that at ICP > 20 mmHg, compliance was linearly correlated to cerebral perfusion pressure (CPP) suggesting failure of the autoregulatory mechanism (Protella et al. 2002).

Phase-contrast magnetic resonance imaging (MRI) measurements of systolic CSF peak velocity in the aqueduct of Sylvius is a sensitive method to detect minor changes in cerebral compliance. It has been reported that systolic CSF peak velocity decreases when CSF pressure was experimentally increased by continuous positive airway pressure (CPAP). In anaesthetized patients, hypercapnia increases systolic CSF peak velocity in comparison with normocapnia (Kolbitsch et al. 2002).

1.4 Pressure Waves

Waves occur synchronously with the cardiac cycle and respiration. Waves synchronized with positive pressure ventilation are supposed to be caused by an increase in intrathoracic pressure. Cyclic variation of cerebral pial arteriolar diameter also occurs. The amplitude of these variations is greater during normal arteriolar tone than during vasodilatation caused by hypercapnia (Daley et al. 2002).

Lundberg (1960) described A-waves, B-waves and C-waves. A-waves are characterized as large plateau-like formations recurring at intervals of varying length with duration of 5–20 min and pressure increase of maximally 100 mmHg. A-waves occur in space-occupying lesions. They are associated with an increase in CBV (Risberg et al. 1969), which again may be caused by changes in CPP in patients with intact autoregulation (Rosner and Becker 1984). Experimentally, spontaneous activity of the locus coeruleus complex is suppressed during plateau waves, while the activity of neurons from the cholinoceptive pontine area is increased (Maeda et al. 1989). Other studies indi-

cate that a lesion in the ventral noradrenergic system evoked ICP changes resembling plateau-waves, while activation of the same system by glutamate microinjection produced a decrease in ICP (Maeda et al. 1993). Thus, activity within the cholinergic basal forebrain, as well as the central noradrenergic system, contributes to ICP changes resembling plateau-waves (Maeda and Miyazaki 1998).

B-waves are defined as rhythmic oscillations, with ICP increase above 20 mmHg, occurring more or less regularly at a frequency of 0.5–2 per minute often synchronously with respiration (Lundberg 1960). B-waves are provoked by a decrease in CPP (Rosner and Coley 1986). Concomitance between B-waves and alternating electroencephalogram (EEG) tracings has been documented in patients with traumatic brain injury (Guieu et al. 1979; Munari and Calbucci 1979). Lescot et al. (2005) proposed that a neuropacemaker was the origin of B-waves, which increases the cerebral metabolic rate of oxygen ($CMRO_2$) and CBV, and leads to secondary increases in ICP.

C-waves are defined as rhythmic oscillations occurring with a frequency of 4–8 per minute with amplitude from non-discernable to 20 mmHg. C-waves are related to rhythmic variations of systemic arterial pressure described as Traube-Hering-Mayer waves. The ventrolateral medullary surface is considered as one synaptic relay involved in the generation of arterial blood oscillation (Haxhiu et al. 1989).

1.5 Critical Levels of Intracranial Pressure

Monro (1823) and Kellie (1824) defined the principles of increased ICP. Provided that the fontanels and sutures are closed, the Monro Kellie doctrine states the following: (1) the brain is enclosed in a non-expandable case of bone; (2) the brain parenchyma is nearly incompressible; (3) the volume of the blood in the cranial cavity is therefore nearly constant; and (4) a continuous outflow of venous blood from the cranial cavity is required to make room for continuous incoming arterial blood.

The tolerance to intracranial hypertension depends on the pathophysiology. Thus, high ICP levels are tolerated fairly well as regards neurological status and consciousness, if the pressure increase is developed over months or years and the high pressure is not accompanied by major shifts of the intracranial content. This is observed in obstructive hydrocephalus and slow-growing tumours. On the other hand, if intracranial hypertension is caused by haematomas or cytotoxic oedema, secondary to ischaemia, and is accompanied by a major shift of the intracranial compartments, it is tolerated badly. According to Eide (2003) the actual size or changes in size of the cerebral ventricles are no reliable predictors of ICP or changes in ICP. Thus, great caution should be exercised when predicting ICP on the basis of the size of the cerebral ventricles on cranial CT scanning.

1.5.1 *Experimental Studies*

In baboons, ischaemic oedema (cytotoxic oedema) is a threshold phenomenon that develops when cerebral blood flow (CBF) is reduced below 20 ml/100 g/min (Symon et al. 1979). However, oedema formation is also dependent on the duration of the ischaemic period and whether ischaemia is complete or incomplete (Ito et al. 1979; Schuier and Hossmann 1980; Todd et al. 1986). Studies in dogs of brain tissue- and CSF oxygen tension indicate that CPP below 80 mmHg is critical. Below this level brain tissue oxygen tension decreases. In the CPP range of 40–60 mmHg a sharp decline in oxygen tensions was found indicating development of cerebral ischaemia (Maas et al. 1993).

In rabbits the critical level at which ICP rises is PaO_2 level of 50 mmHg. Below this level ICP rises steeply (North et al. 1993).

In cats subjected to epidural balloon insufflations CBF increased when ICP began to rise. At ICP levels of 20–30 mmHg CBF and CBV started to decrease. Decompression of the balloon led to an abrupt decrease in ICP and a transient increase in CBF and CBV, after which both CBF and CBV recovered to control values (Kojima et al. 1993).

In cats posttraumatic hypoventilation exacerbates the ICP increase and reduces the pressure/volume index. It is supposed that these events accelerate neuronal damage and produce more extensive brain oedema (Shima and Marmarou 1993).

1.5.2 *Human Studies*

Cushing (1903) described the haemodynamic response to a high ICP as arterial hypertension accompanied by bradycardia. Tachycardia, however, is also observed and in a recent clinical study arterial hypertension and tachycardia was found to be a better indicator of impaired cerebral perfusion during neuroendoscopy (Kalmar et al. 2005).

During craniotomy, the critical level of ICP for cerebral swelling after opening of dura is 10 mmHg. This threshold has been demonstrated in supratentorial (Bundgaard et al. 1998) and infratentorial tumours (Jørgensen et al. 1999). In a later study it was demonstrated that when ICP exceeds 13 mmHg a 95% risk of cerebral swelling through the opening of dura occurs, whereas at ICP < 5 mmHg only 5% of patients had cerebral swelling (Rasmussen 2004c).

Studies of ICP in patients with severe head injury indicate that pressure levels above 30–40 mmHg for several hours are associated with a poor outcome (Troupp 1967; Vapalahti et al. 1969; Cold et al. 1975; Changaris et al. 1987). In a study of 160 patients with severe head injury Miller et al. (1977) found intracranial hypertension (ICP > 10 mmHg) in 82% of the patients and in 97% of

the patients with a mass lesion. Although ICP > 40 mmHg was only observed in 10% of the patients, intracranial hypertension was found to be a primary reason for death in 50% of the patients.

The relationships between ICP, the pulse wave amplitude and CPP indicate a gradual increase in amplitude with CPP decreasing from 75 to 30 mmHg. For CPP below 30 mmHg there is a sharp decrease in amplitude. This change indicates critical disturbance in cerebral circulation (Czosnyka et al. 1994).

In the American Guidelines (2000; http://www.braintrauma.org) the following recommendations are proposed: "There are insufficient data to support a treatment standard for this topic". As an option the American Guidelines propose: that "intracranial pressure (ICP) treatment should be initiated at an upper threshold of 20–25 mmHg". "Interpretation and treatment of ICP based on any threshold should be corroborated by frequent clinical examination and cerebral perfusion pressure data".

1.6 Intracranial Pressure: Impact on Mortality

Although ICP monitoring may guide therapy and is frequently part of the management of patients with severe traumatic brain injury, randomized studies demonstrating improved outcome in patients subjected to ICP monitoring are not available. In a non-randomized study, however, including patients with intracranial haemorrhage, patients subjected to ICP monitoring had an improved outcome (Valentin et al. 2003).

1.7 Intracranial Pressure After Intracranial Surgery

In a retrospective study including 514 consecutive patients with predominantly cerebral tumours ICP was monitored postoperatively. After supratentorial and infratentorial surgery 18.4% and 12.7% had postoperative sustained ICP elevation exceeding 20 mmHg, respectively. Risk factors for postoperative ICP elevation were resection of glioblastoma, repeat surgery and protracted surgery. The most common computed tomography (CT) findings in patients with elevated ICP were brain oedema and bleeding in the tumour bed (Constantini et al. 1988).

1.8 Approaches to Control of Intracranial Hypertension

The operative approach to correction of intracranial hypertension may be restricted if the main reason for intracranial hypertension is cerebral swelling

as a consequence of brain oedema or increased CBV. The control of intracranial hypertension under such circumstances is based on the control of intracranial blood volume either via control of cerebral venous distension (central venous pressure, neck compression, dihydroergotamine) or control by neurophysiological mechanisms including the chemical ($PaCO_2$, PaO_2 indomethacin, theophyllamine), neurogenic or hormonal (catecholamine), metabolic (hypnotics, analgesics, hypothermia) and autoregulatory control of cerebral circulation. Finally, control of cerebral tissue water content is possible by osmotic-acting drugs such as mannitol, diuretics and hypertonic saline.

In this chapter, non-surgical principles of control of ICP will be reviewed. New principles of prevention of ischaemic damage of the brain will shortly be commented on with emphasis on their influence on ICP and/or the pressure/volume relationship.

1.9 Control of Cerebral Blood Volume and Intracranial Pressure

In adults the intracranial blood volume is about 60–80 ml with 2/3 in the capillary and venous bed and 1/3 in the arterial vessels. With an average global CBF of 50 ml/100 g/min, about 700–1,000 ml blood (20% of cardiac output) passes through the cerebrum per minute. As CBF, under normal situations, is precisely adjusted to metabolic demand, adjustment of CBV by changes in the cerebral vascular resistance (hypocapnia, indomethacin, theophyllamine) may be potentially detrimental. On the other hand, a decrease in the cerebral venous blood volume does not influence oxygen delivery. As the blood content in venous vessels is double that of the arterial bed, the potentials of manipulation of the venous blood volume theoretically should have a greater impact on ICP.

1.9.1 *Head Elevation*

In one study, the decrease in ICP during head elevation was smaller than the decline in blood pressure leading to a decrease in CPP. Under these circumstances elevation of the head might precipitate ICP waves of the B-type (Rosner and Coley 1986). In another study, head elevation was not accompanied by a change in CPP because the decrease in ICP corresponded to that of blood pressure (Feldman et al. 1992). Routine nursing of patients with severe head injury at 30 degrees of head elevation within 24 h after trauma leads to a consistent reduction of ICP with preserved CPP (Ng et al. 2004).

A decrease in CBF with patients in the standing position, amounting to approximately 14–21% of flow in recumbence, has been reported (Scheinberg and Stead 1949; Tindall et al. 1967). In comatose patients CBF decreases gradu-

ally with head elevation from 0 to 45 degrees, from 46 to 29 ml/100 g/min. During head elevation, the difference between arterial pressure zeroed at the foramen of Monro and jugular pressure was the major determinant of CBF regardless of head position (Moraine et al. 2000). Dynamic cerebral autoregulation is preserved initially after head-up tilt in normal subjects, but deteriorates in patients with vasovagal syncope (Carey et al. 2001). ICP reduction after a change in body position is significantly greater in patients with free CSF flow through the craniospinal junction than in patents with Chiari's malformation, indicating the impairment of CSF displacement into the spinal canal in the latter (Poca et al. 2006).

1.9.2 *Reverse Trendelenburg Position*

In supine-positioned patients with supratentorial cerebral tumours 10 degrees reverse Trendelenburg position (10° rTp) decreases ICP from 9.5 to 6 mmHg without affecting CPP (Larsen et al. 2002). Similar changes were observed in prone-positioned patients with cerebellar or occipital tumours (Tankisi et al. 2002) and patients with cerebral aneurysm (Tankisi et al. 2006). The ICP-lowering effect of 10° rTp occurs within 1 min after change in position, and mean arterial blood pressure (MABP), CPP and ICP are stable during the following 10 min (Haure et al. 2003).

Repeated measurements of ICP and CPP at neutral position and varying degrees of rTp between 5 and 15 degrees can be obtained within a few minutes, and a decision concerning optimal position, as regards both the level of CPP and ICP, can be drawn. Five degrees rTp reduces ICP without affecting CPP, but a decrease in CPP was observed when further tilting was obtained. The optimal tilting of the operating table, as regards both the fall in ICP and acceptable fall in CPP, was determined to be 15° rTp (Tankisi and Cold 2007).

1.9.3 *Head Flexion, Rotation and Tilting*

Changes in head position, including maximal flexion and lateral rotation, leads to an increase in ICP, and elevation of the head give rises to a fall in ICP (Nornes and Magnäs 1971; Hulme and Cooper 1976; Kenning et al. 1981; Urlesberger et al. 1991; Yoshida et al. 1991; Williams and Coyne 1993; Meixensberger et al. 1997; Hung et al. 2000). The ICP increase during head rotation is reduced by concomitant head elevation (Hung et al. 2000). The most alarming increase in ICP, however, is observed during head-down position (Hulme and Cooper 1976; Lee 1989; Feldman et al. 1992; Schneider et al. 1993; Yoshida et al. 1993; Mavrocordatos et al. 2000). The mechanisms are intracranial venous distension and an increase in CBV (Mchedlishvili 1988; Schreiber et al. 2002). During

bilateral radical neck dissection measurement of ICP indicates a marked increase in ICP immediately after internal jugular vein ligation with a maximum peak at 30 min. Pressure levels of 40 mmHg were observed as well as systemic arterial hypertension in response to the elevated ICP (Weiss et al. 1993).

Some studies indicate that moderate flexion of the head, 15–30 degrees, is associated with a decrease in ICP owing to the improved venous drainage (Kanter et al. 1993). In another study tilting of the head at a steep angle from neutral position (head-tilt position) was compared with the "sniffing position". The sniffing position was found to be superior to the head-tilt position as regards ICP and CPP (Yoshida et al. 1993).

1.9.4 *Central Venous Pressure, Intraabdominal Pressure and Body Position*

An increase of central venous pressure (CVP), whatever the reason, may contribute to intracranial hypertension and changes in pressure/volume index. Experimental studies indicate that reduction in brain compliance can be secondary to elevation of CVP following resuscitation from haemorrhagic shock (Hariri et al. 1993). Thus, fluid volume replacement in patients with head injury should be done with careful attention to CVP.

In pigs a significant and linear increase in ICP with increased intraabdominal pressure has been demonstrated. This tendency is augmented during head-down position (Josephs et al. 1994; Rosenthal et al. 1997; Halvorson et al. 1998), but is ameliorated when apneumic retractors are applied (Este-McDonald et al. 1995). During prone position the intraabdominal pressure increases (Hering et al. 2001). This effect may lead to an increase in ICP. In one study the prone position resulted in an increase in ICP but improved CPP in patients with subarachnoid haemorrhage (SAH) or traumatic brain injury (Nekludov et al. 2006); in another study turning of the patients from the supine to the prone position did not influence ICP or CPP (Thelandersson et al. 2006).

Acutely increased intraabdominal pressure displaces the diaphragm cranially, narrowing the inferior vena cava, and increasing CVP and thereby ICP and decreasing CPP. The ICP-increasing effect is supposed to be effected by venous stasis and increased pressure in the sagittal sinus with decreased reabsorption of CSF (Bloomfield et al. 1997; Rosenthal et al. 1998).

1.9.5 *Endotracheal Suction and Tracheotomy*

In patients with acute traumatic head injury the endotracheal suction procedure, in well-sedated subjects, is accompanied by an increase in ICP, CPP and jugular venous saturation. In comparison, in patients who coughed

or moved in response to suctioning there was a slight decrease in CPP and venous saturation (Gemma et al. 2002).

In patients with severe brain damage tracheotomy is accompanied by an increase in ICP. Careful monitoring and patient selection is recommended (Stocchetti et al. 2000).

1.10 Positive End-Expiratory Pressure and Continuous Positive Airway Pressure

Coughing, Valsalva manoeuvre, application of PEEP and CPAP, and neck compression are supposed to increase ICP. The mechanisms should be an increase in cerebral venous pressure. Even application of a cervical collar for immobilization might increase ICP (Raphael and Chotai 1994).

In rabbits subjected to elevation of ICP by an epidural balloon, it was demonstrated that the volume needed to reach the deflection point of the volume/pressure course was lower, when PEEP at 10 cmH_2O was applied, compared to the values at PEEP zero. The study suggested that PEEP decreased intracranial compliance (Feldman et al. 1997).

The effect of CPAP on cerebral flow velocity is conflicting. Haring et al. (1994), in volunteers, found that 12 cmH_2O CPAP caused a significant increase in middle cerebral artery velocity. In contrast Bowie et al. (2001) did not find any significant change in velocity during application of 5 and 10 cmH_2O CPAP.

The effect of PEEP on ICP in the clinical setting are conflicting. When patients are maintained in the 30-degree head-up position, PEEP improves arterial oxygenation without increasing ICP (Frost 1977). In another study, including patients with head injury, SAH and hydrocephalus, PEEP at 5 cmH_2O did not alter ICP, and the clinical relevance of ICP increase at PEEP levels of 10 and 15 cmH_2O was questionable, because CPP did not change and remained > 60 mmHg. Furthermore, in patients with stroke (Georgiadis et al. 2001) and patients with increased ICP (McGuire et al. 1997) higher levels of PEEP did not change ICP or CPP. In a recent study application of PEEP at 10 and 15 cmH_2O produced an increase in ICP without significant effect on CPP (Videtta et al. 2002). Generally, PEEP is considered as a valuable form of therapy for the comatose patient with pulmonary disorders such as pneumonia or pulmonary oedema (Frost 1977). The effect of PEEP were studied in patients with severe head injury and acute lung injury. PEEP did not induce any change in CPP and CBF, but ICP was correlated to static elastance of the respiratory system due to alveolar overdistension (Mascia et al. 2000). The same group analysed the effect of PEEP in patients with head injury and acute lung injury, and found that when PEEP induced alveolar hyperinflation leading to an increase in $PaCO_2$, ICP increased, whereas when PEEP caused recruitment ICP was unchanged (Mascia et al. 2005). These findings are in agreement with a study by Kolbitsch et al.

(2000). They found that application of CPAP breathing at 6 cmH_2O had no influence on cerebral compliance. In contrast, CPAP at 12 cmH_2O increased CSF peak velocity measured by phase-contrast MRI. An increase in CBV, which impairs systolic craniocaudal CSF displacement, was considered the most likely underlying mechanism.

Warnings against PEEP are also based on a study in volunteers indicating that CPAP of 12 cmH_2O increased CSF pressure from 7 to 11 mmHg (Hörmann et al. 1994). In the sitting position the combination of head flexion and rotation with institution of PEEP might cause a dangerous increase in ICP (Lodrini et al. 1989).

1.11 Dihydroergotamine (DHE)

Dihydroergotamine (DHE) increases peripheral vascular resistance (PVR), mainly by constriction of the venous capacitance vessels (Mellander and Nordenfelt 1970; Müller-Schweinitzer and Rosenthaler 1987).

In a porcine model of intracranial hypertension DHE administered for 60 min caused a lasting decrease in ICP probably achieved by a decrease in CBV due to constriction of both arterial and venous capacitance vessels (Nilsson et al. 1995).

Dihydroergotamine is a potent constrictor of human basilar arteries in vitro. In normal adults, DHE does not influence CBF (Andersen et al. 1987). Neither does Hydergine, a mixture of three ergot alkaloids, alter CBF even after intraarterial carotid injection (McHenry et al. 1971; Olesen and Skinhøj 1972).

Grände (1989) reported that DHE 0.25 mg intravenously decreased ICP in head-injured patients. The duration of this effect was about one hour and after this period ICP was stabilized at a lower level. Further studies from the same group and others concluded that the decrease in ICP was accompanied by a 30% increase in CBF, a decrease in $AVDO_2$, an increase in CPP and a 6% decrease in CBV (Ryding et al. 1990). In severe head injuries the effect of DHE on ICP is not correlated to CO_2 reactivity. Thus, a decrease in ICP was obtained by DHE in patients with or without impaired CO_2 reactivity (Asgeirsson et al. 1995).

Dihydroergotamine was used at dose of 0.25 mg during craniotomy for cerebral tumours subjected to isoflurane-nitrous oxide anaesthesia. In accordance with the study in head injury patients a significant increase in MABP was observed. ICP, however, increased significantly as well. In several patients, increase in MABP was associated with an increase in CBF, and a fall in $AVDO_2$, suggesting that these patients had impaired cerebral autoregulation. Thus, the increase in ICP was associated with an increase in both CBF and MABP (Bundgaard et al. 2001).

1.12 The Lund Model

The main concept is that opening of the blood-brain barrier upsets the normal regulation of brain volume and aggravetes oedema formation. Dihydroergotamine combined with metoprolol, clonidine and prostaglandin has been introduced in the treatment of severe head injury. Metoprolol and clonidine elicit only a minor effect on cerebral haemodynamics in severely injured patients (Asgeirsson et al. 1995).

The patients were subjected to moderate hyperventilation (30–33 mmHg) and thiopental sedation (0.5–3.0 mg/kg/h). Both metoprolol and clonidine are supposed to decrease hydrostatic capillary pressure and reduce fluid filtration across the damaged blood-brain barrier. DHE in doses declining from 0.8 μg/kg/h to 0.1 μg/kg/h are administered to reduce ICP by precapillary and venous vasoconstriction. Low-dose prostaglandin infusion 0.5–0.8 ng/kg/min is given to improve microcirculation around the contusion, and to heal the disrupted blood-brain barrier (Grände 1989). This treatment has since been modified with more focus on details in treatment of these patients (Table 1 in Grände 2006).

Preliminary results with this regime seemed promising (Asgeirsson et al. 1994, 1995), however 15 years after its introduction clinical controlled studies have not been performed. Recently data suggested that if pressure autoregulation is intact then Brain Trauma Foundation management is associated with a better outcome than Lund Therapy, but if pressure autoregulation is lost then Lund Therapy is superior at improving outcomes (Howells et al. 2005). It is time to perform rigorous testing of therapeutic strategies for the treatment of severe head trauma (Andrews and Citerio 2006).

1.13 Hyperventilation (HV)

Hypercapnia has been used in the neurosurgical clinic in cases where an increase in CBF is desired, especially during carotid endarterectomy. There is

Table 1.1 Effects of hyperventilation

Beneficial effects	Detrimental effects
Decrease in ICP	Cerebral oligaemia in focal or watershed areas
Respiratory alkalosis neutralizing metabolic acidosis	Decrease in diastolic filling and cardiac output
Normalization of cerebral autoregulation	Decrease in MABP and CPP
Inverse steal phenomenon (Robin Hood)	Water and salt retention
Reduction of CSF formation	Inhibition of oxygen delivery to the tissues Bohr effect
	Lung injury

no doubt, however, that hypercapnia as a general rule is detrimental when intracranial compliance is exhausted. Instead attention will be paid to hypocapnia, which in experimental as well as clinical studies effectively reduces ICP. Hypocapnia, has been used therapeutically in patients with intracranial hypertension (Table 1.1; for review see Laffey and Kavanagh 2002).

1.13.1 *Cerebral Blood Flow, Cerebral Blood Volume and Intracranial Pressure*

Rosomoff (1963) studied changes in CBV and CSF volume after 30 min of hypocapnia to $PaCO_2$ 20 mmHg in dogs and found a fall in CBV and a compensatory increase in CSF volume. The changes in CBV caused by hypo- and hypercapnia are correlated to changes in CBF. In the monkey regional CBV (rCBV) ranges from 3.8 to 9.2 ml/100 g over the corresponding $PaCO_2$ range of 19 to 92 mmHg. The change in CBV was calculated to be 0.046 ml/mmHg $PaCO_2$ (Phelps et al. 1973). These results were confirmed by Grubb et al. (1974) (0.041 ml/100 g/mmHg $PaCO_2$). Several studies in normal humans and in patients with head injury, cerebral tumours, apoplexy and SAH have shown an increase in cerebrovascular resistance (CVR) and a decrease in CBF during hyperventilation. As a consequence, ICP is reduced. The fall in ICP follows the changes in end-tidal CO_2 and $PaCO_2$, being pronounced during the first 2–3 min. The maximal decrease in ICP is recorded about 15 min after hyperventilation. Following hyperventilation $CMRO_2$ is unchanged.

With MRI technology CBV at normal $PaCO_2$ is 42 µL/g and 29 µL/g for grey and white matter, respectively (Ulatowski et al. 1999). In the normal brain CBV changes by 0.04–0.05 ml/100 g/mmHg $PaCO_2$. In grey and white matter values of 0.053 and 0.043 ml/100 g/mmHg $PaCO_2$ have been found (Greenberg et al. 1978).

In patients with severe head injury a CBV of only 0.5 ml was necessary to produce an ICP change of 1 mmHg (Yoshihara et al. 1995). In another study a change in CBV of 0.72±0.42 ml was found when $PaCO_2$ was changed by 1 mmHg (Stocchetti et al. 1993).

During active hyperventilation cerebral venous drainage is not impaired. During massive passive hyperventilation in dogs a high positive airway pressure impedes cerebral venous drainage, increases cerebral venous pressure and consequently might increase ICP (Kitahata et al. 1971).

1.13.2 *Steal and Inverse Steal Phenomenon*

Studies of focal ischaemia indicate a decrease in focal pial blood pressure during hypercapnia (Brawley et al. 1967; Symon 1970). This phenomenon is caused by a redistribution of blood flow from regions with a relatively high ICP and low

CO_2 reactivity to regions with a high CO_2 reactivity and relatively low tissue pressure, referred to as a steal phenomenon. In patients with apoplexy and cerebral tumours, hypercapnia might provoke a steal phenomenon by promoting a decrease in CBF in the focal region of incomplete ischaemia (Palvölgyi 1969; Paulson 1970).

The occurrence of the inverse steal phenomenon is of considerable interest and has focused the attention on hypocapnia as a therapeutic tool in experimental brain ischaemia. Although studies in MCAO indicate an increase in lactic acidosis and a decrease in ATP in the focal region (Michenfelder and Sundt 1973), other experimental studies indicate that hypocapnia might redistribute blood flow from healthier regions with low tissue pressure and high CO_2 reactivity to more injured regions with high pressures and relatively low CO_2 reactivity. This reaction is called the inverse steal phenomenon. Preliminary studies in dogs and cats suggested that the size of an infarct was reduced if hypocapnia was applied prior to the insult (Soloway et al. 1968). However, later experimental studies have not corroborated this finding (Soloway et al. 1971). Other studies in isoflurane-anaesthetized rats subjected to MCAO do not provide evidence of a hypocapnia-induced inverse phenomenon (Ruta et al. 1993).

In patients with severe head injury, apoplexy and brain tumours, an inverse steal phenomenon or Robin Hood phenomenon has been observed during hypocapnia (Palvölgyi 1969; Paulson 1970; Pistolese et al. 1972; Fieschi et al. 1974; Cold et al. 1977b; Obrist et al. 1984). However, regions with inverse reactions are scattered over the cerebral hemisphere and sparsely localized to abnormal radiological findings (Cold et al. 1977b). Darby et al. (1988), in a study with enhanced xenon scanning, demonstrated that hypocapnia might provoke a pronounced CBF increase probably resulting in cerebral oedema.

In 1996 Dings et al. introduced measurement of brain tissue oxygen tension in patients with severe head injury. In many cases hypocapnia was associated with an increase in tissue oxygen tension during the first day after trauma.

1.13.3 *Bohr Effect*

Alkalosis increases the affinity of haemoglobin for oxygen and displaces the dissociation curve to the left (Bohr effect). This mechanism is counteracted by a rapid increase in lactate production (Wasserman 1994), an increase in 2,3-dephosphoglycerate (DPG) mutase and reduced activity of DPG phosphatase (Nunn 1987), which result in an increased activity of 2.3-DPG, resulting in a normalization of the dissociation curve over a period of several hours.

The decrease in oxygen delivery capacity caused by hypocapnia is partly caused by the decrease in CBF (part 75%) and partly by a shift of the dissociation curve of oxyhaemoglobin (part 25%) (Cain 1963; Gotoh et al. 1965; Harp and Wollman 1973).

1.13.4 *Risk of Ischaemia*

This issue has been debated vigorously during the last decade. The monitored data include regional CBF (rCBF), jugular venous saturation, $AVDO_2$ and brain tissue oxygen tension. A definition of hyperaemia, where CBF outstrips the metabolic demand of the tissue, is used by Bruce et al. (1979) and Obrist et al. (1984). Their studies were primarily based on the $CMRO_2$/CBF relationship ($AVDO_2$) and jugular venous saturation. Real CBF data were used by Cold (1989a) in adult trauma patients, and Skippen et al. (1997) in paediatric head injury patents. Data based on jugular venous saturation are problematic. The two jugular veins have been shown to drain asymmetric parts of the brain, and a significant difference in oxygen saturation in the same patient has been described (Stocchetti et al. 1994). In addition, jugular bulb saturation, by definition, is unable to detect regional areas of ischaemia.

In immature rats hypocapnia increases anaerobic metabolism (Vannucci et al. 1997) and in newborn piglets hypocapnia augments production of cytotoxic excitatory amino acids (Graham et al. 1996). In the pig microdialysis model, hypocapnia decreases brain glucose and increases brain lactate concentration indicating anaerobic metabolism. Hypercapnia has no influence on glucose or lactate (van Hulst et al. 2004). During controlled hyperventilation in non-traumatized pigs no significant change in brain tissue oxygen tension was observed. In contrast, hypercapnia resulted in an increase in brain tissue oxygen tension (van Hulst et al. 2002).

In awake, unsedated patients, active hyperventilation to $PaCO_2$ 20 mmHg induces changes in EEG compatible with cerebral ischaemia (Morgan and Ward 1970). These changes disappeared when hyperbaric oxygenation was provided (Reivich et al. 1966). During hypocapnia EEG slowing is observed when jugular venous oxygen tension is about 22 mmHg (Gotoh et al. 1965). The threshold at which deterioration in consciousness occurs and EEG signs compatible with cerebral hypoxaemia are observed is a jugular venous oxygen tension of about 19–23 mmHg. These low tensions occur at PaO_2 ranging between 26 and 30 mmHg and at a $PaCO_2$ level of 19–23 mmHg. In humans subjected to extreme hypocapnia, a moderate increase in $CMR_{glucose}$ has been found, indicating anaerobic cerebral metabolism (Alexander et al. 1968). This change occurs at CBF levels ranging from 10 to 20 ml/100 g/min, and at jugular venous oxygen tensions of 20 mmHg (Gotoh et al. 1965). In the acute phase of head injury rCBF and global CBF are low (Fieschi et al. 1974; Bouma et al. 1991), and low CBF, in the early phase of head injury, is associated with a poorer outcome (Jaggi et al. 1990; Bouma et al. 1992). Severe cerebral oligaemia accompanying hyperventilation is observed in patients with severe head injury, and in patients with acute brain lesions where hyperventilation decreases rCBF below the ischaemic threshold of 18–20 ml/100 g/min (Cold 1989a; Meixensberger et al. 1993; Stringer et al. 1993). Hyperventilation is also followed by a substantial decrease in jugular bulb saturation (Fortune et al. 1995) and, although normalization of

ICP occurs, it is accompanied by significantly reduced cerebral oxygenation (von Helden et al. 1993; Unterberg et al. 1997). However, in other studies jugular bulb saturation decreases, but not to dangerously low values (Coles et al. 2002; Oertel et al. 2002). In patients with head injury brain tissue oxygen tension might decrease to low values, indicating cerebral ischaemia (van Santbrink et al. 1996; Unterberg et al. 1997; Meixensberger et al. 1998; Fandino et al. 1999; Gopinath et al. 1999; Carmona Suazo et al. 2000; Imberti et al. 2000, 2002). In other studies the fall in brain tissue oxygen tension was not significant (Schneider et al. 1998), and even an increase in oxygen tension has been reported (Gopinath et al. 1999; Imberti et al. 2000, 2002).

It has been proposed that hyperventilation can be optimized on the basis of the level of jugular venous saturation, aiming to normalize ICP and prevent low values of jugular bulb saturation (Cruz 1993, 1998; Cruz et al. 1995). In a recent review the authors concluded that careful use of hyperventilation for the short-term control of ICP remains a useful tool (Stocchetti et al. 2005).

In patients with cerebral contusion the penumbra surrounding the contused region has a high CO_2 reactivity, and the authors hypothesized that hypocapnia may provoke cerebral ischaemia in this vulnerable zone (McLaughlin and Marion 1996). Studies of brain tissue oxygen tension indicate that hyperventilation may reduce oxygen tensions to very low values (Dings et al. 1996). Likewise, manual bagging causes cerebral oligaemia, and precipitates compensatory hypoperfusion with a fall in cerebral venous saturation (Procaccio et al. 1993).

1.13.5 *Adaptation to Prolonged Hyperventilation*

Hyperventilation causes an increase in arterial pH, but only a small increase in brain pH. The increase in perivascular pH results in vasoconstriction. The stability of brain pH results from processes that counteract changes in intracellular pH. The early processes consist of physiochemical buffering by the CO_2/HCO_3^- system, the imidazole groups of histidine residues of proteins and the free and bound forms of phosphate. Active and passive transport mechanisms such as the Na^+/H^+ exchanger, the Cl^-/HCO_3^- exchanger, the H^+/lactate cotransporter and the H^+ and Na^+/HCO_3^- cotransporters are also included. The latter processes are metabolic pathways that generate or consume H^+ ions, of which increased glycolytic production of lactic acid is the most prominent feature.

In studies in dogs and goats, adaptation to prolonged continuous hypocapnia occurs within 2–3 h (Raichle et al. 1970; Albrecht and Ruttle 1987). Prolonged hypocapnia decreases the rate of formation of CSF. After an initial decrease at 30 and 60 min, however, formation of CSF returns to pre-hypocapnic values (Hochwald et al. 1976; Martins et al. 1976; Artru and Hornbein 1987). In dogs with an intracranial mass-expanding lesion, prolonged hypocapnia initially gives rise to a decrease in CBV. However, the CSF-pressure lowering effect is sustained by a reduction in CSF volume, despite re-expan-

sion of CBV. In the same model brain water content did not contribute to changes in CSF pressure and volume (Artru 1987).

The adaptation to prolonged hypocapnia has been investigated in patients with apoplexy. The half-life of the adaptation mechanism of CSF-pH and CSF bicarbonate averages 6 h, and adaptation is said to be complete within 24–30 h (Christensen 1974). Studies using a non-invasive Doppler ultrasound technique and calculation of the instantaneous mean blood velocity during hypocapnia in normal subjects indicate that blood velocity showed adaptation within 10 min after induction of hypocapnia (Ellingsen et al. 1987).

Cerebral haemodynamic responses to hyperventilation are different in normoxic and hyperoxic conditions. Thus, the CO_2 reactivity is lower with normoxia than hyperoxia, and CBF recovery is more rapid with normoxia than hyperoxia (Johnston et al. 2003). The modulation of the pH control mechanisms is influenced by increased breakdown of hypoxia inducible factor-1 (Minchenko et al. 2002), increased free radical production (Mak et al. 2002) or a direct effect of oxygen on cell membrane proteins (Haddad and Jiang 1997).

In an uncontrolled study of patients with severe head injury no signs of CSF-pH adaptation within periods of 6–24 h were disclosed. It was suggested that ischaemia prevented the CSF-pH adaptation (Cold et al. 1977a). When hyperventilation is used for several days to reduce ICP in the presence of brain oedema, withdrawal of hypocapnia should be cautious as intracranial hypertension very often reappears (Havill 1984). Mechanism of adaptation is supposed to play a role in this rebound intracranial hypertension.

1.13.6 *Hyperventilation in Premature, Neonates and Paediatric Patients*

In pre-term infants severe hypocapnia, even of relatively short duration, may elicit neurological abnormalities (Greisen et al. 1987). Neurovascular factors that predispose the immature brain include poorly developed cerebral vascular supply to vulnerable regions (De Reuck 1984), antioxidant depletion by excitatory amino acids (Oka et al. 1993) and the effects of lipopolysaccharide (Gilles et al. 1976) and cytokines (Yoon et al. 1997) that potentiate destruction of white matter. Furthermore, abrupt termination of hyperventilation results in cerebral hyperaemia, which may cause intracranial haemorrhage in prematures (Gleason et al. 1989).

In paediatric patients with severe head injury, diffuse brain swelling occurs with high frequency (Bruce et al. 1979). Increase in blood volume attributed to partial or complete impairment of cerebral autoregulation and dysfunction of the blood-brain barrier allowing pathological vasodilatation have been proposed (Bruce et al. 1979). Evidence for this assumption has never emerged. Nevertheless, vasoconstrictory therapy to decrease CBV has been suggested as particularly appropriate in paediatric patients with head injury. Hyperventilation to a $PaCO_2$ level below 25 mmHg has been standard therapy in many pae-

diatric units. In a study by Skippen et al. (1997), 23 paediatric head injury patients were followed with Xe-CT scanning, jugular bulb saturation and ICP monitoring. They found that there is a very little evidence of "absolute" hyperaemia in their patients. Furthermore, they found CBF values < 18 ml/100 g/min even in normocapnic patients. The percentage of areas with oligaemic flow increased during hypocapnia. In children with diabetic ketoacidosis cerebral low $PaCO_2$ and treatment with bicarbonate is associated with the occurrence of cerebral oedema (Glaser et al. 2001).

1.13.7 *Hyperventilation as a Lifesaving Procedure*

In patients with intracranial hypertension, hypocapnia effectively reduces ICP and CBF. It is accepted that the fall in ICP is caused by vasoconstriction of cerebral arterioles and a secondary decrease in CBV. Although the decrease in CBV is small in comparison with the total brain volume, hypocapnia can be lifesaving in patients with a mass-expanding cerebral lesion. Acute hyperventilation is, therefore, an important tool in the management of acute intracranial hypertension (Lundberg et al. 1959; Bozza et al. 1961; Slocum et al. 1961). On the other hand, hyperventilation must be used cautiously because it might provoke a dangerous decrease in CBF especially in regions with low CBF (Cold 1989b). Ideally the use of prolonged artificial hyperventilation should be guided by measurement of rCBF, $AVDO_2$, venous saturation or tissue oxygen tension.

1.13.8 *Guidelines*

There are insufficient data to support a level I recommendation for hyperventilation. Level II, prophylactic hyperventilation ($PaCO_2$ of 25 mmHg or less), is not recommended. Level III hyperventilation is recommended as a temporary measure for the reduction of elevated ICP. Hyperventilation should be avoided during the first 24 h after injury when CBF is often critically reduced. If hyperventilation is used, jugular venous oxygen saturation (SjO_2) or brain tissue oxygen tension ($PbrO_2$) measurement is recommended to monitor oxygen delivery.

1.14 Indomethacin

1.14.1 *Experimental Studies*

Indomethacin is a blocker of cyclooxygenase and thereby prostaglandin synthesis. Indomethacin acts as a cerebral vasoconstrictor and reduces CBF while

$CMRO_2$ remains unchanged (Pichard and MacKenzie 1973; Sakabe and Siesjö 1979; Dahlgren et al. 1981; Wennmalm et al. 1981). In the anaesthetized baboon, PET studies indicate that indomethacin resulted in a marked and homogeneous decrease in CBF in every region analysed and a moderate reduction in CBV. $CMRO_2$ displayed a small increase in thalamus and pons, and oxygen extraction fraction increased greatly in all structures studied (Schumann et al. 1996).

A bolus dose of indomethacin reduces ICP and increases CPP during both propofol and isoflurane anaesthesia in sheep. The ICP-decreasing effect is, however, more pronounced with isoflurane (Rasmussen et al. 2006).

Studies of canine basilar arteries indicate that prostaglandin mediates cerebral oedema (Shohami et al. 1987). In cats subjected to focal ischaemia (Dempsey et al. 1985) and rats subjected to freezing lesions (Yen and Lee 1987) indomethacin reduces cerebral oedema. Also the rapid accumulation of cyclooxygenase degrading products during reperfusion is blocked by indomethacin (Gaudet et al. 1980). In other experimental studies of focal ischaemia (Harris et al. 1982; Awad et al. 1983; Sutherland et al. 1988; Suzuka et al. 1989) and traumatic head injury (Shapira et al. 1988), indomethacin administration was not followed by a decrease in cerebral oedema.

Indomethacin reduces cerebral infarct size in focal ischaemia (Sasaki et al. 1988), enhances post-ischaemic reperfusion after MCAO (Shigeno et al. 1985) and reduces cerebral fluid compression injury (Hallenbeck and Furlow 1979). Furthermore, in rats subjected to fluid percussion trauma pretreatment with indomethacin improves recovery (Kim et al. 1989).

Other experimental studies suggest that the infarct size in focal cerebral ischaemia was not influenced by indomethacin (Harris et al. 1982; Koide et al. 1986).

1.14.2 *Human Studies*

Studies of non-steroid drugs indicate that ibuprofen (Patel et al. 2000) and diclofenac (Jones and Dinsmore 2002) do not change CBF. In comparison, indomethacin is a strong cerebral vasoconstrictor. In healthy volunteers, the decrease in CBF after a bolus dose of indomethacin followed by continuous infusion is sustained. During hypoxia and during hypercapnia CBF increases indicating normal regulation of CBF (Jensen et al. 1993). In healthy volunteers 0.1, 0.2 and 0.3 mg/kg/h indomethacin decreased CBF to about 45 ml/100 g/min (Jensen et al. 1996). During sensorimotor activation indomethacin reduces the CBF increase otherwise observed, but does not affect the increase in $CMRO_2$ (St Lawrence et al. 2003).

The vasoconstrictor effect of indomethacin has been used in the treatment of intracranial hypertension in patients with head injury. In a preliminary study, indomethacin 30 mg was followed by an immediate decrease in ICP for

about one hour. The fall in ICP was accompanied by a decrease in CBF, an increase in $AVDO_2$ and $AVD_{lactate}$, while the $CMRO_2$ was unchanged (Jensen et al. 1991). In another study the effect of a bolus dose (30 mg) of indomethacin on ICP was comparable with the effect of a 1.5-kPa decrease in $PaCO_2$ (Dahl et al. 1991, 1996). Considerable rCBF decrease has been observed after i.v. indomethacin in patients with head injury, also in focal regions where CBF is decreased. However, only a transient increase in $AVD_{lactate}$ has been observed (Jensen et al. 1991).

In patients subjected to craniotomy for cerebral tumours, indomethacin immediately and within seconds after i.v. administration decreased ICP accompanied by a decrease in CBF (Bundgaard et al. 1996). On the other hand prophylactic indomethacin treatment, administered before induction of anaesthesia, does not significantly decrease ICP in patients with cerebral tumours anaesthetized with propofol-fentanyl (Rasmussen et al. 2004a). Administration of indomethacin during propofol anaesthesia is not associated with evidence of ischaemic damage in patients with brain tumours as evaluated by diffusion-weighted imaging (Rasmussen et al. 2004b).

Only one case study of apoplexy is available, indicating a patient with raised ICP where conventional therapies had failed. Indomethacin (50-mg bolus) led to a fall in ICP and an increase in CPP (Schwarz et al. 1999).

In hepatic failure swelling of astrocytes is a common feature and may result in cerebral oedema with intracranial hypertension. There is accumulating evidence that there are high circulating levels of ammonia resulting from the splanchnic vascular bed, and this is a key mediator of these complications (Schenker et al. 1967). Ammonia crosses the blood-brain barrier (Ott and Larsen 2004), influences neurotransmitter trafficking (Filipo and Butterworth 2002) and ammonia concentration correlates to brain water content and ICP in the experimental setting (Takahashi et al. 1990; Olafsson et al. 1995).

In an experimental setting it has been demonstrated that indomethacin prevents the development of ammonia-induced cerebral oedema (Chung et al. 2001). In patients with hepatic failure bolus injection of indomethacin reduces ICP and increases CPP (Clemmensen et al. 1997; Raghavan and Marik 2006) without compromising cerebral perfusion or oxidative metabolism, as indicated by microdialysis values of glutamate and lactate. Indomethacin did not restore cerebral autoregulation (Tofteng and Larsen 2004).

1.15 Metabolic Control of Cerebral Blood Flow

Metabolic control of ICP is based on the concept that CBF is adjusted to the metabolic demand of the brain tissue. If the metabolic demand of the tissue decreases, CBF and volume will decrease, and the ICP will decline. Metabolic regulation of ICP is effected by hypothermia and drugs that reduce the metabolic rate of oxygen in the brain (hypnotics, analgesics). As hypnotic and anal-

gesic treatments depress the respiration, patients subjected to these treatments are intubated and respiration is supported by a ventilator. As this treatment is often supplemented with treatment with muscle relaxants, the effect of muscle relaxants on ICP will also be discussed.

1.15.1 *Hypothermia*

1.15.1.1 Experimental Studies

Hypothermia decreases $CMRO_2$ and CBF proportionally. In dogs the temperature coefficient Q_{10} (defined as the ratio of metabolic rates at two temperatures differing by 10°C) was 2.2 at temperatures between 37 and 27°C. Below 27°C the Q_{10} was doubled to 4.5 suggesting that the relationship of $CMRO_2$ to brain temperature is variable depending on the functional state of the brain; below 27°C progressive functional depression is supposed to account for the high Q_{10} value (Michenfelder and Milde 1991).

Hypothermia exerts a protective effect on the brain in hypoxic hypoxia (Carlsson et al. 1976), global ischaemia (Chopp et al. 1989), incomplete ischaemia (Hoffman et al. 1991) and in experimental head injury (Clifton et al. 1991). It has been suggested that even a small decrease in temperature of 1–3°C has a protective effect in experimental brain ischaemia (Busto et al. 1989) and an improvement of the blood-brain barrier has been observed (Dietrich et al. 1990). On the other hand, in rats, even small increments in temperature in ischaemic brain tissue seem to accentuate histopathological damage (Kitagawa et al. 1991).

According to Nakamura et al. (2003) rapid increase of brain temperature during re-warming is accompanied by increased extracellular lactate and glutamate. An effect on neuronal cytoskeleton, indicated by an increase of MAP-2 immunoreactivity of the CA1 neurons, was also observed 1 week, but not 1 month after hypothermia.

1.15.1.2 Clinical Studies

A barbiturate in combination with hypothermia might effectively control intracranial hypertension in some patients with severe head injury (Shapiro et al. 1974). Likewise, the combination of barbiturate and hypothermia might accentuate the protective effect in brain ischaemia (Nordström and Rehncrona 1979). On the basis of the experimental studies the use of hypothermia has been discussed and suggested in the intensive care of patients suffering from brain ischaemia (Cohen 1981).

Hypothermia has been used in the treatment of cerebral ischaemia in humans (Connolly et al. 1962) during extracorporeal circulation (duCailar et al.

1964), after circulatory arrest (White 1972), during neurosurgical operations (Uihlein et al. 1966; White et al. 1967) and in the treatment of severe head injury (Sedzimir 1959, Shapiro et al. 1974). Later on, the once common use of hypothermia was abandoned, because studies of hypothermia in the treatment of acute stroke did not prove any beneficial effect. On the contrary, a detrimental effect was observed in primates and dogs (Michenfelder and Milde 1977; Steen et al. 1979).

Mild hypothermia, however, has again been introduced in the treatment of intracranial hypertension in severe head injury. A decrease in ICP accompanied by a decrease in CBF, $AVDO_2$ and $CMRO_2$ have been found (Marion et al. 1993; Shiozaki et al. 1993), and a decrease in $CMR_{lactate}$ has been found (Metz et al. 1996). These changes are accompanied by a moderate decrease in cardiac index, a fall in platelet count and an increased level of serum lipase with signs of pancreatitis (Metz et al. 1996). In an allocated study hypothermia was found to improve outcome (Clifton et al. 1993). In a recent randomized study Marion et al. (1997) found that patients kept at 33°C for 24 h after the injury did not show improved outcome in comparison with normothermic patients.

1.15.1.3 Guidelines

In 2007 American Guidelines there are insufficient data to support level I and level II recommendations for prophylactic hypothermia. The level III recommendation states that pooled data indicate that prophylactic hypothermia is not significantly associated with decreased mortality when compared with normothermic controls. However, preliminary findings suggest that a greater decrease in mortality risk is observed when target temperatures are maintained for more than 48 h.

Prophylactic hypothermia is associated with significantly higher Glasgow Outcome Scale (GOS) scores when compared to scores for normothermic controls.

1.15.2 *Hypnotic Agents*

In experimental as well as human studies it has been documented that hypnotic agents, including barbiturate, benzodiazepines, etomidate and propofol, increase cerebrovascular resistance and reduce CBF and ICP (Pierce et al. 1962; Michenfelder 1974; Stullken et al. 1977; Larsen et al. 1981; Cold et al. 1986; Stephan et al. 1987). These effects are caused through a metabolic suppression of $CMRO_2$. The metabolic suppression is dose-dependent until the EEG is isoelectric. Beyond this level no further suppression of $CMRO_2$ or CBF occurs (Michenfelder 1974; Kassell et al. 1980; Milde et al. 1985). Hypnotics have been used in the control of intracranial hypertension (Gordon 1970; Hunter 1972; Shapiro et al. 1973).

1.15.3 *Vasodilatation*

A direct vasodilatory effect of barbiturate has been found on cerebral vessels (Altura and Altura 1975; Edvinsson and McCulloch 1981; Marin et al. 1981). Thus, Edvinsson and McCulloch (1981) in feline middle cerebral arteries found that maximum contractions effected by potassium, noradrenalin and prostaglandin F2a were reduced in the presence of pentobarbital. Gross and Abel (1985) in a rabbit basilar artery model found that concentrations of 3×10^{-5} thiopental caused relaxation of norepinephrine-induced contraction. In the monkey Tsuji and Chiba (1986, 1987) demonstrated a biphasic vascular response, with an initial vasoconstriction followed by a vasodilatation in a dose-dependent manner. It is supposed that this effect modifies the ICP-lowering effect of barbiturate when $CMRO_2$ and electrical and functional capacity are low.

1.15.4 *Cerebral Metabolic Rate of Oxygen*

In severe head injury (Bruce et al. 1973; Cold 1978; Obrist et al. 1979) and comatose patients with SAH (Grubb et al. 1977; Voldby et al. 1985) $CMRO_2$ is decreased severely, often to values averaging 50% of the values obtained in awake adults. Accordingly, the effect of barbiturate on CBF and $CMRO_2$ is decreased or absent (Messeter et al. 1986; Cold 1989b). Thus, in the acute phase of head injury the barbiturate reactivity, as measured by the decrease in $CMRO_2$ after a bolus dose of 5 mg/kg, seems to be dependent on the $CMRO_2$ level before thiopental injection (Cold 1989a), and in comatose patients with a 50% decrease in $CMRO_2$ the barbiturate reactivity averaged zero (Dahl et al. 1991).

1.15.5 *Sedation*

Chronic administration of barbiturate has been used in the intensive care management of apoplexy, severe head injury and cerebral aneurysm. As a consequence of respiratory obstruction/failure, risk of aspiration and failure of reflexes combined with unconsciousness, these patients are often intubated and eventually hyperventilated. This regime is supported by sedation with hypnotics/analgesics in order to prevent coughing, stress and anxiety. For sedation pentobarbitone or thiopental are administered at hourly intervals. Alternatively, continuous-infusion thiopental, propofol or midazolam are used. Etomidate is not used for continuous sedation because of its inhibitory effect on adrenal steroid genesis.

Propofol sedation was compared with morphine combined with midazolam sedation in patients with severe head injury. Propofol led to a fall in $AVDO_2$ from 6 to 3 ml O_2/100 ml. However, there was no effect on MABP, ICP or CPP, and outcome was similar in the two groups (Stewart et al. 1994). In a study of head injury, bolus doses of propofol 1.5 mg/kg were compared with thiopental 3 mg/kg. The ICP-reducing effects were comparable. However, the MABP-reducing effect was more pronounced and lasted a longer period when propofol was used (Merlo et al. 1993). Hypnotic drugs (thiopental, propofol or midazolam) for sedation or ICP reduction should be administered by continuous infusion, and continuous monitoring of CPP and cerebral venous saturation are recommended (Andrews et al. 1993).

1.15.6 *Intracranial Hypertension*

On the basis of the regulatory effect of hypnotic agents on acute intracranial hypertension (Shapiro et al. 1974; Sidi et al. 1983) and the abundance of documentation of a protective effect in acute focal and incomplete ischaemia, prolonged hypnotic sedation has been used prophylactically in severe head injury. In several uncontrolled studies barbiturate-coma treatment has been claimed to prevent or attenuate intracranial hypertension and improve outcome (Rockoff et al. 1979; Saul and Ducker 1982; Eisenberg et al. 1988). In other uncontrolled studies these findings are not supported (Yano et al. 1986). Ward et al. (1985), however, did not find any improvement of outcome in a controlled study where barbiturate was administered in doses sufficient to suppress the EEG to burst suppression level for several days. In the barbiturate-treated group the incidence of arterial hypotension and septicaemia were higher than in the control group. Likewise, Abramson et al. (1983) did not find any beneficial effect of barbiturate in a controlled study of thiopentone administered to patients after cardiac arrest.

1.15.7 *Guidelines*

In the 2007 American Guidelines, there are insufficient data to support a level I recommendation for the use of anaesthetics, analgesics and sedatives. Level II, prophylactic administration of barbiturates to induce burst suppression EEG, is not recommended. High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Haemodynamic stability is essential before and during barbiturate therapy. Propofol is recommended for the control of ICP, but not for improvement in mortality or 6-month outcome. High-dose propofol can produce significant morbidity.

1.16 Analgesics

1.16.1 *Spontaneous Ventilation*

Morphine and analogue drugs should be administered with extreme caution in the spontaneously breathing patient with exhausted intracranial compliance. On the other hand, these drugs are used in SAH and in the postoperative course after craniotomy. Careful monitoring of conscious state, respiration, blood pressure and eventually gas analysis (PaO_2, $PaCO_2$) or capnometry/oximetry is mandatory. Even a small dose of morphine (3 mg i.v.) might provoke a decrease in $AVDO_2$ suggesting a state of hyperaemia (Cold and Felding 1993).

1.16.2 *Controlled Ventilation*

In the ventilator-treated patient morphine and fentanyl do not increase CBF or ICP. On the contrary, a decrease in ICP is repeatedly observed. This is caused by the sedative effect giving rise to a decrease in CO_2 production, and a decreased level of circulating catecholamine, which otherwise increases cerebral oxygen uptake and CBF when the blood-brain barrier is disrupted (MacKenzie et al. 1976; Berntman et al. 1978; Artru et al. 1981). An additive effect of hypnotics and analgesics on cerebral oxygen uptake may also play a role.

1.16.3 *Sufentanil, Alfentanil*

Sufentanil and alfentanil should be used with reservation because animal experiments indicate that sufentanil provokes a prolonged period of CBF and CBV increase (Milde et al. 1990). Comparative studies of fentanyl, alfentanil and sufentanil in patients subjected to craniotomy indicate that the use of the two latter drugs was accompanied by a decrease in CPP and an increase in CSF pressure (Marx et al. 1989). Cerebral autoregulation may play a role, because correction of blood pressure normalized ICP. Both sufentanil and alfentanil elicit a decrease in blood pressure. As a consequence, a decrease in CVR and an increase in CBV may occur. Under these circumstances an increase in ICP is observed.

1.17 Muscular Relaxation

In experimental (Cottrell et al. 1983; Lanier et al. 1986) as well as human studies (March et al. 1980) succinylcholine increases ICP. The rise in ICP is caused

by activation from peripheral impulses from the muscles (Lanier et al. 1989). Non-depolarizing agents such as pancuronium, atracurium and vecuronium do not increase ICP (Lanier et al. 1985; Giffin et al. 1986; Rosa et al. 1986).

1.18 Osmotic-Acting Drugs, Plasma Expanders and Diuretics

1.18.1 *Electrolytes and Proteins and the Blood-Brain Barrier (BBB)*

Cerebral tissue is protected by the blood-brain barrier, which allows the passive diffusion of non-electrolytes inclusive of water. The extracellular space in cerebral tissue is negligible under normal circumstances. The electrophysical balance between intra- and extracellular milieu is adjusted with a high intracellular potassium concentration and a high extracellular sodium concentration.

In acute hyperosmolar states there is loss of intracellular water with cell shrinkage followed by gradual restoration of brain volume via the generation of non-electrolyte osmotically active intracellular solute. In the hypo-osmolar state, there is cellular expansion, which is corrected over time by loss of intracellular solute. Low Pl-sodium concentration is accompanied by an increase in cerebral tissue water content. During extreme hyponatraemia brain oedema may develop. If the blood-brain barrier is disrupted an increase in extracellular space with filtration of plasma proteins also occurs.

Patients with severe head injuries might have impaired peripheral circulation, even when normotensive. Volume infusion with crystalloid improves oxygen transport without increasing ICP (Scale et al. 1994).

Changes in protein concentration do not influence the volume of the extracellular space whether the blood-brain barrier is disrupted or not, because the architecture of the extracellular space does not allow any expansion.

1.18.2 *Hydroxyethyl Starch and Hyperosmolar/ Hyperoncotic Solutions*

Following haemorrhagic shock (Kramer et al. 1986; Vollmar et al. 1994) and posttraumatic muscular lesions (Mittlmeier et al. 2003) hyperosmotic and hyperoncotic solutions restore impaired microcirculation related to haemodilution-associated improved rheology, reduced swelling of endothelial cells and increased capillary diameter. Likewise, following traumatic brain injury hyperoncotic/hyperosmolar solutions restore impaired microcirculation and decrease posttraumatic oedema (White and Likavec 1992; Kempski et al. 1996; Qureshi and Suarez 2000) by shifting free water into the intravascular lumen, thereby reducing posttraumatic endothelial swelling (Mazzoni et al. 1988), decreasing capillary resistance and improving the rheological properties of the

blood (Mittlmeier et al. 2003), reducing rolling and sticking of white blood cells to the capillary wall in the early phase following experimental brain injury (Nolte et al. 1992; Härtl et al. 1997), and improving pericontusional perfusion and reducing lesion volume following experimental brain injury (Thomale et al. 2004). An early bolus of hyperosmolar/hyperoncotic solution improves long-term outcome after global cerebral ischaemia in rats (Noppens et al. 2006).

In patients with CT signs of blood-brain barrier impairment, penetration of HES into the CSF does not occur (Dieterich et al. 2003).

1.19 Mannitol

1.19.1 *Osmotic Gradient*

In patients with intracranial hypertension, early studies of intravenous infusion of mannitol showed that this drug effectively reduces ICP (Wise and Chater 1962). After fast intravenous infusion of 0.5–1 g/kg ICP is reduced after 2–5 min. The ICP-reducing effect is of hours duration, depending on the dose and the infusion rate (James 1980).

The osmotic effect of mannitol is dependent on the osmotic gradient in blood (Shenkin et al. 1962). The faster the concentration difference of mannitol occurs between plasma and extracellular fluid, the stronger and the longer the reduction in ICP (Takagi et al. 1993). A difference in osmotic gradient exceeding 10 mOsm always gives rise to a reduction in ICP (Marshall et al. 1978). The decrease in ICP is correlated to the decrease in the water content in brain tissue (Nath and Galbraith 1986).

Long-term administration of mannitol, however, increases spinal fluid osmolarity in patients with SAH or severe head injury. Consequently, it has been advocated to measure CSF osmolarity regularly in patients receiving mannitol for longer than 24 h (Polderman et al. 2003).

1.19.2 *Experimental Studies*

Following mannitol infusion in cats, blood viscosity decreases immediately. The greatest decrease occurs at 10 min. At 75 min a rebound increase in viscosity occurs. The pial vessel diameter decreased simultaneously, the largest decrease being at 10 min. The changes in pial vessels were interpreted as an autoregulatory process (Muizelaar et al. 1983). Further studies indicate that if cerebral autoregulation is impaired, mannitol infusion is followed by a decrease in ICP, while ICP is unchanged in studies where the

autoregulation is intact (Muizelaar et al. 1984). The authors hypothesized that changes in blood viscosity might give rise to compensatory changes in the degree of constriction in cerebral vessels. In studies of vessel diameters with the cranial window technique in cats, it was concluded that mannitol in clinically relevant doses does not exert significant constriction on cerebral vessels. Mannitol therefore exerts its effect on ICP through its osmotic effect, rather than by a direct effect on CBV (Auer and Haselsberger 1987).

Studies of mannitol infusion at normal ICP in baboons (Johnstone and Harper 1973) and dogs (Kassell et al. 1982) have shown an increase in CBF, while CBF is unchanged in animals subjected to intracranial hypertension by an epidural balloon (Johnstone and Harper 1973). In the same study mannitol infusion was followed by an increase in $CMRO_2$.

Studies of cryogenic oedema in the cat indicate that a single dose of mannitol decreases cerebral oedema. However, a repeated dose of mannitol leads to increased water content in oedematous regions (Kaufmann and Cardoso 1992). In rats subjected to cryogenic cortical injury, multiple doses of mannitol did not aggravate total hemispheric swelling or global water content (von Berenberg et al. 1994).

In a rat model of ischaemic cortical infarction, repeated mannitol infusions resulted primarily in a decrease in brain water content of the infarct and in the ipsilateral hemisphere (Paczynski et al. 1997).

Mannitol has a beneficial effect in experimental cerebral ischaemia (Little 1978; Watanabe et al. 1979). In studies of experimental cytotoxic oedema mannitol induces a normalization of EEG (James 1978). Studies in rabbits subjected to MCAO have shown that mannitol administration improves CBF in regions of ischaemia, and that a gradual decline in intercellular pH is prevented (Meyer et al. 1987). Shirane and Weinstein (1992) found that mannitol intensified reperfusion hyperaemia after 30 min temporary ischaemia in rats. Both mannitol and glycerol improve parameters of cerebral energy metabolism during ischaemia and up to 8 h after reperfusion in the gerbil brain (Tsuda et al. 1998). In cats mannitol improves post-ischaemic recovery of blood flow (Tanaka and Tomonaga 1987). In the rats subjected to MCAO the combination of hypothermia plus mannitol have a great neuroprotective effect (Kazan et al. 1999), and in rats subjected to forebrain ischaemia mannitol considerably ameliorated the ischaemic injury (Sutherland et al. 1988). In a swine model of retractor brain ischaemia, mannitol plus nimodipine is superior to either agent alone in maintaining both CBF and evoked potential (Andrews and Muto 1992).

In rats with MCAO mannitol provides neuroprotection by preventing both necrosis and apoptotic components of cell death (Korenkov et al. 2000). Mannitol at clinical concentrations, however, induces apoptosis in endothelial cells (Malek et al. 1998; Famularo 1999), an effect antagonized by adrenomedullin (Kim et al. 2002). One pathway of mannitol-mediated apoptosis is through the degradation of focal adhesion kinase and Akt, and that insulin-like growth factor I protects the cells from apoptosis by blocking the activation of caspases (Kim and Feldman 2002).

Other experimental studies of cerebral ischaemia have failed to demonstrate any enhancement of CBF by mannitol (Seki et al. 1981; Pena et al. 1982).

1.19.3 *Human Studies*

Studies of central haemodynamics in patients undergoing craniotomy have shown that mannitol infusion is followed by an increase in blood volume, CVP, pulmonary artery wedge pressure and cardiac output and a decrease in the concentration of haemoglobin, plasma sodium and the peripheral resistance (Rudehill et al. 1983; Brown et al. 1986). The concentration of plasma potassium decreases after mannitol 1 g/kg and increases after 2 g/kg (Manninen et al. 1987).

An increase in CBV a few minutes after mannitol infusion has been demonstrated (Ravussin et al. 1986a). Following mannitol infusion blood viscosity decreases for at least 2 h, suggesting an enhancement of cerebral microcirculation (Burke et al. 1981). Accordingly, studies of cerebral circulation indicate an increase in CBF occurring after 10–20 min and lasting for up to 24 h, and a variable increase in $CMRO_2$ (Jafar et al. 1986).

The effect of mannitol on ICP has been studied in patients with cerebral tumours and aneurysms. In patients with normal ICP a transient but significant increase in ICP followed by a steady decrease towards values below control were found. In contrast; in patients with intracranial hypertension ICP decreased immediately after mannitol infusion (Ravussin et al. 1986b). In a clinical trial, patients with acute subdural haematoma had a better outcome and improved control of intracranial hypertension when treated with high doses of mannitol (Cruz et al. 2001).

Other studies suggest that the effect of mannitol is at least partly dependent on other haemodynamic mechanisms. Thus, patients with CPP > 70 mmHg responded relatively poorly to mannitol, while ICP decreased in patients with CPP < 70 mmHg, suggesting that at CPP > 70 mmHg the vasoconstriction is already nearly at maximum. Under this circumstance mannitol is unable to increase resistance further (Rosner and Coley 1987). In general, administration of large doses of mannitol is safe in the presence of intracranial hypertension (Abou-Madi et al. 1993).

In neurointensive patients the volume/pressure relationship improves after mannitol, often without change in ICP (Miller and Leech 1975).

1.19.4 *Mannitol in Acute Head Injury*

Early administration of mannitol (1.4 g/kg) in the emergency room is associated with improved clinical outcomes for adult comatose patients with acute,

non-missile, intraparenchymal temporal lobe haemorrhages and associated abnormal pupillary widening (Cruz et al. 2002). Cruz et al. (2004), in a randomized trial, also demonstrated successful use of mannitol treatment (1.4 g/kg) in patients with Glasgow Coma Scale (GCS) scores of 3 and bilateral abnormal papillary widening.

1.19.5 *Mannitol in Cerebral Infarct*

Theoretically, mannitol use in large cerebral infarctions may preferentially shrink non-infarcted cerebral tissue, thereby aggravating midline shift and worsening neurological status. That mannitol can accumulate in ischaemic brain tissue has been demonstrated (Maioriello et al. 2002). Acute mannitol used in patients with cerebral oedema after a large hemispheric infarction, however, does not alter midline tissue shifts or worsen neurological outcome (Manno et al. 1999), and improvement of evoked potentials has been demonstrated after mannitol treatment in patients with ischaemic stroke (Onar and Arik 1997). In contrast a Cochrane database review concludes that there is currently no evidence to decide whether the routine use of mannitol in acute stroke would result in any beneficial or harmful effect, and that the routine use of mannitol in patients with acute stroke is not supported by any evidence from randomized trials (Bereczki et al. 2001).

1.19.6 *Mannitol and the Blood-Brain Barrier*

Osmotic opening of the brain-blood barrier by infusion of hyperosmolar solutions like mannitol has repeatedly been demonstrated. In patients with cerebral tumours hyperosmolar blood-brain barrier disruption with mannitol is used to overcome the relative inaccessibility of infiltrating glioma cells to chemotherapy. It has been argued that opening of tight junctions is the dominant mode of leakage in hyperosmolar opening. The opening of the barrier is independent of energy-producing metabolism. It is supposed that osmotic barrier opening is the result of passive shrinkage of endothelial cells and the surrounding tissue (Greenwood et al. 1988). As a result of the impaired barrier function mannitol diffuses into the cells. In this respect it is of interest that HES macromolecules protect against blood-brain barrier disruption after intracarotid injection of mannitol in rats (Chi et al. 1996).

In patients with space-occupying cerebral processes, the blood-brain barrier may be disrupted. Under these circumstances mannitol may permeate into the cerebral tissue, and even into an ischaemic insult (Maioriello et al. 2002).

1.19.7 *Rebound Phenomenon*

Cells are able to create osmotically active particles. These particles reduce the transcellular osmotic gradient (Jennett and Teasdale 1981).

After discontinuing the mannitol infusion the osmotic gradient is reversed because mannitol is excreted through the urine, decreasing the concentration in the plasma. Consequently, the concentration of mannitol is found to be higher in the extracellular and intracellular compartments as compared with the concentration in the blood. This rebound phenomenon gives rise to water influx into brain cells, and an increase in ICP (McQueen and Jeanes 1964).

1.19.8 *Guidelines*

In the Guidelines for the Management of Severe Traumatic Brain Injury (2007), the following recommendations are suggested:

A. Level I: There are insufficient data to support a level I recommendation for hyperosmolar therapy.
B. Level II: Mannitol is effective for control of raised ICP at doses of 0.25–1 g/kg body weight. Arterial hypotension (systolic blood pressure < 90 mmHg should be avoided.
C. Level III: Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes. Hypovolaemia, however, should be avoided by fluid replacement. Serum osmolality should be kept below 320 mOsm because of concern for renal failure. Euvolaemia should be maintained by adequate fluid replacement. A Foley catheter is essential in these patients. Intermittent boluses may be more effective than continuous infusion.

In the European guidelines osmotic therapy, preferably mannitol given as repeated infusion, is advocated. Serum osmolality should be maintained < 315 mOsm. Other agents, such as glycerol or sorbitol are not advocated. If osmotherapy has insufficient effect, furosemide can be given additionally (Maas et al. 1997).

In a Cochrane database review Schierhout and Roberts (2000) conclude that there are insufficient data to recommend one form of mannitol infusion over another. Mannitol therapy for raised ICP may have a beneficial effect on mortality when compared to pentobarbital treatment. ICP-directed treatment shows a small beneficial effect compared to treatment directed by neurological signs and physiological indicators. There are insufficient data on the effectiveness of pre-hospital administration of mannitol to preclude either a harmful or a beneficial effect on mortality.

1.20 Glycerol

Glycerol is an alternative to mannitol in the treatment of intracranial hypertension. Glycerol is effective by the oral and i.v. routes. Haemolysis can be provoked but is avoided by reducing the concentration and infusion rate (Quandt and Reyes 1984). In one study equipotent doses of mannitol and glycerol were used in children with intracranial hypertension. Mannitol was found to be superior to glycerol (MacDonald and Uden 1982). In a study of adult patients with intracranial hypertension a greater and longer lasting pressure reduction was found when glycerol was used (Smedema et al. 1993). In another study by Biestro et al. (1997) glycerol and mannitol were compared in patients with head injury. At 1 and 2 h after infusion both agents induced an effective decrease on ICP and increase in CPP. The results suggested that mannitol would be most indicated as a bolus to control sudden rises in ICP, whereas glycerol would be most indicated as a basal treatment.

1.21 Hypertonic Saline

1.21.1 *Experimental Studies; Central Haemodynamics*

Pigs subjected to haemorrhagic hypotension were resuscitated with hypertonic saline or Ringer's solution. Normalization of blood pressure and oxygen delivery were faster with hypertonic saline (Schmoker et al. 1991). An improved cardiac performance has likewise been observed (Kien et al. 1991a).

In dogs subjected to haemorrhagic hypotension, resuscitation with either 7.2% saline or 20% HES was used. Both fluids restored MABP and cardiac output equally. At 60 min after resuscitation, however, cardiac output decreased in the hypertonic resuscitated group. ICP, CPP and CBF were similar in both groups (Whitley et al. 1991).

In dogs transtentorial herniation was produced by creating a supratentorial intracerebral haemorrhage with autologous blood injection. The state of transtentorial herniation was unresponsive to hyperventilation. Hypertonic saline, however, reversed the transtentorial herniation, normalized ICP and increased CBF as well as $CMRO_2$ (Qureshi et al. 2002).

In a blinded, randomized study in swine hypertonic saline/dextran caused an immediate, transient acidaemia, which primarily was due to hyperchloraemic, hypokalaemic metabolic acidosis with normal anion gap. The acidaemia was transient because of the offsetting alkalotic effects of decreasing serum protein, normalization of electrolytes and the transient nature of an increase in CO_2 tension (Moon and Kramer 1995).

1.21.2 *Intracranial Pressure, Cerebral Blood Flow and Blood-Brain Barrier*

During resuscitation of animals with acute haemorrhage the ICP level is lower in animals treated with hypertonic saline (Prough et al. 1985, 1991; Ducey et al. 1990; Schmoker et al. 1991). Under this circumstance hypertonic saline also reduces water content in cerebral tissue (Todd et al. 1985), but not in the injured part of the brain (Wisner et al. 1990), CBF improves (Todd et al. 1985; Whitley et al. 1988; Prough et al. 1991; Schmoker et al. 1991; Schürer et al. 1992) and brain tissue oxygen tension normalizes (Schürer et al. 1992).

In cats subjected to fluid percussion injury and mild haemorrhage hypotension, rCBF does not increase sufficiently to restore cerebral oxygen delivery or normalize EEG activity (DeWitt et al. 1996). Studies of rCBF and regional glucose utilization in rats indicate a perfect coupling after resuscitation, although the ratio glucose utilization/rCBF was reset to a higher level (1.5 ml/mmol in the control group, contra 2.7 ml/mmol in the hypertonic saline group) (Waschke et al. 1996). Hypertonic saline injures healthy and glutamate-injured rat hippocampus neurons, but does not affect astrocytes (Himmelseher et al. 2001).

It is supposed that the improvement of CBF and the decrease in ICP are caused by a reduction in the cellular volume of uninjured brain parenchyma, endothelial cells and erythrocytes (Shackford et al. 1992). However, hypertonic saline disrupts the blood-brain barrier (Durwald et al. 1983), and rapid infusion of hypertonic saline might cause acute hypotension by a decrease in total peripheral resistance (Kien et al. 1991b).

1.21.3 *Comparative Studies Between Hypertonic Saline and Mannitol*

In a canine model of intracranial haemorrhage the effect of 3% and 23.4% hypertonic saline was compared with mannitol (1 g/kg). Hypertonic saline, in both concentrations, is as effective as mannitol in the treatment of intracranial hypertension. Hypertonic saline has a longer duration of action, particularly when used in 3% solution (Qureshi et al. 1999). In rats subjected to cortical cryogenic lesion, hypertonic saline was more effective in reducing ICP than equiosmolar mannitol, and in mannitol-treated animals rebound intracranial hypertension was observed (Mirski et al. 2000). In rabbits subjected to cryogenic lesion, infusion of hypertonic saline induces a decrease in ICP (Härtl et al. 1993). Berger et al. (1995) studied the effect of 7.2% saline/dextran or 20% mannitol in rabbits subjected to focal lesion of vasogenic oedema. They found that hypertonic saline/dextran was as effective as mannitol in reducing ICP.

1.21.4 *Human Studies*

In a double-blind randomized trial Vassar et al. (1993) used Ringer's solution, 7.5% saline, 7.5% saline combined with dextran 70, and 7.5% saline combined with 12% dextran. Patients with systolic pressure < 90 mmHg were included. They found that hypertonic saline was associated with an increase in blood pressure and an increase in survival at hospital discharge. Patients with low baseline GCS seemed to benefit most from 7.5% NaCl. Hypertonic NaCl without added dextran 70 was as effective as the solution that contained dextran 70. There was, however, no significant effect on neurological outcome after 6 months in hypotensive trauma patients randomized to 250 ml 7.5% NaCl or 250 ml lactated Ringer's solution in addition to conventional fluid therapy (Cooper et al. 2004).

In a randomized trial equipotent rapid infusion of hypertonic saline and mannitol was compared. Hypertonic saline caused a greater ICP decrease than mannitol, and had a longer duration of effect than mannitol (Battison et al. 2005).

Although experimental studies indicate that hypertonic saline is not superior to mannitol in its ability to reduce ICP in cryogenic brain oedema (Scheller et al. 1991), hypertonic saline has been used successfully in children with head injury (Fisher et al. 1992; Khanna et al. 2000), in patients with intractable intracranial hypertension (Worthley et al. 1988) and in patients with brain stem trauma.

Zornow (1996) in an editorial concludes that hypertonic saline reduces ICP and brain volume, and can be used safely in humans with minimal potential for morbidity. On the other hand, Schell et al. (1996) summarize that further studies are needed to measure the functional outcome rather than early parameters of CNS function. In addition hypertonic NaCl has a defined risk including the potential detrimental effects of hypernatraemia (lethargy, seizure and coma), tearing of bridging veins, and development of subdural haematoma, central pontine myelinolysis, cardiac failure and arrhythmia.

1.22 Furosemide

In cats furosemide induces an inhibition of CSF production and a concurrent reduction of ICP. These changes are thought to enhance the clearance of vasogenic oedema (Reulen et al. 1977). In dogs with intracranial hypertension furosemide has no effect on CSF formation rate (Miller et al. 1986). In cats subjected to cold injury furosemide effectively reduces the amount of brain oedema (Long et al. 1976). In dogs subjected to cold injury furosemide decreases brain water content in normal dogs, but not in nephrectomized dogs, indicating that the effect of furosemide is mediated by diuresis (Marshall et al.

1982). In a recent study in rats, however, furosemide alone did not change brain water content at any dose (Thenuwara et al. 2002).

In dogs mannitol and furosemide, when used together, produce a greater and more sustained fall in ICP than mannitol alone (Pollay et al. 1983; Roberts et al. 1987). In the same animal infusion of mannitol followed by furosemide 15 min later resulted in the most profound and sustained ICP reduction (Roberts et al. 1987). In the rats furosemide in doses of 2–8 mg/kg enhances the effect of mannitol on plasma osmolality, resulting in a greater reduction of brain water content. This effect was only observed when mannitol was administered in doses of 4 and 8 g/kg (Thenuwara et al. 2002).

Adding furosemide to hypertonic saline decreases brain water content without causing more increase of osmolality and Na^+ than that caused by hypertonic saline alone (Mayzler et al. 2006).

In clinical studies furosemide does not provoke an initial increase in ICP and does not change serum osmolality or electrolytes to the same degree, as does mannitol (Cottrell et al. 1977). Furosemide decreases CSF formation rate and increases CSF absorption capacity (Sklar et al. 1980).

In patients, with brain tumour or cerebral aneurysm, subjected to a rapid infusion of mannitol (1.4 g/kg) or the same dose combined with furosemide (0.3 mg/kg), brain shrinkage was greater and more consistent with mannitol plus furosemide than with mannitol alone. Rapid electrolyte depletion of sodium was observed with the combination of the two drugs and must be corrected (Schettini et al. 1982).

In patients with intracranial hypertension, the combination of Ringer's solution and furosemide 250 mg resulted in a definite improvement in general condition occurring after 24 h. Forced diuresis with high doses of furosemide is suggested as treatment of choice for acute cerebral oedema (Thilmann and Zeumer 1974).

1.23 Corticosteroids

Glucocorticoids are useful in the resolution of altered vascular permeability in experimental brain oedema. Steroids reduce CSF production (Weiss and Nulsen 1970), attenuate free radical production, and have other beneficial effects in experimental models (Pappius and McCain 1969; Bracken et al. 1985, 1990). The net effect is a reduction of ICP.

In patients with brain tumours steroids result in a marked clinical improvement, also in the perioperative period to patients undergoing craniotomy (French and Galicich 1964; Renaudin et al. 1973). There is evidence in both animals and humans that corticosteroid administration may exacerbate ischaemic brain injury as a result of increases in blood glucose concentration (Norris 1976; Koide et al. 1986; Wass and Lanier 1996). Even a single dose of 10 mg dexamethasone intraoperative in non-diabetic patients undergoing

craniotomy produces a significant increase in blood glucose over a 4-h period (Pasternak et al. 2004; Lukins and Manninen 2005). Using Xe-CT scanning an inverse correlation of daily dose, cumulative dose and duration of dexamethasone treatment with rCBF was demonstrated in patients with cerebral tumours (Van Roost et al. 2001).

In patients with severe head injury Gobiet et al. (1976) compared low-dose and high-dose Decadron therapy, and documented a beneficial effect in patients on high-dose therapy. A beneficial effect was also found by Faupel et al. (1976) in a double-blind trial. Subsequently, six major studies were performed. None of these revealed substantial benefits of steroid therapy (Gobiet et al. 1976; Cooper et al. 1979; Gudeman et al. 1979; Braakman et al. 1983; Dearden et al. 1986). In a multicenter study, the CRASH trial, the risk of death from all causes within 2 weeks was higher in patients allocated to corticosteroids (CRASH trial collaboration 2004). The final result of the CRASH study has recently been published. The mortality rate was significantly greater with methylprednisolone (25.7% vs 22.3% for placebo) (Edwards et al. 2005).

In the American Guidelines for the Management of Severe Traumatic Brain Injury (2007) and the European EBIC guidelines (Maas et al. 1997), glucocorticoids are not recommended in the treatment of severe head injury. Level I recommendation of American Guidelines 2007: The use of steroids is not recommended for improving outcome or reducing ICP. In patients with moderate or severe traumatic brain injury (TBI), high-dose methylprednisolone is associated with increased mortality and is contraindicated.

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Chapter 2
Material Included in the Database

Georg Emil Cold

Abstract
Since 1994 we have performed perioperative measurement of subdural ICP combined with arterial and jugular blood pressure and gas analysis in primarily elective patients subjected to craniotomy. ICP was measured with a 22G needle connected to a pressure transducer via a polyethylene catheter. Until now (2006), 1,833 patients have been included in our database.

In this chapter the extensive material of the database is disclosed. Patients were entered consecutively over the years, some included as part of controlled trials and some as part of the normal daily routine. The demographics of the patient population are described, likewise the diagnosis, including tumour (if any) localization. The anaesthetics used and ICP-reducing procedures are summarized and the method for ICP monitoring discussed.

Cerebral haemodynamics and the level of ICP are of importance in the surgical management of space-occupying cerebral lesions. At high ICP surgical access to deep cerebral structures is impeded, and pressure by self-retaining specula may decrease cerebral perfusion regionally. Likewise, swelling/herniation of cerebral tissue through the opening of dura may be deleterious by preventing venous outflow from brain tissue, and increases ICP regionally. Thereby, a vicious circle may develop with increasing cerebral oedema and ischaemia, further impeding the surgical access. Preoperative measurement of ICP or other cerebral haemodynamic parameters, however, is rarely a part of the combined surgical or anaesthesiological procedure with the exception when part of a clinical investigation.

Since 1994 we have performed perioperative measurement of subdural ICP combined with arterial and jugular blood pressure and gas analysis in primarily elective patients subjected to craniotomy. ICP was measured with a 22G needle connected to a pressure transducer via a polyethylene catheter. Until May 2006, 1,833 patients have been included in our database. The number of patients per year, and the distribution of men/women are indicated in Table 2.1.

Table 2.1 Number of patients and female/male distribution related to year in 1,833 patients subjected to craniotomy

Year	Number	Women	Men	Percent women
1994	89	48	41	53.9
1995	88	46	42	52.3
1996	131	59	72	45.0
1997	132	57	75	43.2
1998	124	67	57	54.0
1999	143	81	62	56.6
2000	153	77	76	50.3
2001	171	110	61	64.3
2002	157	83	74	52.9
2003	148	66	82	44.6
2004	149	65	84	43.6
2005	207	98	109	47.3
2006	141	68	73	48.2
Total	1,833	925	908	
Percent		50.5	49.5	

Table 2.2 Distribution of age in 1,833 patients subjected to craniotomy

Years	Number	Percent of total
0–10	50	2.7
11–20	53	2.9
21–30	106	5.8
31–40	217	11.8
41–50	377	20.6
51–60	514	28.0
61–70	397	21.7
71–80	111	6.1
81–90	8	0.4
Total	1,833	

In total 1.833 patients were studied, of whom 50.5% were women. The number of patients increased from 89 in 1994 to 207 patients in 2005.

In Table 2.2 the distribution of patients is related to age. Few studies of ICP were performed in children (total 5.6% below the age of 21 years). Between the ages of 51 and 60 years recordings from 514 patients (28.0%) were analysed.

2.1 Diagnosis of Tumour, Localization of Cerebral Aneurysm and Hunt and Hess Gradation

In Table 2.3 the diagnoses of the patients are presented. The three largest groups were supratentorial cerebral tumours (1,326 patients, 72.3%), cerebral aneurysm (225 patients, 12.3%) and infratentorial tumours (150 patients, 8.2%).

Table 2.3 Distribution of patients (number and percent) related to diagnosis in 1,833 patients subjected to craniotomy

	Number	Percent
Supratentorial cerebral tumours	1,326	72.3
Infratentorial cerebral tumours	150	8.2
Cerebral aneurysm	225	12.3
Arteriovenous malformation	28	1.5
Traumatic head injury	15	0.8
Trigeminus neuralgia	26	1.4
Cerebral cyst	14	0.8
Cerebral abscess	10	0.5
Chronic subdural haematoma	7	0.4
Liquorrhea	6	0.3
Cerebral infarct	3	0.2
Parkinson disease	3	0.2
Intracerebral haematoma	11	0.6
Encephalitis	6	0.3
Disseminated sclerosis	3	0.2
Total	1,833	

The localization of cerebral aneurysm related to year is indicated in Table 2.4 (see page 62). After the introduction of coil treatment in 2003 the number of patients subjected to cerebral aneurysm surgery declined. In Table 2.5 (see page 62) patients with cerebral aneurysm are related to Hunt and Hess (H&H) gradation performed immediately before induction of anaesthesia. Sixty-three patients (28.0%) had unruptured aneurysm. In H&H groups I–III the distribution of patients differed from 16.9% to 31.6% of total. Only 4 patients in the H&H group IV were investigated.

2.2 Anaesthesia

In Table 2.6 (see page 63) the number of patients in each diagnostic group is related to choice of anaesthesia. Propofol-fentanyl was used in 1,076 patients (58.7%), propofol-remifentanil was used in 464 patients (25.3%), isoflurane-fentanyl was used in 204 patients (11.1%) and sevoflurane-fentanyl in 76 patients (4.1%). Seven patients were anaesthetized with halothane and 1 with midazolam. In 5 patients ICP was monitored before induction of anaesthesia.

Table 2.4 Number of patients with cerebral aneurysm related to localization of aneurysm and year in 225 patients subjected to craniotomy

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Total
Media	9	5	5	8	5	4	5	4	11	8	10	11	5	90
Arteria communicans anterior	7	2	9	7	7	3	1	1	3	4	4	6	2	56
Carotis	9	9	10	11	3	2	7	4	2			3	2	62
Basilaris	2											5	2	9
Other	1								4	1		1	1	8
Total	28	16	24	26	15	9	13	9	20	13	14	26	12	225

Table 2.5 Patients with cerebral aneurysm related topreoperative Hunt and Hess evaluation

Hunt and Hess gradation	Total	Percent of total
H&H 0	63	28.0
H&H I	49	21.8
H&H II	71	31.6
H&H III	38	16.9
H&H IV	4	1.8
Total	225	100

Table 2.6 The distribution of anaesthesia in patients subjected to craniotomy. The diagnoses are related to anaesthetic technique. Maintenance of anaesthesia during ICP recordings included propofol-fentanyl, propofol-remifentanil, isoflurane-fentanyl, sevoflurane-fentanyl, halothane-fentanyl, midazolam-fentanyl and local anaesthesia (awake)

	Propofol -fentanyl	Propofol -remifentanil	Isoflurane -fentanyl	Sevoflurane -fentanyl	Halothane-fentanyl	Midazolam-fentanyl	Awake	Total
Supratentorial tumours	762	342	142	71	7		2	1,326
Infratentorial tumours	87	50	12	5				150
Cerebral aneurysm	133	51	36			1		225
Arteriovenous malformation	18	4	6					28
Traumatic head injury	15	0	0					15
Trigeminus neuralgia	20	6	0					26
Cerebral cyst	9	3	2					14
Cerebral abscess	8	2	0					10
Chronic subdural haematoma	4	0	3					7
Liquorrhea	4	2	0					6
Cerebral infarct	2	1	0					3
Parkinson's disease	0	0	0				3	3
Intracerebral haematoma	11	0	0					11
Encephalitis	2	2	2					6
Disseminated sclerosis	1	1	1					3
Total	1,076	464	204	76	7	1	5	1,833

2.3 Intracranial Pressure-Reducing Procedures

In Table 2.7 the ICP-reducing procedures are summarized. In total 549 patients underwent ICP-reducing procedures either because ICP exceeded 10 mmHg and/or because the neurosurgeon, by touch of his/her fingers, estimated that dural tension was increased. The ICP-reducing method was decided by the anaesthesiologist in concert with the surgeon. In 188 patients 10° rTp was used and 168 patients were subjected to hyperventilation. In 74 patients decompression by ventricular fluid drainage or puncture of cystic tumour was performed. Mannitol treatment was used in 56 cases, intravenous indomethacin in 51 patients, propofol bolus injection in 8 patients and dihydroergotamine in 4 patients.

Table 2.7 ICP-reducing procedures used in connection with subdural ICP measurements

Procedure	Number of patients	Percent of total (1,833)
Reverse Trendelenburg position	188	10.3
Hyperventilation	168	9.2
Decompression (drainage or puncture of cyst)	74	4.0
Mannitol	56	3.1
Indomethacin	51	2.8
Propofol bolus	8	0.4
Dihydroergotamine	4	0.2
Total	549	30.0

2.4 Discussion

Perioperative ICP monitoring for elective tumour craniotomy is rarely used today, one reason being that preoperative corticosteroids in many cases normalize ICP. Another reason is that electronic monitoring devices used for ICP monitoring are expensive, and the sterilization procedure if possible is time consuming. Furthermore, if the ventricular cavities are compressed, intraventricular catheterization for ICP monitoring, which is considered the "gold standard", may be difficult. Lastly, the application of perioperative ICP monitoring, although of interest for the anaesthesiologist, is dependent on the surgeons attitude and cooperation.

During craniotomy subdural ICP measurement is easily performed. If the surgical team in advance is supplied with a 22G cannula and catheter for connection to a pressure transducer, subdural ICP can be measured within one minute. Furthermore, it is possible to follow changes in ICP during

ICP-reducing therapy such as hyperventilation, indomethacin administration, rTp, mannitol treatment and surgical decompression. Subdural ICP monitoring is a stronger predictor of intraoperative brain swelling than the neuroradiological findings or estimation of dural tension by the neurosurgeon (Rasmussen et al. 2004).

Compared with other ICP-monitoring techniques subdural ICP measurement has limitations. First, a technique that continuously follows ICP during craniotomy would be optimal, because precautions based on both ICP and CPP would secure optimal cerebral perfusion throughout anaesthesia and avoid ischaemic episodes. This is especially relevant at the beginning of the procedure: during intubation, after induction of anaesthesia where blood pressure often fluctuates, during head fixation where an increase in blood pressure might provoke cerebral oedema and in the subsequent period of surgical preparation without surgical stimulation. Finally during incision and galea removal, where the surgical stimulation is very intense, the blood pressure often increases significantly. Nevertheless, preoperative insertion of an epidural transducer or an intraventricular catheter for ICP monitoring is rarely used in elective craniotomy. Large dural lesions limit the use of subdural ICP, but not the use of epidural or intraventricular ICP monitoring. However, small dural lesions (below 2 cm in length) do not limit the use of subdural ICP monitoring.

If dural tension is increased ICP is increased as well, with high probability. At an ICP exceeding 13 mmHg cerebral swelling occurs with 95% probability, and at ICP values greater than 26 mmHg severe brain swelling occurs with 95% probability (Rasmussen et al. 2004). Under this circumstance the use of ICP-reducing therapy might be considered. In the present material, including 1,833 patients, the combination of increased dural tension and ICP exceeding 10 mmHg was registered in 594 patients (32.4%). In this situation ICP-reducing therapy should be considered before opening of dura in order to reduce the risk of cerebral swelling/herniation. Surgical drainage of CSF by an intraventricular catheter, evacuation of cystic processes, change in position from supine to 10° rTp and indomethacin bolus injection might reduce subdural ICP effectively within 1 min, while the maximal effects of hyperventilation and mannitol treatment occur after 10–15 min. The data collected in the present prospective study have clearly given that important information. Besides analysis of the ICP-reducing effects by different techniques, the method provides important information of ICP in tumour patients, where analysis of ICP in relation to anaesthetic technique is one example. Thus, in patients anaesthetized with propofol-fentanyl ICP was significantly lower compared with the ICP in patients anaesthetized with isoflurane-fentanyl or sevoflurane-fentanyl (Petersen et al. 2003). The relationship between pre-anaesthetic Hunt and Hess evaluation and ICP is another example where data collection has provided information. Thus, in patients with unruptured cerebral aneurysms and patients with subarachnoid haemorrhage classified as Hunt and Hess I, the ICP was low and dural tension was normal, while ICP was significantly increased in

patients classified as Hunt and Hess II and III (Tankisi et al. 2006). In these patients drainage of ventricular fluid easily controls intracranial hypertension, otherwise early mannitol treatment or 10° rTp adjusted just before opening of dura should be considered.

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Chapter 3
Method

Niels Juul, Georg Emil Cold

Abstract
Since 1994 we have followed the principles of current neuroanaesthesia, including measurement of subdural ICP and cerebral perfusion pressure, and the data have been prospectively registered. In the first study of the procedure we described the method of subdural ICP monitoring during anaesthesia and found a fairly good correlation in paired subdural ICP measurements and almost identical pressure waves and levels of ICP.

In this chapter the method for subdural ICP monitoring and the monitoring of other physiological parameters that we utilize are described in detail. The anaesthetic techniques used, both inhaled and intravenous, are discussed. The scale for the surgeons' estimation of dural tension is disclosed, and the comparative studies mentioned in subsequent chapters are briefly described. A short summary of the statistical methods used is added.

Since 1994 we have followed the principles of current neuroanaesthesia, including measurement of subdural ICP and CPP, and the data have been prospectively registered. In the first study of the procedure we described the method of subdural ICP monitoring during anaesthesia, and found a fairly good correlation in paired subdural ICP measurements, and almost identical pressure waves and levels of ICP (Cold et al. 1996). In subsequent publications we described the influence of anaesthetic methods, and methods for evaluation of dural tension and degree of cerebral swelling after opening of dura (Bundgaard and Cold 2000; Petersen et al. 2003). Measurements of CBF and $CMRO_2$ were described (Bundgaard et al. 1996, 1998). Methods in connection with subdural ICP monitoring during rTp were published by Tankisi et al. (2002). Measurement of transcranial Doppler sonographics was used and described by Rasmussen et al. (2004). In the following the principles of methods used in studies of subdural ICP and cerebral haemodynamics are summarized.

3.1 Neuroradiological Examination in Patients with Cerebral Tumours

From the latest CT or MR scanning the localization of the tumours and midline shifts were registered. The maximum tumour area was calculated using the formula for area of an ellipse (area = abπ, where a is half the length and b is half the width of the tumour).

3.2 Localization of Aneurysm and Hunt and Hess Gradation

The localization of the aneurysm was classified with preoperative four-vessel angiography. Classification according to the Hunt and Hess scale was done just before induction of anaesthesia.

3.3 Anaesthesia and Monitoring

If premedication was deemed necessary, diazepam 5–10 mg was administered perorally. If preoperative steroid and/or anticonvulsant treatment were instituted they were given together with diazepam. Any other daily medication was given at the discretion of the attending anaesthesiologist.

Monitoring before induction consisted of automated non-invasive blood pressure (NIBP, oscillometric blood pressure), continuous electrocardiogram and pulse oximetry. After induction of anaesthesia end-tidal CO_2 and concentration of inspired and expired anaesthetic gas were monitored continuously (Datex AS3, Helsinki, Finland). Controlled ventilation (fraction of inspired oxygen (FiO_2) 50–60% by oxygen/air) was applied at a $PaCO_2$ between 30 and 40 mmHg, inspiratory peak pressure < 20 cm H_2O and a respiratory frequency between 10 and 20/min. The level of $PaCO_2$ was achieved by continuous monitoring of pulmonary ventilation and end-tidal CO_2, and verified by arterial blood gas analysis. A Foley catheter was placed in the urinary bladder, and rectal temperature was continuously monitored. A radial artery catheter was inserted for continuous blood pressure monitoring and blood sampling. A catheter was introduced into the bulb of the internal jugular vein for pressure monitoring and blood sampling. The location of the catheter was checked by x-ray. Bupivacaine 2.5 mg/ml with epinephrine or lidocaine with epinephrine were used for infiltration of the scalp. Train-of-four stimulation was used to monitor muscular relaxation, which was achieved by a continuous infusion of atracurium.

The anaesthetic procedures included the following.

Group 1: Propofol-Fentanyl

Anaesthesia was induced with propofol 1–3 mg/kg given over 1 min and fentanyl 3–4 μg/kg. Lidocaine 1 mg/kg was administered over 1 min followed by muscular relaxation by atracurium 0.5 mg/kg. Anaesthesia was maintained with infusions of propofol 6–10 mg/kg/h and fentanyl 2–3 μg/kg/h. Just before incision of the scalp doses of propofol 1 mg/kg and/or fentanyl 1–2 μg/kg/h were supplemented, if necessary. The infusion rates of propofol and fentanyl were unchanged during the ICP measurements and during the estimation of dural swelling.

Group 2: Isoflurane-Fentanyl

Anaesthesia was induced with propofol 1–3 mg/kg given over 1 min and fentanyl 2–3 μg/kg. Lidocaine and atracurium were administered as in group 1. Anaesthesia was maintained with isoflurane (maximally 1.5 minimal alveolar concentration (MAC)) and fentanyl 2–3 μg/kg/h. Just before incision of the scalp fentanyl 1–2 μg/kg/h was supplemented, if necessary. The dose of isoflurane and the infusion rate of fentanyl were unchanged during the ICP measurements and during the estimation of dural swelling.

In Chapter 11, study 1, and in the study in Chapter 12, isoflurane was administered with nitrous oxide 50–67% and fentanyl.

Group 3: Sevoflurane-Fentanyl

Anaesthesia was induced with propofol 1–3 mg/kg given over 1 min and fentanyl 2–3 μg/kg. Lidocaine and atracurium were administered as in group 1. Anaesthesia was maintained with sevoflurane (maximally 1.5 MAC) and fentanyl 2–3 μg/kg/h. Just before incision of the scalp fentanyl 1–2 μg/kg/h was supplemented, if necessary. The dose of sevoflurane and the infusion rate of fentanyl were unchanged during the ICP measurements and during the estimation of dural swelling.

Group 4: Propofol-Remifentanil

Anaesthesia was induced using 1–3 mg/kg propofol supplemented with 0.5–1 μg/kg remifentanil during 1 min followed by 0.1–0.15 mg/kg cisatracurium for muscular relaxation. Anaesthesia was maintained with 0.2–0.5 μg/kg/min remifentanil and 4–8 mg kg/h propofol. The infusion rates of propofol and remifentanil were unchanged during the ICP measurements and during the estimation of dural swelling.

In patients with supratentorial cerebral tumours the effect of anaesthesia on ICP, MABP, CPP and jugular bulb pressure (JBP), and the effect of hyperventilation are indicated in Chapter 10. The same parameters in patients with cerebral aneurysm are indicated in Chapter 19.

3.4 Fluid Administration and Regulation of Blood Pressure

During the first hour of anaesthesia isotonic saline 15 ml/kg was administered, and followed by 2–4 ml/kg/h. If systolic blood pressure decreased > 20 mmHg colloids, in the form of either Haes-Steril 6% (hydroxyethyl starch; Fresenius Kabi, Uppsala, Sweden) or 5% dextran in saline, were administered, if needed, eventually supplemented with ephedrine 5–10 mg intravenously. Packed erythrocytes, albumin or fresh frozen plasma were not given before the ICP measurements.

3.5 Subdural Intracranial Pressure and Cerebral Perfusion Pressure

Subdural ICP was measured during surgery by use of the following method. After removal of the bone flap ICP was measured subdurally by an intravenous needle (22G/0.8 mm), which was connected to a pressure transducer via a polyethylene catheter. The transducer was placed in the same sagittal plane as the dura, and zero point adjustment was performed with the tip of the needle placed at the point of intended insertion of the dura. The needle was introduced through the dura until a continuous recording of ICP with typical cardiac and respiratory waves appeared. After 1 min of stabilization the integrated mean value of subdural pressure was used as an estimate of ICP. The needle was left in situ until the study was finished, and during the measurement no surgical intervention was performed. Simultaneously the integrated value of MABP was recorded via the radial artery catheter. The mid-axillary line was used for zero point adjustment for the arterial blood pressure.

The CPP was calculated as the difference between MABP and ICP. The surgeons were blinded as regards the values of ICP, MABP and JBP. The

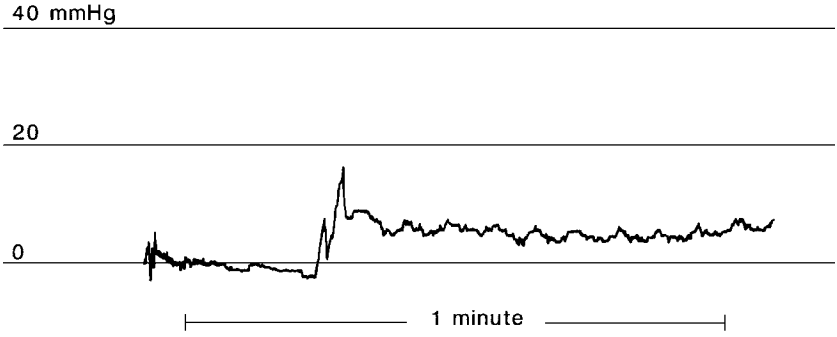

Fig. 3.1 Recording of subdural ICP, with zero-point adjustment, perforation of dura mater and cardiac and respiratory waves

measurement of subdural ICP was normally finished after 1 min. In Figure 3.1 subdural ICP is illustrated with cardiac and respiratory waves.

In Chapter 21 studies of subdural or spinal pressure during spinal surgery are described. In these studies the distance between the skin and the surface of the spinal dura was measured, and the transducer was placed according to this distance.

3.6 Catheterization of the Internal Jugular Vein and Blood Gas Analyses

A jugular bulb catheter was inserted percutaneously at the level of the cricoid. In order to avoid puncture of the carotid artery, catheterization was performed with the head in neutral position (Sulek et al. 1996) and with the patient positioned in 5–10° rTp. This position dilates the jugular vein (Clenaghan et al. 2005). The catheter was introduced 12–14 cm in the cranial direction. Correct cranial position was verified by ascertaining an increase in jugular pressure following neck compression and by unrestrained blood withdrawal. In some cases a lateral x-ray of the neck was exposed to verify correct position of the catheter. The catheter was connected to a transducer and placed in the same sagittal plane as the transducer connected to the needle for subdural ICP measurement.

Blood was withdrawn simultaneously from the arterial and jugular catheters for measurement of PaO_2, $PaCO_2$, pH, glucose lactate, Na^+, K^+ and Ca^{++} (ABL 555 and ABL 700; Radiometer, Copenhagen, Denmark). $AVDO_2$ was calculated as the difference between arterial and jugular venous oxygen content. Furthermore, the arteriovenous difference of $PaCO_2$ ($AVD\text{-}CO_2$), pH (AVD-pH), lactate (AVD-lactate (mmol/L)), Na^+ ($AVD\text{-}Na^+$ (mmol/L)), K^+ ($AVD\text{-}K^+$ (mmol/L)) and Ca^{++} ($AVD\text{-}Ca^{++}$ (mmol/L)) were calculated.

3.7 Measurement of Cerebral Blood Flow and Cerebral Metabolic Rate of Oxygen

Two angular detectors were placed on each side of the head. As tracer, ^{133}Xe (3–4 mCi i.v.) was used. CBF was measured over a period of 10 min as initial slope index using 10-min clearance curves with a Novo Cerebrograph 10. Correction for rest activity and recirculation was performed. The average of the two CBFs was used. $CMRO_2$ was calculated according to the formula $CMRO_2 = CBF \times AVDO_2$. CBF is measured in Chapter 11, study 1 (indomethacin), Chapter 12 (dihydroergotamine) and Chapter 9 (sevoflurane). In the study of dihydroergotamine (Chapter 12) the CVR was calculated using the formula $CPP = CBF \times CVR$.

3.8 Measurement of Flow Velocity

Transcranial Doppler ultrasonography was used in study 2 in Chapter 11 (indomethacin). In this study middle cerebral artery flow velocity was measured bilaterally. The artery was identified at a depth varying between 45 and 55 mm. The flow velocity was monitored beat-to-beat using a 2-MHz pulsed Doppler probe (TC 2000S; EME Überlingen, Germany). Transcranial Doppler frequency spectra, converted into flow velocity (cm/s), were calculated automatically over 4–5 consecutive cardiac cycles. The mean middle cerebral artery blood flow velocity was recorded and, because flow velocity fluctuates with respiration, the value during end-expiration was used.

3.9 Effect of Hyperventilation and Indomethacin

After the initial ICP measurement the pulmonary ventilation was increased by 30% for 10 min. The measurements were repeated 11 min after the first measurements. CO_2 reactivity was calculated as % change $AVDO_2$/$\Delta PaCO_2$ mmHg (Chapter 10) or % change $AVDO_2/\Delta PaCO_2$ kPa (Chapter 13).

In some comparable studies the effect of indomethacin and hyperventilation was analysed by comparing the changes in ICP or changes in $AVDO_2$.

3.10 Estimation of Dural Tension and Cerebral Swelling

Before subdural ICP measurement the surgeon made a tactile evaluation of the dural tension. The neurosurgeons were blinded as regards choice of anaesthesia and the ICP value obtained. The tensions were categorized as follows: (1) very slack, (2) normal, (3) increased tension and (4) pronounced increased tension.

The degree of brain swelling during hyperventilation was evaluated by the neurosurgeon after opening of dura. Swelling was estimated as: (1) no swelling, (2) moderate swelling of the brain and (3) pronounced swelling of the brain.

3.11 Measurement of Intracranial Pressure During Tilting of the Operating Table

The arterial and jugular pressure (JP) transducers were placed on the same horizontal plane as the ICP transducer to eliminate the influence of hydro-

static pressure difference during tilting of the operating table. CPP was calculated as the difference between MABP and subdural ICP. After reference measurements of ICP, MABP and JP in neutral position, the operating table was tilted 5° head-down (5° rTp), with whole-body trunk tilting without flexion of the hips. In this position all pressure transducers were readjusted to the same horizontal level of the dural perforation. The degree of tilting was adjusted using a spirit level fixed to the operating table. A laser pointer fixed to the transducer table was used to place the transducers in the same horizontal plane as the subdural needle. The measurement procedure was repeated after readjustment of the table to 10° and 15° rTp. In accordance with previous investigations performed in our clinic, in which MABP, ICP, CPP and JBP were stable within 1 min after tilting to 10° rTp, the pressure measurements were performed 1 min after a change in position. The effect of rTp on ICP, MABP, CPP and JBP are summarized in Chapter 15.

3.12 Comparative Studies of Intracranial Pressure-Reducing Methods

Data from patients with supratentorial tumours were extracted from our database for the period 1997–2006. The following criteria were used as inclusion in the study: The neurosurgeon estimated that the dura tension was increased and/or ICP exceeded 10 mm Hg at the initial measurement. The following ICP-reducing techniques were used.

3.12.1 *Hyperventilation*

The minute ventilation of the ventilator was increased by 20–50% for 5 min. In order to keep the peak respiratory pressure below 20 cmH_2O, the respiratory rate was eventually increased. Before and 5 min after the increase in minute ventilation subdural ICP and MABP were recorded, and arterial gas tensions were monitored. Thirty patients were included.

3.12.2 *Ten Degrees Reverse Trendelenburg Position*

After reference measurements of ICP, CPP and MABP in neutral position, the table was adjusted to 10° rTp (whole body trunk tilting without flexion at the hips) and all pressure transducers were re-adjusted to the same level of dural perforation. As a result of a recent study, indicating stable CPP and ICP within 1 min after tilting to 10° rTp, the measurements were performed 1 min after change in position. Sixteen patients were included.

3.12.3 *Mannitol Treatment*

Over about 5 min, 0.5–1.0 g/kg mannitol was administered intravenously. ICP and CPP were recorded before and 5 min after conclusion of mannitol infusion. Nineteen patients were included.

3.12.4 *Indomethacin*

Indomethacin 0.5 mg/kg was administered i.v. as a bolus dose. ICP and CPP were recorded for 5 min, and arterial gas analysis was performed before and 5 min after indomethacin. Fifteen patients were included.

3.12.5 *Surgical Decompression*

Surgical decompression was performed either by drainage via a ventricular catheter inserted during the operation (n=3) or by evacuation of fluid from cystic tumours (n=10). ICP and CPP were recorded before and after decompression, and the volume of fluid from drainage was recorded. Thirteen patients were included.

3.13 Studies of the Effect of Central Analgetics in Patients with Cerebral Tumours

During propofol-fentanyl anaesthesia patients subjected to craniotomy for supratentorial cerebral tumours were subjected to a bolus dose of alfentanil in the following doses: 10, 20 and 30 μg/kg alfentanil followed by an infusion of 10, 20 and 30 μg/kg/h. ICP and CPP were measured continuously before and after administration (Chapter 13). In the same chapter the effects of i.v. fentanyl bolus dose, and remifentanil bolus dose were investigated.

3.14 Studies of Propofol Bolus Dose

In Chapter 14 the effect of an i.v. bolus dose of propofol was studied during propofol-fentanyl and during propofol-remifentanil anaesthesia.

3.15 Patients Subjected to Controlled Studies

After informed consent and before premedication, a sealed numbered envelope indicating anaesthetic procedure or test drug/placebo was opened.

3.16 Statistical Analysis

In intra- and intergroup studies the statistical analyses were as follows: Data within groups were tested for normal distribution. The normality test and equal variance test were applied and one-way ANOVA was used for analysis if these tests were passed. The Tukey test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis one-way analysis of variance on ranks and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance showed that the data were not normally distributed. These data included subdural ICP, MABP and $AVDO_2$. Bonferroni's test was applied for statistical analysis. In other studies where only two groups were compared the *t*-test was used if the normality test was passed; if not Mann-Whitney's test was used for intergroup differences and Wilcoxon's test for intragroup changes. The chi-square test was used for statistical analysis of demographic data, localization, size and histopathological diagnosis of the tumours, preoperative steroid administration and position of the head. Difference in tension of dura and the degree of cerebral swelling were tested by the chi-square test in 2×4 or 2×3 tables. For correlation studies Pearson's product moment correlation and linear regression were performed. Means and standard deviation (SD) were calculated in some studies and median and range in others, according to the distribution of the data. $P<0.05$ was considered statistically significant.

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Chapter 4
Comparative Studies of Intracranial Pressure in Patients With and Without Space-Occupying Lesions

Lisbeth Krogh and Georg Emil Cold

Abstract

Anaesthesia for craniotomy has to be carried out with emphasis on haemodynamic stability, a sufficient cerebral perfusion pressure and avoidance of agents or procedures that increase ICP. The patients presented to a current neuroanaesthesiological practice come with a multitude of intracranial pathologies, ranging from discrete unruptured aneurisms to significantly sized tumours that create a midline shift. It is important to relate the ICP measured in patients with space-occupying lesions to the ICP in patients without lesions. Studies of ICP during craniotomy in patients without space-occupying intracerebral lesions, however, are few.

In this chapter data on two populations, one with supratentorial glioblastomas and the other without space-occupying lesions, are presented. Differences between the groups, in ICP and other relevant data obtained, are discussed and the relationship between neuroradiological data and measured ICP correlated.

Anaesthesia for craniotomy has to be carried out with emphasis on haemodynamic stability, a sufficient CPP and avoidance of agents or procedures that increase the ICP. In a randomized study in patients undergoing craniotomy for supratentorial tumours it was concluded that anaesthesia with propofol-fentanyl is to be preferred from anaesthesia with either isoflurane-fentanyl or sevoflurane-fentanyl, because subdural ICP and the degree of cerebral swelling after opening of dura were significantly lower and CPP significantly higher during propofol-fentanyl compared with isoflurane-fentanyl or sevoflurane-fentanyl (Petersen et al. 2003).

Other studies indicate that in patients with space-occupying lesions undergoing supratentorial craniotomy, the degree of cerebral swelling after opening of dura is highly correlated to subdural ICP monitored immediately before opening of dura (Cold et al. 1996; Bundgaard et al. 1998; Rasmussen et al. 2004).

It is important to relate the ICP measured in patients with space-occupying lesions with ICP in patients without lesions. Studies of ICP during craniotomy in patients without space-occupying intracerebral lesions, however, are few. In patients with unruptured cerebral aneurysm, anaesthetized with either propofol-fentanyl or propofol-remifentanil, ICP averaged 2.9 mmHg with the operating table in neutral position; a fall to 0.4 mmHg was found when the table was turned to 10° rTp (Tankisi et al. 2006).

In the present study two populations (one without space-occupying lesion, the other patients with supratentorial glioblastoma) were anaesthetized with either propofol-fentanyl or propofol-remifentanil. Subdural ICP, CPP and jugular pressure were monitored.

Study Outline

Aims 1: To study ICP, CPP and JBP in patients with or without space-occupying lesions. 2: To study the relationship between neuroradiological data (maximal area of tumour, volume of tumour and midline shift) as presented in patients subjected to craniotomy, and to correlate these data with subdural ICP obtained during craniotomy.

Patients The data were collected during the period between 1997 and 2005. Subdural ICP was monitored in 107 patients subjected to propofol-fentanyl and 65 patients subjected to propofol-remifentanil. Of these patients, 132 patients had supratentorial glioblastoma and 40 patients had either unruptured cerebral aneurysm (30 patients) or were operated on for trigeminus neuralgia (10 patients).

Method Concerning neuroradiological findings, histopathology, anaesthetic maintenance dose and monitoring (MABP, ICP, CPP, jugular pressure, arterial gas analysis), degree of dural tension and swelling after opening of dura, see Chapter 3.

Statistical analysis Data within groups were tested for normal distribution. The *t*-test was used if the normality test was passed; if not Mann-Whitney's test was used for intergroup differences and Wilcoxon's test for intragroup changes. The chi-square test was used for statistical analysis of demographic data, localization, size and histopathological diagnosis of the tumours, preoperative steroid administration and position of the head. Difference in tension of dura and the degree of cerebral swelling were tested by the chi-square test in 2×4 or 2×3 tables. $P<0.05$ was considered statistically significant.

Results In patients with glioblastoma anaesthetized with either propofol-fentanyl or propofol-remifentanil no significant differences were found as regards male/female distribution, age, weight, height, rectal temperature,

PaO_2, jugular venous saturation, $AVDO_2$, neuroradiological findings (maximal area of the tumour, volume of the tumour and midline shift) and $PaCO_2$. The same applies to patients without space-occupying lesions anaesthetized with propofol-fentanyl or propofol-remifentanil (Tables 4.1 and 4.2). The maintenance dose of propofol was significantly higher in propofol-fentanyl- compared with propofol-remifentanil-anaesthetized patients (Table 4.1). In patients with glioblastoma ICP averaged 9.7 mmHg (median 9.0 mmHg) when anaesthetized with propofol-fentanyl, while ICP in propofol-remifentanil-anaesthetized patients averaged 6.7 mmHg (median 6.0 mmHg) ($P<0.05$). In patients without space-occupying lesions ICP averaged 4.3 mmHg (median 5.0 mmHg) when anaesthetized with propofol-fentanyl. This value was significantly lower compared with ICP in patients with glioblastoma ($P<0.05$). In patients without space-occupying lesions ICP averaged 4.4 mmHg (median 4.0 mmHg) when anaesthetized with propofol-remifentanil. This value was not significantly different from patients with glioblastoma subjected to the same anaesthesia (Table 4.3).

In patients with glioblastoma as well as patients without space-occupying lesions both MABP and CPP were significantly lower during anaesthesia with propofol-remifentanil- compared with propofol-fentanyl-anaesthetized patients (Table 4.3). In patients with glioblastoma anaesthetized with propofol-fentanyl jugular pressure was significantly higher (mean 5.4 mmHg) compared with propofol-remifentanil-anaesthetized patients with glioblastoma (mean 2.6 mmHg). No significant difference was found in patients without space-occupying lesions, where mean jugular pressure averaged 3.7 and 3.4 mmHg, respectively (Table 4.2). In patients with glioblastoma the degree of dural tension and swelling after opening of dura were more pronounced in propofol-fentanyl- compared with propofol-remifentanil-anaesthetized patients, with $P=0.042$ (dural tension) and 0.037 (degree of swelling), respectively. In propofol-fentanyl-anaesthetized patients with glioblastoma dural tension and degree of cerebral swelling were significantly different from patients without space-occupying lesions, with P values of 0.001 and <0.001, respectively. In propofol-remifentanil-anaesthetized patients with glioblastoma the degree of dural tension did not differ significantly from patients without space-occupying lesion ($P=0.254$), but the degree of swelling differed significantly ($P<0.001$) (Table 4.4). In patients with glioblastoma as well as patients without space-occupying lesions, whether anaesthetized with propofol-fentanyl or propofol-remifentanil, significant correlations were disclosed between jugular pressure and ICP (correlation coefficients varied from 0.3064 to 0.5800) (Table 4.5). In patients anaesthetized with propofol-fentanyl significant positive correlations were found when neuroradiological data (maximal area of tumour, volume of tumour and midline shift) were correlated to subdural ICP. The corresponding correlations in patients anaesthetized with propofol-remifentanil were also positive but insignificant (Table 4.6).

Table 4.1 Data include patients with supratentorial glioblastoma and patients without space-occupying lesions (unruptured cerebral aneurysm or trigeminus neuralgia). Patients were anaesthetized with propofol-fentanyl or propofol-remifentanil

	Number	Men/ women		Age (year)	Weight (kg)	Height (cm)	Propofol dose (mg//h)
Patients with glioblastoma							
Propofol -fentanyl	89	54/35	Mean±SD	55±11	75±14	174±9	670±186
			Median	56	73	174	700
			Range	17–76	42–120	154–193	250–1,400
Propofol -remifentanil	43	24/19	Mean±SD	52±11	79±15	174±8	400±101*
			Median	55	83	175	400
			Range	52–107	65–119	156–190	250–700
Patients without tumour							
Propofol -fentanyl	18	7/11	Mean±SD	57±11	73±18	175±9	719±199
			Median	57	74	178	700
			Range	37–75	50–124	157–186	300–1,250
Propofol -remifentanil	22	3/19	Mean±SD	53±10	73±14	174±8	425±111*
			Median	53	72	166	400
			Range	27–66	50–98	158–188	200–700

*$P<0.05$ within groups (glioblastoma or patients without space-occupying lesions)

Table 4.2 Data include patients with supratentorial glioblastoma, and patients without space-occupying lesions (unruptured cerebral aneurysm or trigeminus neuralgia). Patients were anaesthetized with propofol-fentanyl or propofol-remifentanil

		Temperature (°C)	PaO_2 (kPa)	Venous saturation (%)	$AVDO_2$ (mmol/L)	Jugular pressure (mmHg)
Patients with glioblastoma						
Propofol -fentanyl	Mean±SD	35.9±0.6	27±10	57±11	3.2±0.9	5.4±4.0
	Median	36.0	26	56.4	3.2	5.0
	Range	34.1–37	10–66	37.3–91	0.9–5.7	−4 to 17
Propofol -remifentanil	Mean±SD	35.9±0.3	24±6	54±8	3.3±0.7	2.6±3.6*
	Median	35.8	24	52.4	3.5	2.5
	Range	35–36.5	12–38	42.7–72	1.8–4.4	−4 to 10
Patients without tumour						
Propofol -fentanyl	Mean±SD	35.8±0.5	27±10	53±13	3.4±1.1	3.7±3.4
	Median	36	24	52	3.4	4.0
	Range	35–37.1	13–42	37.6–88	0.8–5.3	−2 to 12
Propofol -remifentanil	Mean±SD	35.7±0.4	23±6	52±10	3.2±0.8	3.4±3.4
	Median	35.8	24	53	3.0	3.0
	Range	35–36.3	12–33	33.6–65	2.2–5.1	−3 to 10

*$P<0.05$ within groups (glioblastoma or patients without space-occupying lesions)

Table 4.3 Patients with supratentorial glioblastoma, and patients without space-occupying lesions (unruptured cerebral aneurysm or trigeminus neuralgia. Patients were anaesthetized with propofol-fentanyl or propofol-remifentanil

		Tumour area (cm^2)	Tumour volume (cm^3)	Midline shift (mm)	$PaCO_2$ (kPa)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
Patients with glioblastoma								
Propofol	Mean±SD	17±8	33±22	8.3±5.9	4.5±0.5	85±13	9.7±6.2	75±14
-fentanyl	Median	15.7	26	9.0	4.5	83	9.0	74
	Range	3–42	3–98	0–25	2.7–5.5	56–119	0–34	36–111
Propofol	Mean±SD	15±7	30±19	7.3±6.3	4.5±0.4	74±14*	6.7±4.7*	67±14*
-remifentanil	Median	14.6	26.7	5.0	4.5	70	6.0	65
	Range	3–28	3–71	0–20	3.9–6.0	52–113	0–21	43–100
Patients without tumour								
Propofol	Mean±SD	0	0	0	4.6±0.4	86±12	4.3±3.3**	82±12
-fentanyl	Median				4.6	85	5.0	80
	Range				3.9–5.3	64–106	−2 to 12	58–101
Propofol	Mean±SD	0	0	0	4.6±0.5	74±9*	4.4±2.9	69±10*
-remifentanil	Median				4.5	74	4.0	69
	Range				3.7–5.7	60–93	0–9	51–91

*$P<0.05$ within groups (glioblastoma or patients without space-occupying lesions)

**$P<0.05$ between propofol-fentanyl-anaesthetized patients with and without space-occupying lesions

Table 4.4 Data indicate tension of dura before opening and degree of brain swelling after opening of dura in patients with supratentorial glioblastoma and patients without space-occupying lesions anaesthetized with either propofol-fentanyl or propofol-remifentanil. Number (%) of patients is indicated

	Supratentorial glioblastoma present		No space-occupying lesion	
	Propofol -fentanyl	Propofol -remifentanil	Propofol -fentanyl	Propofol -remifentanil
Tension of dura				
Normal tension	42 (47.2%)	30 (69.8%)	17 (94.4%)	19 (86.3%)
Moderate tension	40 (44.9%)	10 (23.3%)	1 (5.6%)	3 (13.6%)
Pronounced tension	7 (7.9%)	3 (7.0%)	0 (0.0%)	0 (0.0%)
Degree of swelling				
No swelling (group 1)	41 (46.1%)	30 (69.8%)	17 (94.4%)	21 (95.5%)
Moderate swelling (group 2)	32 (36.0%)	9 (20.9%)	1 (5.6%)	1 (4.5%)
Pronounced swelling (group 3)	16 (17.9%)	4 (9.3%)	0 (0.0%)	0 (0.0%)

Table 4.5 ICP related to JBP. Correlation coefficient, significance (*P* value) and linear regression are indicated

	Correlation coefficient (*r*)	*P* value	Linear regression
Glioblastoma			
Propofol-fentanyl	0.3064	0.003	ICP=7.38 + 0.51 × JBP (mmHg)
Propofol-remifentanil	0.3969	0.025	ICP=5.23 + 0.52 × JBP (mmHg)
Without tumour			
Propofol-fentanyl	0.5800	<0.001	ICP=1.19 + 0.86 × JBP (mmHg)
Propofol-remifentanil	0.4714	0.027	ICP=3.03 + 0.40 × JBP (mmHg)

Conclusion In propofol-fentanyl- and propofol-remifentanil-anaesthetized patients no significant differences in ICP and CPP were found in patients without space-occupying tumours. In contrast, in patients with glioblastoma both ICP and jugular pressure were significantly higher in propofol-fentanyl-anaesthetized patients compared with patients anaesthetized with propofol-remifentanil.

Discussion

The significantly higher ICP and CPP found in the propofol-fentanyl-anaesthetized patients, compared with the propofol-remifentanil-anaesthetized patients were not caused by differences in $PaCO_2$, tumour size or midline shift.

Table 4.6 ICP correlated to neurological findings (maximal area of tumour, volume of tumour and midline shift). Correlation coefficient, significance (*P* value) and linear regression are indicated

	Correlation coefficient (*r*)	P value	Linear regression
Correlation between maximal area of tumour and subdural ICP			
Propofol-fentanyl	0.4240	<0.001	ICP=4.55 + 0.34 × area (cm^2)
Propofol-remifentanil	0.3558	0.019	ICP=3.15 + 0.23 × area (cm^2)
Correlation between volume of tumour and subdural ICP			
Propofol-fentanyl	0.4530	<0.001	ICP=5.71 + 0.14 × volume (cm^3)
Propofol-remifentanil	0.3698	0.015	ICP=4.17 + 0.52 × volume (cm^3)
Correlation between midline shift of tumour and ICP			
Propofol-fentanyl	0.3359	0.003	ICP=7.36 + 0.38 × midline shift (mm)
Propofol-remifentanil	0.0810	0.606	Not significant

Accordingly, both dural tension before opening and the degree of cerebral swelling after opening of dura were less pronounced in patients anaesthetized with propofol-remifentanil. The difference in ICP was surprising because the maintenance dose of propofol was significantly lower in the propofol-remifentanil-anaesthetized patients compared with patients undergoing anaesthesia with propofol-fentanyl. According to experimental and clinical studies, propofol induces a dose-related decrease in $CMRO_2$ and CBF, and consequently a lower ICP level should be expected in the propofol-fentanyl group (Moss and Price 1990; Pinaud et al. 1990; Ramani et al. 1992; Alkire et al. 1995). In a comparative study of fentanyl and remifentanil, ICP and CPP did not differ significantly when administered in equipotent doses together with nitrous oxide to patients with supratentorial space-occupying lesions (Guy et al. 1997). Furthermore, recent studies indicate that the CO_2 reactivity is preserved during remifentanil-nitrous oxide anaesthesia (Baker et al. 1997), and the CO_2 reactivity is similar during remifentanil-nitrous oxide and fentanyl-nitrous oxide anaesthesia (Ostapkovich et al. 1998).

The significant difference in subdural ICP might be explained by the difference in CPP, which, dependent on the status of cerebral autoregulation, might influence ICP. On the one hand, a fall in ICP is a consequence of a low CPP if cerebral autoregulation is abolished. On the other hand, an increase in ICP is suspected if cerebral autoregulation is intact. As cerebral autoregulation was not tested in the present study, it is impossible to answer whether autoregulation-induced changes in ICP, caused by different levels of CPP, can explain the difference in ICP levels between the two groups. The differences in ICP might

also be caused by differences in JBP between the two anaesthetic groups. In support of this, we found that JBP was significantly lower during propofol-remifentanil anaesthesia compared with the propofol-fentanyl anaesthesia, and significant correlations between JBP and subdural ICP were observed in patients with glioblastoma as well as in patients without space-occupying lesions. Thus, ICP seems to be dependent on the level of JBP in patients undergoing craniotomy in propofol-fentanyl or propofol-remifentanil anaesthesia. This finding is supported by other studies indicating that 5° or 10° rTp is accompanied by a decrease in both JBP and subdural ICP (Rolighed Larsen et al. 2002; Tankisi et al. 2002, 2006; Haure et al. 2003). The fall in ICP during rTp is thought to be due to a decrease in intracranial blood volume caused by augmented venous outflow (Lovell et al. 2000).

In patients anaesthetized with either propofol-fentanyl or propofol-remifentanil significant positive correlations were also disclosed between maximal area of the tumour or volume of the tumour and subdural ICP. The *P* values were lower and the powers were higher in patients with glioblastoma anaesthetized with propofol-fentanyl compared with glioblastoma patients anaesthetized with propofol-remifentanil. The difference in number of patients in the two anaesthetic groups did not explain the discrepancy, because the correlation coefficients and powers were still of the same numerical size, even when the number of patients in the propofol-fentanyl group was reduced to the first 43 investigations, a number in correspondence with the number in the propofol-remifentanil group.

In awake patients without cerebral pathology ICP averages 11 mmHg (range 7–15 mmHg) (Albeck et al. 1991). In the present study the level of ICP in patients without space-occupying lesions averaged 4.3 and 4.4 mmHg in patients anaesthetized with propofol-fentanyl and propofol-remifentanil, respectively. The difference in ICP between the awake and anaesthetized state is supposed to be caused by propofol that in experimental (Vandesteene et al. 1988; Ramani et al. 1992; Watts et al. 1998) and clinical studies (Madsen 1991; Stephan et al. 1987) reduces cerebral oxygen uptake, CBF and ICP.

Furthermore, the low ICP may be caused by hypocapnia (Petersen et al. 2003). In the present study, both the estimation of dural tension and the degree of cerebral swelling after opening of dura are semiquantitative as well as subjective. Nevertheless, these estimates were used because the presence of brain swelling increases retractor pressure resulting in low regional perfusion pressure (Hongo et al. 1987; Rosenørn 1987), thereby increasing the risk for development of cerebral ischaemia. Furthermore, brain swelling makes surgical access difficult. Another limitation in the present study is the lack of randomization. Data, however, were collected prospectively and continuously between the years 1997 and 2005. In this period subdural ICP monitoring and jugular bulb catheterization were performed in 132 patients with supratentorial glioblastoma, of which 89 patients were anaesthetized with propofol-fentanyl and 43 patients with propofol-remifentanil. The anaesthetic groups were not of equal size, propofol-fentanyl being the largest group. Propofol-remifentanil

was used over the period 2000–2005, while propofol-fentanyl was used over the entire period. The maintenance dose of propofol and CPP differed significantly, which makes interpretation of the results difficult. The staff of neurosurgeons and anaesthesiologists involved in craniotomy, however, was almost the same over the period. The same applies to preoperative care, principles of steroid treatment and the operating and monitoring conditions.

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Chapter 5
Studies of Regional Subdural Pressure Gradients During Craniotomy

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Abstract

Intracranial pressure monitoring is based on the premise that the intracranial space is one compartment without pressure differences between brain regions. To what extent the pressure within the subarachnoid space correlates with pressures in other brain regions and whether an increase in pressure within the brain substance is transmitted to the rest of the brain and to the subarachnoid and ventricular cerebrospinal fluid are debated.

In this chapter we summarize and discuss four studies dealing with regional subdural pressure gradients during craniotomy. The first study refers to studies of pressure gradients between subdural ICP and pressures within the neuroaxis, including intraventricular pressure and lumbar spinal pressure. The second study refers to subdural pressure gradients within the surgical field in patients with supratentorial tumour, the third study to pressure gradients within the surgical field in patients with infratentorial tumour, and the fourth study to changes in subdural ICP during opening of dura.

The existence of intercompartmental pressure gradients in conditions of intracranial hypertension has been reported in experimental (Kaufmann and Clark 1970; Takizawa et al. 1986) and clinical studies (Langfitt et al. 1964a, b; Johnston and Rowan 1974). These pressure gradients occur between supratentorial and infratentorial compartments across the tentorium cerebelli or between infratentorial and spinal compartments across the foramen magnum, and develop because displaced brain tissue obstructs the subarachnoid space. Pressure gradients between supratentorial and infratentorial spaces have also been demonstrated in the absence of transtentorial herniation (Smyth and Henderson 1938) and it has been demonstrated that even with patent CSF flow and without tentorial herniation, pressure gradients as high as 12 mmHg exist (Soni 1974).

Concerning intracompartmental pressure gradients, several experimental studies have indicated that gradients occur within the supratentorial compartment between the two hemispheres after cryogenic damage (Langfitt et al. 1964b; Weinstein et al. 1968; Reulen and Kreysch 1973; Symon et al. 1974; Brock et al. 1975; Reulen et al. 1977; Furuse et al. 1981) or after cerebrovascular occlusion (Brock et al. 1972; Iannotti et al. 1985) in one of the hemispheres. Even pressure gradients within one hemisphere have been reported (Wolfla et al. 1996). Clinical research, however, involving head-injured patients has yielded conflicting results. Weaver et al. (1982) documented markedly asymmetric pressures between hemispheres in patients with unilateral mass lesions, and Park et al. (1989) found significant differences in ICP, where the location of higher pressure predicted the region of major pathology. In contrast, Yano et al. (1987) studied comparative ICPs in head-injured patients and found no differences in comparative ICPs, despite the difference in severity of the lesions between the right and left hemispheres.

Intracranial pressure monitoring is based on the premise that the intracranial space is one compartment without pressure differences between brain regions. To what extent the pressure within the subarachnoid space correlates with pressures in other brain regions, and whether an increase in pressure within the brain substance is transmitted to the rest of the brain and to the subarachnoid and ventricular CSF, are debated.

During craniotomy opening of dura occasionally may be followed by herniation of cerebral tissue. This swelling is secondary to a high ICP, where the pressure difference between the intracranial compartment and the ambient pressure forces cerebral tissue through the opening of dura. In some patients this process is self-limiting, where decompression like suction of CSF balances the development of brain herniation. In patients with fast-developing mass-expansion of tumour tissue, haematoma or oedema, cerebral swelling develops so rapidly that evacuation of cerebral tissue may be necessary to provide access to deeper structures. Furthermore, venous engulfment with development of cerebral oedema and ischaemia may develop in the herniated tissue. We therefore found it of interest to measure changes in subdural ICP in the operating field during opening of dura.

In this chapter we summarize and discuss four studies. The first study refers to studies of pressure gradients between subdural ICP and pressures within the neuroaxis, including intraventricular pressure and lumbar spinal pressure. The second study refers to the subdural pressure gradient within the surgical field in patients with supratentorial tumour, the third study to pressure gradients within the surgical field in patients with infratentorial tumour, and the fourth study to changes in subdural ICP during opening of dura. The second and the third studies have been presented by Bundgaard and Cold in Br J Neurosurg (2000) 14:229–234.

Study 1: Studies of Pressure Gradients Between Subdural Intracranial Pressure and Pressures Within the Neuroaxis, Including Intraventricular Pressure and Lumbar Spinal Pressure

Aim Toinvestigate pressure gradients within the neuroaxis.

Method In 13 patients undergoing supratentorial craniotomy in the supine position for SAH (n=9), tumour (n=3) and intraventricular haematoma (n=1). A ventricular catheter was inserted preoperatively. After exposure of the dura, subdural ICP and intraventricular pressure were measured with the transducers placed in the same horizontal plane. In 6 patients subjected to fossa posterior surgery in the prone position for tumour (n=3), haematoma (n=2) and arteriovenous malformation (n=1), intraventricular pressure and subdural ICP in the posterior fossa were measured simultaneously. In 5 patients (4 patients with SAH and 1 patient with trigeminus neuralgia) a lumbar spinal catheter was inserted and subdural ICP and lumbar spinal pressures were measured simultaneously.

Statistical analysis Median and range were calculated. Non-parametric tests (Wilcoxon and Mann-Whitney) were used for statistical analyses within and between groups. Linear regression and correlation analysis (Spearman's rho) were used.

Results The results are given in Tables 5.1, 5.2 and 5.3 and Fig. 5.1. The values of subdural ICP were higher compared with intraventricular pressure and spinal pressure. The mean values for difference in pressures were 0.1 mmHg when comparing supratentorial subdural ICP with intraventricular pressure,

Table 5.1 Values of subdural ICP and intraventricular pressure in patients undergoing supra- and infratentorial surgery

Patient number	Supratentorial subdural ICP (mmHg)	Intraventricular pressure (mmHg)	Difference in pressures (mmHg)
1	3	7	−4
2	13	17	−4
3	6	6	0
4	10	10	0
5	5	6	−1
6	22	12	10
7	7	5	2
8	13	13	0
9	5	5	0
10	0	2	−2
11	1	1	0
12	7	7	0
13	0	0	0
Mean±SD	7.1±6.2	7.0±4.9	0.1±3.4

Table 5.2 Values of infratentorial subdural ICP and intraventricular pressure in patients undergoing infratentorial surgery

Patient number	Infratentorial subdural ICP (mmHg)	Intraventricular pressure (mmHg)	Difference in pressure (mmHg)
1	7	5	2
2	10	5	5
3	9	6	3
4	14	10	4
5	19	12	7
6	15	7	8
Mean±SD	12.3±4.5	7.5±2.9	4.8±2.3

Table 5.3 Values of subdural ICP and spinal pressure in patients undergoing supratentorial surgery

Patient number	Subdural ICP (mmHg)	Spinal pressure (mmHg)	Difference in pressure (mmHg)
1	10	7	3
2	11	5	6
3	8	1	7
4	9	2	7
5	10	0	10
Mean±SD	9.6±1.1	3.0±2.9	6.6±2.5

4.8 mmHg when comparing infratentorial subdural ICP with intraventricular pressure, and 6.6 mmHg when comparing supratentorial subdural ICP with spinal pressure.

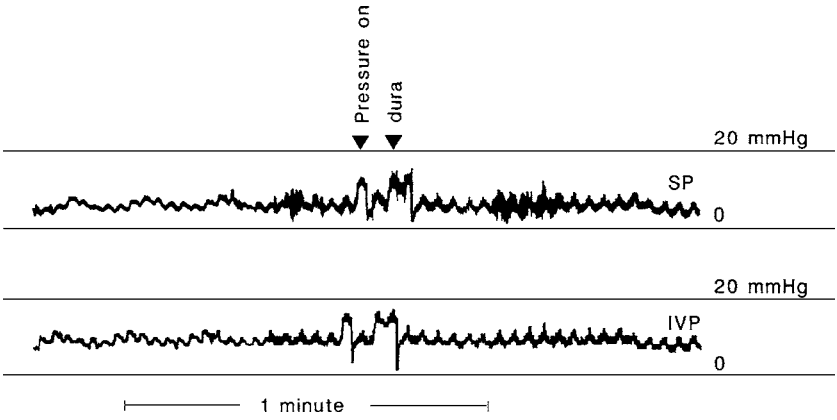

Fig. 5.1 Simultaneous recording of subdural (SP) and intraventricular (IVP) pressures

Conclusion This study indicates that between compartments of the neuroaxis differences in pressures exist, with the smallest differences within the supratentorial compartment, higher differences between the supra- and infratentorial compartments, and the highest difference between the supratentorial and spinal compartments.

Study 2: Subdural Intracranial Pressure Gradients Within the Supratentorial Surgical Field

Aim To measure gradients of subdural ICP in the sagittal and horizontal plane within the surgical field during craniotomy.

Method Thirty-seven patients with supratentorial space-occupying lesions were subjected to craniotomy in the supine position. Twenty-nine patients had

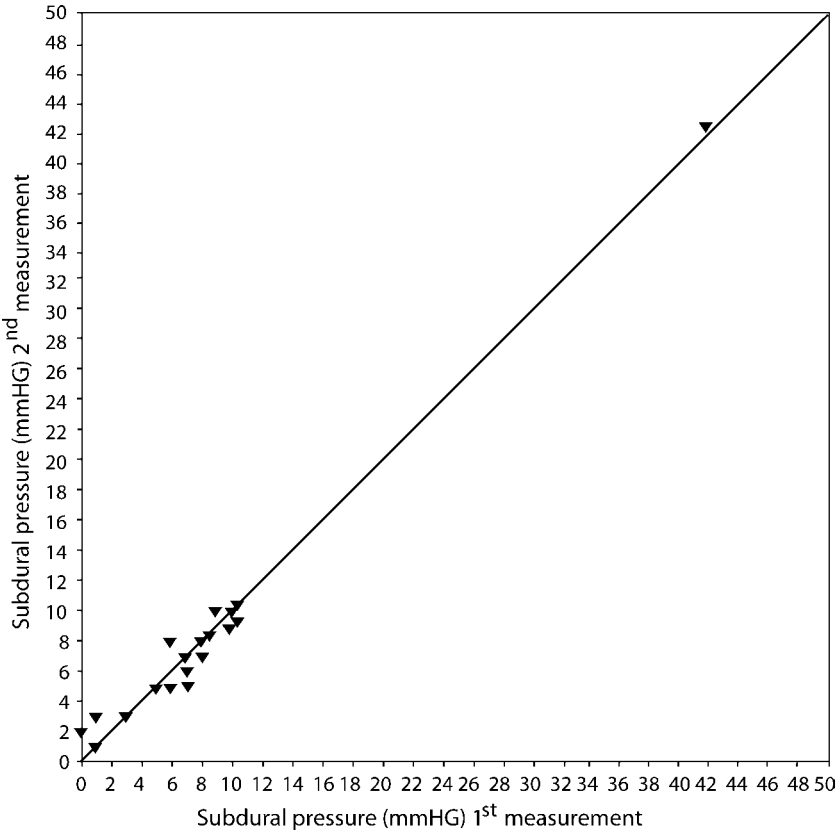

Fig. 5.2 Correlation between paired subdural pressure measurements in the same horizontal plane in 19 patients with supratentorial cerebral tumours

a brain tumour, 5 patients had SAH and were operated on for cerebral aneurysm in the acute phase within 1 week after the haemorrhage and 3 had an arteriovenous malformation. Propofol-fentanyl or isoflurane-nitrous oxide-fentanyl anaesthesia was used for maintenance of anaesthesia. Subdural ICP were measured twice in each patient. In 19 patients the two measurements were performed in the same horizontal plane with a distance of approximately 2–4 cm, and in 18 patients the two measurements were performed in the same vertical plane. The distances between the two vertical measurements of subdural pressure were measured by use of a laser light placed on a ruler. For details concerning induction and maintenance of anaesthesia and monitoring, see Chapter 3.

Statistical analysis Median and range were calculated. Non-parametric tests (Wilcoxon and Mann-Whitney) were used for statistical analyses within and between groups. Linear regression and correlation analysis (Spearman's rho) were used.

Results In the study period (5 min) no surgical intervention occurred apart from the subdural pressure measurements. The patients were in steady-state and no changes in mean arterial blood pressure or $PaCO_2$ were observed. In the study of paired subdural pressure measurements in the same horizontal plane, a good correlation between the measurements was found ($y=0.976x+0.197$, $r=0.992$, $P<0.001$) (Fig. 5.2).

In the study of paired subdural pressure measurements in the same vertical plane, the graphical representation of the results indicate that there is a corre-

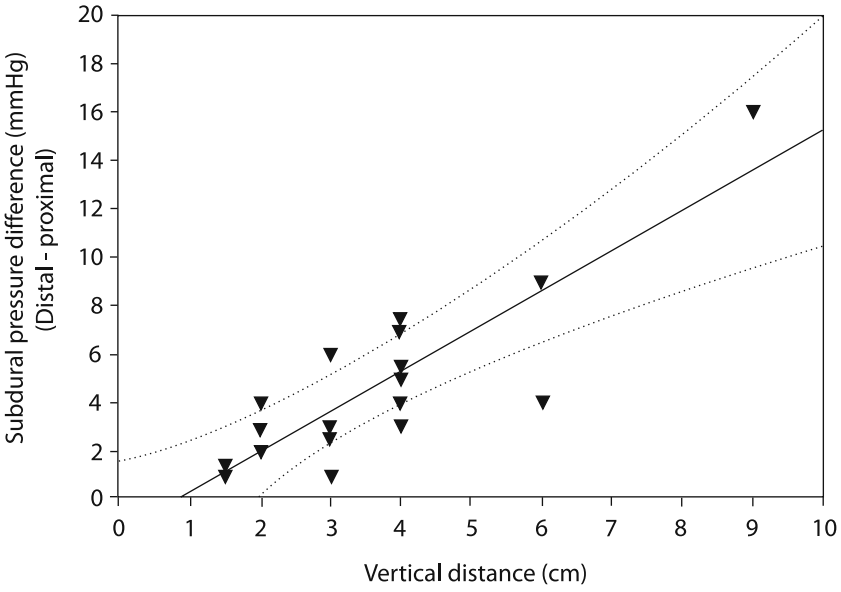

Fig. 5.3 Correlation between the vertical distance (cm), and the difference in subdural ICP in 18 patients with supratentorial space-occupying lesions

lation between the vertical distance of the two measurements and the difference in subdural pressure, with the highest subdural pressure in the most downward portion of the brain (r=0.85, P<0.001) (Fig. 5.3).

Conclusion No difference in subdural pressure was observed in the horizontal plane. A correlation between pressure on the vertical axis with the highest pressure in the caudal regions of the brain exists.

Study 3: Subdural Intracranial Pressure Gradients Within the Surgical Field in Infratentorial Surgery

Aim To measure the difference in subdural ICP in the horizontal plane in patients with midline and unilateral cerebellar tumour.

Method Sixteen patients with cerebellar tumours were subjected to posterior fossa surgery in the prone position. Ten patients had a tumour in one cerebellar hemisphere (group 1) and 6 patients had a midline cerebellar tumour or tumour in both cerebellar hemispheres (group 2). Propofol-fentanyl or isoflurane-nitrous oxide-fentanyl anaesthesia was used for maintenance of anaesthesia. Subdural pressures were measured bilaterally in the horizontal plane over the right and left cerebellar hemispheres. For details concerning maintenance of anaesthesia and monitoring, see Chapter 3.

Statistical analysis Median and range were calculated. Non-parametric tests (Wilcoxon and Mann-Whitney) were used for statistical analyses within and between groups. Linear regression and correlation analysis (Spearman's rho) were used.

Table 5.4 Group 1. Paired measurements of subdural ICP on the tumour side and the contralateral side, and differences in pressures are indicated

Patient number	ICP tumour side (mmHg)	ICP contralateral side (mmHg)	Difference in pressure(mmHg)
1	37	28	9
2	16	14	2
3	5	2	3
4	13	7	6
5	22	12	10
6	28	12	16
7	16	13	3
8	36	27	9
9	18	13	5
10	32	27	5
Median	20	13*	5.5
Range	(5–37)	(2–18)	(2–16)

*P=0.002 between median subdural pressure on tumour side and the contralateral side

Table 5.5 Group 2. Paired measurements of subdural pressure in 6 patients with midline cerebellar tumour

Patient number	ICP right cerebellar hemisphere (mmHg)	ICP left cerebellar hemisphere (mmHg)	Difference in pressure (mmHg)
1	11	11	0
2	14	15	1
3	14	13	1
4	34	36	2
5	10	11	1
6	23	22	1
Median	14	14	1
Range	(10–34)	(11–36)	(0–2)

No statistical significant difference found

Results In patients with tumour in one cerebellar hemisphere, subdural pressure measured over the cerebellar hemisphere ipsilateral to the tumour side was significantly higher than subdural pressure measured on the contralateral side (median 20 and 13 mmHg, P=0.002) (Table 5.4). In contrast, in patients with midline cerebellar tumours no difference was found in the median subdural pressure (14 mmHg) (Table 5.5). A significant difference between median subdural pressure differences in the groups was found (P=0.002) (Fig. 5.4).

Conclusion Unilateral cerebellar tumours exert local pressure in the ipsilateral hemisphere.

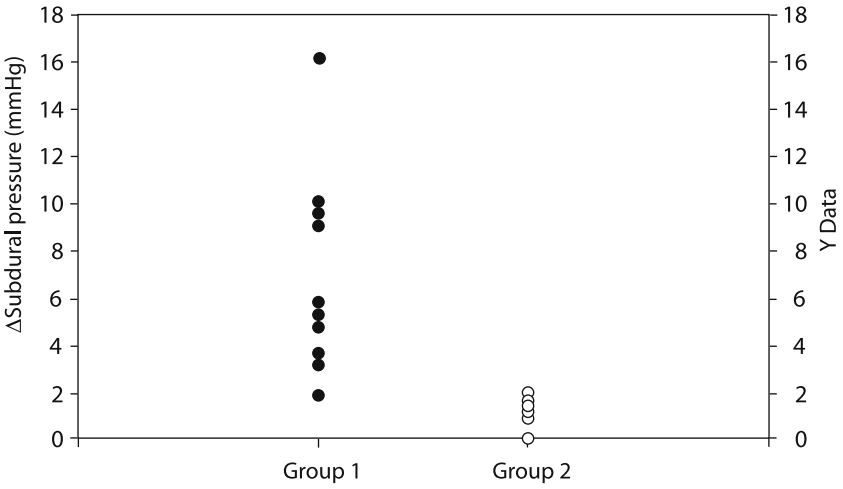

Fig. 5.4 Numerical differences in subdural pressure in 16 patients with cerebellar tumours. Numerical difference in subdural pressure from the left and right cerebellar hemisphere in 10 patients with tumour in one cerebellar hemisphere (group 1; n=10). Numerical differences in subdural pressure from the left and right cerebellar hemisphere in 6 patients with midline cerebellar tumour (group 2; n=6). P=0.002 between median subdural pressure differences in the two groups

Study 4: Changes in Subdural Intracranial Pressure During Opening of Dura

Aim To measure subdural ICP during opening of dura.

Method In 21 patients with supratentorial cerebral tumours subdural ICP was measured continuously 2 min before opening of dura, and 3–5 min after opening of dura. Subdural ICP was measured at a distance of about 1 cm from the initial opening of dura close to the bone margin.

Statistical analysis Median and range were calculated. Non-parametric tests (Wilcoxon and Mann-Whitney) were used for statistical analyses within and between groups.

Results In 8 patients with median ICP of 6 mmHg (range 2–9 mmHg) herniation never occurred, and opening of dura was followed by a rapid decline of subdural ICP over 2–3 min. In 9 patients with median subdural ICP of 10 mmHg (range 8–17 mmHg) cerebral swelling developed after dural incision, but severe herniation with venous engorgement/oedema was not observed. In these patients subdural ICP decreased slowly but steadily over 3–5 min. In four patients with median subdural ICP of 16 mmHg (range 12–32 mmHg) before opening of dura, severe herniation developed. An initial decrease in subdural ICP was followed by a secondary increase occurring 2–3 min after opening of dura. In these patients cerebral swelling was uncontrolled and evacuation of cerebral tissue was necessary to gain access to deeper structures (Table 5.6).

Conclusion The risk of cerebral swelling after opening of dura is dependent on ICP. Severe cerebral swelling was only observed at subdural ICP > 12 mmHg before opening of dura.

Discussion

Clinical and diagnostic inferences drawn from ICP-monitoring devices frequently make the assumption that ICP is uniform throughout the subarachnoid space, although the relevant pathology observed on CT or MRI is often found to be asymmetrical, but only few clinical studies are available.

Nearly all the research concerning cerebral pressure gradients has been performed experimentally on the basis of fluid infusion to imitate a rapidly expanding intracranial mass. It is reasonable that differential pressures must exist in relation to a rapidly expanding intracranial mass whose rate of expansion exceeds the rate of the adaptive capacity of the cranial space. Whether slowly expanding lesions are able to create pressure differences or not, is questionable. One problem is related to the methodology of ICP measurements. In slowly expanding lesions, where the capacity of adaptive compliance mechanisms is not exhausted, the pressure gradients are so localized and small that they are almost immeasurable. However, regional pressure gradients are important factors influencing CPP, rCBF and oedema mobilization.

Table 5.6 Changes in subdural ICP 2 min before and 3–5 min after opening of dura

Patient number	ICP, −1 min (mmHg)	ICP, zero (mmHg)	ICP, 1 min (mmHg)	ICP, 2 min (mmHg)	ICP, 3 min (mmHg)	ICP, 4 min (mmHg)	ICP, 5 min (mmHg)
Patients where subdural ICP decreases to zero within 5 min							
1	2	2	1	0			
2	2	2	1	0			
3	5	4	2	1	0		
4	6	6	5	5	4	3	0
5	7	7	6	5	4	3	0
6	8	8	0				
7	8	8	6	2	0		
8	9	9	6	2	0		
Patients where subdural ICP decreases to levels ranging from 3 to 7 mmHg							
1	8	8	7	7	5	5	4
2	9	9	7	7	5	5	4
3	10	10	10	8	3	3	3
4	10	10	7	4	4	4	3
5	10	10	10	8	6	4	3
6	11	11	11	9	8	6	5
7	11	11	11	10	8	6	5

Table 5.6 *(continued)*

Patient number	ICP, −1 min (mmHg)	ICP, zero (mmHg)	ICP, 1 min (mmHg)	ICP, 2 min (mmHg)	ICP, 3 min (mmHg)	ICP, 4 min (mmHg)	ICP, 5 min (mmHg)
Patients where subdural ICP remains higher than 9 mmHg							
1	12	12	12	20	30	28	25
2	16	16	9	9	9	12	15
3	16	16	14	12	20	13	10
4	32	32	30	23	15	17	20

Under normal conditions, there is no evidence of a naturally occurring subdural space (Haines et al. 1993). It is supposed that the pressures measured in the present study originated either from the dural border cell layer or from the subarachnoid space. It is impossible to determine from which space the pressures were measured.

Satisfactory records were obtained in all patients within 1 min. Cardiac and respiratory waves were present immediately after insertion of the needle. The reproducibility of the subdural pressure was high, as evaluated by the studies of subdural pressures performed twice and simultaneously in the same horizontal plane. The pressures never differed more than 2 mmHg, and the regression line ($y=0.976x+0.197$, $r=0.992$, $P<0.001$) was close to the line of identity.

Pressure gradients within the neuroaxis were demonstrated in study 1, where pressure gradients between supratentorial subdural ICP and ventricular pressure were smaller than pressure gradients between the supra- and infratentorial compartments, while pressure gradients between the supratentorial and spinal compartments were greatest. These findings question the use of spinal pressure in studies of intracranial space-occupying lesions.

The pressure gradients originating from a space-occupying process were studied by measuring differences in subdural pressures over the right and the left cerebellar hemispheres in 16 patients operated on in the prone position for cerebellar tumours. We distinguished between patients with tumour in one cerebellar hemisphere and patients with midline cerebellar tumours. Subdural pressure measured over the cerebellar hemisphere ipsilateral to the tumour side was significantly higher than subdural pressure measured on the contralateral side ($P=0.002$). A pressure difference as high as 16 mmHg was seen in one patient. In patients with midline cerebellar tumours subdural pressure gradients never exceeded 2 mmHg. Our results are in accordance with other studies. Cairns expressed the opinion that intracranial pressure produced by a tumour may be greater in the brain adjacent to the tumour (Cairns (1939). Weaver et al. (1982) documented markedly asymmetric pressures between hemispheres in patients with unilateral mass lesions, and Broaddus (1989) found that the location of higher pressure was predicted by the region of major pathology. The influence of a supratentorial tumour on subdural pressure was not evaluated in the present study. However, it is likely that pressure gradients due to a mass-expanding process are also present in the supratentorial compartment within the area of the exposed dura.

The actual pathophysiological mechanisms of pressure gradients in the brain are debated. During expansion of an intracranial mass, vascular compression, ischaemia of brain tissue and oedema adjacent to the lesion may occur. Formation of vasogenic brain oedema is associated with an increase in local brain tissue pressure in the white matter adjacent to the lesion site (Reulen and Kreysch 1973). It has been argued that local differences of brain water content, regional blood flow and brain tissue elastance are responsible for pressure gradients between and within hemispheres, in the presence of an expanding intracranial lesion (Ecker 1955; Lundberg 1960; Miller and Garibi

1972; Leech 1974; Symon et al. 1974; Miller et al. 1975; Piek et al. 1988). Furthermore, the pressures are influenced by obstruction of the venous vascular bed in response to increased ICP (Ecker 1955; Lundberg 1960). In addition, the physical properties of the dura mater and its attachment to the cranium play a role (Langfitt and Elliott 1967).

Other pressure gradients, not originating from an intracranial mass lesion, normally exist within the cranial vault. Tissue pressure is the sum of hydrostatic, osmotic and oncotic pressure gradients. However, it is technically challenging to record each of the components. The hydrostatic pressure measured by current techniques is more analogous to the term total tissue pressure because it also includes osmotic and oncotic forces (Rosner 1996).

The hydrostatic pressure of blood varies normally within the intact skull depending on the size of the vessel and the resistance of the vascular bed. Our results indicate that gravity might influence the regional subdural pressure in the open area of the craniotomy. A vertical pressure gradient was observed with the highest subdural pressure in the most downward portion of the brain (Fig. 5.3). It is probable, however, that the measured subdural pressure in addition to gravity was influenced by the presence of the underlying space-occupying process.

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Chapter 6
Subdural Intracranial Pressure and Degree of Swelling After Opening of Dura in Patients with Supratentorial Tumours

Mads Rasmussen and Georg Emil Cold

Abstract

During craniotomy for a mass-expanding cerebral process such as tumour or haematoma, opening of dura mater represents a critical moment. Cerebral swelling through the craniotomy can seriously jeopardize surgical access and increase the risk of cerebral ischaemia with possible worsening of the outcome. Traditionally, preoperative CT data together with the neurological examination and level of consciousness are used to assess the risk of high ICP. As a consequence, the neurosurgeon together with the anaesthesiologist may decide whether ICP-reducing therapy is indicated before opening of the dura and exposing of the brain.

In this chapter two studies of the relationship between subdural ICP and the degree of cerebral swelling after opening of dura mater are presented. The first study examined the relationship between subdural ICP before opening of the dura mater and the dural tension and degree of brain swelling in patients undergoing craniotomy for cerebral tumours or subarachnoid haemorrhage. In the second study we further investigated the relationship between subdural ICP and the degree of brain swelling in a larger population of patients.

During craniotomy for a mass-expanding cerebral process like tumour or haematoma, opening of dura mater represents a critical moment. Cerebral swelling through the craniotomy can seriously jeopardize surgical access and increase the risk of cerebral ischaemia with possible worsening of the outcome. Traditionally, preoperative CT data with estimation of tumour size, midline shift and oedema formation together with the neurological examination and level of consciousness are used to assess the risk of intracranial hypertension. As a consequence, the neurosurgeon together with the anaesthesiologist, may decide whether ICP-reducing therapy is indicated before opening of dura and exposing the brain.

In this chapter two studies of the relationship between subdural ICP and the degree of cerebral swelling after opening of dura will be presented. The first study has been presented by Bundgaard et al. in Acta Neurochir Suppl (1998) 71:276–278 and the second study has been presented by Rasmussen et al. in J Neurosurg (2004) 101:621–626.

Study 1: Subdural Monitoring of ICP During Craniotomy: Thresholds of Cerebral Swelling/Herniation

Aim To correlate ICP immediately before opening of dura mater with the tendency to cerebral swelling/herniation after opening of dura mater, and to define thresholds for cerebral swelling/herniation. Furthermore to correlate the surgeons tactile estimation of dural tension to the degree of cerebral swelling/herniation after opening of dura mater.

Patients One hundred and seventy-eight patients subjected to craniotomy for either supratentorial cerebral tumour (n=126) or subarachnoid haemorrhage (n=52) were included in the study.

Method Subdural ICP was measured before opening of dura. The degree of dural tension immediately before opening of dura was estimated (for details see Chapter 3). The degree of cerebral swelling after opening of dura was estimated by the surgeon and classified in accordance with Chapter 3: group 1: the brain below the level of dura; group 2: the brain at the level of dura, without swelling; group 3: moderate swelling of the brain; group 4: pronounced swelling of the brain. One hundred and six patients underwent propofol-fentanyl anaesthesia and 72 patients were subjected to isoflurane-nitrous oxide-fentanyl anaesthesia.

Statistical analysis Median, 5% and 95% confidence intervals (CI) of the subdural ICP are indicated. The Mann-Whitney test was used to analyse intergroup data and the Kruskal-Wallis one-way analysis of variance on ranks was used to compare groups. P<0.05 was considered significant.

Results Pair-wise multiple comparisons showed a significant difference in subdural ICP between all groups except between group 1 and group 2 and group 3 and group 4. At subdural ICP < 7 mmHg cerebral swelling/herniation rarely occurred after opening of dura. At subdural ICP > 10 mmHg, cerebral swelling/herniation occurred with high probability (Figure 6.1).

The 178 patients were divided into subgroups according to pathology (subarachnoid haemorrhage versus cerebral tumours), anaesthetic agents (isoflurane-nitrous oxide-fentanyl contra propofol-fentanyl) and the level of $PaCO_2$ (< 4.0 kPa, > 4.0 kPa). No significant intergroup difference in the subdural ICP levels were disclosed (Tables 6.1–6.3). Generally, a good correlation between tactile estimation of dural tension and the degree of cerebral swelling after opening of dura was found. However, in 15 patients (8.5%) where swelling/herniation were disclosed the neurosurgeon predicted normal tension of dura,

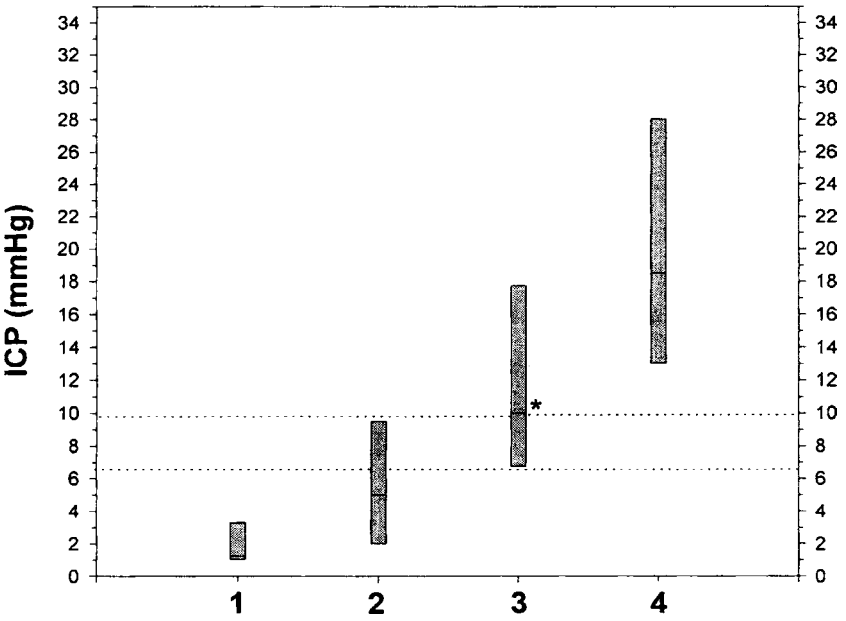

Fig. 6.1 Degree of cerebral swelling/herniation correlated to subdural ICP (N = 178). 1 The brain below the level of dura (n = 10). 2 no swelling or herniation of the brain (n = 107). 3 Swelling or herniation of the brain (n = 43). 4 Pronounced herniation of the brain (n = 18). The dotted lines indicate the thresholds for cerebral swelling/herniation. At ICP below the bottom line cerebral swelling or herniation rarely occur. At ICP above the top line cerebral swelling or herniation occur with high probability. Median and 5% to 95% confidence intervals are indicated. *Indicate $p < 0.05\%$ (comparison between 2 and 3)

Table 6.1 Relationship between level of ICP and degree of cerebral swelling after opening of dura in patients with cerebral tumours and patients with subarachnoid haemorrhage. No significant differences in the levels of ICP in the respective swelling groups were found between patients with cerebral tumour and subarachnoid haemorrhage. Group A: cerebral tumour (*n*=126), mean $PaCO_2$ 4.5 kPa, MABP 77 mmHg. Group B: subarachnoid haemorrhage (*n*=52), mean $PaCO_2$ 4.3 kPa, MABP 77 mmHg

	Degree of cerebral swelling			
	Group 1	Group 2	Group 3	Group 4
Group A				
Number	5	78	30	13
Median ICP (mmHg) (5% and 95% CI)	1 (1–4)	5 (1–10)	11 (6–21)	18 (11–31)
Group B				
Number	5	29	13	5
Median ICP (mmHg) (5% and 95% CI)	1 (1–4)	5 (1–13)	10 (6–19)	21 (13–30)

Table 6.2 Relationship between level of ICP and degree of cerebral swelling after opening of dura in patients anaesthetized with isoflurane-nitrous oxide-fentanyl or propofol-fentanyl. No significant differences in the levels of ICP in the respective swelling groups were found between patients with cerebral tumour and subarachnoid haemorrhage. Group A: isoflurane-nitrous oxide anaesthesia (n=72, mean $PaCO_2$ 4.3 kPa, MABP 73 mmHg). Group B: propofol-fentanyl anaesthesia (n=106, mean $PaCO_2$ 4.5 kPa, MABP 80 mmHg)

	Degree of cerebral swelling			
	Group 1	Group 2	Group 3	Group 4
Group A				
Number	4	36	19	13
Median ICP (mmHg) (5% and 95% CI)	2 (1–4)	5 (1–12)	12 (6–19)	17 (11–31)
Group B				
Number	6	71	24	5
Median ICP (mmHg) (5% and 95% CI)	1 (1–4)	5 (1–10)	11 (6–20)	23 (13–30)

Table 6.3 Relationship between level of ICP and degree of cerebral swelling after opening of dura in patients with $PaCO_2$ level of ≤ 4.0 kPa and > 4.0 kPa. No significant differences in the levels of ICP in the respective swelling groups were found between patients with cerebral tumour and subarachnoid haemorrhage. Group A: mean $PaCO_2$ ≤ 4.0 kPa, MABP 79 mmHg (n=50). Group B: mean $PaCO_2$ > 4.0 kPa, MABP 80 mmHg (n=128)

	Degree of cerebral swelling			
	Group 1	Group 2	Group 3	Group 4
Group A				
Number	5	28	10	7
Median ICP (mmHg) (5% and 95% CI)	1 (1–4)	5 (1–10)	9 (5–15)	20 (17–30)
Group B				
Number	6	79	33	10
Median ICP (mmHg) (5% and 95% CI)	1 (1–4)	5 (1–11)	10 (6–21)	17 (10–32)

and in 13 patients (7.5%) the neurosurgeon estimated increased tension of the dura but no swelling or herniation occurred after opening of dura.

Conclusion Generally a good correlation between the tactile estimation of dural tension and the degree of cerebral swelling after opening of dura was found. In 8.5% of patients, however, the neurosurgeons were unable to predict the occurrence of cerebral swelling. In contrast, at subdural ICP < 7 mmHg cerebral swelling rarely occurred, while at subdural ICP > 10 mmHg cerebral

swelling occurred with high probability. The subdural ICP levels at which cerebral swelling occurred were independent of pathology, anaesthetic regime and level of $PaCO_2$.

Study 2: Craniotomy for Supratentorial Brain Tumours: Risk Factors for Brain Swelling After Opening of Dura Mater

Aim The primary aim was to determine risk factors, including subdural ICP, patient characteristics, histopathology, neuroradiology, anaesthetic regimen and perioperative physiological data, predictive for brain swelling through the dural opening. As a secondary aim we wanted to define subdural ICP thresholds of brain swelling.

Method Data were collected prospectively and included demographic, anaesthetic, physiological and radiographic data from patients subjected to elective craniotomy in the supine position for supratentorial brain tumours. Since January 1994 we have routinely performed measurement of subdural ICP for elective craniotomy. Data were collected in the period from March 1994 to January 2003, and included 975 patients. Two hundred and eighty-three records were excluded because data concerning one or more of the independent variables were missing leaving 692 patients for the analysis. Preoperative CT or MR images classified the location of the tumour and extent of the midline shift. The neuroradiological examination was usually performed within 30 days of the operation. To estimate tumour size the maximum cross-sectional area was calculated on the basis of the CT or MR images using the formula for the area of an ellipse (area = $ab\pi$, where a is half the length and b is half width of the tumour). Histopathological diagnosis was obtained from the neuropathology report. A radial artery catheter was inserted for continuous blood pressure monitoring and blood sampling. Controlled ventilation (FiO_2 40–50% by oxygen/air) was applied, and the patients were ventilated with $PaCO_2$ and PaO_2 levels attempted to be between 4–5 kPa and >13 kPa, respectively. The level of $PaCO_2$ was achieved by continuous monitoring of pulmonary ventilation and end-tidal CO_2 and verified by arterial blood gas analysis. Four different anaesthetic regimes were used at our Department as "standard" anaesthesia for supratentorial craniotomy (see Chapter 3 for details): isoflurane-fentanyl, sevoflurane-fentanyl, propofol-fentanyl and propofol-remifentanil.

Subdural ICP was measured according to the description in Chapter 3. The integrated mean value of subdural pressure was used as an estimate of ICP. CPP was calculated as the difference between MABP and ICP. Blood was withdrawn simultaneously from the arterial catheter for measurement of arterial oxygen tension and $PaCO_2$. The number of subdural ICP readings with corresponding arterial blood samples ranged from 1 to 3 in each patient, depending on whether ICP-reducing therapy (see below) was instituted. The measurements were performed during a 2- to 15-min time-frame, depending on the number of measurements.

The degree of cerebral swelling was evaluated by the neurosurgeon after opening of dura. Swelling was estimated as follows: (1) the brain below the level of dura; (2) the brain at the level of dura; (3) moderate swelling of the brain; (4) pronounced swelling of the brain.

In study 1 we demonstrated that subdural ICP ≥ 10 mmHg is associated with a high probability of cerebral swelling through the dural opening. Consequently, we developed a guideline at our Department to stepwise institute hyperventilation ($PaCO_2$ attempted to be between 3 and 4 kPa), osmotherapy (mannitol 0.5–1 g/kg), 5–15° rTp or indomethacin (bolus dose of 0.2–0.4 mg/kg) to reduce ICP when perioperative recordings of ICP ≥ 10 mmHg were obtained. These therapies were instituted in random order in cooperation with the neurosurgeon. None of these therapeutic measures were incorporated in the study. The data selected for analysis from each patient therefore represent the last recording of ICP, haemodynamic and ventilatory values performed immediately before opening of dura and estimation of the degree of brain swelling.

Statistical analysis The outcome variable was dichotomized as the presence (patients classified as having moderate or pronounced brain swelling) or absence (patients classified as having the brain below or at the level of the dura) of cerebral swelling through the dural opening during craniotomy. Several continuous (age, weight, tumour size, midline shift, ICP, MABP, CPP) and categorical (sex, histopathology, tumour localization, anaesthetic regime) independent variables were chosen that potentially contribute to perioperative brain swelling (Table 6.4).

A multivariate logistic regression was performed to determine the predictors of intraoperative brain swelling. The listed independent variables might contribute to the degree of subdural ICP. Consequently the logistic regression analysis was performed with and without adjustment for ICP.

The results of the logistic regression analysis are presented as odds ratios (OR) with confidence intervals and P values. For a continuous variable x, the odds ratio is a measure of the risk change associated with a unit change in x. This estimate is obtained as the logarithm of the slope estimate from the logistic regression analysis. A P value <0.05 was considered to be significant. To illustrate the impact of ICP on the risk of brain swelling, a logistic regression curve was computed using the equation $P = P(x_1) = \exp(b_0 + b_1x_1)/[1 + \exp(b_0 + b_1x_1)]$ where P is the probability of brain swelling, b_0 and b_1 are the intercept and slope estimates from the logistic regression analysis and x is the ICP. The surgical access during craniotomy often depends on the degree of brain swelling observed. Therefore, the population of patients with brain swelling was selected and divided into two groups: those with moderate brain swelling and those with pronounced brain swelling. Logistic regression analysis was further used to calculate the impact of ICP on the risk of severe brain swelling using the above-mentioned equation.

Table 6.4 Risk factors included in the analysis of perioperative brain swelling

Risk factor	Number	Mean±SD	Percent of total
Age (years)	692	50.0±15.0	
Weight (kg)	692	73.0±16.0	
Men/women	340/352		49.0/51.0
Histopathology			
Glioblastoma	197		28.5
Meningioma	153		22.1
Metastasis	102		14.7
Glioma	182		26.3
Other	58		8.4
Tumour localization			
Frontal	266		38.4
Parietal	136		19.6
Temporal	197		28.5
Occipital	15		2.2
Central	76		11.0
Other	2		0.3
Tumour size (cm^2)	692	13.3±10.0	
Midline shift (mm)	692	5.4±5.8	
Anaesthesia			
Sevoflurane-fentanyl	52		7.5
Isoflurane-fentanyl	120		17.3
Propofol-fentanyl	457		66.0
Propofol-remifentanil	63		9.1
Physiological parameters			
$PaCO_2$ (kPa)	692	4.4±1.0	
MABP (mmHg)	692	81.0±14.0	
Subdural ICP (mmHg)	692	7.0±5.5	
CPP (mmHg)	692	73.0±15.0	

Results A total of 692 patients were included in this study. Classification of the patients according to the degree of brain swelling is demonstrated in Table 6.5. The logistic regression analysis identified four independent predictors of intraoperative brain swelling (Table 6.6). Subdural ICP was the strongest predictor of intraoperative brain swelling (OR=1.9, 95% CI=1.72–2.10, $P<0.0001$).

Table 6.5 Classification of brain swelling in 692 patients undergoing craniotomy for cerebral tumour

Classification of swelling	Number of patients (% of total)
Brain below the level of dura	59 (8.5%)
Brain at the level of dura	386 (55.8%)
Moderate brain swelling	205 (29.6%)
Pronounced brain swelling	42 (6.1%)

Table 6.6 Risk factors for intraoperative brain swelling after opening of dura in 692 patients with cerebral tumour. Odds ratios are presented without (OR) and with (OR_{adj}) adjustment for subdural ICP. The 95% CI and probability values are listed for each OR_{adj}

Risk factor	OR	OR_{adj}	CI_{adj}	P $value_{adj}$
Age (years)	0.99	1.01	0.99–1.03	0.13
Weight (kg)	1.02	1.01	0.99–1.03	0.16
Men/women	1.08	1.12	0.67–1.83	0.65
Histopathology				
Glioblastoma	1.60	2.10	1.01–4.30	0.047*
Meningioma	1.00	1.00		
Metastasis	2.1	2.9	1.3–6.9	0.011*
Glioma	1.10	1.66	0.77–3.60	0.19
Other	1.10	1.34	0.50–3.60	0.56
Tumour localization				
Frontal	1.00	1.00		
Parietal	1.03	0.74	0.38–1.43	0.37
Temporal	0.97	0.85	0.48–1.52	0.58
Occipital	5.29	3.05	0.49–19.1	0.23
Central	1.90	1.43	0.46–4.51	0.54
Tumour size (cm^2)	1.01	1.01	0.98–1.03	0.68
Midline shift (mm)	1.02	1.06	1.02–1.11	0.008*
Anaesthesia				
Sevoflurane-fentanyl	1.67	1.28	0.50–3.03	0.66
Isoflurane-fentanyl	2.18	1.34	0.72–2.52	0.36
Propofol-fentanyl	1.00	1.00		
Propofol-remifentanil	0.73	1.57	0.63–3.89	0.33
Physiological parameters				
MABP (mmHg)	1.00	1.00	0.98–1.02	0.96
Subdural ICP (mmHg)		1.90	1.72–2.10	0.0001*
CPP (mmHg)	0.973	0.990	0.96–0.98	0.82

*$P<0.05$

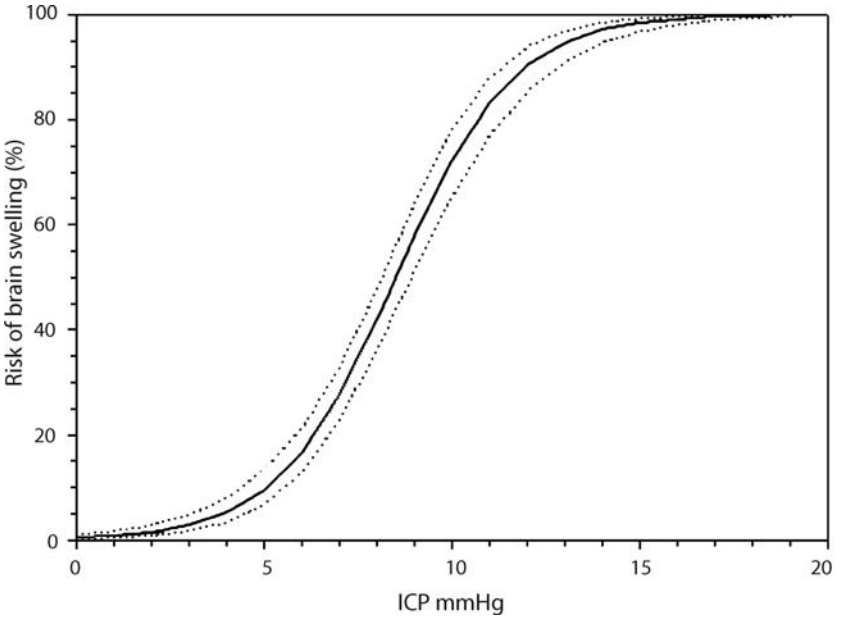

Fig. 6.2 Logistic regression curve with 95% point-wise confidence intervals depicting the relationship between subdural ICP and the percentage risk of brain swelling after opening of dura in 692 patients

The degree of midline shift (OR=1.06, 95% CI=1.02–1.11, *P*=0.008), a histopathological diagnoses of glioblastoma (OR=2.1, 95% CI=1.01–4.3, *P*=0.047) and metastasis (OR=2.9, 95% CI=1.3–6.9, *P*=0.01) were independent predictors of brain swelling. The relation between ICP and the risk of moderate and severe brain swelling including 95% confidence intervals is shown in Figure 6.2. At ICP < 5 mmHg brain swelling rarely occurred (5% probability). At ICP > 13 mmHg brain swelling occurred with 95% probability.

Conclusion Subdural ICP is the strongest predictor of intraoperative brain swelling. It is possible to define thresholds of cerebral swelling. At a subdural ICP < 5 mmHg, brain swelling rarely occurred (5% probability); at ICP > 13 mmHg, brain swelling occurred with 95% probability.

Discussion

In the first study we demonstrated that the subdural ICP levels at which cerebral swelling occurred were independent of pathology (cerebral tumour contra aneurysm), anaesthetic regime (propofol-fentanyl contra isoflurane-nitrous oxide-fentanyl) and level of $PaCO_2$. In the second study we demonstrated that subdural ICP and, to a lesser degree midline shift and histopathological diag-

nosis (glioblastoma and metastasis), significantly predicted the risk of cerebral swelling after opening of dura in patients with supratentorial cerebral tumours. Furthermore, subdural ICP threshold levels for moderate and severe brain swelling were defined.

In preliminary studies including patients subjected to craniotomy for supra- and infratentorial tumours, a significant correlation was found between subdural ICP and the degree of cerebral swelling (Cold et al. 1996; Jørgensen et al. 1999). In the first study, including 178 patients undergoing craniotomy for supratentorial tumours or subarachnoid haemorrhage, a good correlation was found between subdural ICP and the degree of cerebral swelling after opening of dura mater (Bundgaard et al. 1998). Thus, at subdural ICP < 7 mmHg cerebral swelling rarely occurred, while at ICP > 10 mmHg cerebral swelling occurred with high probability. These thresholds were independent of the pathophysiology (tumour contra subarachnoid haemorrhage), the anaesthetic agents (propofol-fentanyl contra isoflurane-fentanyl) and the $PaCO_2$ level obtained during the subdural ICP measurement. The upper threshold defined in the first study is in accordance with the threshold defined in the second study where an ICP > 10 mmHg was associated with an 83% risk of cerebral swelling (Rasmussen et al. 2004). Furthermore, at ICP > 13 mmHg brain swelling occurred with a 95% probability. However, in contrast to the first study cerebral swelling rarely occurred at ICP < 5 mmHg (5% probability), and ICP < 7 mmHg was associated with a 16% risk of brain swelling. These differences may be explained by the different statistical methods and the number of patients analysed.

The surgical access during craniotomy is impeded when severe brain swelling occurs. In the second study severe brain swelling occurred with a 95% probability at ICP > 26 mmHg. This threshold is higher than reported by Todd et al. (1993) where an ICP of 18 (SD~18) mmHg was associated with severe brain swelling in a sample of 11 patients. The large difference in standard deviation, ICP measurement technique (see below) and a small patient sample size may account for this difference.

Studies of epidural ICP measured through the first burr hole correlates significantly with the degree of cerebral swelling in patients with supratentorial tumours (Todd et al. 1993). The epidural ICP threshold at which cerebral swelling occurs appears to be higher compared with the thresholds obtained with subdural ICP. The ICP technique (epidural contra subdural ICP) may account for this difference. However, other factors may contribute. In the second study a considerable number of patients received ICP-reducing therapy prior to opening of dura. In all of these cases ICP readings were performed repeatedly in an attempt to reduce ICP to ≤ 10 mmHg. In most cases we observed that these therapies reduced ICP to a certain extent. We were, however, only able to estimate the degree of cerebral swelling once in each patient and therefore we cannot provide data whether these interventions reduced the degree of brain swelling. Because we only included the last subdural ICP measurement before opening of the dura, it is likely that the 5% and 95% ICP thresholds for brain swelling would be lower in a patient population which did

not receive ICP-reducing therapy. The time interval between epidural ICP measurement through the first burr hole and opening of dura, roughly estimated at about 10–20 min, may interfere because factors influencing ICP, including level of $PaCO_2$ and blood pressure, may differ. Furthermore, cerebral decompression after removal of the bone flap is accompanied by a fall in ICP (Rasmussen et al. 2003), with the size of the craniotomy being likely to influence subdural ICP recordings. After removal of the bone flap subdural ICP is influenced by gravity (Bundgaard and Cold 2000). Thus, ICP in the most declive part of the craniotomy is highest. Furthermore, subdural ICP is influenced by the mass-expanding lesion, being highest if measured in the immediate vicinity of the tumour. Moreover, subdural ICP measurement is a better predictor for the occurrence of brain swelling compared with estimation of dural tension by the neurosurgeon (Cold et al. 1996; Bundgaard et al. 1998). Taking these observations into consideration we therefore hypothesize that subdural ICP is a better estimate of risk of cerebral swelling than estimation of dural tension, intraventricular ICP and epidural ICP, which is measured in the fringe of the craniotomy opening, and consequently at a certain distance from the mass-expanding lesion.

The safety of our ICP measurement technique requires comments. A small subarachnoid haemorrhage after opening of the dura was observed in 0.6% of our patient population. This may be caused by the surgical incision, but we cannot exclude that the haemorrhage was caused by the insertion of the needle. However, in all of these cases ICP was within acceptable limits (mean value of 8 mmHg, data not shown) and the operation progressed without complications. Thus, the incidence of traumatic subarachnoid haemorrhage did not affect the operating conditions. In addition, no visible traumatic lesions of the cortical tissue below the insertion point of the needle was observed.

In previous studies of patients with supratentorial brain tumours, tumour size, ventricular effacement and shift of midline structures are not reliable predictors of elevated ICP measured during craniotomy (Bedford et al. 1982; Todd et al. 1993). In contrast, the degree of cerebral oedema, surrounding the tumour is correlated to ICP (Bedford et al. 1982). Likewise, contralateral ventricular dilatation is an early indicator of intracranial hypertension (Narotam et al. 1993). The significant predictive value of midline shift as well as the non-predictive value of tumour size, found in the present study, must be regarded critically. A mean of 1 week elapsed between the CT scanning and the craniotomy. In this period, the growth of tumour and the formation of cerebral oedema may increase midline shift. On the other hand, corticosteroid treatment may decrease shift of midline structures. We did not estimate the degree of cerebral oedema or the degree of contralateral ventricular dilatation, which in other studies have been documented to correlate to ICP, because estimation would be based on a graduation and not an exact area or volume. Thus, findings from study 2 do not mitigate the need for a more meticulous CT scan-based estimation of tumour size and degree of cerebral oedema immediately before craniotomy; such data would provide more valuable predictive information about

the predictive value of CT findings and the related occurrence of degree of brain swelling.

In the second study we demonstrated that patients with glioblastoma and metastasis had a significantly higher odds ratio compared with a diagnosis of meningioma. This observation is explained by the benign nature of the slow-growing meningioma, where cerebral oedema rarely contributes to the mass effect of the tumour.

Unfortunately, we are not able to provide data concerning outcome in these patients. Parameters such as tumour type, tumour location, preoperative morbidity, age and sex may have a strong influence on outcome. Thus, to assess whether prediction of cerebral swelling with measurement of subdural ICP has any influence on surgical outcome would require a large-scale randomized study.

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Chapter 7
Subdural Intracranial Pressure, Cerebral Haemodynamics, Dural Tension and Degree of Swelling After Opening of Dura in Patients with Infratentorial Tumours

Mads Rasmussen and Georg Emil Cold

Abstract

The prone position is often recommended for surgery in patients with space-occupying lesions localized in the occipital region or the posterior fossa. Compared to the supratentorial compartment, space-occupying lesions in the smaller infratentorial compartment may have a different influence on subdural ICP and the tendency to brain swelling. In addition, positioning the patient in either the supine, lateral or prone position may influence the level of subdural ICP.

In this chapter we present two studies. In the first study we present data concerning the relationship between the ICP and the degree of brain swelling in patients undergoing infratentorial surgery. In the second study we focus on whether placing the patient in the supine, lateral or prone position has any influence on subdural ICP during surgery for occipital tumours.

The prone position is often recommended for surgery in patients with space-occupying lesions localized in the occipital region or the posterior fossa. However, it has repeatedly been observed that subdural ICP in supine-positioned patients with supratentorial tumours (Rolighed Larsen et al. 2002; Haure et al. 2003; Petersen et al. 2003) is lower compared with ICP in prone-positioned patients subjected to posterior fossa surgery (Jørgensen et al. 1999; Tankisi et al. 2002) or surgery for tumours localized in the occipital region (Tankisi et al. 2002). Theoretically, the prone position causes a higher pressure in the intracerebral venous system, due to the declive position of the head. This suggestion is in accordance with studies indicating a fall in cerebral blood volume during head-up position in awake and anaesthetized subjects (Lovell et al. 2000). Other studies indicate that the prone position results in an increase in abdominal pressure (Hering et al. 2001), and experimental studies

have demonstrated that raised intraabdominal pressure increases ICP (Halverson et al. 1998; Rosenthal et al. 1998). Another possibility is that a space-occupying lesion in the smaller infratentorial compartment causes a higher increase in ICP compared with space-occupying lesions in the greater supratentorial compartment. Accordingly, the volume/pressure curve in the infratentorial segment, compared with the supratentorial compartment, is displaced to the left.

In patients with supratentorial tumours a significant relationship was found between the degree of cerebral swelling after opening of dura mater and subdural ICP measured immediately before opening of dura (Rasmussen et al. 2004). In 32 patients subjected to fossa posterior surgery in the prone position the degree of cerebral swelling was related to the level of subdural ICP (Jørgensen et al. 1999). The results indicated that at subdural ICP < 10 mmHg brain swelling rarely occurred, while at ICP > 10 mmHg some degree of cerebral swelling occurred with high probability (Jørgensen et al. 1999). In the present study, which included 109 patients, the relationship between the degree of cerebral swelling after opening of dura and subdural ICP measured immediately before opening of dura was studied in patients subjected to infratentorial cerebral surgery.

In this chapter two studies of patients subjected to craniotomy for infratentorial tumours are presented.

Study 1: The Relationship Between Intracranial Pressure and the Degree of Brain Swelling in Patients Subjected to Infratentorial Surgery

Aim To study the relationship between ICP and the occurrence of brain swelling and to define thresholds for ICP associated with brain swelling in a larger population of adult patients undergoing infratentorial craniotomy.

Method One hundred and nine adult patients subjected to infratentorial surgery were studied. The material included 98 patients with infratentorial tumours, 3 patients with arteriovenous malformations and 8 patients subjected to craniotomy for trigeminus neuralgia. Nine patients were operated in the supine position, 19 patients in the lateral position and 81 patients in the prone position. Propofol-fentanyl was used in 79 patients, propofol- remifentanil in 24 patients and isoflurane-fentanyl in 6 patients. Subdural ICP was measured immediately before opening of dura. Cerebral Perfusion Pressure was calculated as the difference between MABP and ICP. Arterial blood was analysed for $PaCO_2$ and PaO_2. The maximal area and the volume of the intracerebral process were calculated from CT/MRI scans. The degree of dural tension before opening of dura and the degree of cerebral swelling after opening of dura were estimated by the neurosurgeon. Accordingly, four groups were defined: group 1: the brain below the opening of dura mater; group 2: the brain does not swell, but the surface of the brain is at the same level as the opening of

dura mater; group 3: there is moderate swelling of the brain without strangulation at the border of dura mater; group 4: pronounced swelling of the brain with strangulation of brain tissue.

Statistical analysis Between groups normality test and equal variance test were applied. If normality tests were passed, one-way analysis of variance was used. Tukey's test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis analysis of variance on ranks and multiple comparisons (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. Means (SD) are indicated for normally distributed data and median (range) for non-normally distributed data. $P<0.05$ was considered statistically significant. In order to define thresholds for ICP associated with brain swelling the outcome variable (brain swelling) was dichotomized as the presence (patients classified as having either moderate or pronounced brain swelling) or absence (patients classified with brain below or at the level of dura) of cerebral swelling through the dural opening. Subsequently, a logistic regression curve was calculated using the equation $P = P(x_1) = \exp(b_0 + b_1x_1)/[1 + \exp(b_0 + b_1x_1)]$ where P is the probability of brain swelling, b_0 and b_1 are the intercept and slope estimates from the logistic regression analysis and x is the ICP.

Results With the exception of the weight of the patients, where patients in group 4 had a higher weight compared to patients in group 2, no significant differences were disclosed as regards age of the patients, male/female distribution, the level of $PaCO_2$, PaO_2, rectal temperature, MABP or CPP (Tables 7.1 and 7.4).

The maximal area of the intracranial processes increased from group 1 over group 2 to group 3, the median levels being 5.2, 5.9 and 11.2 cm^2 in the respective groups and 8.8 cm^2 in group 4. The differences in area in the respective groups were not significant. The volume of the processes followed the same tendency, the median (range) being 4.0 (0–13) cm^3 in group 1, 5.1 (0–40) cm^3 in group 2, 13 (0–79) cm^3 in group 3, against 9.3 (2–29) cm^3 in group 4, the only significant difference being between group 1 and group 3 (Table 7.2).

Table 7.1 Demographic and neuroradiologic data correlated to estimated brain swelling. The number of patients in each group is shown in the first row. The percentage of total is indicated in parentheses. Demographic data (age, weight) are given as mean ± SD. Neuroradiological data (tumor area and tumor volume) are given as median (range).

	Group 1 (brain below dura)	Group 2 (brain at the level of dura)	Group 3 (moderate swelling)	Group 4 (pronounced swelling)
Number	10 (9.2%)	35 (32.1%)	42 (38.5%)	22 (20.2%)
Male/female	5/5	18/17	19/23	11/11
Age	51±15	48±17	50±13	49±13
Weight	71±18	70±15	71±15	83±18*
Tumour area (cm^2)	5.2 (0–13)	5.9 (0–26)	11.2 (0–35)	8.8 (3–22)
Tumour volume (cm^3)	4.0 (0–13)	5.1 (0–40)	13 (0–79)#	9.3 (2–29)

*P<0.05 compared to group 2
#P<0.05 compared to group 1

Table 7.2 Maximal tumour area and volume of tumours related to the degree of cerebral swelling after opening of dura. Medians (ranges) are indicated

	Group 1 (brain below dura)	Group 2 (no swelling)	Group 3 (moderate swelling)	Group 4 (pronounced swelling)
Maximal area of tumour (cm^2)	5.2 (0–13)	5.9 (0–26)	11.2 (0–35)	8.8 (3–22)
Volume of tumour (cm^3)	4.0 (0–13)	5.1 (0–40)	13* (0–79)	9.3 (2–29)

*$P<0.05$ between groups 1 and 3

The major groups of pathological diagnosis included metastasis, meningioma and angioma. Astrocytoma was only diagnosed in groups 2, 3 and 4, and patients with trigeminus neuralgia were not represented in group 4. The number of patients in each group was too small to recognize significant differences in distribution (Table 7.3).

The level of ICP increased significantly with increasing degrees of dural swelling. The median (range) being 0.5 (−1 to 7) mmHg in group 1, 6.0 (−1 to 13) mmHg in group 2, 13.5 (7–24) mmHg in group 3 and 21.0 (15–37) mmHg in group 4. The difference in ICP between groups 1 and 2 was not significant, but between the groups 2, 3 and 4 and the groups 1, 3 and 4 significant differences in ICP were disclosed (Table 7.4).

At ICP levels < 7 mmHg cerebral swelling was not observed. Moderate cerebral swelling was observed in all patients when ICP exceeded 13 mmHg. Pronounced cerebral swelling was observed in all patients at ICP > 24 mmHg. In order to identify specifically the thresholds of ICP for the occurrence of brain swelling a logistic regression analysis was performed. The logistic regression analysis identified that an ICP equal to or greater than 13 mmHg was associated with a 95% probability of brain swelling. At an ICP less than 6 mmHg, brain swelling occurred with a 5% probability (Figure 7.1).

Table 7.3 Pathology of infratentorial tumours related to the degree of cerebral swelling after opening of dura

	Group 1 (brain below dura)	Group 2 (no swelling)	Group 3 (moderate swelling)	Group 4 (pronounced swelling)
Metastasis	4	10	22	8
Meningioma	1	3	4	4
Angioma	1	7	3	7
Astrocytoma	0	5	0	1
Trigeminus neuralgia	2	3	3	0
Arteriovenous malformation	0	2	1	0
Other pathology	2	5	7	2

Table 7.4 The levels of rectal temperature, $PaCO_2$, PaO_2, MABP, CPP and ICP related to the degree of brain swelling after opening of dura. Mean±SD are indicated for normally distributed data and median (range) for non-normally distributed data

	Group 1 (brain below dura)	Group 2 (no swelling)	Group 3 (moderate swelling)	Group 4 (pronounced swelling)
Temperature (°C)	36.2±0.9	35.8±0.4	35.8±0.6	36.0±0.5
$PaCO_2$ (kPa)	4.5±0.5	4.4±0.6	4.3±0.4	4.4±0.4
PaO_2 (kPa)	23.0±5.9	28.0±9.5	28.0±8.3	27.0±6.6
MABP (mmHg)	77.0±13.0	84.0±15.0	87.0±15.0	89.0±17.0
Median ICP (mmHg) (range)	0.5 (−1.0 to 7.0)	6.0 (−1.0 to 13.0)	13.5* (7.0–24.0)	21.0* (15.0–27.0)
CPP (mmHg)	76.0±13.0	79.0±16.0	72.0±13.0	68.0±19.0

*$P<0.05$ compared with all lower groups

Conclusion In this study a significant relationship was found between subdural ICP and the degree of cerebral swelling after opening of dura. In patients with ICP below 7 mmHg no swelling of the brain was observed. Moderate brain swelling was found if ICP exceeded 13 mmHg, and pronounced swelling developed at ICP exceeding 24 mmHg. Specific thresholds for ICP were calculated. A 95% and 5% risk of brain swelling was observed at ICP ≥ 13 mmHg and at ICP < 6 mmHg. Thresholds for ICP associated with brain swelling are close to thresholds defined in patients undergoing supratentorial surgery.

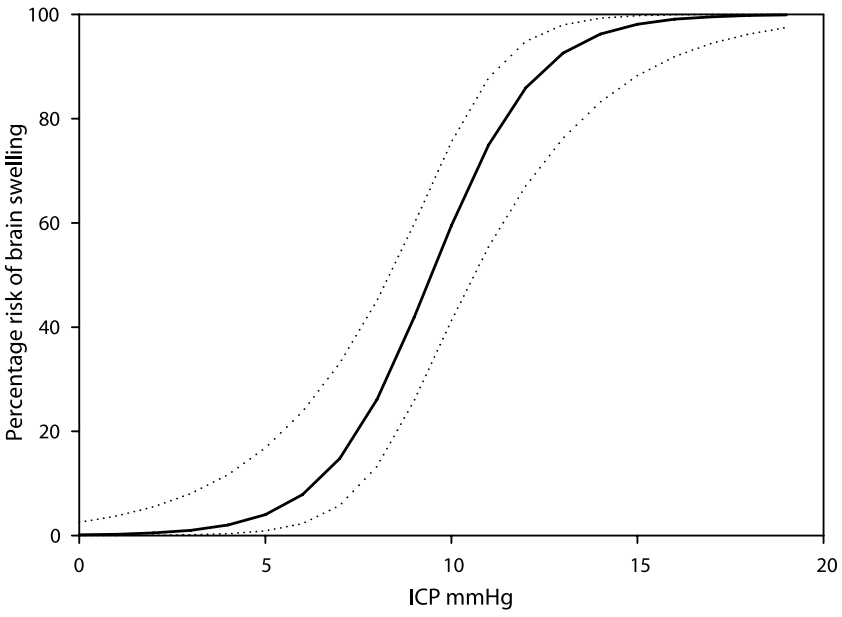

Fig. 7.1 Risk of brain swelling after opening of the dura at different ICP levels

Study 2: Patients Subjected to Craniotomy for Occipital Tumours with Special Reference to Position

Aim To measure subdural ICP in anaesthetized patients with occipital tumours positioned in the supine, lateral or prone position.

Method Thirty-three patients were operated in the prone position, 9 in the supine position and 20 in the lateral position. Anaesthesia was maintained with either propofol-fentanyl or propofol-remifentanil. As regards anaesthetic methods, neuroradiological and pathological data, monitoring of subdural ICP and cerebral haemodynamics, see Chapter 3. Subdural ICP and JBP were measured before opening of dura. CPP was calculated as the difference between MABP and ICP. The neurosurgeon estimated the degree of dural tension before opening of dura and the degree of cerebral swelling immediately after opening of dura.

Statistical analysis Between groups normality test and equal variance test were applied. If the normality tests were passed, one-way analysis of variance was used. Tukey's test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis analysis of variance on ranks and multiple comparisons (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. Means (SD) are indicated. $P<0.05$ was considered statistically significant.

Results No significant difference was found between the three positions as regards demographic data (age, height, weight, sex), neuroradiological data (maximal area of tumour, volume of the tumour or midline shift). Neither did the maintenance dose of propofol differ significantly (Table 7.5).

No significant difference was found as regards $PaCO_2$ or CPP. ICP averaged 18.7, 13.2 and 11.0 mmHg in prone-positioned, supine-positioned and laterally positioned patients, respectively ($P<0.001$ between positions). In the prone position JBP averaged 10.9 mmHg against 6.1 mmHg in the lateral position and 6.0 mmHg in the supine position. ICP and JBP were significantly higher in the prone position compared with the values observed in the lateral position. Likewise, ICP and JBP were significantly higher in prone-positioned patients compared with patients positioned otherwise (Table 7.6). Dural tension and degree of swelling were significantly more pronounced in the prone position compared with patients positioned otherwise (Table 7.7). In both propofol- fentanyl- and propofol-remifentanil-anaesthetized patients the level of ICP followed the same tendency with higher ICP levels in the prone position compared with the supine and lateral positions. The differences in ICP between positions were significant in propofol-remifentanil- anaesthetized patients ($P<0.001$), but not in propofol-fentanyl-anaesthetized patients ($P=0.07$). In prone-positioned patients a significant positive correlation was disclosed between JBP and subdural ICP ($ICP = 5.762 + 1.13 \times JBP$; $r=0.6541$, $P=0.002$, power 0.897). In the combined group of laterally and supine-positioned patients, the correlation between JBP and ICP was insignificant ($P=0.405$).

Table 7.5 Data concerning demography, neuroradiological findings and anaesthesia in prone-, laterally, supine- and lateral + supine-positioned patients with occipital tumours. Mean±SD are indicated

	Prone position	Lateral position	Supine position	Lateral+supine position
Number	33	20	9	29
Men/women	15/18	16/4	4/5	20/9
Age (years)	52.8±16.2	46.0±20.6	55.7±12.2	52.7±15.6
Weight (kg)	74.3±17.0	72.2±11.3	75.7±11.5	74.6±11.4
Height (cm)	172.0±7.0	172.0±8.0	176.0±9.0	175.0±8.0
Radiology				
Maximal area of tumour (cm^2)	13.5±7.6	11.3±6.3	11.3±6.3	11.5±6.9
Volume of tumour (cm^3)	23.6±17.8	19.8±16.5	19.8±16.5	19.8±15.3
Midline shift (mm)	4.9±5.9	3.8±4.9	2.9±4.6	3.5±4.7
Anaesthesia				
Propofol (mg/h)	618.0±199.0	552.0±246.0	656.0±174.0	584.0±192.0

Table 7.6 $PaCO_2$, ICP, CPP and JBP in prone-, laterally, supine- and lateral + supine-positioned patients with occipital tumours. Mean±SD are indicated

	Prone position	Lateral position	Supine position	Lateral+supine position
$PaCO_2$ (kPa)	4.4±0.5	4.7±0.4	4.4±0.6	4.6±0.5
ICP (mmHg)	18.7±6.8*	11.0±5.4	13.2±7.5	11.7±6.1
CPP (mmHg)	64.1±14.0	69.3±13.0	73.6±11.3	70.6±19.0
JBP (mmHg)	10.9±4.8*	6.1±5.1	6.0±1.4	6.1±4.8

*$P<0.05$ from prone position

Table 7.7 Degree of dural tension and degree of cerebral swelling after opening of dura in prone-, laterally, supine- and lateral + supine-positioned patients with occipital tumours. Number of patients is indicated (*$P<0.05$ from normal tension)

	Prone position	Lateral position	Supine position	Lateral+supine position
Tension of dura				
Normal	6	3	10	13
Increased	12	4	9	13
Pronounced	15*	2	1	3
Cerebral swelling				
None	4	3	9	12
Moderate	6	4	10	14
Pronounced	22*	2	1	3

Conclusion In the present study ICP and JBP were significantly higher in the prone position compared with the supine and lateral position. These findings suggest that the high ICP found in prone-positioned patients is partially caused by an increase in cerebral venous blood volume.

Discussion

The level of ICP is of importance in the surgical management of space-occupying cerebral lesions. At high ICP surgical access to deep cerebral structures is impeded, and pressure by self-retaining specula may decrease cerebral perfusion regionally (Albin et al. 1977; Hongo et al. 1987; Rosenørn 1987). Likewise, swelling/herniation of cerebral tissue through the opening of dura may be deleterious by preventing venous outflow from brain tissue. Thereby, a vicious circle may develop with increasing cerebral oedema and ischaemia, and surgical access is impeded or even prevented.

In preliminary studies in patients with supratentorial tumours (Cold et al. 1996; Bundgaard et al. 1997) and infratentorial tumours (Jørgensen et al. 1999) of the relationship between subdural ICP, the degree of dural tension and the degree of cerebral swelling after opening of dura, it has been documented that the subdural ICP correlates better to the degree of cerebral swelling/herniation as compared with the tactile estimation of dural tension by the neurosurgeon. One reason may be the experience of the neurosurgeon; another reason may be that the thickness of dura makes interpretation of dural tension, as an indicator of intracranial hypertension, difficult. If ICP is below 5–7 mmHg cerebral swelling rarely occurs, while subdural ICP above 13 mmHg is accompanied by moderate cerebral swelling, and at ICP above 26 mmHg pronounced cerebral swelling occurs after opening of dura (Cold et al. 1996; Jørgensen et al. 1999; Rasmussen et al. 2004). The threshold of swelling is independent of the level of $PaCO_2$, choice of anaesthesia and diagnosis (tumour versus aneurysm surgery) (Bundgaard et al. 1997).

In recent studies subdural ICP was high in prone-positioned patients with infratentorial space-occupying lesions (Jørgensen et al. 1999; Tankisi et al. 2002), compared with subdural ICP observed in patients with supratentorial space-occupying processes (Petersen et al. 2003; Rolighed Larsen et al. 2002).

The first study included 109 patients subjected to infratentorial surgery. One hundred and one patients had mass lesions due to tumour (n=98) or arteriovenous malformation (n=2), while 8 patients were without space-occupying lesions, being operated for trigeminus neuralgia. In patients with ICP below 7 mmHg no swelling of the brain was observed. Moderate brain swelling was found if ICP exceeded 13 mmHg and pronounced swelling developed at ICP exceeding 24 mmHg. It is remarkable that these thresholds are similar or very close to those found in patients subjected to surgery for supratentorial space-occupying lesions where the respective thresholds for swelling were as follows: At ICP < 5 mmHg brain swelling occurred with 5% probability, at ICP

exceeding 13 mmHg brain swelling occurred with 95% probability and at an ICP exceeding 26 mmHg severe cerebral swelling occurred with 95% probability (Rasmussen et al. 2004). The percentage of patients in the respective swelling groups were 9.2%, 32.1%, 35.5%, and 20.2%. In comparison the percentages in patients with supratentorial brain tumours were 8.5%, 55.8%, 29.6% and 6.1% (Rasmussen et al. 2004). The proportions of observations in the two studies vary significantly ($P<0.001$), indicating that the occurrence of cerebral swelling in infratentorial surgery is higher compared with supratentorial tumour surgery, but that the corresponding levels of ICP in each group are identical in patients subjected to infratentorial and supratentorial surgery. In patients subjected to craniotomy in the prone position, ICP averaged 18.3 mmHg for patients with occipital tumours and 21.0 mmHg for those with infratentorial tumours (Tankisi et al. 2002). These levels of ICP were identical with the ICP levels observed in another study of infratentorial tumours (Jørgensen et al. 1999). In comparison, the levels of ICP are considerably lower in patients subjected to supratentorial surgery in the supine position, where subdural ICP averaged 7.5, 7.0 and 10.9 mmHg (Haure et al. 2003; Petersen et al. 2003; Rasmussen et al. 2004). Likewise, an increase in ICP occurs in head injury patients when turned from the supine to the prone position (Lee 1989).

The high levels of ICP found during intracranial surgery in prone-positioned patients are associated with a high jugular venous pressure averaging 14.3 and 12.1 mmHg in patients with occipital tumours and infratentorial tumours, respectively (Tankisi et al. 2002). In comparison JBP averaged 8 mmHg in patients operated on in the supine position (Rolighed Larsen et al. 2002). During change in position to 10° rTp a decrease in ICP and jugular venous pressure is observed within 1 min (Tankisi et al. 2002). These findings suggest that the high jugular venous pressure partly causes the high ICP found in prone-positioned patients. Accordingly, a fall in cerebral blood volume during head-up position in awake and anaesthetized subjects has been demonstrated (Lovell et al. 2000). The prone position also results in an increase in ICP and a fall in CPP in patients with subarachnoid haemorrhage and acute respiratory distress syndrome (ARDS) (Reinprecht et al. 2003). Furthermore, the abdominal pressure increases (Hering et al. 2001), and in experimental studies an increase in intraabdominal pressure increases ICP (Halverson et al. 1998; Rosenthal et al. 1998). Accordingly, in patients with severe head injury ICP is higher in prone-positioned patients compared with supine-positioned patients (Lee 1989), and a rise in ICP occurs when patients with subarachnoid haemorrhage and ARDS are turned from the supine to the prone position (Reinprecht et al. 2003). One reason could be that the gravity of the brain increases ICP in the underlying brain tissue in prone-positioned patients. This has been documented in supine-positioned patients subjected to craniotomy for supratentorial tumours (Bundgaard and Cold 2000). However, it cannot be the reason in prone-positioned patients with occipital tumours, because the occipital lobe is positioned superior to other supratentorial brain structures. Another reason could be that tumour size in the smaller infratentorial com-

partment gives rise to a more pronounced ICP increase. A third reason might be that intracranial blood volume increases in the prone position, because of the declive position of the head. This reason is supported by the observation that the abdominal pressure increases in prone-positioned patients (Hering et al. 2001; Reinprecht et al. 2003), and by experimental studies showing that an increase in intraabdominal pressure is accompanied by an increase in ICP (Halverson et al. 1998; Rosenthal et al. 1998).

In the second study presented in this chapter, the position of the space-occupying lesion in the infra- contra supratentorial compartment is eliminated, because only patients with occipital processes were included. At the neurosurgeons discretion three different positions, including supine, lateral and prone, were analysed, and the values of subdural ICP and JBP were compared. Significantly higher subdural ICP and JBP were observed in prone-positioned patients, compared with patients positioned laterally, or patients positioned in a combined group including both laterally positioned patients and supine-positioned patients. In prone-positioned patients the correlation between JBP and ICP was positive and significant. Furthermore, the degree of dural tension and the degree of cerebral swelling was more pronounced in prone-positioned patients, compared with patients in the supine position and the lateral position. The use of two anaesthetic procedures, including propofol-fentanyl and propofol-remifentanil, might influence the significant differences in ICP. However, ICP in the respective anaesthetic groups followed the same tendency, with a higher ICP in prone-positioned patients compared with ICP in supine- and laterally positioned patients, and with a significant difference in ICP in propofol-remifentanil-anaesthetized patients, but not in propofol-fentanyl-anaesthetized patients.

A positive correlation between JBP and ICP has previously been documented in patients subjected to supratentorial craniotomy in either propofol-fentanyl or propofol-remifentanil anaesthesia (Chapter 8, study 3). Furthermore, studies of the effect of rTp in prone-positioned patients (Tankisi et al. 2002) and supine-positioned patients (Haure et al. 2003; Rolighed Larsen et al. 2002) have shown a decrease in both jugular venous pressure and ICP when the operating table is tipped to a head up position.

To avoid cerebral swelling after opening of dura, subdural ICP measurement is a guide. Recently, thresholds of ICP at which moderate or pronounced cerebral swelling occurs have been defined. These thresholds are identical in supratentorial (Rasmussen et al. 2004; Chapter 6) and infratentorial surgery (Chapter 7). Thus at ICP below 5–7 mmHg cerebral swelling rarely occurs, while at ICP exceeding 13 mmHg some degree of cerebral swelling occurs with high probability, and at ICP > 26 mmHg pronounced swelling occurs. Therefore, if ICP exceeds 13 mmHg therapeutic measures to reduce ICP should be initiated. Comparative studies of therapeutic methods in the treatment of perioperative intracranial hypertension are discussed in Chapter 17.

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Chapter 8
Subdural Intracranial Pressure During General Anaesthesia for Craniotomy in Patients with Supratentorial Cerebral Tumours

Lise Schlünzen and Georg Emil Cold

Abstract

Supratentorial cerebral tumours represent the bulk of intracranial pathological processes presented in most clinics. Some patients have small tumours in important deep areas and others have large tumours creating midline shift but situated close to the surface of the brain. Regardless of pathology the team treating the patient must work to create the best possible environment in the surgical field, thus giving the patient optimal chances for curative surgery. The choice of anaesthetic agent is known to influence both cerebral blood volume and other cerebral haemodynamic parameters.

In this chapter three studies of patients with supratentorial tumours are presented. Two of the studies investigate the anaesthetic techniques and the influence on cerebral haemodynamics, and the third includes the histopathological diagnosis of the tumour and relates this to the measured parameters

Anaesthesia for craniotomy has to be carried out with emphasis on haemodynamic stability, a sufficient CPP and avoidance of agents or procedures that increase the ICP. Experimental and clinical studies of cerebral haemodynamics, including CBF, $CMRO_2$ and ICP, have been carried out during isoflurane (Adams et al. 1981; Madsen et al. 1987a, b; Algotsson et al. 1988; Gordon et al. 1988; Olsen et al. 1994; Talke et al. 1996; Artru et al. 1997), sevoflurane (Scheller et al. 1988; Artru et al. 1997; Bundgaard et al. 1998; Talke et al. 1999) and propofol anaesthesia (Moos and Price 1990; Pinaud et al. 1990; Ramani et al. 1992; Alkire et al. 1995; Oshima et al. 2002). Clinical studies indicate that when isoflurane (Madsen et al. 1987a, b; Algotsson et al. 1988; Olsen et al. 1994) or sevoflurane (Artru et al. 1997; Bundgaard et al. 1998; Mielck et al. 1999) are administered CBF and $CMRO_2$ are reduced as compared to values obtained in awake normocapnic subjects. An increase

in ICP has been found during anaesthesia with isoflurane (Adams et al. 1981; Talke et al. 1996) and sevoflurane (Talke et al. 1999), and an increase in CBF has been disclosed during isoflurane (Olsen et al. 1994) and sevoflurane anaesthesia (Bundgaard et al. 1998). However, in other studies of isoflurane (Madsen et al. 1987a, b; Artru et al. 1997) and sevoflurane (Scheller et al. 1988; Artru et al. 1997; Schlünzen et al. 2004), global CBF and ICP are unchanged. In contrast, a dose-related decrease in CBF, $CMRO_2$ and ICP has been found during propofol anaesthesia (Moss and Price 1990; Pinaud et al. 1990; Ramani et al. 1992; Alkire et al. 1995).

Only a few clinical comparative studies of ICP are available. In a prospective trial of three anaesthetic techniques for elective supratentorial craniotomy (isoflurane-nitrous oxide, fentanyl-nitrous oxide and propofol-fentanyl), epidural ICP measured through the first burr hole did not differ significantly, but more patients in the isoflurane-nitrous oxide group had ICP ≥ 24 mmHg than in the other two groups (Todd et al. 1993). In contrast, a significantly lower ICP and higher CPP were found in tumour patients anaesthetized with propofol-fentanyl compared with isoflurane-fentanyl or sevoflurane-fentanyl, and in the same study the degree of dural tension and brain swelling after opening of dura were less pronounced in patients allocated to propofol-fentanyl (Petersen et al. 2003). Other studies of lumbar CSF pressure for neurosurgical anaesthesia disclosed contrasting results, no difference during propofol versus thiopental-isoflurane (Ravussin et al. 1991), but significantly lower ICP during propofol anaesthesia compared to isoflurane and sevoflurane anaesthesia (Moss and Price 1990; Talke et al. 1996).

In this presentation the randomized study by Petersen et al. (2003) is recapitulated. Moreover, based on our database, further studies are presented where special attention has been paid to the relation between pathology and ICP (the second part of the study), and the level of ICP related to jugular venous pressure (the third part of the study).

Study 1: Subdural Intracranial Pressure and Cerebral Haemodynamics in Patients with Supratentorial Cerebral Tumours Randomized to Either Propofol-Fentanyl, Isoflurane-Fentanyl or Sevoflurane-Fentanyl Anaesthesia

Aims The primary aims of the present study were to investigate whether significant differences in subdural ICP and cerebral haemodynamics existed between the three anaesthetic regimes (propofol-fentanyl, isoflurane-fentanyl and sevoflurane-fentanyl) and to study the incidence of cerebral swelling after opening of dura.

Method One hundred and seventeen patients were enrolled in the study. Forty-one patients were allocated to the propofol-fentanyl group, and the iso-

flurane-fentanyl and sevoflurane-fentanyl groups were allocated 38 patients each. Concerning neuroradiological findings, anaesthetic maintenance doses and monitoring, see Chapter 3.

Statistical analysis Data within groups were tested for normal distribution. Within groups the paired *t*-test or Wilcoxon signed rank test was used. Between groups the normality test and equal variance test were applied. Intergroup analyses included one-way analysis of variance. The Tukey test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis analysis of variance on ranks, and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. The chi-square test was used for statistical analysis of proportions of observation within neuroradiological, histopathological findings and the degrees of dura tension and brain swelling. Medians (ranges) are indicated. $P<0.05$ was considered statistically significant.

Results Data concerning neuroradiological findings, pathology and anaesthesia are summarized in Table 8.1. No significant differences were found as regards demographic, histopathology and neuroradiological findings. Data obtained after removal of the bone flap are indicated in Table 8.2. Subdural ICP and jugular saturation were significantly lower while MABP and CPP were significantly higher during propofol-fentanyl compared to isoflurane-fentanyl and sevoflurane-fentanyl. The distributions of the tactile estimate of dural tension are indicated in Table 8.3. Dural tension was significantly lower during propofol-fentanyl compared with the isoflurane-fentanyl.

Table 8.1 Data including demographics, neuroradiological data, pathology and anaesthesia. Numbers or mean (SD) are indicated

	Propofol-fentanyl	Isoflurane-fentanyl	Sevoflurane-fentanyl
Number of patients	41	38	38
Men/women	20/21	16/22	20/18
Age (years)	55 (14)	55 (10)	53 (11)
Midline shift (mm)	5.5 (5.4)	4.2 (4.0)	4.4 (4.1)
Maximal area of tumour (cm^2)	13.7 (3.4)	13.9 (14.7)	14.8 (13.7)
Glioblastoma	16	10	16
Meningioma	8	12	12
Glioma	10	8	3
Metastasis	4	5	6
Other tumours	3	3	1
Maintenance of propofol (mg/kg/h)	9.2 (1.8)	0	0
Fentanyl (μg/kg/h)	2.2 (0.7)	1.9 (0.4)*	2.0 (0.4)
MAC of volatile agent	0	0.9 (0.1)	1.0 (0.0)

*$P<0.05$ compared with propofol-fentanyl

Table 8.2 Data obtained in patients subjected to craniotomy for cerebral tumours after removal of the bone flap. Mean (SD) are indicated

	Propofol-fentanyl	Isoflurane-fentanyl	Sevoflurane-fentanyl
Rectal temperature (°C)	35.8 (0.4)	36.0 (0.6)	35.9 (0.7)
$PaCO_2$ (mmHg)	34.5 (3.0)	34.5 (3.0)	36.0 (3.0)
PaO_2 (mmHg)	203 (68)	197 (66)	179 (67)
MABP (mmHg)	86 (14)	73 (10)	76 (10)
Subdural ICP (mmHg)	7.5 (4.9)	13.0 (7.5)*	13.2 (7.1)*
CPP (mmHg)	78 (15)	60 (12)*	63 (8)*
Jugular saturation (%)	57 (10)	65 (11)*	65 (12)*

*$P<0.05$ compared with propofol-fentanyl

Table 8.3 Degree of dural tension in patients subjected to craniotomy for cerebral tumours after removal of the bone flap. Numbers (%) are indicated

Dural tension	Propofol-fentanyl	Isoflurane-fentanyl*	Sevoflurane-fentanyl
Dura very slack	4 (9.8)	1 (2.6)	1 (2.6)
Normal tension	22 (53.7)	11 (28.9)	14 (36.8)
Increased tension	13 (31.7)	20 (52.6)	21 (55.3)
Pronounced increased	2 (4.9)	6 (15.8)	2 (5.3)

*$P<0.05$ compared with propofol-fentanyl

Conclusion The study indicates that subdural ICP and jugular saturation are significantly lower and CPP higher in propofol-fentanyl-anaesthetized patients compared with patients anaesthetized with isoflurane-fentanyl or sevoflurane-fentanyl. Moreover, the degree of dural tension was less pronounced in patients subjected to propofol-fentanyl anaesthesia compared with isoflurane-fentanyl anaesthesia.

Study 2: Subdural Intracranial Pressure and Cerebral Haemodynamics in Patients Operated on in the Supine Position for Supratentorial Glioblastoma, Meningioma and Metastasis

Aim To investigate whether the histopathology of supratentorial brain tumours (glioblastoma, meningioma and metastasis) influenced the level of subdural ICP and cerebral haemodynamics during maintenance anaesthesia with propofol-fentanyl, isoflurane-fentanyl and sevoflurane-fentanyl.

Method Data from supine-positioned patients with supratentorial cerebral tumours, including glioblastoma (n=272), metastasis (n=250) or meningioma (n=163), were included in the present study. Four anaesthetic procedures were compared: Propofol-fentanyl (n=393), propofol-remifentanil (n=128), isoflu-

rane-fentanyl (n=107) and sevoflurane-fentanyl (n=57). Concerning histopathology, neuroradiological findings, anaesthesia maintenance doses and monitoring during anaesthesia, see Chapter 3.

Statistical analysis Data within groups were tested for normal distribution. Within groups the paired t-test or Wilcoxon signed rank test was used. Between groups the normality test and equal variance test were applied. Intergroup analyses included one-way analysis of variance. The Tukey test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis analysis of variance on ranks, and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. The chi-square test was used for statistical analysis of proportions of observation within neuroradiological, histopathological findings and the degrees of dura tension and brain swelling. Medians (ranges) are indicated. P<0.05 was considered statistically significant.

Results In Table 8.4 the distribution of localization of the tumours in the four different diagnostic groups are indicated. Frontal and temporal localization dominated, followed by parietal localization. In patients with meningioma basal localization was represented. In each anaesthetic group the percentage of glioblastoma was highest. Thus, in the propofol-fentanyl group 43.8% were operated on for glioblastoma, in the propofol-remifentanil group 36.3%, in the isoflurane-fentanyl group 37.6% and in the sevoflurane-fentanyl group 50%. In total 685 patients were included in the study.

In Table 8.5 the maintenance doses of anaesthetics are indicated. In all diagnostic groups the doses of propofol were significantly lower in the propofol-remifentanil group compared with the propofol-fentanyl group. The degrees of dural tension are indicated in Table 8.6. The percentages of patients with pronounced dural tension were generally lower with propofol-fentanyl (4.5–9.2%) or propofol-remifentanil (7.3–14.3%) anaesthesia compared with isoflurane-fentanyl (12.5–28%) or sevoflurane-fentanyl (9.5–21.5%) anaesthetia. Conversely, the percentages of patients with normal dural tension were higher in patients anaesthetized with propofol-fentanyl (52.4–60%) and propofol-remifentanil (61.0–71.4%) compared with isoflurane-fentanyl (34.3–46.9%) or sevoflurane-fentanyl (28.6–50%).

In Table 8.7 the level of midline shift, maximal area of tumour, volume of tumour, $PaCO_2$, PaO_2, rectal temperature, MABP, ICP and CPP are related to diagnostic groups and anaesthetic technique. Within each diagnostic group no significant differences in neuroradiological parameters were found between anaesthetic groups. No significant differences as regards $PaCO_2$, PaO_2 or rectal temperature were found between the four anaesthetic techniques. In patients with glioblastoma significant differences between ICP were found. The mean values of ICP during isoflurane-fentanyl (12.7 mmHg) or sevoflurane-fentanyl anaesthesia (13.1 mmHg) were significantly higher than during propofol-fentanyl (9.7 mmHg), which was significantly higher compared with propofol-remifentanil (6.7 mmHg). In patients with meningioma anaesthetized

Table 8.4 Histopathology and localization of tumour in patients subjected to craniotomy. Four different anaesthetic techniques were used.

Anaesthesia	Diagnosis	Frontal	Parietal	Temporal	Central	Hemispheric	Basal	Total	Percent
Propofol	Glioblastoma	56	32	65	12	5	0	170	43.3
-fentanyl	Metastasis	32	30	32	3	0	0	97	24.6
	Meningioma	55	32	21	3	0	15	126	32.1
Propofol	Glioblastoma	16	11	16	2	1	0	46	35.9
-remifentanil	Metastasis	15	7	10	1	0	0	33	25.8
	Meningioma	21	10	5	0	0	13	49	38.3
Isoflurane	Glioblastoma	11	12	11	0	0	0	34	31.8
-fentanyl	Metastasis	8	9	3	1	0	2	23	21.5
	Meningioma	20	12	13	1	0	4	50	46.7
Sevoflurane	Glioblastoma	8	7	7	0	0	0	22	38.6
-fentanyl	Metastasis	2	4	4	0	0	0	10	17.5
	Meningioma	9	10	3	0	0	3	25	43.9
Total		253	176	190	23	6	37	685	

Table 8.5 Maintenance dose of anaesthesia related to diagnosis (glioblastoma, metastasis or meningioma) in patients with supratentorial tumours. Four different anaesthetic techniques were used

Anaesthesia	Diagnosis	Maintenance dose of propofol (mg/h)	Maintenance dose of fentanyl (μg/h)	Maintenance dose of remifentanil (mg/h)	Isoflurane (MAC)	Sevoflurane (MAC)
Propofol -fentanyl	Glioblastoma	669±186	133±34	0	0	0
	Metastasis	603±170	127±35	0	0	0
	Meningioma	610±186	129±36	0	0	0
Propofol -remifentanil	Glioblastoma	397±88*	0	2.25±0.65	0	0
	Metastasis	396±106*	0	1.94±0.72	0	0
	Meningioma	385±107*	0	1.86±0.66	0	0
Isoflurane -fentanyl	Glioblastoma	0	125±36		0.71±0.29	
	Metastasis	0	113±40		0.86±0.31	
	Meningioma	0	120±42		0.89±0.23	
Sevoflurane -fentanyl	Glioblastoma	0	128±33	0	0	0.76±0.16
	Metastasis	0	156±68	0	0	0.70±0.12
	Meningioma	0	135±37	0	0	0.87±0.18

*$P<0.05$ compared with propofol-fentanyl

Table 8.6 Histopathology related to estimation of dural tension. The patients were subjected to four different anaesthetic procedures. Number (%) of patients are indicated

Anaesthesia	Diagnosis	Total number	Normal tension	Increased tension	Pronounced increased tension
Propofol -fentanyl	Glioblastoma	170	88 (51.8)	70 (41.2)	12 (7.0)
	Metastasis	97	55 (56.7)	37 (38.1)	5 (5.1)
	Meningioma	126	75 (59.5)	42 (33.3)	9 (7.1)
	Total	393	218 (55.5)	149 (37.9)	26 (6.6)
Propofol -remifentanil	Glioblastoma	46	29 (63.0)	14 (30.4)	3 (6.5)
	Metastasis	33	23 (69.7)	7 (21.1)	3 (9.1)
	Meningioma	49	38 (77.6)	7 (14.3)	4 (8.2)
	Total	128	90 (70.3)	28 (21.9)	10 (7.8)*
Isoflurane -fentanyl	Glioblastoma	34	11 (32.4)	13 (38.2)	10 (29.4)
	Metastasis	23	8 (34.8)	10 (43.5)	5 (21.7)
	Meningioma	50	20 (40.0)	22 (44.0)	8 (16.0)
	Total	107	39 (36.4)	45 (42.1)	23 (21.5)*,**
Sevoflurane -fentanyl	Glioblastoma	22	6 (27.3)	13 (59.1)	3 (13.6)
	Metastasis	10	4 (40.0)	5 (50.0)	1 (10.0)
	Meningioma	25	13 (52.0)	5 (20.0)	7 (28.0)
	Total	57	23 (40.4)	23 (40.4)	11 (19.3)*,**

*Significantly different distribution compared with propofol-fentanyl
**Significantly different distribution compared with propofol-remifentanil

with either isoflurane-fentanyl or sevoflurane-fentanyl ICP averaged 11.3 and 12.2 mmHg, respectively. These values were significantly higher compared with the ICP registered in propofol-remifentanil-anaesthetized patients (7.6 mmHg). In the same diagnostic group sevoflurane-fentanyl-anaesthetized patients had a significantly higher ICP (12.2 mmHg) compared with patients subjected propofol-fentanyl anaesthesia (8.0 mmHg). In all diagnostic groups, except patients with metastasis anaesthetized with isoflurane-fentanyl, the levels of CPP were significantly higher in propofol-fentanyl-anaesthetized patients. Within each anaesthetic group no significant differences in subdural ICP or cerebral haemodynamics were disclosed. Table 8.8 indicates the pooled data, irrespective of diagnosis. The four anaesthetic groups are indicated. No significant intergroup differences were disclosed as regards neuroradiological data (maximal tumour area, tumour volume and midline shift) or levels of $PaCO_2$. The level of ICP was significantly lower during propofol-remifentanil (6 mm Hg) and propofol-fentanyl anaesthesia (8 mmHg) compared with isoflurane-fentanyl (11.0 mmHg) and sevoflurane-fentanyl anaesthesia (11.0 mm Hg). Furthermore, the level of ICP in propofol-remifentanil-anaesthetized patients was lower than during propofol-fentanyl anaesthesia. The level of CPP was significantly higher during propofol-fentanyl anaesthesia (74 mmHg) compared with propofol-remifentanil (65 mmHg), isoflurane-fentanyl (65 mm Hg) and sevoflurane-fentanyl anaesthesia (62 mmHg).

Table 8.7 The levels of midline shift, volume of tumour, $PaCO_2$, PaO_2, rectal temperature, MABP, ICP and CPP in supratentorial cerebral tumours (glioblastoma, metastasis and meningioma). Four anaesthetic techniques were used. Mean±SD are indicated

	Diagnosis	Midline shift (mm)	Volume of tumour (cm^3)	$PaCO_2$ (kPa)	PaO_2 (kPa)	Rectal temperature (°C)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
Propofol	Glioblastoma	8.4±5.8	33±22	4.5±0.5	27±9.6	35.9±0.6	85±13	9.8±6.2	75±14
-fentanyl	Metastasis	4.5±5.1	14±16	4.6±0.5	25±8.0	35.9±0.5	82±15	9.0±5.4	73±15
	Meningioma	5.7±7.0	31±49	4.4±0.4	26±8.6	36.1±0.5	85±14	8.0±6.7	77±15
Propofol	Glioblastoma	7.3±6.5	30±19	4.5±0.4	24±6.3	35.9±0.3	74±13*	6.8±4.5*	67±14*
-remifentanil	Metastasis	4.8±6.5	20±21	4.6±0.4	23±7.7	35.9±0.5	75±12	7.8±5.2	67±14*
	Meningioma	5.2±7.2	37±58	4.4±0.3	26±7.4	35.8±0.5	70±10*	7.0±7.9	63±13*
Isoflurane	Glioblastoma	4.6±4.1	29±21	4.6±0.4	26±9.0	36.2±0.5	75±7.4*	12.6±7.6**	63±8.9*
-fentanyl	Metastasis	3.6±4.1	11±10	4.6±0.6	23±7.8	36.2±0.4	74±9.4	11.7±6.0**	62±11*
	Meningioma	2.4±4.1	31±64	4.5±0.4	27±8.3	35.9±0.6	77±11*	11.0±6.1*,**	66±13*
Sevoflurane	Glioblastoma	4.5±4.4	27±20	4.6±0.7	23±6.5	36.0±0.6	77±10*	13.3±7.8**	64±11*
-fentanyl	Metastasis	3.6±4.0	16±17	4.6±0.6	27±10	35.8±0.6	69±12*	9.8±5.9	59±11*
	Meningioma	4.0±4.8	23±16	4.5±0.3	29±13	36.0±0.6	74±11*	12.6±6.0*,**	61±12*

*Significant difference from propofol-fentanyl
**Significant difference from propofol-remifentanil

Table 8.8 Patients with supratentorial tumours (glioblastoma, meningioma and metastasis). Neuroradiological data (maximum areas of tumour, volume of tumour and midline shift), $PaCO_2$, MABP, ICP and CPP are indicated. Mean±SD are indicated

Anaesthesia	Number of patients	Women/Men	Tumour volume (cm^3)	Midline shift (mm)	$PaCO_2$ (kPa)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
Propofol -fentanyl	393	207/186	28.0±33.0	6.6±6.3	4.5±0.5	84.0±14.0	9.0±6.3	75.0±15.0
Propofol -remifentanil	128	79/49	30.0±31.0	6.3±6.8	4.5±0.4	73.0±12.0*	7.2±6.1*	66.0±14.0*
Isoflurane -fentanyl	107	58/49	26.0±21.0	4.9±4.1	4.6±0.5	76.0±10.0*	11.6±6.6*,**	64.0±11.0*
Sevoflurane -fentanyl	57	34/23	23.0±18.0	4.1±4.5	4.6±0.4	74.0±11.0*	12.4±6.7*,**	62.0±11.0*

*Significant difference ($P<0.05$) compared with propofol-fentanyl
**Significant difference compared with propofol-remifentanil

Conclusion During supratentorial tumour surgery ICP and dural tension are lowest during propofol-remifentanil anaesthesia, followed by propofol-fentanyl and anaesthesia with either isoflurane-fentanyl or sevoflurane-fentanyl. CPP, however, is significantly higher during propofol-fentanyl compared with the other three groups. Within each anaesthetic group no significant differences in subdural ICP or cerebral haemodynamics were disclosed.

Study 3: Studies of Subdural Intracranial Pressure and Jugular Bulb Pressure in Patients with Supratentorial Tumours Anaesthetized with Propofol-Fentanyl or Propofol-Remifentanil

Aim To investigate the relationship between JBP and subdural ICP/cerebral haemodynamics in patients anaesthetized with either propofol-fentanyl or propofol-remifentanil.

Method Patients with supratentorial tumours (glioblastoma, meningioma or metastasis) received either maintenance anaesthesia with propofol-fentanyl (n=188) or propofol-remifentanil (n=85). Subdural ICP, MABP and JBP were monitored immediately before opening of the dura. Arterial blood and jugular venous blood were analysed for $PaCO_2$, PaO_2, venous saturation (SATv) and $AVDO_2$. CPP was calculated as MABP – ICP. Rectal temperature was monitored. From the preoperative CT scan the maximal area of the tumour and the volume of the tumour were calculated. For details concerning histopathology, neuroradiological findings, maintenance of anaesthesia and monitoring, see Chapter 3.

Statistical analysis Data within groups were tested for normal distribution. Within groups the paired t-test or Wilcoxon signed rank test were used. Between groups the normality test and equal variance test were applied. Intergroup analyses included one-way analysis of variance. The Tukey test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis analysis of variance on ranks, and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. The chi-square test was used for statistical analysis of proportions of observation within neuroradiological, histopathological findings and the degrees of dura tension and brain swelling. Median and ranges are indicated. $P<0.05$ was considered statistically significant.

Results No significant difference was found as regards demographic data (age, weight, height, sex), serum-Na^+, serum-K^+, $PaCO_2$, PaO_2 or rectal temperature. The propofol maintenance dose was significantly lower in propofol-remifentanil-anaesthetized patients. The distribution of tumour diagnosis, localization of tumour, the midline shift and the area and volume of the tumours did not differ significantly between propofol-fentanyl and propofol-remifentanil-anaesthetized patients.

During propofol-fentanyl anaesthesia the median (ranges) of MABP 84 (52–128) mmHg, ICP 8.0 (2–38) mmHg, CPP 75 (36–118) mmHg and JBP 5.0 (4–17) mmHg were significantly higher than the values obtained during propofol-remifentanil: MABP 70 (52–118) mmHg, ICP 6.0 (−3 to 36) mmHg, CPP 65 (27–115) mmHg and JBP 2.0 (−4 to 13) mm Hg, respectively. Jugular venous oxygen saturation (SATv) was significantly higher in the propofol-fentanyl group 55.5% (36–91%) compared with the propofol-remifentanil group 51.4% (34–80%). In contrast the values of $AVDO_2$ were significantly lower during propofol-fentanyl 3.2 (0.9–5.7) mmol/L compared with the propofol-remifentanil group 3.5 (1.4–4.8) mmol/L (Table 8.9).

The estimation of tension of dura and the degrees of brain swelling after opening of dura are indicated in Table 8.10. In the propofol-fentanyl group the percentages of patients with normal tension of dura (52.1%) and patients without swelling after opening of dura (53.2%) were significantly different from the propofol-remifentanil group, where 70.6% had normal tension of dura and 70.6% were without swelling. In both groups the correlations between maximal area of tumour and ICP, the correlations between midline shift and ICP, and the correlations between JBP and ICP were significant (Table 8.11). In contrast, the correlations between CPP and jugular venous saturation, and between CPP and $AVDO_2$ were insignificant in both groups (Table 8.11).

Table 8.9 Median and ranges of MABP, subdural ICP, CPP, JBP, jugular venous saturation (SATv) and $AVDO_2$ in patients with supratentorial tumours anaesthetized with either propofol-fentanyl or propofol-remifentanil

Anaesthesia		MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	JBP (mmHg)	SATv (%)	$AVDO_2$ (mmol/L)
Propofol	Median	84	8.0	75	5.0	55.5	3.2
-fentanyl	Range	52–128	2–38	36–118	4–17	36–91	0.9–5.7
Propofol	Median	70*	6.0*	65*	2.0*	51.4*	3.5*
-remifentanil	Range	52–118	−3 to 36	27–115	−4 to 13	34–80	1.4–4.8

*$P<0.05$

Table 8.10 Tension of dura and degree of brain swelling after opening of dura in patients with supratentorial tumour anaesthetized with either propofol-fentanyl or propofol-remifentanil. Number (%) of patients is indicated

	Propofol-fentanyl	Propofol-remifentanil
Tension of dura		
Normal tension	98 (52.1)	60 (70.6)
Increased tension	76 (40.4)	17 (20.0)
Pronounced increased tension	14 (7.5)	8 (9.4)
Degree of brain swelling		
No swelling	100 (53.2)	60 (70.6)
Moderate swelling	61 (32.4)	18 (21.2)
Pronounced swelling	27 (14.4)	7 (8.2)

Table 8.11 Linear regression, correlation coefficient *r* and *P* values for the relationship between ICP contra neuroradiological findings (maximal area, volume and midline shift of tumour) and JBP

		Propofol-fentanyl	Propofol-remifentanil
Number of patients		188	85
ICP contra maximal area of tumour (cm^2)	Linear regression	ICP=5.52 + 0.24 × area	ICP=5.24 + 0.18 × area
	Coefficient (*r*)	0.3283	0.2471
	Significance	*P*<0.001	*P*=0.0230
ICP contra volume of tumour (cm^3)	Linear regression	ICP=7.01 + 0.07 × volume	Not significant
	Coefficient (*r*)	0.2670	Not significant
	Significance	*P*<0.001	Not significant
ICP contra midline shift (mm)	Linear regression	ICP=7.05 + 0.29 × midline shift	ICP= 4.74 + 0.48 × midline shift
	Coefficient (*r*)	0.2580	0.4295
	Significance	*P*<0.001	*P*<0.001
ICP contra JBP (mmHg)	Linear regression	ICP=6.49+0.46 × JBP	ICP=5.42+0.73 × JBP
	Coefficient (*r*)	0.2822	0.3411
	Significance	*P*<0.001	*P*<0.001

Conclusion In this prospective but non-randomized study significant differences between propofol-fentanyl- and propofol-remifentanil-anaesthetized patients were disclosed, comprising significantly lower ICP, CPP, JBP and jugular venous saturation values in patients anaesthetized with propofol combined with remifentanil. The results suggest that the low jugular venous pressure and the low CPP may influence ICP, and that the low $AVDO_2$ is a result of a low CPP during propofol-remifentanil anaesthesia.

Discussion

A dose-related decrease in CBF, $CMRO_2$ and ICP has been found during propofol anaesthesia (Moss and Price 1990; Pinaud et al. 1990; Ramani et al. 1992; Alkire et al. 1995). Cerebral autoregulation is better preserved during propofol anaesthesia than with isoflurane (Strebel et al. 1995) or sevoflurane (McCulloch et al. 2000). The CBV is higher during inhalation anaesthesia compared with propofol anaesthesia (Todd and Weeks 1996; Cenic et al. 2002), and jugular venous saturation is lower during propofol compared with isoflurane (Jansen et al. 1999; Petersen et al. 2003) or sevoflurane anaesthesia (Nandate et al. 2000; Petersen et al. 2003; Kawano et al. 2004; Yoshitani et al. 2005). The first randomized study presented here strongly suggests that in the clinical situation propofol-fentanyl anaesthesia for cerebral tu-

mour surgery is superior to anaesthesia with both isoflurane or sevoflurane both combined with fentanyl, because ICP is significantly lower and CPP significantly higher, and the degree of dural tension and degree of cerebral swelling after opening of dura are less pronounced (Petersen et al. 2003).

After a bolus dose of remifentanil ICP is unchanged but MABP and CPP fall (Warner et al. 1996). Compared with fentanyl both blood pressure and heart rate are lower during remifentanil anaesthesia (Twersky et al. 2001). Remifentanil in anaesthetic doses reduces regional CBF (Klimscha et al. 2003), transcranial flow velocity (Paris et al. 1998) and preserves CO_2 reactivity (Baker et al. 1997; Ostapkovich et al. 1998; Klimscha et al. 2003), which is not significantly different from anaesthesia with fentanyl as analgesic (Ostapkovich et al. 1998).

Three comparable studies of the effects of fentanyl and remifentanil in patients with supratentorial tumours are available. In a randomized study, including 18 patients, nitrous oxide-oxygen 2/1 was used as anaesthesia. The effects of continuous infusion of either fentanyl or remifentanil on CBF, measured by the intravenous ^{133}Xe method, and brain relaxation were compared. With no significant difference in $PaCO_2$, CBF was 37 ml and 36 ml/100 g/min in the remifentanil and fentanyl groups, respectively, and brain relaxation was comparable between groups (Ostapkovich et al. 1998). In another study where nitrous oxide was used as anaesthesia, 16 patients were allocated to fentanyl and 17 patients to remifentanil. Epidural ICP averaged 14 and 13 mmHg, CPP 76 and 78 mmHg and $PaCO_2$ 29 and 28 mmHg, and cerebral swelling was recorded in 65% and 58% of patients, respectively (Guy et al. 1997). In comparison, significant differences in ICP, CPP and both dura tension and the degree of brain swelling were found in the present study. Differences in anaesthetic technique (nitrous oxide contra propofol), dosages of fentanyl and remifentanil, number of patients and level of mean blood pressure might explain the discrepancy between the two studies. In the second prospective, but non-randomized study, including in total 619 patients, comparisons of ICP, CPP and dural tension were performed in patients with supratentorial tumours subjected to either propofol-fentanyl, propofol-remifentanil, isoflurane-fentanyl or sevoflurane-fentanyl. ICP were significantly higher and CPP significantly lower with isoflurane-fentanyl- or sevoflurane-fentanyl-anaesthetized patients compared with patients anaesthetized with propofol-fentanyl or propofol-remifentanil. Furthermore, ICP and CPP were significantly lower in patients subjected to propofol-remifentanil anaesthesia (mean values 7.6 and 65 mmHg, respectively), compared with patients anaesthetized with propofol-fentanyl (mean values 9.0 and 75 mmHg, respectively). The average maintenance doses of propofol, fentanyl and remifentanil were comparable with the doses used in the present study. Likewise, the levels of $PaCO_2$, ICP and CPP during propofol-fentanyl and propofol-remifentanil anaesthesia were identical with those obtained in the present study. The significantly higher values of ICP and CPP found in the propofol-fentanyl-anaesthetized patients, compared with the propofol-remifentanil group were not caused by differences in $PaCO_2$, tumour size or midline shift. Recent studies indicate that the

CO_2 reactivity is preserved during remifentanil-nitrous oxide anaesthesia (Baker et al. 1997), and the CO_2 reactivity is similar during remifentanil-nitrous oxide and fentanyl-nitrous oxide anaesthesia (Ostapkovich et al. 1998). The difference in ICP was surprising because the maintenance dose of propofol was significantly lower in the propofol-remifentanil group. According to experimental and clinical studies, propofol induces a dose-related decrease in $CMRO_2$ and CBF (Moss and Price 1990; Pinaud et al. 1990; Ramani et al. 1992; Alkire et al. 1995). Consequently, lower CBV and a lower ICP level should be expected in the propofol-fentanyl group.

The significant difference in subdural ICP might be explained by the difference in CPP, which, dependent on the status of cerebral autoregulation, might influence ICP. If cerebral autoregulation is abolished a low CPP is accompanied by a decrease in ICP. Cerebral autoregulation is not influenced by propofol (Strebel et al. 1995) or fentanyl (Hoffman et al. 1992). It is well known that cerebral autoregulation is abolished close to the site of cerebral tumours (Kuroda et al. 1982), but loss of cerebral autoregulation remote from the tumour site is also common (Endo et al. 1977) while global loss of autoregulation rarely occurs (Pálvölgyi 1969). As cerebral autoregulation was not tested in the present study, it is impossible to deny that the difference in ICP was caused by differences in CPP. In favour of this explanation is the observation that the median value of CPP was very close to the lower point of cerebral autoregulation, which otherwise is considered to be 60 mmHg, but higher values have been demonstrated in healthy volunteers (Schmidt et al. 1991; Olsen et al. 1994). At CPP below the lower value of cerebral autoregulation, CBF and CBV are positively correlated to CPP, and collapse of cerebral vessels with reduction of CBV and ICP might occur.

Differences in ICP might also be caused by a difference in JBP between the two anaesthetic groups. It has been demonstrated that tilting of the operating table to rTp in supine-positioned patients (Rolighed Larsen et al. 2002; Haure et al. 2003; Tankisi et al. 2006) and in prone-positioned patients (Tankisi et al. 2002) is accompanied by a decrease in ICP and JBP. The mechanism is supposed to be a decrease in intracranial blood volume caused by drainage of blood from the intracerebral compartment. In the third study presented here a significant difference in JBP was found, with a median of 5 mmHg in the propofol-fentanyl group against 2 mmHg in the propofol-remifentanil group. Furthermore, significant correlations between JBP and ICP were found in both anaesthetic groups. It therefore seems reasonable to suggest that the lower ICP observed in propofol-remifentanil-anaesthetized patients to some degree was caused by a lower JBP in this group.

In the third study, jugular venous oxygen saturation was lower and $AVDO_2$ higher in the propofol-remifentanil group and values of venous saturation as low as 36% and 34% were observed in the propofol-fentanyl and propofol-remifentanil groups, respectively. Although the correlations between CPP and jugular venous saturation, and CPP and $AVDO_2$ were insignificant, it cannot be excluded that the lower values of venous satura-

tion and high values of $AVDO_2$ in the propofol-remifentanil group were caused by the lower level of CPP in the remifentanil group. In some patients the value of jugular venous saturation was considerably below 40%, which otherwise is supposed to be associated with development of cerebral ischaemia (Gopinath et al. 1996). A re-definition of the lower limit of jugular venous saturation during propofol seems justified. At least in studies of diffusion-weighted MRI jugular venous saturation below 40% is not associated with evidence of cerebral ischaemia damage in patients anaesthetized with propofol (Rasmussen et al. 2004).

Two of the presented studies have limitations because they were not randomized. Data, however, were collected prospectively and continuously between the years 1997 and 2005. In this period subdural ICP monitoring was performed in 1,151 patients with supratentorial tumour, 685 of which had glioblastoma, metastasis or meningioma. The anaesthetic groups were not of equal size, propofol-fentanyl being the largest group. Propofol-remifentanil was used over the period 2000–2005, while propofol-fentanyl was used over the entire period. The maintenance dose of propofol and CPP differed significantly, which made interpretation of the results difficult. The staff of neurosurgeons and anaesthesiologists involved in craniotomy, however, was almost the same over the period. The same applies to preoperative care, principles of steroid treatment and the operating and monitoring conditions.

The clinical implications are as follows: The first two studies indicate that as regards ICP, CPP, dural tension and degree of swelling after opening of dura, propofol-fentanyl and propofol-remifentanil anaesthesia are the be preferred to isoflurane-fentanyl or sevoflurane-fentanyl. The third study indicates a preference for propofol-remifentanil compared with propofol-fentanyl because ICP was lower and the degree of dural tension and degree of swelling were less pronounced during propofol-remifentanil compared with propofol-fentanyl anaesthesia. However, CPP was also lower and close to or below the lower point of autoregulation defined elsewhere. Furthermore, jugular venous saturation was lower and $AVDO_2$ higher in propofol-remifentanil-anaesthetized patients. The third study also suggests that the low ICP in propofol-remifentanil-anaesthetized patients might be caused by a lower jugular venous bulb pressure, but the low CPP theoretically also might be a causal factor. Thus, further comparative studies of the effect of propofol-fentanyl and propofol-remifentanil on ICP seem justified, especially, studies where the doses of propofol are comparable and studies where MABP is adjusted to the same level during anaesthesia.

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Chapter 9
Effect of Sevoflurane on Subdural Intracranial Pressure and Cerebral Haemodynamics During Craniotomy

Georg Emil Cold and Helle Bundgaard

Abstract

Volatile anaesthetics act as cerebral vasodilators with the potential to increase cerebral blood flow, cerebral blood volume and ICP. In experimental studies sevoflurane is a less potent vasodilator than isoflurane and halothane, and sevoflurane has been advocated for neurosurgical anaesthesia. However, concerning the effect of ICP, the results in experimental studies are conflicting.

In this chapter we discusses sevoflurane and the dose-related changes in cerebrovascular resistance, cerebral blood flow, subdural ICP and relative CO_2 reactivity in patients undergoing craniotomy for cerebral tumour.

Volatile anaesthetics act as cerebral vasodilators with the potential to increase CBF, CBV, ICP (Drummond et al. 1986). In experimental studies, sevoflurane is a less potent vasodilator than isoflurane and halothane, and sevoflurane has been advocated for neurosurgical anaesthesia (Scheller et al. 1988, 1990; Takahashi et al. 1993; Baker 1997). However, concerning the effect of ICP, the results in experimental studies are conflicting. In rabbits (Scheller et al. 1988) and cats (Kotani et al. 1992; Sugioka 1992) sevoflurane elicits an increase in ICP. In dogs with normal intracranial compliance, however, the changes in ICP are not significant (Takahashi et al. 1993). The results of clinical studies are also conflicting. A dose-related increase in the CBF equivalent $1/AVDO_2$ has been reported (Kuroda et al. 1996). In patients undergoing transsphenoidal hypophysectomy without evidence of mass effect, sevoflurane at 0.5 and 1 MAC increases lumbar CSF pressure (Talke et al. 1999). In contrast, no dose-related changes in velocity of the middle cerebral artery were found (Kuroda et al. 1997), and ICP is unchanged from baseline during administration of 0.5–1.5% sevoflurane (Artru et al. 1997).

In patients without cerebral diseases autoregulation is intact during 1.2 MAC sevoflurane (Cho et al. 1996). In a study of hypotensive anaesthesia induced by prostaglandin E_1 autoregulation was intact as well (Kitaguchi et al. 1992). In another study, in patients subjected to extra-intracranial by-pass anastomosis, cerebral autoregulation was intact (Kitaguchi et al. 1993). Studies of dynamic cerebral autoregulation with transcranial Doppler sonographics indicate that during 1.5 MAC sevoflurane dynamic autoregulation was better preserved during sevoflurane than during isoflurane anaesthesia (Summors et al. 1999).

In patients without cerebral diseases (Cho et al. 1996), cardiac patients (Mielck et al. 1999), patients with cerebral tumours (Inada et al. 1996) and patients subjected to extra-intracranial by-pass anastomosis (Kitaguchi et al. 1993) the CO_2 reactivity is intact during sevoflurane anaesthesia. In patients subjected to craniotomy for supratentorial cerebral tumours, the CO_2 reactivity was higher for sevoflurane and isoflurane, compared with propofol-anaesthetized patients (Petersen et al. 2003).

In the present study, the dose-related changes in CVR, CBF, $CMRO_2$, subdural ICP and relative CO_2 reactivity were analysed in patients undergoing craniotomy for cerebral tumour.

Effect of Sevoflurane on Intracranial Pressure, Cerebral Blood Flow and Cerebral Metabolism

Data from this study are based on Bungaard et al. (1998).

Aim The dose-response of CVR, CBF, $CMRO_2$, CO_2 reactivity and subdural ICP of sevoflurane was studied in patients undergoing craniotomy for cerebral tumour.

Method Twenty adult patients undergoing craniotomy for supratentorial cerebral tumour participated in the study. Only patients with midline shift < 10 mm on preoperative CT were included. The patients were randomized into two groups according to the anaesthetic procedure. In group 1 (n=10) 0.7 MAC sevoflurane supplemented with Fentanyl 2 μg/kg/h was used for maintenance of anaesthesia. In group 2 (n=10) sevoflurane 1.3 MAC with the same fentanyl dose was used. CBF was measured with ^{133}Xe as tracer with two angular detectors placed on each side of the head. CBF was calculated as the initial slope index. The average values of CBF from the two detectors were used. A jugular catheter was inserted according to Chapter 3. Samples of arterial and jugular bulb blood were analysed for oxygen content and $AVDO_2$ was calculated as the difference in oxygen content between arterial blood and jugular bulb blood. $CMRO_2$ was calculated as the product of $AVDO_2$ and CBF. CVR was calculated according to the formula CPP = CBF × CVR. The relative CO_2 reactivity was calculated as the % change $AVDO_2$/change $PaCO_2$ (%/mmHg).

Table 9.1 Parameters in two groups of patients measured during maintenance anaesthesia with 0.7 MAC sevoflurane (group 1) and 0.7 followed by 1.3 MAC sevoflurane (group 2)

	$PaCO_2$ (kPa)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	$AVDO_2$ (mmol/L)	CBF (ml/100 g/min)	CVR (mmHg/ml min 100 g)	$CMRO_2$ (ml O_2/100 g/min)
Group 1								
0.7 MAC	4.8±0.3	69±6	11±7	58±11	2.4±0.7	31±10	2.2±1.0	1.7±0.6
0.7 MAC	4.9±0.3	68±4	11±8	57±10	2.2±0.7	30±10	2.2±0.7	1.5±0.6
Group 2								
0.7 MAC	5.0±0.3	80±11	11±7	69±15	2.1±0.9	29±10	2.7±1.2	1.3±0.3
1.3 MAC	5.0±0.4	77±9	12±8	66±15	1.9±0.9	34±12*	2.3±1.2*	1.3±0.4

*$P<0.05$ within group

Table 9.2 Changes in $PaCO_2$, $AVDO_2$ and subdural ICP before and after 5 min hyperventilation in patients undergoing anaesthesia with 0.7 and 1.3 MAC sevoflurane. The relative CO_2 reactivity is also shown. Mean±SD are indicated

	ΔPaCO$_2$ (mmHg)	ΔAVDO$_2$ (mmol/L)	ΔICP (mmHg)	Relative CO$_2$ reactivity (%/mmHg)
Sevoflurane 0.7 MAC	5.6±1.8	0.6±0.5	3.0±2.1	3.3±3.1
Sevoflurane 1.3 MAC	6.1±0.9	0.3±0.3	3.0±2.7	2.2±1.8

The duration of hyperventilation was 5 min. Subdural ICP, CBF and $CMRO_2$ were measured twice as follows: In group 1 both measurements were performed with 0.7 MAC sevoflurane. In group 2, the first measurement was performed with 0.7 MAC sevoflurane and the second with 1.3 MAC sevoflurane.

Statistic analysis Mean±SD are calculated. The unpaired *t*-test was used to analyse intergroup difference, and the paired *t*-test for intragroup changes. If the test for normal distribution failed, Mann-Whitney's test and the Wilcoxon test were used for unpaired and paired data.

Results No intergroup differences were found as regards demographic data, perioperative values of $PaCO_2$, PaO_2, rectal temperature, neuroradiological examination (tumour size and midline shift) or data concerning histopathology. In group 1 no time-dependent changes in subdural ICP, CPP, CBF, CVR, $AVDO_2$ and $CMRO_2$ were found. In group 2, an increase in sevoflurane concentration from 0.7 to 1.3 MAC resulted in a significant increase in CBF from 29±10 to 34±12 ml/100 g/min, and a significant decrease in CVR from 2.7±0.9 to 2.3±1.2 mmHg/ml min 100 g (Table 9.1, see page 149). During hyperventilation $PaCO_2$ decreased significantly in both groups. This was accompanied by a significant decrease in $AVDO_2$ and ICP. The relative CO_2 reactivities were 3.3±3.1 and 2.2±1.8%/mmHg during 0.7 and 1.3 MAC sevoflurane, respectively (Table 9.2).

Conclusion The present study confirms that sevoflurane is a cerebral vasodilator, as sevoflurane increases CBF and decreases CVR in a dose-dependent manner. However, in the present study the cerebral vasodilatation was not accompanied by an increase in subdural ICP. The CO_2 reactivity is preserved during 0.7 as well as 1.3 MAC sevoflurane maintenance anaesthesia.

Discussion

The major findings in this study were as follows: During normocapnic maintenance anaesthesia with 0.7 MAC sevoflurane supplemented with fentanyl no time-dependent alterations in CBF, subdural ICP, CVR and $CMRO_2$ were

observed. However, a significant increase in CBF and a significant decrease in CVR were shown when sevoflurane concentration was increased from 0.7 to 1.3 MAC.

These values of CBF and $CMRO_2$ are comparable to CBF and $CMRO_2$ measured by the Kety and Schmidt technique with argon as tracer in normocapnic patients with ischaemic cerebrovascular disease anaesthetized with 1.5% sevoflurane (Kitaguchi et al. 1993). Furthermore, CBF and $CMRO_2$ were approximately 40% lower than CBF measured by the Kety and Schmidt technique in awake healthy volunteers (Madsen et al. 1993). These findings indicate that sevoflurane, supplemented with fentanyl, even in low MAC concentration induces a substantial suppression of cerebral oxygen uptake. A dose-dependent decrease in $CMRO_2$, following increase in MAC concentration from 0.7 to 1.3 MAC, was expected because anaesthetics in general suppress $CMRO_2$ dose dependently (Michenfelder 1974; Newberg et al. 1983). Accordingly, CBF and $CMRO_2$ are coupled with a reduction of flow and metabolism averaging 38% and 47%, respectively, during 1 MAC sevoflurane in cardiac patients (Mielck et al. 1999). However, with these low values of $CMRO_2$ a dose-dependent decrease was not found, probably because a 50% decrease is accompanied by isoelectric activity, and oxygen consumption is only used for maintenance of cellular membrane potential.

In accordance with Kuroda et al. (1997) time-dependent alterations in CBF, $CMRO_2$ and subdural ICP were not observed in the present study. A dose-related increase in CBF and a decrease in CVR, however, were disclosed, while subdural ICP and CPP were unchanged. The increases in CBF and the fall in CVR indicate that sevoflurane is a cerebral vasodilator. Under these circumstances, the reason for the unchanged subdural ICP might be a favourable cerebral compliance, where changes in CBV, caused by the increased sevoflurane concentration, did not elicit a measurable ICP increase. A reasonable explanation may also be that all patients were fully conscious, that only patients with midline shift < 10 mm were included, that the individual levels of subdural ICP were relatively low, meaning that the actual ICP pressures were localized on the flat part of the volume/pressure curve, and that the majority of patients were in treatment with steroid.

In clinical studies in patients without cerebral diseases (Cho et al. 1996) and in patients subjected to extra-intracranial by-pass anastomosis, cerebral autoregulation was intact during sevoflurane anaesthesia (Kitaguchi et al. 1993). It is well known, however, that cerebral autoregulation is abolished regionally and globally in patients with brain tumour. The status of cerebral autoregulation might not seem to influence the results in the present study because CPP was unchanged in both groups.

The relative CO_2 reactivity was calculated as % change $AVDO_2$/change in $PaCO_2$ in accordance with Obrist et al. (1984). CBF is inversely proportional to $AVDO_2$ on the assumption that $CMRO_2$ is constant during hyperventilation (Michenfelder and Theye 1969), and hyperventilation has been reported to have no effect on $CMRO_2$ (Åkeson et al. 1993). The relative CO_2 reactivity aver-

aged 3.3 and 2.2%/mmHg at 0.7 and 1.3 MAC sevoflurane, respectively. These values are less than the values obtained with the initial slope ^{133}Xe method in awake subjects during normocapnic conditions (average 4%/mmHg) (Olesen et al. 1971) and in patients undergoing craniotomy for cerebral tumour in 1 MAC sevoflurane supplemented with fentanyl, where the relative CO_2 reactivity averaged 4.6%/mmHg (Petersen et al. 2003). Higher CO_2 reactivities during sevoflurane anaesthesia have also been documented patients with ischaemic cerebral disease (Kitaguchi et al. 1993) and in another study in patients with cerebral tumour (Inada et al. 1996). Methodological differences, differences in level of $PaCO_2$, blood pressure and the use of nitrous oxide may explain the discrepancy. Using the definition proposed by Obrist et al. (1984), the relative CO_2 reactivity is preserved at values > 1%/mmHg. Accordingly, in the present study the CO_2 reactivity was preserved at 0.7 as well as 1.3 MAC sevoflurane.

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Chapter 10
Effect of Hyperventilation on Subdural Intracranial Pressure

Lise Schlünzen and Georg Emil Cold

Abstract

Hyperventilation has been used in the treatment of patients with intracranial pathologies for decades. In the neurointensive care unit the use of hyperventilation is on retreat due to the risk of cerebral ischaemia. During surgery the situation is somewhat different because of the shorter duration of hyperventilation and the close monitoring of physiological parameters.

In this chapter the results of three studies regarding the effect of hyperventilation on subdural ICP and cerebral haemodynamics during four anaesthetic regimes are presented. The inhalation agents most often used in western countries, isoflurane and sevoflurane, as well as the total intravenous anaesthetic regimes of propofol-fentanyl and propofol-remifentanil, and the influence on ICP during hyperventilation are discussed.

In Chapter 8 studies of ICP and cerebral haemodynamics in patients subjected to craniotomy for cerebral tumours are summarized. Four anaesthetic regimes, including propofol-fentanyl, isoflurane-fentanyl, sevoflurane-fentanyl and propofol-remifentanil, were studied. As regards ICP at the time of opening of dura ICP was significantly higher during isoflurane-fentanyl and sevoflurane-fentanyl compared with propofol-fentanyl, but lower during propofol-remifentanil than during propofol-fentanyl.

Continuous remifentanil infusion combined with propofol provides stable central haemodynamics, but clinical data concerning ICP and other measures of cerebral haemodynamics are few. In clinical practice in our clinic the maintenance dose of propofol is higher during propofol-fentanyl- compared with propofol-remifentanil-anaesthetized patients subjected to craniotomy. As a consequence it is expected that the suppression of cerebral metabolism and thereby CBF is more pronounced during propofol-fentanyl anaesthesia. Consequently, ICP theoretically should be lower. Moreover, the lower blood pressure during propofol-remifentanil anaesthesia should decrease CPP. If cerebral autoregulation is predominantly intact this decrease should increase

ICP. In contrast, ICP should decrease if cerebral autoregulation is lost. As the effect of hyperventilation on ICP is influenced by cerebral autoregulation as well as the depression of cerebral oxygen uptake, and anaesthetics influence both factors, studies of hyperventilation during different anaesthetic regimes seem justified. Moreover, studies of the combination of hyperventilation, which acts via cerebral vasoconstriction, and mannitol treatment, acting via osmotic forces, are of interest, and especially in cases where hyperventilation alone does not reduces ICP below the threshold for occurrence of brain swelling after opening of dura.

In this chapter the results of three studies of the effect of hyperventilation on subdural ICP and cerebral haemodynamics during four anaesthetic regimes are presented. Results of the first study have been presented by Petersen et al. in Anesthesiology (2003) 98:329–336.

Study 1: Comparative Study of the Effect of Hyperventilation During Propofol-Fentanyl, Isoflurane-Fentanyl and Sevoflurane-Fentanyl Anaesthesia on Cerebral Haemodynamics

Aim To study the effect of hyperventilation on cerebral haemodynamics in patients subjected to craniotomy for supratentorial cerebral tumours during anaesthesia with propofol-fentanyl, isoflurane-fentanyl or sevoflurane-fentanyl.

Method In an open label study 117 patients with supratentorial cerebral tumours were randomized to propofol-fentanyl (group 1), isoflurane-fentanyl (group 2) or sevoflurane-fentanyl anaesthesia (group 3). Principles for anaesthesia (induction and maintenance) are indicated in Chapters 3 and 8. Principles for neuroradiological and pathological findings and monitoring are indicated in Chapter 3. Normo- to moderate hypocapnia was applied, the target level of $PaCO_2$ being 30–40 mmHg. MABP was stabilized with i.v. ephedrine (2.5–5 mg), if necessary. Subdural ICP, MABP, CPP, $AVDO_2$ and internal jugular vein oxygen saturation (SjO_2) were monitored before and after a 10-min period of hyperventilation, and the CO_2 reactivity was calculated. Furthermore, the tension of dura before and during hyperventilation, and the degree of cerebral swelling during hyperventilation and after opening of dura were estimated by the neurosurgeon. Data concerning neurological findings, pathology and demographics are summarized in Chapter 8, study 1.

Statistical analysis Based on a previous non-randomized study of ICP during three different anaesthetic techniques, given a minimum detectable difference of 3.6 mmHg, expected SD of 5.0 mmHg, power of 0.80 and a significance level of $P<0.05$, the total number of patients was calculated to be 114 patients. Data within groups were tested for normal distribution. The normality test and equal variance test were applied, one-way ANOVA was used for analysis if these tests were passed, and Tukey's test was used for pair-wise multiple com-

parison procedures. The Kruskal-Wallis one-way analysis of variance on ranks and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. These data included subdural ICP, MABP and $AVDO_2$. Bonferroni's test was applied for statistical analysis. The chi-square test was used for statistical analysis of demographic data, localization, size and histopathological diagnosis of the tumours, preoperative steroid administration and position of the head between the groups. Difference in tension of dura and the degree of cerebral swelling were tested by the chi-square test. For correlation studies Pearson's product moment correlation and linear regression were performed. Mean±SD were calculated. $P<0.05$ was considered statistically significant.

Results No significant differences between the three anaesthetic groups were disclosed as regards neurological findings, pathology and demographics. During hyperventilation ICP decreased significantly in all groups. ICP was sinificantly lower while MABP and CPP were significantly higher during propofol-fentanyl compared to isoflurane-fentanyl and sevoflurane-fentanyl

Table 10.1 Data obtained before and during hyperventilation, changes in parameters before and during hyperventilation, and CO_2 reactivity. Mean±SD are indicated. No significant differences were disclosed between the isoflurane and sevoflurane groups

	Propofol	Isoflurane	Sevoflurane
Before hyperventilation			
MABP (mmHg)	86.0±14.0	73.0±10.0	76.0±10.0
ICP (mmHg)	7.5±4.9	13.0±7.5*	13.2±7.1*
CPP (mmHg)	78.0±15.0	60.0±12.0*	63.0±8.0*
JBP (mmHg)	7.0±3.5	8.5±4.3	8.9±3.9
$PaCO_2$ (mmHg)	34.5±3.0	34.5±3.0	36.0±3.0
PaO_2 (mmHg)	203.0±68.0	197.0±66.0	179.0±67.0
SATv (%)	57.0±10.0	65.0±11.0*	65.0±12.0*
$AVDO_2$ (mmol/L)	3.1±0.8	2.5±0.8*	2.5±0.8*
Temperature (°C)	35.8±0.4	36.0±0.6	35.9±0.7
During hyperventilation			
MABP (mmHg)	87.0±13.0	71.0±12.0	74.0±11.0
ICP (mmHg)	5.8±4.6	9.8±6.3*	9.4±6.6*
CPP (mmHg)	82.0±14.0	61.0±11.0*	64.0±10.0*
JBP (mmHg)	6.3±3.4	8.1±4.0	8.4±4.2
$PaCO_2$ (mmHg)	28.5±3.0	29.3±2.3	30.8±3.0*
SATv (%)	52.0±11.0	57.0±12.0*	56.0±12.0*
$AVDO_2$ (mmol/L)	3.6±0.9	3.0±0.9*	3.2±0.8
ΔICP (mmHg)	1.7±2.2	3.2±3.7*	3.4±3.7*
$\Delta PaCO_2$ (mmHg)	6.1±2.0	5.0±2.0*	4.9±2.2*
ΔCPP (mmHg)	3.3±6.1	1.5±7.4	0.2±8.7
CO_2 reactivity (% change $AVDO_2/\Delta PaCO_2$ (mmHg))	2.0±1.4	3.6±2.6*	4.6±3.2*

*$P<0.05$ compared with the propofol group

anaesthesia. Hyperventilation was accompanied by a significant increase in $AVDO_2$ in all groups. During propofol-fentanyl anaesthesia $AVDO_2$ was significantly higher compared with isoflurane-fentanyl anaesthesia, but not significantly different from sevoflurane-fentanyl anaesthesia. $PaCO_2$ was significantly higher in the sevoflurane group compared with the propofol group.

The CO_2 reactivity was significantly lower during propofol-fentanyl compared with isoflurane-fentanyl and sevoflurane-fentanyl anaesthesia. Although the difference in $PaCO_2$ was significantly greater during propofol-fentanyl anaesthesia, the reduction in ICP during hyperventilation was significantly smaller compared with isoflurane-fentanyl and sevoflurane-fentanyl anaesthesia, respectively (Table 10.1).

The distributions of the tactile estimate of dural tension before and during hyperventilation, and the estimates of brain swelling after opening of dura are indicated in Table 10.2. Before and during hyperventilation dural tension was significantly lower during propofol-fentanyl compared with isoflurane-fen-

Table 10.2 Degree of dural tension before hyperventilation and during hyperventilation, and the degree of brain swelling after opening of dura. Number and percentage are indicated. No significant differences between the isoflurane and sevoflurane groups were disclosed

	Propofol	Isoflurane	Sevoflurane
Tension of dura before hyperventilation			
Dura slack	4 (9.8%)	1 (2.6%)	1 (2.6%)
Normal tension	22 (53.7%)	11 (28.9%)	14 (36.8%)
Moderately increased tension	13 (31.7%)	20 (52.6%)	21 (55.3%)
Pronounced increase in tension	2 (4.9%)	6 (15.8%)	2 (5.3%)
Significance compared with propofol		$P<0.05$	Not significant
Tension of dura during hyperventilation			
Dura slack	7 (17.1%)	2 (5.3%)	2 (5.3%)
Normal tension	24 (58.5%)	16 (42.1%)	23 (60.5%)
Moderately increased tension	8 (19.5%)	14 (36.8%)	13 (34.2%)
Pronounced increase in tension	2 (4.9%)	6 (15.8%)	0 (0.0%)
Significance compared with propofol		$P<0.05$	Not significant
Brain swelling			
No swelling	30 (73.2%)	16 (42.1%)	21 (53.3%)
Moderate swelling	11 (26.8%)	16 (42.1%)	14 (36.8%)
Pronounced swelling	0 (0.0%)	6 (15.8%)	3 (7.9%)
Significance compared with propofol		$P<0.05$	Not significant

tanyl anaesthesia. After opening of the dura the degree of cerebral swelling was found to be more prominent during isoflurane-fentanyl and sevoflurane-fentanyl anaesthesia compared with propofol-fentanyl anaesthesia.

Correlation studies No significant correlations were found between $PaCO_2$ and ICP, between $\Delta PaCO_2$ and ΔICP or between MABP and ICP in the respective groups. Neither did we find any significant correlation between neuroradiological data (tumour size, midline shift) and subdural ICP obtained before hyperventilation, or between the anaesthetic maintenance dose of fentanyl and subdural ICP.

Conclusion The study indicates that before as well as during hyperventilation, subdural ICP and $AVDO_2$ are lower and CPP higher in propofol-anaesthetized patients compared with patients anaesthetized with isoflurane or sevoflurane. These findings were associated with less tendency for cerebral swelling after opening of dura in the propofol group. The CO_2 reactivity in patients anaesthetized with isoflurane and sevoflurane was significantly higher than in the propofol group. The differences in subdural ICP between the groups are presumed to be caused by differences in the degree of vasoconstriction elicited by the anaesthetic agents, but autoregulatory mechanisms caused by differences in CPP cannot be excluded.

Study 2: Comparative Study of the Effect of Hyperventilation During Propofol-Fentanyl and Propofol-Remifentanil Anaesthesia on Cerebral Haemodynamics

Aim To study the effect of hyperventilation on cerebral haemodynamics in patients subjected to craniotomy for supratentorial cerebral tumours in anaesthesia with either propofol-fentanyl or propofol-remifentanil.

Method Subdural ICP, MABP, CPP, $PaCO_2$, SATv, JBP, and $AVDO_2$ were compared in 52 patients scheduled to propofol-fentanyl (P/F) anaesthesia and 53 patients to propofol-remifentanil (P/R) anaesthesia. The measurements were performed before and immediately after a 5-min period of hyperventilation. Principles for anaesthesia (induction and maintenance), and principles for neuroradiological and pathological findings and monitoring are indicated in Chapter 3.

Statistical analysis Based on a previous non-randomized study of ICP during three different anaesthetic techniques, given a minimum detectable difference of 3.6 mmHg, expected SD of 5.0 mmHg, power of 0.80 and a significance level of $P<0.05$, the total number of patients was calculated to be 114 patients. Data within groups were tested for normal distribution. The normality test and equal variance test were applied, one-way ANOVA was used for analysis if these tests were passed, and Tukey's test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis one-way analysis of variance on

ranks and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. These data included subdural ICP, MABP and $AVDO_2$. Bonferroni's test was applied for statistical analysis. The chi-square test was used for statistical analysis of demographic data, localization, size and histopathological diagnosis of the tumours, preoperative steroid administration and position of the head between the groups. Difference in tension of dura and the degree of cerebral swelling were tested by the chi-square test. For correlation studies Pearson's product moment correlation and linear regression were performed. Mean±SD were calculated. $P<0.05$ was considered statistically significant.

Results Demographic data, neurological findings, including maximal area of the tumour and midline shift, were comparable between the two groups. Neither did electrolytes, haemoglobin, blood pressure on admission, histopathological data nor distribution of tumour localization differ significantly between groups. The maintenance dose of propofol was 8.9 mg/kg/h in the

Table 10.3 Data obtained before and during hyperventilation, changes in parameters before and during hyperventilation, and CO_2 reactivity. Mean±SD are indicated

	Propofol -fentanyl	Propofol -remifentanil	*P* values
Before hyperventilation			
Temperature (°C)	35.8±0.5	35.8±0.4	0.924
$PaCO_2$ (kPa)	4.6±0.4	4.5±0.3	0.289
PaO_2 (kPa)	27.2±8.3	25.2±7.0	0.196
MABP (mmHg)	86.0±13.0	76.0±14.0	<0.001
ICP (mmHg)	6.8±4.8	6.2±3.9	0.690
CPP (mmHg)	80.0±14.0	69.0±14.0	<0.001
JBP (mmHg)	6.8±4.0	2.7±3.4	<0.001
Jugular oxygen saturation (%)	56.8±9.6	53.2±10.5	0.044
$AVDO_2$ (mmol/L)	3.2±0.7	3.4±0.7	0.262
During hyperventilation			
$PaCO_2$ (kPa)	3.8±0.5	3.9±0.3	0.641
MABP (mmHg)	87.0±13.0	74.0±13.0	<0.001
ICP (mmHg)	5.1±4.6	4.3±3.8	0.475
CPP (mmHg)	82.0±14.0	70.0±13.0	<0.001
JBP (mmHg)	6.2±4.0	2.6±3.3	<0.001
Jugular oxygen saturation (%)	51.2±10.6	47.7±10.8	0.070
$AVDO_2$ (mmol/L)	3.6±0.8	3.7±0.7	0.402
$\Delta PaCO_2$ (kPa)	0.74±0.26	0.70±0.20	0.615
ΔICP (mmHg)	1.6±1.6	2.0±1.4	0.088
ΔCPP (mmHg)	1.8±5.3	2.0±1.4	0.670
CO_2 reactivity (% change $AVDO_2/\Delta PaCO_2$ (mmHg))	2.0±1.4	1.9±1.4	0.670

propofol-fentanyl group, against 5.8 mg/kg/h in the propofol-remifentanil group (P<0.001). No significant differences between groups were found as regards $PaCO_2$, PaO_2, $AVDO_2$ or rectal temperature.

During hyperventilation ICP averaged 5.1 and 4.3 mmHg in the propofol-fentanyl and propofol-remifentanil groups, respectively (P=0.475). MABP and CPP were 87 and 82 mmHg in the propofol-fentanyl group against 74 and 70 mmHg in the propofol-remifentanil group. In intergroups, differences in MABP and CPP were significant (P<0.001). SATv or $AVDO_2$ did not differ significantly between groups. As regards changes in $PaCO_2$ ($\Delta PaCO_2$ mmHg), MABP (ΔMABP mmHg), ICP (ΔICP mmHg), CPP (ΔCPP mmHg) and the CO_2 reactivity no significant intergroup differences were disclosed (Table 10.3). No significant differences as regards the degree of dural tension or the degree of cerebral swelling after opening of dura were disclosed either before or during hyperventilation.

Conclusion No difference in ICP during hyperventilation between patients anaesthetized with propofol-fentanyl or propofol-remifentanil was found. MABP and CPP were significantly lower in the patients anaesthetized with propofol-remifentanil.

Study 3: Is It Possible to Reduce Subdural Intracranial Pressure Below 10 mmHg by Hyperventilation Eventually Supplemented with Mannitol Treatment?

Aim To evaluate if hyperventilation eventually supplemented with mannitol treatment is able to reduce subdural ICP below 10 mmHg in patients subjected to craniotomy for supratentorial cerebral tumours.

Method Twenty-nine patients with supratentorial cerebral tumours (glioblastoma (n=12), meningioma (n=6), astrocytoma (n=7), other tumours (n=4)) were included in the study. For maintenance of anaesthesia propofol-fentanyl was used. After exposure of dura subdural ICP, MABP and arterial gas analyses were performed. These measurements were repeated after 5 min hyperventilation. If subdural ICP was ≥ 10 mmHg, mannitol 1 g/kg was administered over 5 min, and the measurements were repeated 15 min after the start of mannitol treatment. After opening of dura the degree of brain swelling was evaluated by the surgeon.

Statistical analysis Median and range are presented. Mann-Whitney's test was used for intergroup analyses. P<0.05 signifies statistical significance.

Results Before hyperventilation, the median level of subdural ICP was 9 mmHg (range −2 to 20 mmHg). In 16 of 29 patients (55%) subdural ICP < 10 mmHg was observed, and the tension of dura was estimated as normal. In the remaining 13 patients with subdural ICP ≥ 10 mmHg, dural tension was normal in 5 patients and increased in 8 patients. After 5 min hyperventilation

Table 10.4 $PaCO_2$, MABP, subdural ICP and CPP in 29 patients with cerebral tumours before and during hyperventilation

Variable	Before hyperventilation	During hyperventilation	Significance
$PaCO_2$ (kPa)	4.9 (4.1–5.6)	4.1 (3.2–4.8	$P<0.05$
MABP (mmHg)	81.0 (58.0–118.0)	83.0 (59.0–155.0)	Not significant
ICP (mmHg)	9.0 (−2.0 to 20.0)	7.0 (−3.0 to 14.0)	$P<0.05$
CPP (mmHg)	72.0 (49.0–98.0)	76.0 (54.0–103.0)	$P<0.05$

Table 10.5 $PaCO_2$, MABP, subdural ICP and CPP before mannitol and 15 min after mannitol (1 g/kg) combined with hyperventilation in 7 patients with ICP ≥ 10 mmHg

Variable	Before mannitol	After mannitol	Significance
$PaCO_2$ (kPa)	3.9 (3.5–4.8)	3.6 (3.3–4.4)	$P<0.05$
MABP (mmHg)	86.0 (71.0–99.0)	85.0 (70.0–106.0)	Not significant
ICP (mmHg)	13.0 (10.0–14.0)	9.0 (4.0–12.0)	$P<0.05$
CPP (mmHg)	73.0 (57.0–103.0)	76.0 (58.0–112.0)	$P<0.05$

a significant decrease in the median level of subdural ICP from 9 mmHg (−2 to 20 mmHg) to 7 mmHg (−3 to 14 mmHg) was observed (Table 10.4). In total, hyperventilation elicited a decrease in subdural ICP in 24 of 29 patients. Dural tension was still increased in 6 patients. In 7 patients with a median subdural ICP of 13 mmHg (10–14 mmHg) mannitol (1 g/kg) was administered, while hyperventilation continued. After 15 min a significant decrease in subdural ICP to median 9 mmHg (4–12 mmHg) was observed (Table 10.5). Two patients still had subdural ICP ≥ 10 mmHg (12 mmHg), and in these patients pronounced brain swelling was observed after opening of dura. In the other patients brain swelling did not occur. In total, moderate brain swelling was observed in 4 patients and pronounced swelling in 2 patients.

Conclusion Addition of mannitol to hyperventilation decreases ICP during craniotomy.

Discussion

In this review the effect of hyperventilation on subdural ICP and cerebral haemodynamics has been analysed during four different anaesthetic procedures, including propofol-fentanyl, propofol-remifentanil, isoflurane-fentanyl and sevoflurane-fentanyl. The principal findings were that hyperventilation decreased subdural ICP significantly independent of anaesthetic method, but the effect differed. Thus, the ICP-reducing effect of hyperventilation was most pronounced during isoflurane-fentanyl and sevoflurane-fentanyl anaesthesia, while the ICP-reducing effect was less pronounced during propofol-fentanyl and propofol-remifentanil anaesthesia. Accordingly, the relative CO_2 reactivity

calculated as the % change $AVDO_2/\Delta P_aCO_2$/mmHg was higher during isoflurane and sevoflurane anaesthesia compared with the CO_2 reactivities obtained during propofol-fentanyl and propofol-remifentanil anaesthesia. These findings correspond to experimental and clinical studies. During isoflurane-nitrous oxide anaesthesia for supratentorial cerebral tumours the CO_2 reactivity is preserved, averaging 4.4%/mmHg $PaCO_2$ (Madsen et al. 1987). In another study including patients subjected to craniotomy for supratentorial cerebral tumours, the relative CO_2 reactivity averaged 3.3% and 2.2% change $AVDO_2/\Delta PaCO_2$/mmHg at concentrations of 0.7 and 1.3 MAC sevoflurane (Bundgaard et al. 1998). In patients without cerebral diseases (Cho et al. 1996), patients with cerebral tumours (Inada et al. 1996), patients with cardiac disease (Mielck et al. 1999) and patients subjected to extra-intracranial by-pass anastomosis (Kitaguchi et al. 1993) the CO_2 reactivity is intact during sevoflurane anaesthesia. In another study it was documented that the CO_2 reactivity in young adults, ranging from 20 to 40 years, is greater than in adults in the range 50–70 years of age (Nishiyama et al. 1999). In dogs subjected to low and moderate doses of propofol, the cerebral autoregulation and CO_2 reactivity were preserved. In contrast, high-dose propofol decreased CPP below the lower point of cerebral autoregulation (Artru et al. 1992). In rabbit's subjected to propofol anaesthesia the cerebrovascular reactivity of blood flow and CBV are markedly decreased during hypocapnia, but maintained during hypercapnia (Cenic et al. 2000). After propofol bolus injection the CO_2 reactivity was preserved (Stephan et al. 1987). This finding was also confirmed in studies with the Doppler technique (Jansen and Kagenaar 1993; Strebel et al. 1994; Ederberg 1998). In a study including healthy adults the slope of the CBF versus $PaCO_2$ was 1.56 ml/100 g/min/mmHg $PaCO_2$ (Fox et al. 1992). During continuous propofol infusion in patients without brain disorders the CO_2 reactivity was also found to be intact (Harrison et al. 1999). In other studies the CO_2 reactivity based on flow velocity was attenuated (Mirzai et al. 2004). Hyperventilation to end-tidal CO_2 values less than 30 mmHg is without effect because flow velocity is unchanged below this level (Karsli et al. 2004).

The low CO_2 reactivity found during propofol-remifentanil and propofol-fentanyl anaesthesia may be for the following reasons. One explanation, at least during propofol-remifentanil anaesthesia, is that the CPP was significantly lower compared with the other three anaesthetic procedures, and close to the lower point of cerebral autoregulation of 60 mmHg. In dogs the CO_2 reactivity is sustained during drug-induced hypotension (Artru and Colley 1984), and during propofol-fentanyl anaesthesia nicardipine-, nitroglycerin- and prostaglandin E_1-induced hypotension attenuate the CO_2 reactivity (Endoh et al. 1999). Studies in rats subjected to intracranial hypertension also indicate that reduced CPP seems to be followed by a decreased CO_2 reactivity (Hauerberg et al. 2001). The low CO_2 reactivity found during hypotension might be considered as a sign of threatening cerebral ischaemia and as such is accompanied by an increase in $AVDO_2$ and a low SATv. In awake healthy humans SjO_2 averages 62% (range 55–75%). In acute head injury $SjO_2 < 50\%$

suggests hypoperfusion, and readings < 40% are supposed to be associated with cerebral ischaemia (Gopinath et al. 1996). In comparison with isoflurane and sevoflurane low values of SATv were disclosed during propofol anaesthesia in patients undergoing coronary by-pass (Nandate et al. 2000), and during craniotomy a 50% incidence of SjO_2 < 50% was found in patients subjected to propofol-fentanyl anaesthesia, but not in patients anaesthetized with isoflurane-nitrous oxide (Moss et al. 1995; Jansen et al. 1999). In the studies presented in this chapter venous saturations were significantly lower during propofol-fentanyl and propofol-remifentanil compared with isoflurane-fentanyl and sevoflurane-fentanyl anaesthesia. After hyperventilation the incidences of low venous saturation (high $AVDO_2$) increased in all groups. The differences in SjO_2 between the respective groups were not explained alone by the difference in the level of blood pressure or CPP, the latter being higher in the propofol-fentanyl group. It must be stressed that a threshold value of SjO_2 indicating impeding cerebral ischaemia has not been defined during clinical anaesthesia. Propofol is generally accepted as an agent with neuroprotective properties and propofol-induced neurological deterioration has never been described. In a recent clinical PET study, no indication of propofol-induced diffusion-weighted ischaemic changes were observed in patients with cerebral tumours (Rasmussen et al. 2004).

In the third study hyperventilation and the combined use of hyperventilation and mannitol treatment were studied in patients with supratentorial cerebral tumours. Although both treatment modalities reduced subdural ICP significantly during the 20-min study, it was not possible to reduce subdural ICP to < 10 mmHg in all patients, and pronounced swelling after opening of dura was observed in two patients. If cerebral swelling is to be omitted, other measures to reduce subdural ICP, such as the use of rTp (Haure et al. 2003; Tankisi and Cold 2007), indomethacin (Bundgaard et al. 1996), surgical decompression, drainage of CSF or evacuation of fluid from cystic processes (see Chapter 17), might be considered appropriate.

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Chapter 11
Effect of Indomethacin on Subdural Intracranial Pressure and Cerebral Haemodynamics

Mads Rasmussen and Georg Emil Cold

Abstract

Treatment options for increased ICP during craniotomy include hyperventilation, bolus injection of barbiturate or other hypnotic agents, mannitol administration and head elevation. However, these interventions are not consistently successful. Indomethacin acts as a potent cerebral vasoconstrictor and decreases cerebral blood flow and ICP without affecting cerebral oxygen consumption. Previous studies in patients with severe head injury suggested that indomethacin may be effective in lowering high ICP resistant to the traditional methods of managing elevated ICP. Administration of indomethacin may be an alternative option for managing increased ICP in patients undergoing craniotomy.

In this chapter two studies concerning indomethacin are presented. The first study includes the effect of perioperative indomethacin on subdural ICP, cerebral blood flow and cerebral metabolic rate of oxygen in patients subjected to craniotomy for cerebral tumour. The second study is a randomized study where we investigated the effect of indomethacin on ICP and cerebral haemodynamics in patients undergoing supratentorial craniotomy.

Treatment options for increased ICP during craniotomy include hyperventilation, bolus injection of barbiturate or other hypnotic agents, mannitol administration and head elevation (Miller and Leech 1975; Bedford et al. 1980; Cenic et al. 2000; Tankisi et al. 2002). Intracranial hypertension can also be treated by surgical drainage of CSF or evacuation of cystic intracranial processes if present. However, these interventions are not consistently successful. Controlled hyperventilation is often of limited value; patients with intracerebral space-occupying lesions may have impaired or abolished cerebrovascular reactivity to changes in $PaCO_2$. The effect of hyperventilation are subject to adaptation (Raichle and Plum 1972) and adverse effects have been reported (Cold 1989; Muizelaar et al. 1991). The effect of mannitol has also been questioned (Kaufmann and Cardoso 1992). Barbiturates may induce cardiovascular depression

with a decrease in CPP, and CSF drainage is often impossible because of difficult access to the ventricular system. In experimental and human studies indomethacin, a fatty acid cyclooxygenase inhibitor, acts as a potent cerebral vasoconstrictor and decreases CBF without affecting cerebral oxygen consumption (Pichard and MacKenzie 1973; Wennmalm et al. 1981; Jensen et al. 1993). In patients with severe head injury and otherwise intractable intracranial hypertension, indomethacin reduces ICP substantially and within a few minutes. This effect is accompanied by a decrease in CBF, while $CMRO_2$ is unchanged (Jensen et al. 1991). In another study of patients with severe acute head injury, the ICP-reducing effect of indomethacin was comparable with the effect of hyperventilation (Dahl et al. 1996). In some patients, however, the ICP-reducing effect of indomethacin was more pronounced than hyperventilation and vice versa (Dahl et al. 1996).

Two studies are presented in this chapter: the first has been presented by Bundgaard et al. in J Neurosurg Anesthesiol (1996) 8:273–279 and the second has been presented by Rasmussen et al. in Anaesthesia (2004) 59:1–9.

Study 1: Effect of Perioperative Indomethacin on Intracranial Pressure, Cerebral Blood Flow and Cerebral Metabolism in Patients Subjected to Craniotomy for Cerebral Tumours

Aim To examine the effect of perioperatively administered indomethacin on subdural ICP, CBF and $CMRO_2$ in patients subjected to craniotomy for supratentorial cerebral tumours.

Methods Twenty adult patients, age 18–70 years, with supratentorial cerebral tumours participated in the study. Anaesthesia was maintained with isoflurane-nitrous oxide-fentanyl. The patients were randomized to receive intravenous indomethacin 50 mg or placebo (0.9% saline) administered after exposure of the dura mater. Subdural ICP was measured after removal of the bone flap and exposure of the dura mater as previously described. Subdural ICP, MABP and CPP were recorded simultaneously and continuously. CBF was measured by the ^{133}Xe method and calculated as the initial slope index using 10-min clearance curves. For measurement of $AVDO_2$ and jugular bulb oxygen saturation (SjO_2) a jugular bulb catheter was inserted. Measurements of ICP, CPP, CBF and $AVDO_2$ were performed before and after administration of indomethacin/placebo. All measurements were performed before opening of dura mater.

Statistical analysis Medians and range were calculated. The Mann-Whitney test was used to analyse data between the two groups, and the Wilcoxon test was used to analyse data within groups. Statistical significance was considered to be $P<0.05$.

Results No significant differences between the two groups were found, as regards demographics (age, weight, gender), tumour volume, time until open-

ing of dura, number of patients receiving preoperative steroid, anaesthetic doses, rectal temperature and $PaCO_2$ level.

Physiological data are shown in Table 11.1 (see page 170). In the placebo group no significant differences were observed in ICP, CBF, CPP, SjO_2 or $AVDO_2$. Indomethacin bolus was accompanied by: an increase in MABP from median 69 mmHg (range 65–83) to 82 mmHg (range 78–93), $P<0.05$; a decrease in subdural ICP from 6.5 mmHg (range 2–27) to 1.5 mmHg (range −1 to 18), $P<0.05$; a decrease in CBF from 39 ml/100 g/min (range 20–31) to 20 ml/100 g/min (range 14–31), $P<0.05$; a decrease in SjO_2 from 69% (range 45–89) to 49% (range 38–83), $P<0.05$; and an increase in $AVDO_2$ from 1.7 mmol/L (range 0.7–2.9) to 3.2 mmol/L (range 1.2–4.2), $P<0.05$.

Conclusion Indomethacin effectively reduces ICP by a cerebral vasoconstrictive effect giving rise to a fall in CBF and SjO_2 and an increase in $AVDO_2$. The effect of i.v. indomethacin on ICP occurs within 1 min, and is accompanied by an increase in MABP and CPP.

Study 2: Effect of Indomethacin on Intracranial Pressure and Cerebral Haemodynamics in Patients Undergoing Craniotomy: A Randomized Prospective Study

Aim To investigate the perioperative effect of indomethacin, administered immediately before induction of anaesthesia, on subdural ICP in patients subjected to craniotomy for supratentorial tumours.

Method We compared the effect of indomethacin (bolus of 0.2 mg/kg followed by infusion of 0.2 mg/kg/h) and placebo on ICP and cerebral haemodynamics in 30 patients undergoing craniotomy for supratentorial brain tumours in propofol-fentanyl anaesthesia. Indomethacin was administered beore induction of anaesthesia and the infusion was terminated after opening of dura. Subdural ICP was measured through the first burr hole and before opening of dura. CBF velocity, CPP, SjO_2), $AVDO_2$ and CO_2 reactivity were measured and dural tension and the degree of brain swelling were estimated.

Statistical analysis Non-parametric data are reported as median (interquartile range). The Mann-Whitney test was used to analyse data between the two groups and the Wilcoxon signed rank test was used to analyse data within groups. Parametric data are reported as mean±SD and Student's *t*-test was used to analyse data between groups. The chi-square test was used for statistical analysis of demographic data, tumour localization, histopathological diagosis, preoperative steroid administration, difference in dural tension and the degree of swelling (no swelling contra swelling).

Table 11.1 Physiological parameters measured before and after administration of indomethacin 50 mg i.v (group 1) or placebo (group 2)

		$PaCO_2$ (kPa)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	SjO_2 (%)	CBF (ml/100g/min)	$AVDO_2$ (mmol/L)	$CMRO_2$ (mlO_2/100 g/min)
Group 1									
Before indomethacin	Median	4.8	69	6.5	63	69	39	1.7	1.6
	Range	3.6–5.6	65–83	2–27	43–71	45–89	20–41	0.7–2.9	0.4–2.6
After indomethacin	Median	4.8	82*	1.5*	80*	49*	20*	3.2*	1.8
	Range	3.4–5.6	78–93	−1 to 18	60–82	38–83	14–31	1.2–4.2	0.4–2.4
Group 2									
Before saline	Median	4.8	75	9.5	67	69	34	2.6	1.6
	Range	4.5–5.6	66–87	4–25	54–74	43–90	11–44	0.9–3.9	0.7–2.5
After saline	Median	4.8	78	8.5	70	70	33	2.2	1.8
	Range	4.5–5.7	68–89	1–22	55–83	46–89	13–39	0.8–3.6	0.6–2.4

*$P<0.05$

Table 11.2 Transcranial Doppler measurements: MABP, $PaCO_2$, SjO_2 and $AVDO_2$ before and after the start of indomethacin infusion and after induction of anaesthesia. Values are median and interquartile range

	Indomethacin (n=15)	Placebo (n=14)
Before start of indomethacin		
Mean middle cerebral artery blood flow velocity (cm/s)	66.0 (56.0–90.0)	70.0 (50.0–73.0)
MABP (mmHg)	101.0 (90.0–112.0)	102.0 (87.0–113.0)
$PaCO_2$ (kPa)	5.2 (4.8–5.5)	5.3 (5.0–5.6)
After start of indomethacin		
Mean middle cerebral artery blood flow velocity (cm/s)	48.0 (37.0–59.0)**	68.0 (53.0–74.0)
MABP (mmHg)	110.0 (101.0–118.0)*	104.0 (86.0–112.0)
$PaCO_2$ (kPa)	5.2 (4.4–5.5)	5.3 (5.1–5.6)
After induction of anaesthesia		
SjO_2 (%)	48.5 (42.9–56.3)*	57.2 (50.2–62.9)
$AVDO_2$ (mmol/L)	4.0 (3.2–4.5)	3.6 (3.3–4.4)
Mean middle cerebral artery blood flow velocity (cm/s)	41.0 (29.0–46.0)*	35.0 (31.0–38.0)*
MABP (mmHg)	80.0 (70.0–84.0)*	76.0 (70.0–91.0)*
$PaCO_2$ (kPa)	4.8 (4.5–5.0)	4.7 (4.4–5.0)*

*P<0.05 within groups
**P<0.05 between groups

Results Patient characteristics and preoperative and anaesthesia data were similar in the two groups. Before induction of anaesthesia indomethacin administration was associated with a significant decrease in CBF velocity and a significant increase in MABP (Table 11.2). After induction of anaesthesia, CBF velocity and the MABP decreased significantly in both groups (Table 11.2). No significant differences in ICP or CPP were seen during the measrements performed through the first burr hole (Table 11.3). After removal of the bone flap, a significant decrease in ICP was observed in both groups without differences between the groups (Table 11.3). Hyperventilation caused a derease in ICP and SjO_2 and an increase in $AVDO_2$ in both groups without intergroup differences (Table 11.3). There was no intergroup difference in CPP, dural tension and degree of brain swelling. CO_2 reactivity measured after induction of anaesthesia was significantly lower in the indomethacin group (P<0.05). After removal of the bone flap no significant difference in CO_2 reactivity was observed (Table 11.4).

Conclusion This study indicates that the ICP-decreasing effect of an indomethacin infusion during propofol-fentanyl anaesthesia is attenuated or absent and is likely to be caused by propofol-induced cerebral vasoconstriction and the subsequent decrease in CBF.

Table 11.3 Subdural ICP, MABP, CPP and other physiological variables measured at the drilling of the first burr hole, after removal of the bone flap, and before and after a 5-min period of hyperventilation. Values are median and interquartile range

Variables	First burr hole		After removal of bone flap		After hyperventilation	
	Indomethacin	Placebo	Indomethacin	Placebo	Indomethacin	Placebo
ICP (mmHg)	9.0 (7.0–13.0)	9.0 (5.0–17.0)	8.0 (5.0–10.0)*	7.0 (4.0–9.0)*	7.0 (5.0–10.0)*	6.0 (2.0–9.0)*
MABP (mmHg)	86.0 (76.0–90.0)	84.0 (77.0–94.0)	87.0 (76.0–94.0)	86.0 (76.0–100.0)	87.0 (76.0–93.0)	90.0 (77.0–102.0)
CPP (mmHg)	77.0 (66.0–85.0)	74.0 (58.0–85.0)	81.0 (68.0–87.0)	80.0 (67.0–93.0)	80.0 (70.0–89.0)	79.0 (72.0–93.0)
Temperature (°C)	35.6 (35.1–36.0)	35.7 (35.2–35.9)	35.8 (35.2–36.1)	35.6 (35.2–36.0)	35.7 (35.2–36.1)	35.6 (35.2–36.0)
$PaCO_2$ (kPa)	4.5 (4.1–4.9)	4.6 (4.3–5.1)	4.4 (4.1–5.1)	4.7 (4.6–5.1)	3.7 (3.4–3.9)*	3.9 (3.7–4.2)*
PaO_2 (kPa)	24.7 (22.2–33.5)	22.1 (19.4–31.4)	23.5 (22.2–27.6)	23.9 (19.7–29.9)	27.5 (24.8–40.7)*	24.3 (20.2–30.7)*
SjO_2 (%)	49.0 (43.0–62.0)	54.0 (49.0–62.0)	46.0 (42.0–57.0)	55.0 (47.0–61.0)	41.0 (38.0–58.0)*	46.0 (41.0–55.0)*
$AVDO_2$ (mmol/L)	3.8 (2.8–5.0)	3.4 (2.6–4.1)	3.6 (2.9–5.0)	3.4 (3.0–4.2)	4.5 (3.5–5.3)*	4.3 (2.9–4.6)*

*$P<0.05$ within groups

Table 11.4 Change in $PaCO_2$, $AVDO_2$ and CO_2 reactivity after induction of anaesthesia and after removal of the bone flap. Values are median and interquartile range

	Indomethacin (n=15)	Placebo (n=15)
After induction of anaesthesia		
Change in $PaCO_2$ (kPa)	1.0 (0.8–1.2)	1.0 (0.5–1.0)
Change in $AVDO_2$ (mmol/L)	0.4 (0.1–0.6)	0.7 (0.3–1.0)
CO_2 reactivity (%/kPa)	9.8 (2.3–14.3)	17.3 (10.5–27.1)**
After removal of bone flap		
Change in $PaCO_2$ (kPa)	0.8 (0.6–1.3)	0.8 (0.7–1.0)
Change in $AVDO_2$ (mmol/L)	0.3 (0.0–0.7)	0.5 (0.1–0.8)
CO_2 reactivity (%/kPa)	12.0 (3.8–16.5)	15.8 (0.0–20.3)

**P<0.05 between groups

Discussion

During craniotomy for cerebral tumours a high ICP may result in cerebral swellng after opening of dura mater (Rasmussen et al. 2004a). This condition can seriously jeopardize surgical access and may increase the risk of cerebral ischaemia with a poor outcome. In the study by Bundgaard et al. (1996) administration of indomethacin was associated with a significant fall in ICP from 6.5 mmHg (median) to 1.5 mmHg (median) and an increase in CPP from 63 to 80 mmHg (median) within 1 min. The reduction in ICP was associated with a significant decrease in CBF from 39 to 20 ml/100 g/min (Bundgaard et al. 1996). The authors did not report whether indomethacin affected the degree of brain swelling through the craniotomy. These findings are in good agreement with previous studies where indomethacin caused a significant reduction in ICP in patients with head injury (Jensen et al. 1991; Biestro et al. 1995; Dahl et al. 1996), in patients with plateau waves associated with head injury (Imberti et al. 2005) and in patients with fulminant hepatic failure (Tofteng and Larsen 2004).

The findings by Bundgaard et al. (1996) in previous studies are in contrast to the study by Rasmussen et al. (2004a) where indomethacin administration immediately before induction of anaesthesia did not influence the level of ICP in propofol-fentanyl-anaesthetized patients with cerebral tumours. Moreover, in the study by Rasmussen et al. the occurrence of brain swelling after opening of dura mater demonstrated a tendency to be higher in the indomethacin group compared with the control group. The two studies also differ by choice of anaesthesia, indomethacin dose and the time interval between administration of indomethacin and the ICP measurements.

A number of studies have demonstrated that the percentage reduction of CBF after administration of propofol is larger than the reduction of $CMRO_2$. These findings suggest that propofol may have a direct cerebral vasoconstricting effect, beyond the associated decrease in $CMRO_2$ leading to a decrease of the $CBF/CMRO_2$ ratio (Vandesteene et al. 1988; Van Hemelrijck

et al. 1990; Ederberg et al. 1998; Jansen et al. 1999). The consequence is a shift to the left on the ICP compliance curve, where changes in CBV by cerebral vasoconstricting agents have less impact on ICP. The study by Rasmussen et al. supports these findings indicated by the substantial decrease in CBF velocity in both groups after induction of propofol-fentanyl anaesthesia without intergroup difference. Thus, additional treatment with indomethacin may have little or no impact on ICP, as observed in this study.

This hypothesis was not supported by a recent experimental study where sheep were randomized to receive indomethacin during either propofol or isoflurane anaesthesia (Rasmussen et al. 2006). Changes in CBF, ICP, MABP, $AVDO_2$ and $PaCO_2$ were measured at specific time points before and after a bolus dose of indomethacin (0.2 mg/kg). Indomethacin caused a reduction in ICP within 15 s during both anaesthetic regimes with the decrease in ICP being significantly more pronounced during isoflurane. Several factors may explain this difference. First, in the human study by Rasmussen et al. (2004a) the indomethacin infusion was administered before anaesthesia induction and terminated after opening of dura mater. The mean time interval between indomethacin administration and the first ICP measurement was 117 min. Baseline recordings of ICP were not performed and the possibility exists that indomethacin initially lowered ICP but failed to sustain the effect during the long infusion time. The authors suggested that indomethacin-induced cerebral vasoconstriction shows adaptation, however, this has not previously been demonstrated (Rasmussen et al. 2004a). Secondly, Rasmussen et al. (2004a) demonstrated a 50% decrease in CBF after induction with propofol compared to a 35% reduction in CBF observed in the experimental study. Thus, propofol-induced cerebral vasoconstriction was possibly near maximal in the study by Rasmussen et al. (2004a), with limited room for further vasoconstriction by indomethacin. Consequently, the differences in the reduction of CBF and degree of vasoconstriction observed in the two studies may explain how indoethacin in the experimental study managed to constrict the resistance vessels further and reduce ICP. Thirdly, differences regarding species, dose-reponse relationships and methods of measuring ICP (subdural versus epidural) may have influenced the results.

The rapid ICP-reducing effect of indomethacin observed in the studies by Bundgaard et al. (1996) and Rasmussen et al. (2006) is similar to that obtained with barbiturates. Thiopentone, however, is accompanied by a fall in CPP (Shapiro et al. 1973). In contrast the effects of hyperventilation and mannitol are only maximal after 10–15 min and 30–60 min, respectively (James 1980; Ravussin et al. 1988). Thus, compared to other treatments of high ICP, indomethacin is unique in effecting an immediate decrease in ICP associated with an increase in CPP.

The dose of indomethacin administered in the study by Rasmussen et al. (2004a) is based on a study in healthy volunteers where indomethacin (bolus 0.2 mg/kg followed by 0.2 mg/kg/h) caused a significant decrease in CBF, ranging between 29% and 37% (Jensen et al. 1996). In the study by Rasmussen

et al. (2004a) indomethacin induced a 29% median decrease in CBF velocity compared to the control group. This finding is in agreement with a clinical study in head-injured patients where indomethacin (bolus of 30 mg followed by 30 mg/h) reduced ICP and caused a reduction in CBF averaging 15–26% (Jensen et al. 1991). However, the reduction in CBF velocity observed in this study was lower compared to the study by Bundgaard et al. (1996) in isoflurane-anaesthetized tumour patients where indomethacin (bolus of 50 mg) induced a 48% median decrease in CBF accompanied by a decrease in ICP. Thus, the effect on CBF velocity induced by the administered dose of indomethacin is comparable to the effects of equal or higher doses administred in other clinical studies where significant decreases in CBF and ICP were observed.

The use of indomethacin is controversial because several studies have demnstrated marked reductions in CBF which may cause cerebral ischaemia (Jensen et al. 1991; Bundgaard et al. 1996; Dahl et al. 1996). To examine whether indomethacin induces severe cerebral ischaemia, diffusion-weighted magnetic resonance imaging (DWI) was performed in nine patients subjected to craniotomy for cerebral tumours (Rasmussen et al. 2004b). DWI is an established MRI technique that is widely used in the diagnosis of acute stroke due to its extreme sensitivity to acute ischaemic damage (Warach et al. 1992). The technique detects the diffusion of water molecules. Due to the altered hindrance of their Brownian motions caused by cytotoxic oedema following ATP depletion, DWI hyperintensities appear within minutes of ischaemic tissue damage. DWI sequences were performed: (1) the day before surgery; (2) before administration of indomethacin; (3) 20 min after administration of indomethacin (bolus of 0.2 mg/kg followed by infusion of 0.2 mg/kg/h) in the propofol-fentanyl-anaesthetized patient; and (4) 2 days after surgery. SjO_2 decreased from an average of 51% to 43% comparable to the findings in the study by Bundgard et al. (1996). However, no ischaemic lesions were detected on the DWI images. This observation is in accordance with Biestro et al. (1995) who reported no evidence of cerebral ischaemia or infarctions on follow-up CT scans after indomethacin administration in patients with severe head injury.

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Chapter 12
Effect of Dihydroergotamine on Subdural Intracranial Pressure and Cerebral Haemodynamics

Helle Bundgaard and Georg Emil Cold

Abstract

Dihydroergotamine (DHE) acts as a non-competitive agonist at vascular 5-hydroxytryptamine receptors. Experimental studies indicate that DHE is a constrictor of the venous capacitance vessels and, in in vitro studies, DHE induces concentration-dependent contraction in human cerebral arteries and veins. Theoretically, DHE is more effective in the treatment of increased ICP than hyperventilation and is less dangerous because it predominantly acts on the cerebral venous pool, which contains a larger blood volume than the arterial pool.

In this chapter DHE and the results of a study dealing with the effect of DHE on arterial blood pressure, subdural ICP, cerebral perfusion pressure, cerebral blood flow and the cerebral metabolism in patients subjected to craniotomy for supratentorial brain tumours is discussed.

Treatments of increased ICP, tension of dura or brain swelling during craniotomy include therapy that increases CVR, such as hyperventilation and indomethacin, hypnotic agents, such as barbiturates or propofol and osmotic therapy (mannitol and hypertonic saline); also CSF drainage and evacuation of cystic processes, head elevation or rTp can be used (Miller and Leech 1975; Bedford et al. 1980; Bundgaard et al. 1996; Cenic et al. 2000; Tankisi et al. 2002). Each of these measures has advantages and disadvantages. Controlled hyperventilation is often of limited value since patients with intracerebral space-occupying lesions may have impaired or abolished cerebrovascular reactivity to changes in $PaCO_2$. The effect of hyperventilation follows the changes in $PaCO_2$, but maximal effect will only occur after 10–15 min and adaption to the effect takes place during continuous hypocapnia (Raichle and Plum 1972); adverse effects such as serious decrease in CBF have been reported (Cold 1989; Muizelaar et al. 1991). A precipitous decrease in CBF has also been found after i.v. indomethacin, but unlike hyperventilation this drug increases CPP. The effect of repeated mannitol infusion has also been questioned, and a rebound effect at a high repeated dose is well known (Kaufmann and Cardoso 1992). Barbitu-

rates and propofol may induce cardiovascular depression with a decrease in CPP, and CSF drainage is often impossible because of difficult access to the ventricular system.

Dihydroergotamine (DHE) acts as a non-competitive agonist at vascular 5-hydroxytryptamine receptors (Glusa and Markwardt 1984; Müller-Scheweinitzer and Rosenthaler 1987; Müller et al. 1988). Experimental studies indicate that DHE is a constrictor of the venous capacitance vessels (Mellander and Nordenfelt 1970; Müller-Scheweinitzer and Rosenthaler 1987) and, in in vitro studies, DHE induces concentration-dependent contraction in human cerebral arteries and veins (Nilsson et al. 1997). The Lund group have shown that in patients with severe head injury a bolus dose of DHE reduces ICP and increases CPP (Grände 1989; Asgeirsson et al. 1994, 1995). The ICP-reducing effect of DHE starts within 1 min after i.v. injection, reaching its maximal effect after 8–20 min, and the effect remains stable for up to 90 min (Asgeirsson et al. 1995). Theoretically, the effect of DHE is more effective in the treatment of increased ICP than hyperventilation and is less dangerous because it predominantly acts on the cerebral venous pool, which contains a larger blood volume than the arterial pool (Mellander and Johansson 1968; Mellander and Nordenfelt 1970), and because the arterial constrictor effect is less pronounced.

Data in this chapter have been presented by Bundgaard et al. in J Neurosurg Anesthesiol (2001) 3:195–201.

Effect of Dihydroergotamine on Intracranial Pressure, Cerebral Blood Flow and Cerebral Metabolism in Patients Undergoing Craniotomy for Brain Tumours

Aim To test the effect of a single bolus of DHE on ICP during craniotomy.

Method Twenty adult patients, median age 49 years (range 23–63 years) underwent craniotomy for supratentorial cerebral tumours in the supine position. Only patients with midline shift < 10 mm at preoperative CT scan participated in the study. For maintenance of anaesthesia isoflurane (end-tidal % 0.2–1.5%) and nitrous oxide (50–60%) supplemented with fentanyl was used. In a double-blind design, the patients were randomized to receive either 0.25 mg DHE as a bolus dose (group 1) or placebo physiological saline (group 2). The measurements were performed after exposure of the dura. CBF was measured by the ^{133}Xe technique and calculated as the initial slope index from 10-min clearance curves. Two angular detectors were placed on each side of the head, and the average CBF of the two detectors was used. Subdural ICP, jugular blood and arterial blood samples were analysed for gas analysis and $AVDO_2$. $CMRO_2$ was calculated as the product of $AVDO_2$ and CBF. The CVR was calculated according to the formula: CPP = CBF × CVR. Subdural ICP and cerebral haemodynamics were measured twice in each patient. The first measurement was performed before administration of DHE or placebo and the second 30 min later. (For details concerning method, see Chapter 3.)

Statistical analysis Median and range were calculated. The Mann-Whitney rank sum test was used to analyse the difference between groups, and the Wilcoxon signed rank test and Friedman repeated measures analysis of variance on ranks were used to analyse data within groups. $P<0.05$ signifies significant difference.

Results No significant differences were found between the two groups as regards demographic (age, weight, gender), neuroradiological findings (maximal area of tumour, midline shift, localization of tumour) or histopathological data. The concentration of anaesthesia was kept constant during the study period. The physiological variables during the measurements are indicated in Table 12.1. Before administration of DHE or placebo, no significant differences were found between the two groups. In group 1 DHE bolus injection was followed by a significant increase in subdural ICP from 9.5 mmHg (range 3–21 mmHg) to 11.5 mmHg (range 5–24 mmHg) and a significant increase in CPP from 65 mmHg (range 49–77 mmHg) to 72 mmHg (range 57–100 mmHg). Simultaneously, a significant increase in MABP was found.

Table 12.1 Parameters obtained in group 1, where measurements were obtained before 0.25 mg DHE and 30 min after DHE administration. In group 2 the variables were measured before and after i.v. administration of normal saline (placebo). Median and range are indicated

	Group 1		Group 2	
	Before DHE	After DHE	Before placebo	After placebo
Temperature (°C)	36.2 (35.6–36.5)	36.2 (35.7–36.5)	36.0 (36.3–37.0)	36.0 (35.3–37.0)
$PaCO_2$ (kPa)	4.8 (4.4–5.1)	4.9 (4.5–5.1)	4.9 (4.4–5.0)	4.9 (4.4–5.1)
MABP (mmHg)	74.0 (67.0–84.0)	87.0* (67.0–112.0)	75.0 (69.0–105.0)	73.0 (62.0–113.0)
ICP (mmHg)	9.5 (3.0–21.0)	11.5* (5.0–24.0)	8.0 (2.0–20.0	8.0 (0.0–11.0)**
CPP (mmHg)	65.0 (49.0–77.0)	72.0* (57.0–100.0)	71.0 (60.0–95.0)	68.0 (56.0–103.0)
CBF (ml/100 g/min)	27.0 (23.0–56.0)	30.0 (24.0–63.0)	30.0 (25.0–54.0)	32.0 (27.0–55.0)
CVR mmHg/ml/min/100 g	2.2 (1.1–3.0)	2.5 (0.9–3.3)	2.4 (1.3–3.3)	2.2 (1.0–3.3)
$AVDO_2$ (mmol/L)	2.4 (1.0–3.5)	2.6 (1.0–3.3)	2.3 (0.6–3.5)	2.3 (0.5–3.5)
$CMRO_2$ (ml O_2/100 g/min)	1.8 (1.1–2.3)	2.1 (1.2–2.4)	1.9 (0.8–2.3)	2.0 (1.1–2.3)
Venous saturation (%)	68.0 (53.0–89.0)	67.0 (57.0–88.0)	70.0 (44.0–96.0)	71.0 (45.0–97.0)

*$P<0.05$ within group
**$P<0.05$ between groups

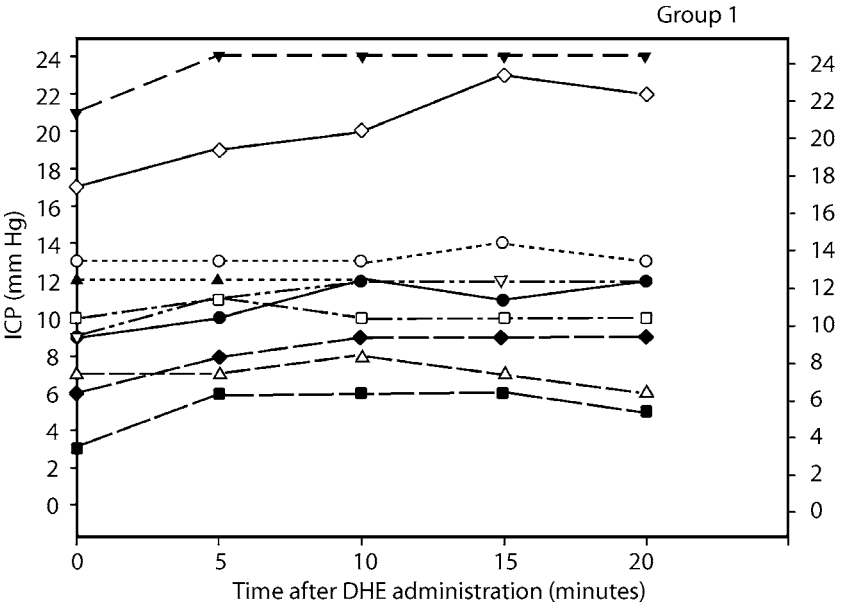

Fig. 12.1 Subdural ICP in relation to time in group 1 patients after 0.25 mg DHE i.v. as bolus

In group 2 (placebo group) no significant differences in the variables were detected.

In group 1 a substantial increase in both subdural ICP and MABP was observed 30 min after administration of DHE, while no changes in subdural ICP or MABP were observed in the placebo group (Figure 12.1).

Conclusion No ICP-decreasing effect of a bolus dose of DHE was found when administered to patients with brain tumours during isoflurane-nitrous oxide anaesthesia. Corresponding increases in MABP and ICP suggest that abolished cerebral autoregulation might explain why DHE was associated with an ICP increase.

Discussion

In the present study it was not possible to confirm the ICP-decreasing effect of a bolus dose DHE, as observed previously in patients with severe head injury (Grände 1989; Asgeirsson et al. 1994, 1995). In contrast, a significant increase in subdural ICP was observed, accompanied by an increase in MABP and CPP.

In a porcine model of intracranial hypertension (Nilsson et al. 1995) and in studies of patients with severe traumatic brain lesion (Grände 1989; Asgeirsson et al. 1994, 1995) DHE effectively reduces ICP and increases MABP, CPP and CVR. These studies suggest that the ICP-reducing effect of DHE results from

a reduction in CBV caused predominantly by an increase in constriction of the intracranial venous blood pool. The difference in results in our study was not caused by a change in surgical activity and eventually cerebral stimulation, because surgical activity was postponed during the measuring, and $CMRO_2$ did not change significantly. In addition $PaCO_2$, PaO_2 and rectal temperature did not change significantly after DHE administration. The difference in results may be caused by the difference in sedation (anaesthesia). DHE acts as a non-competitive agonist at vascular 5-hydroxytryptamine receptors (Glusa and Markwardt 1984; Müller-Scheweinitzer and Rosenthaler 1987; Müller et al. 1988) and sensitises venous smooth muscle cells to the vasoconstrictor effect of biogenic amines (Müller-Scheweinitzer 1984). Theoretically, inhalation anaesthetics block this effect. If so, it is unlikely that this effect was caused by nitrous oxide used in the current study, because indirect evidence of a cerebral venous constrictor effect by DHE was found in pigs anaesthetized with nitrous oxide (Nilsson et al. 1995). Furthermore, in the present study an increase in blood pressure was observed that either could be caused by an increase in cardiac output or an increase in peripheral resistance. At least, the dose of DHE was sufficient to increase blood pressure and subdural ICP in the current study, without affecting CVR, CBF or cerebral oxygen consumption. The increase in blood pressure, however, might augment cerebral vasoconstriction via cerebral autoregulation. If cerebral autoregulation predominantly is preserved, an increase in blood pressure elicits cerebral vasoconstriction and thereby a decrease in ICP. In contrast an increase in blood pressure might be accompanied by an increase in ICP when cerebral autoregulation is abolished. Although cerebral autoregulation was not tested in our patients, this possibility exists because abolished cerebral autoregulation has been documented in several studies of patients with cerebral tumour and because both nitrous oxide and isoflurane, by acting as cerebral vasodilators, abolish cerebral autoregulation (Todd and Drummond 1984; van Aken et al. 1986). Both experimental studies (McPherson and Traystman 1988) and clinical studies (Olsen et al. 1994) indicate that cerebral autoregulation is intact at 1 MAC isoflurane, but defective at 2 MAC isoflurane. In this context, the end-expiratory concentrations of isoflurane in the present study, ranging between 0.2% and 1.5%, seem too low to have any influence on cerebral autoregulation.

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Chapter 13
Effect of a Bolus Dose of an Analgetic on Subdural Intracranial Pressure and Cerebral Haemodynamics During General Anaesthesia for Craniotomy in Patients with Supratentorial Cerebral Tumours

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Abstract

Many studies regarding the effects of synthetic opioids on ICP, arteriovenous oxygen difference, mean arterial blood pressure and the CO_2 reactivity have been carried out. Contradictory results have been obtained. This, however, is most likely due to different study designs and to different patient populations studied. The overall result seems to be that these opioids depress the blood pressure in a dose-related way. This blood pressure decrease may affect the cerebral parameters depending on whether cerebral autoregulation is intact or not.

In this chapter three studies regarding analgetic boluses and the influence on the cerebral haemodynamics are presented. A bolus dose of alfentanil during propofol-fentanyl maintenance, a bolus dose of remifentanil during propofol-remifentanil anaesthesia and a bolus dose of fentanyl during propofol-fentanyl anaesthesia were studied.

The opioids fentanyl, alfentanil, sufentanil and remifentanil are all used for induction as well as for maintenance of anaesthesia in patients with space-occupying lesions. In the patient with spontaneous breathing these drugs may increase ICP dangerously due to a depressing effect on the respiratory drive and consequently lead to an increasing $PaCO_2$.

Clinical studies comprising artificially ventilated patients gave contradictory results with regard to changes in ICP, while decreases in MABP and CPP are found to be relatively constant. The magnitude of these effects is related to the choice of opioid and the dose used.

Several synthetic opioids, for example alfentanil, are administered for maintenance of anaesthesia either as a continuous infusion and/or as bolus doses to depress sympathetic stimulation. Studies on the effect on ICP of alfentanil administered during craniotomy have, however, given somewhat contradictory

results. Thus, in a study comparing the effect on ICP of fentanyl, sufentanil and alfentanil administered to patients with supratentorial tumours, fentanyl did not change lumbar CSF pressure, while administration of sufentanil and most markedly alfentanil was followed by an increase in lumbar CSF pressure and a decrease in MABP and CPP (Marx et al. 1989). In another human study comprising patients with brain tumour, CSF pressure remained unchanged in patients who received nitrous oxide whether or not fentanyl was administered for maintenance of anaesthesia. However, in the patients who received alfentanil, a gradual increase in ICP was found (Jung et al. 1990). This is consistent with the observation by Mayberg et al. (1993) who found a small ICP increase after an alfentanil dose of 50 μg/kg and with the observation by Moss (1992) who found that alfentanil increased ICP in patients with suspected normal pressure hydrocephalus. The increase in ICP occurred immediately after alfentanil administration and was accompanied by a fall in blood pressure. It was presumed that cerebral autoregulatory mechanisms, leading to vasodilation and hence to an increase in ICP, were activated by the decrease in arterial pressure. In contrast to this result, alfentanil did not change ICP in children undergoing shunt revision (Marcovitz et al. 1990). Neither did alfentanil change ICP from pre-anaesthetic levels in a study on patients with supratentorial tumours, where thiopentone was used for induction of anaesthesia (Hung et al. 1992). In artificially ventilated patients with closed head injury, injection of alfentanil before suction of the airways did not change ICP. In that study, however, decreases in blood pressure and CPP were observed (Hanowell et al. 1993). These findings are also in accordance with studies using transcranial Doppler sonography, where no change in vessel diameter in the middle cerebral artery was found, indicating that alfentanil did not alter the vessel tonus (Schregel et al. 1992). In a study comprising patients subjected to craniotomy for supratentorial tumours the effects of remifentanil 0.5 μg/kg and alfentanil 1.0 μg/kg, respectively, on ICP and MABP were compared. Neither of these opioids caused significant changes in ICP, but both drugs were associated with a dosage-dependent decrease in MABP (Warner et al. 1996).

Four clinical studies on the effect of remifentanil administered to patients undergoing craniotomy for cerebral tumours are available:

1. In a clinical study of patients undergoing supratentorial craniotomy a dose-dependent decrease in CPP was observed. ICP, however, did not change, and the effect of remifentanil did not differ from those of equipotent doses of alfentanil (Hindman et al. 1994).
2. In another study of patients subjected to craniotomy for supratentorial tumours the effect of remifentanil 0.5 μg/kg and alfentanil 1.0 μg/kg on ICP and MABP were compared. Neither of these opioids caused significant changes in ICP, but both drugs were associated with a dosage-dependent decrease in MABP (Warner et al. 1996).
3. Continuous infusion of either remifentanil 0.03 μg/kg/min or fentanyl 0.2 μg/kg/min was compared. The anaesthesia was induced with thiopental

and maintained with nitrous oxide supplemented with one of the opioids. ICP and CPP were identical in the two groups. MABP was highest in the fentanyl group (Guy et al. 1997).

4. Anaesthesia supplemented with remifentanil 0.2 μg/kg/min, alfentanil 20 μg/kg/h or fentanyl 2 μg/kg/h was compared in patients undergoing craniotomy. There were no differences among the groups as regards heart rate and MABP. ICP was not monitored (Coles et al. 2000).

   Compared with fentanyl, emergence is more rapid with remifentanil (Balakrishnan et al. 2000). To our knowledge, the effect of a bolus dose of remifentanil on subdural ICP and cerebral haemodynamics in patients undergoing craniotomy in propofol-remifentanil anaesthesia has not so far been studied.

In patients with space-occupying lesions fentanyl may increase ICP (Miller et al. 1975). In many cases the increase in ICP is caused by hypercapnia due to pulmonary hypoventilation. However, an increase in CSF pressure has also been observed in normocapnic volunteers (Benzer et al. 1992). In contrast, some studies indicate that ICP is unchanged during induction of anaesthesia with thiopentone and fentanyl and controlled hyperventilation (Moss et al. 1978). On the other hand in newer studies comprising patients with severe head injury administration of fentanyl in doses of 2 μg/kg was accompanied by a moderate increase in ICP and a fall in MABP and CPP, but no change in $AVDO_2$ (de Nadal et al. 1998, 2000). Thus, due to the inconsistency in the above-mentioned results three studies were carried out. The first study is a blinded and randomized dose-response study which has been presented by Olsen et al. in Acta Anaesthesiol Scand (2005) 49:445–452. The other two studies are non-randomized and both based on the database.

Study 1: Effect of Alfentanil on Subdural Intracranial Pressure, Cerebral Haemodynamics and CO_2 Reactivity During Propofol-Fentanyl Anaesthesia in Patients Subjected to Craniotomy for Supratentorial Cerebral Tumours

Aim To investigate the effect of intravenous bolus doses of alfentanil on subdural ICP and cerebral haemodynamics during propofol-fentanyl anaesthesia in patients subjected to craniotomy for supratentorial cerebral tumours.

Method The study was designed as a randomized and controlled dose-response study and comprised 31 patients with supratentorial cerebral tumours undergoing craniotomy. Maintenance of anaesthesia was obtained with administration of propofol and fentanyl. After removal of the bone flap a bolus dose of alfentanil 10 μg/kg (group 1), 20 μg/kg (group 2) or 30 μg/kg (group 3) was administered followed by an infusion of 10, 20 or 30 μg/kg/h to the patients in groups 1, 2 and 3, respectively. A control group received no alfentanil. Subdural ICP, JBP and cerebral haemodynamics, including CPP and gas analysis from

jugular and arterial blood, were monitored during a 5-min observation period. $AVDO_2$ was calculated as the difference between oxygen content in arterial blood and jugular bulb blood. After the 5-min observation period, the effect of hyperventilation was tested. The CO_2 reactivity was calculated as the $\Delta AVDO_2$ (%)/$\Delta PaCO_2$ (kPa).

The CVR was calculated before and after 5 min of hyperventilation as CPP × $AVDO_2$ × a constant. Percentage change in CVR was calculated as (CVR (before hyperventilation) – CVR (during hyperventilation))/CVR (before hyperventilation).

The degree of dural tension and the degree of brain swelling were evaluated by the surgeon. For details concerning histopathology, neuroradiological findings, anaesthetic maintenance doses, intravenous fluid management and monitoring, see Chapter 3.

Statistical analysis One-way analysis of variance was used when tests for normality and equal variance were passed. If not, the non-parametric Kruskal-Wallis one-way analysis of variance by ranks was used. Tukey's test and Dunn's method were used for multiple comparisons. For analysis within groups, one-way repeated measures analysis of variance was used. If the normality test failed, Friedman's repeated analysis of variance on ranks was used. For pair-wise multiple comparison procedures Dunnett's method was used. A *t*-test was used for analysis between groups, when only two groups were compared. If the normality test failed the Wilcoxon signed rank test was used. $P<0.05$ signifies statistical significance.

Results Two neuroanaesthesiological departments participated in the study. Twenty patients were included from one of the clinics and 11 from the other.

Table 13.1 Demographic data, preoperative variables and neuroradiological findings. Mean±SD are indicated

	Control	Group 1	Group 2	Group 3
Age (years)	42.0±14.0	50.0±10.0	54.0±10.0	45.0±16.0
Weight (kg)	76.0±16.0	71.0±11.0	81.0±11.0	81.0±12.0
Height (cm)	174.0±8.0	174.0±8.0	177.0±9.0	179.0±6.0
Men/women	5/4	5/2	4/3	8/1
MABP (mmHg) before induction	95.0±16.0	99.0±15.0	97.0±14.0	108.0±11.0
Steroid (+/−)	2/7	6/1	4/3	4/5
Glioblastoma	0	3	3	2
Meningioma	0	1	1	0
Metastasis	0	0	1	1
Glioma	4	1	1	4
Other	4	2	1	2
Tumour area (cm^2)	10.0±8.0	18.0±7.0	17.0±10.0	8.0±6.0
Midline shift (mm)	2.7±3.4	6.1±3.5	5.4±4.0	2.8±3.9
Propofol (mg/h)	661.0±141.0	586.0±94.0	642.0±181.0	687.0±160.0
Fentanyl (μg/h)	133.0±43.0	157.0±45.0	169.0±60.0	194.0±71.0
Temperature (°C)	35.6±0.4	35.9±0.7	35.8±0.5	36.0±0.3

Eight patients were allocated to the control group, seven to group 1, seven to group 2 and nine to group 3. Table 13.1 indicates demographic data, anaesthetic maintenance doses before alfentanil administration and histopathology. No statistically significant intergroup differences were disclosed. Following the administration of alfentanil, MABP and CPP decreased in all groups. However, the values of subdural ICP and JBP did not change in any of the groups.

After hyperventilation (from time 5 min to time 10 min) decreases in $PaCO_2$ were found in all groups. A decrease in subdural ICP was found in all groups. No significant intergroup differences in CO_2 reactivity or percentage change in CVR was found (Table 13.2). No intergroup differences were disclosed as regards the degree of dural tension and the degree of brain swelling after opening of dura.

Table 13.2 Change in subdural ICP, MABP, CPP, SjO_2 and $AVDO_2$ in the control group and in groups 1–3 with increasing doses of alfentanil. Time zero to 5 min indicates changes in the 5-min observation period after alfentanil administration. From time 5 to 10 min hyperventilation was applied. The CO_2 reactivity and percentage change in CVR before and after hyperventilation are indicated

	Control	Group 1	Group 2	Group 3
$PaCO_2$ (kPa)				
Time zero	4.6±0.4	4.5±0.4	4.4±0.4	4.8±0.5
Time 10 min	4.0±0.4**	3.7±0.3**	3.9±0.5**	4.2±0.2**
ICP (mmHg)				
Time zero	4.3±2.5	11.7±6.3	9.7±7.9	6.8±3.6
1 min	4.6±2.2	11.1±6.1	9.9±7.9	7.0±3.6
2 min	4.4±1.6	10.9±5.7	9.6±6.4	6.7±3.7
3 min	4.1±2.0	11.4±5.6	9.9±6.7	6.6±3.7
4 min	4.0±1.9	11.7±5.7	9.9±6.5	7.0±3.8
5 min	4.1±2.0	11.7±6.1	9.6±6.7	6.9±3.7
10 min	2.6±2.0**	9.0±5.3**	8.0±6.5**	5.3±4.5**
MABP (mmHg)				
Time zero	89.0±7.0	75.0±10.0	83.0±9.0	85.0±13.0
1 min	90.0±7.0	75.0±9.0	79.0±8.0	76.0±11.0
2 min	89.0±7.0	75.0±8.0	77.0±8.0	69.0±10.0*
3 min	89.0±8.0	72.0±8.0	75.0±9.0	68.0±10.0*
4 min	88.0±7.0	72.0±8.0	75.0±8.0	67.0±10.0*
5 min	88.0±8.0	72.0±9.0	75.0±9.0	69.0±8.0*
10 min	87.0±6.0	74.0±10.0	76.0±8.0	70.0±8.0
CPP (mmHg)				
Time zero	86.0±8.0	64.0±9.0	73.0±8.0	78.0±13.0
1 min	86.0±7.0	64.0±9.0	70.0±9.0	69.0±13.0
2 min	84.0±8.0	64.0±7.0	67.0±7.0	63.0±11.0*
3 min	85.0±9.0	61.0±7.0	65.0±8.0	61.0±11.0*
4 min	84.0±8.0	60.0±9.0	65.0±8.0	60.0±10.0*
5 min	84.0±8.0	60.0±9.0	66.0±10.0	62.0±8.0*
10 min	84.0±6.0	65.0±10.0	68.0±9.0	65.0±8.0

Table 13.2 *(continued)*

	Control	Group 1	Group 2	Group 3
SjO_2 (%)				
Time zero	54.0±15.0	56.0±9.0	50.0±9.0	60.0±9.0
1 min	51.0±9.0	56.0±8.0	50.0±10.0	59.0±12.0
2 min	51.0±9.0	55.0±9.0	47.0±11.0	58.0±12.0
3 min	51.0±8.0	53.0±12.0	50.0±9.0	58.0±12.0
4 min	51.0±8.0	54.0±11.0	49.0±10.0	57.0±14.0
5 min	51.0±9.0	52.0±11.0	49.0±10.0	59.0±12.0
10 min	45.0±9.0**	49.0±8.0	46.0±9.0	55.0±11.0
$AVDO_2$ (mmol/L)				
Time zero	3.6±0.6	3.2±0.9	3.8±0.9	3.3±0.7
1 min	3.6±0.6	3.2±0.7	3.8±1.0	3.2±1.0
2 min	3.6±0.5	3.4±0.9	4.0±1.1	3.4±1.0
3 min	3.6±0.4	3.4±1.2	4.0±1.1	3.3±1.1
4 min	3.6±0.5	3.4±1.1	3.9±1.0	3.4±1.1
5 min	3.6±0.5	3.5±1.1	3.8±1.0	3.3±1.1
10 min	4.0±0.6**	3.8±0.9	4.1±1.0	3.5±1.0
CO_2 reactivity	16.3±6.3	12.6±11.3	15.5±9.9	17.1±17.3
$\%AVDO_2/\Delta PaCO_2$ (kPa)				
% change CVR	12.0±9.0	23.0±20.0	12.0±8.0	15.0±17.0

*$P<0.05$ intergroup differences
**$P<0.05$ after hyperventilation

Conclusion Administration of i.v. alfentanil to propofol-fentanyl-anaesthetized patients with supratentorial cerebral tumours decreases MABP and CPP in a dose-related way, but does not influence subdural ICP, $AVDO_2$, the CO_2 reactivity or the percentage change in CVR.

Study 2: Effect of a Bolus Dose of Remifentanil on Cerebral Haemodynamics During Propofol-Remifentanil Anaesthesia in Patients Subjected to Craniotomy for Supratentorial Cerebral Tumours

Aim To investigate the effect of an intravenous dose of remifentanil on subdural ICP and cerebral haemodynamics.

Method Two groups of 15 patients each were studied. One of the groups was a control group and received only a maintenance dose of remifentanil. Patients in the other group received 10% of the remifentanil maintenance dose per hour as a bolus dose. All patients in both groups were scheduled for craniotomy for supratentorial cerebral tumours and propofol-remifentanil was used for maintenance of anaesthesia. Subdural ICP, MABP and CPP were monitored every minute for 5 min after the bolus dose of remifentanil.

$PaCO_2$, SjO_2 and $AVDO_2$ were measured at time zero and after 5 min (for details concerning histopathology, neuroradiological findings, anaesthesia, intravenous fluid management and monitoring, see Chapter 3).

Statistical analysis One-way analysis of variance was used when tests for normality and equal variance were passed. If not, the non-parametric Kruskal-Wallis one-way analysis of variance by ranks was used. Tukey's test and Dunn's method were used for multiple comparisons. For analysis within groups, one-way repeated measures analysis of variance was used. If the normality test failed, Friedman's repeated analysis of variance on ranks was used. For pair-wise multiple comparison procedures Dunnett's method was used. A *t*-test was used for analysis between groups, when only two groups were compared. If the normality test failed the Wilcoxon signed rank test was used. $P<0.05$ signifies statistical significance.

Results No differences in demographic data, preoperative blood pressure, $PaCO_2$, rectal temperature, neurological data (tumour size, midline shift, localization of tumour) or pathohistology of the tumours were disclosed (see Tables 13.3 and 13.4). The remifentanil bolus dose (averaging 188 µg) induced a statistically significant fall in MABP and CPP for 4 min. No falls werefound in the control group (Table 13.5). The remifentanil administration did not change ICP. In both groups $PaCO_2$, SjO_2 and $AVDO_2$ were unchanged during the 5-min study period (Table 13.6).

Table 13.3 Preoperative demographic data, neuroradiological data, maintenance dose of anaesthesia and parameters related to cerebral haemodynamics in a control group and in a group where 10% of the remifentanil maintenance dose per hour was given intravenously. Data were obtained before the administration of remifentanil bolus. No significant differences were disclosed between groups

	Control group	Remifentanil group
Men/women	6/9	7/8
Weight (kg)	79.0±17.0	74.0±16.0
Preoperative MABP (mmHg)	96.0±6.0	94.0±11.0
Maximal tumour area (cm^2)	11.0±7.0	8.0±6.0
Midline shift (mm)	4.2±0.6	2.0±4.0
Propofol (mg/h)	460.0±135.0	386.0±52.0
Remifentanil (ml/h)	23.5±9.1	18.9±3.4
$PaCO_2$ (kPa)	4.5±0.3	4.6±0.2
Temperature (°C)	35.7±0.4	35.8±0.3
MABP (mmHg)	77.0±15.0	75.0±10.0
ICP (mmHg)	9.5±6.2	7.2±4.6
CPP (mmHg)	68.0±15.0	68.0±12.0
SjO_2 (%)	50.0±8.7	52.0±12.0
$AVDO_2$ (mmol/L)	3.6±0.8	3.6±1.1

Table 13.4 Localization and pathology of the tumours in the control group and in a group where 10% of the remifentanil maintenance dose per hour was given intravenously

	Control group	Remifentanil group
Localization of tumour		
Frontal	2	4
Parietal	4	2
Temporal	4	5
Occipital	1	0
Basal	3	3
Central	1	1
Pathology		
Glioblastoma	3	4
Meningioma	4	1
Metastasis	0	4
Glioma	4	4
Other	4	2

Table 13.5 MABP, ICP and CPP in the control group and in the remifentanil bolus group. Mean values are indicated

Minutes	Control			Remifentanil		
	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
0	77.3	9.5	67.8	74.6	7.2	68.3
1	77.3	9.3	68.1	73.2*	7.2	66.0*
2	77.1	9.3	67.7	71.7*	7.3	64.7*
3	76.5	9.5	67.0	71.0*	7.3	63.9*
4	77.2	9.3	67.8	70.9*	7.3	63.4*
5	77.7	9.4	67.6	71.5*	7.3	64.3

*$P \leq 0.01$ significant difference from 0 min

Table 13.6 SjO_2, $AVDO_2$ and $PaCO_2$ in the control group and the remifentanil bolus group. No significant differences were disclosed within the groups

Minutes	Control			Remifentanil		
	S_jO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)	S_jO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)
0	49.8±8.7	3.6±0.8	4.4±0.3	52.4±12	3.6±1.1	4.6±0.3
5	49.7±8.4	3.6±0.8	4.5±0.4	51.8±13	3.6±1.1	4.5±0.3

Conclusion A bolus dose of remifentanil administered during propofol-remifentanil anaesthesia does not change ICP, SjO_2 or $AVDO_2$, but reduces blood pressure and CPP.

Study 3: Effect of a Bolus Dose of Fentanyl on Cerebral Haemodynamics During Propofol-Fentanyl Anaesthesia in Patients Subjected to Craniotomy for Supratentorial Cerebral Tumours

Aim To investigate the effect of an intravenous dose of fentanyl on subdural ICP and cerebral haemodynamics.

Method Two groups of 15 patients each were studied, a control group receiving no fentanyl and a group in which intravenous fentanyl (1 μg/kg) was administered. All patients were scheduled for craniotomy for supratentorial cerebral tumours, and propofol-fentanyl was used for maintenance of anaesthesia. Subdural ICP, MABP and CPP were monitored every minute for 5 min after a bolus dose of fentanyl. $PaCO_2$, SjO_2 and $AVDO_2$ were measured at time zero and after 5 min (for details concerning histopathology, neuroradiological findings, anaesthesia, intravenous fluid management and monitoring, see Chapter 3).

Statistical analysis One-way analysis of variance was used when tests for normality and equal variance were passed. If not, the non-parametric Kruskal-Wallis one-way analysis of variance by ranks was used. Tukey's test and Dunn's method were used for multiple comparisons. For analysis within groups, one-way repeated measures analysis of variance was used. If the normality test failed, Friedman's repeated analysis of variance on ranks was used.

Table 13.7 Preoperative demographic data, neuroradiological data, maintenance dose of anaesthesia and parameters related to cerebral haemodynamics in a control group and in a group where fentanyl (1 μg/kg) was given intravenously. Data were obtained before the administration of a fentanyl bolus. No significant differences were disclosed between groups

	Control group	Fentanyl group
Men/women	7/8	8/7
Weight (kg)	76.0±16.0	74.0±15.0
Preoperative MABP (mmHg)	95.0±7.0	94.0±10.0
Maximal tumour area (cm^2)	12.0±8.0	10.0±6.0
Midline shift (mm)	3.1±5.4	2.9±3.5
Propofol (mg/kg/h)	8.8±1.7	9.2±2.2
Fentanyl (μg/kg/h)	2.1±0.5	2.4±0.3
$PaCO_2$ (kPa)	4.6±0.2	4.6±0.2
Temperature (°C)	35.6±0.3	35.7±0.3
MABP (mmHg)	84.0±13.0	87.0±11.0
ICP (mmHg)	9.0±5.8	8.5±5.6
CPP (mmHg)	75.0±15.0	78.0±11.0
SjO_2 (%)	52.0±7.6	53.0±7.4
$AVDO_2$ (mmol/L)	3.5±0.7	3.4±0.8

Table 13.8 Localization and pathology of the tumours in the control group and in the group where fentanyl was administered as a bolus dose

	Control group	Fentanyl group
Localization of tumour		
Frontal	4	4
Parietal	3	2
Temporal	5	4
Occipital	2	2
Basal	0	1
Central	1	2
Pathology		
Glioblastoma	6	5
Meningioma	3	3
Metastasis	2	2
Glioma	2	3
Other	2	2

For pair-wise multiple comparison procedures Dunnett's method was used. A *t*-test was used for analysis between groups, when only two groups were compared. If the normality test failed the Wilcoxon signed rank test was used. $P<0.05$ signifies statistical significance.

Results No difference in demographic data, preoperative blood pressure, $PaCO_2$, rectal temperature, neurological data (tumour size, midline shift, localization of tumour) or pathohistology of the tumours were disclosed (see Tables 13.7 and 13.8). During the 5-min observation period fentanyl induced a significant fall in MABP and CPP lasting 4 min, but ICP was unchanged. MABP, ICP and CPP were unchanged in the control group (Table 13.9). In both groups $PaCO_2$, SjO_2 and $AVDO_2$ were unchanged during the 5-min study period (Table 13.10).

Table 13.9 MABP, ICP and CPP in the control group and the fentanyl bolus group. Mean values are indicated

Minutes	Control			Fentanyl		
	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
0	84.3	9.0	75.4	86.8	8.5	78.2
1	83.2	8.8	74.4	86.5	8.5	78.1
2	83.8	9.1	74.2	85.2	8.1	77.1
3	84.4	9.2	75.3	82.2	8.3	73.9
4	84.2	9.0	75.4	81.3	8.4	73.0
5	84.0	8.9	75.2	77.2*	8.2	69.0*

*$P\leq0.01$ significant difference from 0 min

Table 13.10 SjO_2, $AVDO_2$ and $PaCO_2$ in the control group and the fentanyl bolus group. No significant difference was disclosed within the groups

Minutes	Control			Fentanyl		
	S_jO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)	S_jO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)
0	52.1±7.6	3.5±0.7	4.6±0.2	53.4±7.4	3.4±0.8	4.6±0.2
5	50.2±7.9	3.6±0.9	4.6±0.3	52.9±8.8	3.5±0.7	4.6±0.2

Conclusion A bolus dose of fentanyl administered during propofol-fentanyl anaesthesia does not change ICP, SjO_2 or $AVDO_2$, but reduces blood pressure and CPP significantly.

Discussion

The three studies presented in this chapter show identical patterns as regards changes in subdural ICP and cerebral haemodynamics. Bolus injections of the three analgetics (alfentanil, remifentanil and fentanyl) were accompanied by a decrease in blood pressure and CPP, while subdural ICP was unchanged. A dose-response relationship was found with alfentanil as regards the decrease in MABP and CPP. The cerebral haemodynamics, indirectly registered by monitoring the $AVDO_2$ and the SjO_2, were unchanged for all three analgetics during the observation period, and the CO_2 reactivity or changes in CVR were not influenced by increasing doses of alfentanil. The decreases in CPP found after bolus injections of the three analgetics were not accompanied by changes in SjO_2 or $AVDO_2$, indicating that these analgetic drugs did not jeopardize cerebral oxygen delivery (or provoke potential cerebral ischaemia) in spite of the decrease in CPP.

The results of the experimental and clinical studies of the effects of analgetics on CBF and $CMRO_2$ are complex. In cats, fentanyl induces an increase in CBF and $CMRO_2$ (Nilsson and Ingvar 1965; Freeman and Ingvar 1967). In comparison, studies of venous outflow in dogs during nitrous oxide anaesthesia indicate an 18% decrease in $CMRO_2$ and a 47% decrease in CBF after fentanyl 0.006 mg/kg (Michenfelder and Theye 1971). Milde et al. (1989) studied the effect of fentanyl 50 and 100 mg/kg, respectively, on CBF and $CMRO_2$ in dogs, and found that these doses had minimal effect on CBF, oxygen uptake and the energy state of the brain. In studies of pigs, subjected to fentanyl-nitrous oxide anaesthesia and pancuronium relaxation, CBF, $CMRO_2$, CO_2 reactivity and EEG were stable throughout a 100-min period (Åkeson et al. 1993). Studies with a Doppler technique indicate that fentanyl during normocapnia increases flow velocity (Trindle et al. 1993). This effect is abolished during hypocapnia (Kolbitsch et al. 1997). During induction of anaesthesia with fentanyl 100 mg/kg and diazepam 0.4 mg/kg for cardiac surgery a 25% decrease in CBF was observed, while $CMRO_2$ was unchanged. Administration of fentanyl

during controlled ventilation, however, might be accompanied by an increase in ICP and a decrease in blood pressure (Knüttgen et al. 1989). In dogs, alfentanil induces a dose-related decrease in CBF, the CO_2 reactivity is preserved and the upper autoregulatory threshold is shifted to the right (McPherson et al. 1982). Healthy volunteers were subjected to remifentanil infusion (0.1 μg/kg/min) and cerebral parameters were measured with a magnetic resonance (MR) technique. Remifentanil increased rCBF and rCBV in white and grey matter (striatal, thalamic, occipital, parietal, frontal) regions with a parallel decrease in transit time in these regions with the exception of the occipital grey matter. Regional CVR was decreased in all regions studied. The authors concluded that these findings were consistent with cerebral excitement and/or disinhibition (Lorenz et al. 2000). In volunteers remifentanil induces dose-dependent changes in relative rCBF in areas involved in pain processing. Furthermore, at moderate doses of remifentanil rCBF responses were detected in structures known to participate in modulation of vigilance and alertness (Wagner et al. 2001). Using contrast-enhanced MR perfusion measurement in human volunteers, a comparative study of nitrous oxide (50%) and remifentanil (0.1 μg/kg/min) indicated that nitrous oxide produced a greater increase in rCBV in all grey matter regions than did remifentanil. However, the increase in rCBF, especially in the basal ganglia, was less pronounced than during infusion of remifentanil (Lorenz et al. 2002). In patients with head trauma, who were sedated with propofol and sufentanil, a bolus dose of remifentanil (0.5 μg/kg) followed by continuous infusion (0.25 μg/kg/min for 20 min) did not change flow velocity, ICP or CPP (Engelhard et al. 2004). In patients subjected to coronary by-pass graft surgery remifentanil (3 μg/kg/min) reduced flow velocity by 31%. The flow velocity was not changed by 1 μg/kg/min remifentanil (Paris et al. 1998). Thus, based on the cited experimental and clinical studies of CBF and $CMRO_2$, it seems as if a bolus dose of one of the three analgetics administered under maintenance anaesthesia as described either leaves CBF unchanged or reduces CBF and $CMRO_2$. Consequently, a decrease in ICP or an unchanged ICP should be the most reliable finding.

The decrease in blood pressure and CPP, as well as the unchanged ICP found in the three studies presented in this chapter, are in agreement with other studies. Thus, a decrease in MABP and CPP was found in patients with severe head injury, where fentanyl in doses of 2 mg/kg resulted in a fall in MABP and CPP, but did not change $AVDO_2$ (de Nadal et al. 1998, 2000). In another study of patients subjected to craniotomy for supratentorial tumours the effects of remifentanil 0.5 μg/kg and alfentanil 1.0 μg/kg on ICP and MABP were compared. Neither opioid caused significant changes in ICP, but both drugs were associated with a dosage-dependent decrease in MABP (Warner et al. 1996). Alfentanil did not change ICP in children undergoing shunt revision (Marcovitz et al. 1990). In another study alfentanil and thiopentone were used for induction of anaesthesia in patients with supratentorial tumours and ICP remained stable without significant difference from

pre-anaesthetic levels (Hung et al. 1992). In artificially ventilated patients with closed head injury, pretreatment with alfentanil before suction did not change ICP. In this study a decrease in blood pressure and in CPP were observed (Hanowell et al. 1993). These findings are in accordance with studies of transcranial Doppler sonography, indicating that alfentanil does not alter the vessel diameter in the middle cerebral artery (Schregel et al. 1992). However, the unchanged subdural ICP found in the present study is in conflict with some other studies. Thus, in a comparative study in patients with supratentorial tumours fentanyl did not change lumbar CSF pressure, while administration of sufentanil and especially alfentanil was followed by an increase in lumbar CSF pressure, and a decrease in MABP and CPP (Marx et al. 1989). In propofol-sedated patients with head injury the decrease in MABP was accompanied by an increase in ICP after alfentanil administration (Albanese et al. 1999). In another human study of brain tumour patients the CSF pressure remained unchanged in patients who received nitrous oxide with or without fentanyl for maintenance of anaesthesia. In contrast, in the patients who received alfentanil, a gradual increase in lumbar CSF pressure was found (Jung et al. 1990). This is consistent with the result of a study by Mayberg et al. (1993), who found a small ICP increase with an alfentanil dose of 50 μg/kg, and also with the observation by Moss (1992), who found that alfentanil increased ICP in patients with suspected normal pressure hydrocephalus.

Compensatory cerebral vasodilatation has been observed during alfentanil-induced decrease in MABP in orthopaedic patients (Mayberg et al. 1993). This mechanism implies that the cerebral autoregulation is intact. Thus, theoretically, the decrease in CPP should be accompanied by an increase in CBV and ICP, which could explain the increase in ICP found in some studies. In contrast, an increase in CPP should be followed by a decrease in ICP, if cerebral autoregulation is intact. However, cerebral autoregulation is easily disturbed in patients with mass-expanding lesions, such as a brain tumour (Palvölgyi 1969; Endo et al. 1977), and in patients with severe head injury (Fieschi et al. 1974; Enevoldsen et al. 1976; Muizalaar et al. 1989; Jünger et al. 1997). Nevertheless, deliberate blood pressure increase induced by vasopressors is used in the treatment of intracranial hypertension in patients with severe head injury, and this treatment is often accompanied by a decrease in ICP (Rosner and Coley 1986). Another confounding factor is that in several studies where an increase in ICP has been observed after administration of analgetics, anaesthetics disturbing cerebral autoregulation (such as isoflurane or nitrous oxide) have been used (Strebel et al. 1995; Matta et al. 1999; Summors et al. 1999). Most intravenous anaesthetics, for example propofol, do not disturb cerebral autoregulation (Harrison et al. 1999).

In some of the cited studies showing increasing CSF pressure, a lumbar approach was used (Jung et al. 1990). The subdural method used in the studies presented in this chapter seems to be a more relevant method, as cerebral mass-expanding processes probably affect the subdural ICP more than lum-

bar CSF pressure, and obliterations of the CSF flow from the brain to the spinal canal may invalidate the lumbar approach as a reliable method. In the study by Warner et al. (1996) and in the present studies of alfentanil, remifentanil and fentanyl only patients with cerebral tumours were included, and maintenance of anaesthesia was provided with either inhalation agents or propofol supplemented with one of the analgetics. Generally speaking, the results as regards subdural ICP, CPP and $AVDO_2$ were identical. None of the analgetics changed ICP or $AVDO_2$, but decreased CPP in a dose-dependent manner. Based on these studies we find that moderate bolus doses of all three analgetics can be used safely during craniotomy for space-occupying processes. High doses, however, may decrease blood pressure and thereby CPP to levels which, in some patients, may be inappropriate.

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Chapter 14
Effect of a Propofol Bolus Dose on Subdural Intracranial Pressure and Cerebral Haemodynamics During General Anaesthesia for Craniotomy in Patients with Supratentorial Cerebral Tumours

Georg Emil Cold and Niels Juul

Abstract

Like barbiturates, propofol suppresses cerebral blood flow and cerebral metabolic rate of oxygen. As a consequence, a decrease in ICP is also expected. Rapid intraoperative reduction of ICP with thiopental has been demonstrated. In patients with head injury, propofol decreases both ICP and mean arterial blood pressure. Cerebral perfusion pressure, however, decreases as well, making the use of propofol in patients with head injury controversial. In patients subjected to craniotomy for space-occupying lesions in propofol-fentanyl or propofol-remifentanil anaesthesia, the effect of a bolus dose of propofol are poorly studied.

In this chapter the effect of a propofol bolus during maintenance of anaesthesia with either propofol-remifentanil or propofol-fentanyl is studied, and differences in cerebral haemodynamic parameters are discussed.

Like barbiturates, propofol suppresses CBF and $CMRO_2$. As a consequence, a decrease in ICP is also expected. Rapid intraoperative reduction of ICP with thiopental has been demonstrated (Shapiro et al. 1973). In a study of rabbits subjected to intracranial hypertension by an extradural balloon, propofol had a greater effect on ICP than hyperventilation, and the effect of the two treatments was additive (Watts et al. 1998). In patients with head injury, propofol decreases both ICP and MABP. CPP, however, decreases as well, making the use of propofol in patients with head injury controversial (Hartung 1987). In another study it was concluded that propofol 1–2 mg/kg decreased ICP, that the hypotensive effect on blood pressure was mild and that no inadvertent CPP changes were observed (Weinstabl et al. 1990). In patients subjected to craniotomy for space-occupying lesions in propofol-fentanyl or propofol-remifentanil anaesthesia, the effect of a bolus dose of propofol are poorly studied.

Study 1: Effect of a Propofol Bolus Dose on Subdural Intracranial Pressure and Cerebral Haemodynamics in Patients Subjected to Craniotomy for Supratentorial Cerebral Tumours in Propofol-Remifentanil Anaesthesia

Aim We tested the hypothesis that a bolus dose of propofol or remifentanil decreases ICP in patients scheduled for craniotomy during propofol-remifentanil anaesthesia.

Method Two groups of 15 patients each were studied: a control group and a group where 10% of the maintenance dose per hour of propofol was given as a bolus dose. All patients were scheduled for craniotomy for supratentorial

Table 14.1 Preoperative demographic data, neuroradiological data, perioperative data concerning maintenance of anaesthesia and data related to measurement of subdural ICP and cerebral haemodynamics in a control group and a group where propofol was administered as a bolus dose. The perioperative data are obtained before the administration of propofol bolus dose. No significant differences were disclosed between groups

	Control group	Propofol group
Men/women	6/9	7/8
Weight (kg)	79.0±17.0	75.0±15.0
Preoperative MABP (mmHg)	96.0±6.0	94.0±10.0
Maximal area of tumour (cm^2)	11.0±7.0	15.0±15.0
Midline shift (mm)	4.2±6.6	4.2±6.1
Propofol (mg/h)	460.0±135.0	473.0±101.0
Remifentanil (mg/h)	23.5±9.1	23.6±7.3
Temperature (°C)	35.7±0.4	35.9±0.3
$PaCO_2$ (kPa)	4.5±0.3	4.7±0.5
MABP (mmHg)	77.0±15.0	72.0±11.0
ICP (mmHg)	9.5±6.2	5.9±4.8
CPP (mmHg)	68.0±15.0	66.0±10.0
SjO_2 (%)	50.0±8.7	50.0±8.1
$AVDO_2$ (mmol/L)	3.6±0.8	3.3±0.5

Table 14.2 Localization of the tumours in a control group and a group where propofol was administered as a bolus dose. Number of patients is indicated

Localization	Control group	Propofol group
Frontal	2	7
Parietal	4	3
Temporal	4	3
Occipital	1	0
Basal	3	1
Central	1	1

cerebral tumours. Subdural ICP, MABP and CPP were monitored every minute for 5 min after a bolus dose of propofol. $PaCO_2$, SjO_2 and $AVDO_2$ were measured at time zero and after 5 min.

Statistical analysis Within groups the paired *t*-test was used for the analyses of normally distributed data. Between groups, analysis of variance was used. The chi-square test was used to estimate the difference in proportion. Mean±SD are indicated. $P<0.05$ was considered significant.

Results No differences in demographic data, preoperative blood pressure, $PaCO_2$, rectal temperature, neurological data (tumour size, midline shift, localization of tumour) or pathohistology of the tumours were disclosed (Tables 14.1–14.3). Propofol (average dose 47 mg) induced a significant fall in MABP and CPP lasting from 1 min after administration and for the following

Table 14.3 Histopathology in a control group and a group where propofol was administered as a bolus dose

Pathology	Control group	Propofol group
Glioblastoma	3	3
Meningioma	4	5
Metastasis	0	2
Glioma	4	3
Other	4	2

Table 14.4 MABP, ICP and CPP in the control group (n=15) and the propofol bolus group (n=15). Mean values are indicated

Minutes	Control			Propofol		
	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
0	77.3	9.5	67.8	72.3	5.9	66.5
1	77.3	9.3	68.1	67.9*	6.0	62.1*
2	77.1	9.3	67.7	67.8*	6.5	62.1*
3	76.5	9.5	67.0	69.5*	5.7	63.7*
4	77.2	9.3	67.8	69.8*	5.8	63.3*
5	77.7	9.4	67.6	70.1	5.9	64.2

*$P\leq0.01$ significant difference from 0 min

Table 14.5 SjO_2, $AVDO_2$ and $PaCO_2$ before and at 5 min in the control group and the propofol bolus group. No significant difference was disclosed within the groups

Minutes	Control			Propofol		
	$PaCO_2$ (kPa)	SjO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)	SjO_2 (%)	$AVDO_2$ (mmol/L)
0	4.4±0.3	49.8±8.7	3.6±0.8	4.7±0.5	49.9±8.1	3.3±0.5
5	4.5±0.4	49.7±8.4	3.6±0.8	4.6±0.4	49.6±8.3	3.3±0.5

4 min, but subdural ICP was unchanged. In the control group subdural ICP, MABP and CPP were unchanged (Table 14.4). In both groups $PaCO_2$, SjO_2 and $AVDO_2$ were unchanged during the 5-min study period (Table 14.5).

Conclusion A bolus dose of propofol administered during propofol-remifentanil anaesthesia does not change ICP, SjO_2 or $AVDO_2$ but reduces blood pressure and CPP significantly.

Study 2: Effect of a Propofol Bolus Dose on Subdural Intracranial Pressure and Cerebral Haemodynamics in Patients Subjected to Craniotomy for Supratentorial Cerebral Tumours in Propofol-Fentanyl Anaesthesia

Aim We tested the hypothesis that a propofol bolus dose decreases ICP in patients scheduled for craniotomy during propofol-fentanyl anaesthesia.

Method In 11 patients scheduled for craniotomy for cerebral tumours subdural ICP, MABP and CPP were monitored every minute for 5 min after a bolus dose of propofol (10% of maintenance dose per hour). SjO_2 and $AVDO_2$ were measured at time zero and 5 min after propofol injection. Fifteen patients served as control.

Statistical analysis Within groups the paired *t*-test was used for the analysis of normally distributed data. Between groups, analysis of variance was used. The chi-square test was used to estimate the difference in proportion. Mean±SD are indicated. $P<0.05$ was considered significant.

Table 14.6 Preoperative demographic data, neuroradiological data, perioperative data concerning maintenance of anaesthesia and data related to measurement of subdural ICP and cerebral haemodynamics in a control group and a group where propofol was administered as a bolus dose. The perioperative data are obtained before the administration of propofol bolus dose. No significant differences were disclosed between groups

	Control group	Propofol group
Women/Men	7/8	2/9
Weight (kg)	74.0±12.0	77.0±12.0
Maximal tumour area (cm^2)	13.0±10.0	13.0±8.0
Midline shift (mm)	4.8±6.6	3.7±4.2
Propofol maintenance (mg/h)	677.0±190.0	509.0±83.0
Fentanyl maintenance (μg/h)	137.0±40.0	136.0±23.0
$PaCO_2$ (kPa)	4.6±0.4	4.5±0.3
Temperature (°C)	35.7±0.5	35.8±0.4
MABP (mmHg)	90.0±11.0	93.0±11.0
ICP (mmHg)	5.3±3.1	6.7±2.1
CPP (mmHg)	86.0±13.0	86.0±11.0
SjO_2 (%)	55.8±14.1	55.4±6.9

Table 14.7 Localization of the tumours in a control group and a group where propofol was administered as a bolus dose

Localization	Control group	Propofol group
Frontal	7	4
Parietal	2	2
Temporal	4	2
Occipital	0	1
Basal	1	0
Central	1	2

Table 14.8 Histopathology in a control group and a group where propofol was administered as a bolus dose

Pathology	Control group	Propofol group
Glioblastoma	2	4
Meningioma	1	1
Metastasis	2	4
Glioma	9	2
Other	1	0

Table 14.9 MABP, ICP and CPP in the control group and the propofol bolus group. Mean values are indicated

Minutes	Control			Propofol		
	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
0	90.1	5.3	85.5	93.2	6.7	86.2
1	89.9	5.5	84.8	90.4	6.8	83.5
2	89.0	5.6	83.4	86.3*	6.8	79.5*
3	89.5	5.4	84.1	86.7*	6.8	79.9*
4	89.6	5.3	83.3	87.6*	7.0	80.6*
5	89.2	5.3	84.2	88.2*	7.0	81.2*

*$P \leq 0.002$ significant difference from 0 min

Results No differences in demographic data, preoperative blood pressure, $PaCO_2$, rectal temperature, neurological data (tumour size, midline shift, localization of tumour) or pathohistology of the tumours were disclosed (Tables 14.6–14.8). The propofol dose (averaging 51 mg, induced a significant fall in MABP and CPP lasting from 1 min after administration and for the following 5 min. The maximum fall in MABP and CPP averaged 6.9 and 6.8 mmHg, respectively. ICP did not change significantly. In the control group MABP, ICP and CPP were unchanged (Table 14.9). In both groups SjO_2 and $AVDO_2$ were unchanged (Table 14.10).

Table 14.10 $PaCO_2$, SjO_2 and $AVDO_2$ before, and at 5 min in the control group and the propofol bolus group

Minutes	Control			Propofol		
	$PaCO_2$ (kPa)	SjO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)	SjO_2 (%)	$AVDO_2$ (mmol/L)
0	4.6±0.4	55.8±14.1	3.4±0.7	4.5±0.3	55.4±6.9	3.3±0.4
5	4.6±0.4	53.5±10.8	3.5±0.8	4.5±0.3	54.8±7.6	3.3±0.4

Conclusion A bolus dose of propofol administered during propofol-fentanyl anaesthesia does not change ICP, SjO_2 or $AVDO_2$ but reduces CPP significantly.

Discussion

The principal findings in the presented studies are as follows: During maintenance anaesthesia with propofol-fentanyl or propofol-remifentanil a bolus dose of propofol decreases blood pressure and CPP, but leaves ICP unchanged. In contrast, in experimental studies (Watts et al. 1998) and in clinical studies in patients with head injury (Hartung 1987; Weinstabl et al. 1990), a decrease in ICP, eventually accompanied by a decrease in CPP, was found. A decrease in blood pressure and CPP was also observed after a propofol bolus dose of 2.5 mg/kg (Hemelrijck et al. 1992). As cerebral metabolism, cerebral autoregulation and the CO_2 reactivity are influenced by changes in CPP, these factors should be discussed as a reason for the unchanged ICP found in the present studies.

In experimental studies propofol is known to reduce both CBF and $CMRO_2$ (Vandesteene et al. 1988; Werner et al. 1992). A dose-related decrease in CBF and $CMRO_2$ under conditions where blood pressure is maintained has been found (Ramani et al. 1992). In dogs low and moderate doses of propofol decrease the EEG activity and $CMRO_2$, causing an associated decrease of CBF and CSF pressure. Cerebral autoregulation and CO_2 reactivity were found to be preserved. In contrast, high-dose propofol decreases CPP below the lower point of cerebral autoregulation (Artru et al. 1992). In rabbits cerebrovascular reactivity of blood flow and CBV are markedly decreased during hypocapnia, but are maintained during hypercapnia (Cenic et al. 2000). In the rat and pig autoregulation is present during propofol anaesthesia (Werner et al. 1990; Lagerkranser et al. 1997).

In humans propofol, given as a bolus injection, suppresses CBF and $CMRO_2$ (Stephan et al. 1987, 1988). Similar changes in CBF and $CMRO_2$ have been observed during continuous infusion with propofol (Vandesteene et al. 1988), and in a clinical study $CMRO_2$ was reduced about 50% compared with values obtained in awake healthy humans (Madsen et al. 1989). In healthy volunteers $AVDO_2$ is unchanged during continuous propofol induction, suggesting parallel changes in CBF and $CMRO_2$. The decrease in flow velocity, measured with trans-

cranial Doppler, reaches a minimum value of 40% of baseline within 5 min, and the bispectral index (BIS) decreases to a minimum value at around 7 min from the onset of propofol administration (Ludbrook et al. 2002). Several studies have suggested that during propofol anaesthesia, the reduction of CBF is larger than the reduction of $CMRO_2$, resulting in a decrease of the $CBF/CMRO_2$ ratio (Manohar 1986; Scheller et al. 1988, 1990; Mielck et al. 1999). Likewise, other studies indicate that the SjO_2 is low or the $AVDO_2$ is high during propofol anaesthesia (Jansen et al. 1999; Munoz et al. 2002; Petersen et al. 2003), at least when compared with isoflurane anaesthesia (Jansen et al. 1999; Petersen et al. 2003) or sevoflurane anaesthesia (Munoz et al. 2002; Petersen et al. 2003; Kawano et al. 2004). On the other hand, Iwata et al. (2006) found that increasing the dose of propofol did not affect SjO_2. Both during sevoflurane, isoflurane and propofol anaesthesia, hyperventilation aggravates the changes in $AVDO_2$ and SjO_2 (Petersen et al. 2003; Kawano et al. 2004). These findings suggest that maintenance of normocarbia may be critical to maintenance of adequate cerebral perfusion. Kaisti et al. (2002) studied rCBF with positron emission tomography (PET) in volunteers when they were awake and during increasing propofol concentrations of 1, 1.5 and 2 EC_{50}. They found that rCBF during EC_{50} was reduced by 62–70% with minor additional effect when the concentration was further increased. In a similar study they found that at a BIS value of 40 propofol reduced rCBF and $rCMRO_2$ comparably (Kaisti et al. 2003). After propofol bolus injection the CO_2 reactivity was preserved (Stephan et al. 1987). This finding was also confirmed in studies with a Doppler technique (Jansen and Kagenaar 1993; Strebel et al. 1994; Ederberg et al. 1998). In a study including healthy adults the slope of the CBF versus $PaCO_2$ was 1.56 ml/100 g/min/mmHg $PaCO_2$ (Fox et al. 1992). During continuous propofol infusion in patients without brain disorders the CO_2 reactivity was also found to be intact (Craen et al. 1992; Harrison et al. 1999). In other studies the CO_2 reactivity based on flow velocity was attenuated (Mirzai et al. 2004). Hyperventilation during propofol anaesthesia to end-tidal CO_2 values less than 30 mmHg is without effect on CBF because flow velocity is unchanged below this level (Karsli et al. 2004). In a randomized study, including patients with supratentorial cerebral tumours, the CO_2 reactivity was significantly lower during propofol anaesthesia compared with the reactivates obtained during isoflurane and sevoflurane (Petersen et al. 2003). In comparison with sevoflurane (Conti et al. 2006) or 1.5 MAC isoflurane and desflurane anaesthesia cerebral autoregulation is preserved with propofol (Matta et al. 1995; Strebel et al. 1995). In healthy subjects the effect of graded hypercapnia on cerebral autoregulation was tested during sevoflurane and propofol anaesthesia. The threshold of $PaCO_2$ to significantly impair cerebral autoregulation averaged 56 mmHg during sevoflurane anaesthesia and 61 mmHg during propofol anaesthesia (McCulloch et al. 2000).

From the cited studies it seems likely that cerebral autoregulation did not influence the results. If cerebral autoregulation is intact a decrease in CPP should elicit an increase in ICP, while a decrease in ICP was expected if cerebral autoregulation was intact. Furthermore, changes in $PaCO_2$ were not observed in

either study and therefore could be excluded as a factor influencing ICP. A substantial decrease in $CMRO_2$ and CBF during maintenance of anaesthesia, however, seems to be a reasonable explanation why ICP was unchanged. A 50% decrease in $CMRO_2$ has been observed during propofol-fentanyl anaesthesia, and very low values of SjO_2 have been observed as well. Under such circumstances it is unlikely that a bolus dose of propofol might suppress $CMRO_2$ and CBF further, and thereby elicit a fall in CBV and ICP.

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Chapter 15
Effect of Reverse Trendelenburg Position on Subdural Intracranial Pressure and Cerebral Haemodynamics During General Anaesthesia for Craniotomy in Patients with Supratentorial Cerebral Tumours

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Abstract

The effects of head and trunk elevation on cerebral haemodynamics have been investigated in intensive care patients. In most of these studies, head and trunk elevation resulted in decreased ICP. The effect of head elevation on ICP and cerebral haemodynamics during general anaesthesia for craniotomy in patients with cerebral tumours has only been sparsely investigated.

In this chapter data on four studies concerning the reverse Trendelenburg position in patients with significant space-occupying lesions as well as patients with cerebral aneurysms are presented and discussed. The ICP-lowering effect of 10 degrees reverse Trendelenburg position in two groups of prone- and supine-positioned patients are presented. The optimal reverse position is disclosed and the influence of the anaesthetic regime discussed.

The effects of head and trunk elevation (flexion with the hips in a sitting and semi-sitting position) on cerebral haemodynamics have been investigated in intensive care patients. In patients with severe head injury the head-up position reduced ICP in the intensive care setting (Durwald et al. 1983; Rosner and Coley 1986; Porchet et al. 1998; Moraine et al. 2000). In contrast, the head-down position increases ICP compared to the neutral position (Lee 1989; Hung et al. 2000). The effect of head elevation on ICP in anaesthetized patients has only sparsely been investigated. The effect of head elevation on lumbar spinal pressure in anaesthetized patients was studied by Mavrocordatos et al. (2000) who investigated lumbar cerebrospinal pressure and found an increase of around 1 mmHg with a 30° head-up position, depending on the position of the neck. Rolighed

Larsen et al. (2002) studied subdural ICP during craniotomy before and 1 min after a change in position from supine to 10° rTp and found that subdural ICP and MABP decreased significantly, but CPP remained unchanged. In this chapter we present further studies in prone-positioned patients, patients with cerebral aneurysm and in supine-positioned patients of changes in subdural ICP and CPP with the patients in the neutral position and in 5°, 10° and 15° rTp.

This chapter is based on three published studies and one unpublished study: study 1 has been presented by Haure et al. in J Neurosurg Anesthesiol (2003) 15:297–301, study 2 has been presented by Tankisi et al. in Acta Neurochir (2002) 144:665–670 and study 3 has been presented by Tankisi and Cold in J Neurosurg (2007) 106:239–244; study 4 is unpublished.

Study 1: The Intracranial Pressure-Lowering Effect of 10 Degrees Reverse Trendelenburg Position During Craniotomy is Stable During a 10-Minute Period

Aim To study the effect of 10° rTp on subdural ICP, CPP and JBP during a 10-min period during craniotomy.

Method Fifteen adult patients scheduled for craniotomy for supratentorial cerebral tumours were included in the study. After exposure of dura, subdural ICP, MABP, CPP and JBP were monitored continuously before and 10 min after change in position from supine to 10° rTp. The degree of dural tension was evaluated by the surgeon as well. End-tidal CO_2 was monitored during the study period, and arterial and jugular venous blood were analysed for PaO_2, $PaCO_2$, oxygen content and oxygen saturation. $AVDO_2$ was calculated as the difference in oxygen content between arterial and venous blood. (For details concerning methods, see Chapter 3.)

Statistical analysis Mean values, SD and standard error of mean (SE) were calculated. One-way repeated measures of variance was performed. If the test for normality failed, Friedman's repeated measures of analysis on ranks was used to analyse paired data. Dunnett's method was used for pair-wise multiple comparison. $P<0.05$ was considered significant.

Results No significant changes as regards $PaCO_2$, PaO_2, arterial oxygen saturation, SjO_2, $AVDO_2$ or end-tidal CO_2 were disclosed when values before and 10 min after change in position were compared. One minute after change in position, subdural ICP decreased from 10.9 (5.7) mmHg to 7.3 (5.2) mmHg, $P<0.05$, and remained stable during the next 9 min (Fig. 15.1). A significant decrease in MABP was also disclosed after 1 min after change in position from 81 (15) mmHg to 77 (15) mmHg, $P<0.05$, but for the following 9 min MABP remained constant. JBP decreased significantly from 7.7 (1.7) mmHg to 5.5 (2.0) mmHg after 1 min. CPP did not change during the study period being 70 (16) mmHg before and 70 (17) mmHg after change in position (Fig. 15.2).

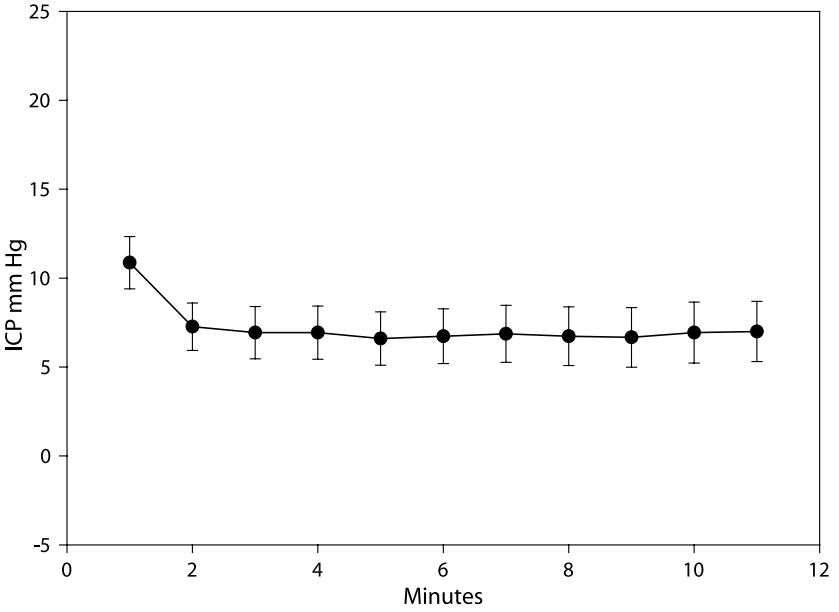

Fig. 15.1 Changes in subdural ICP in the supine position and during a 10-min period of 10° rTp. Means and SE are indicated

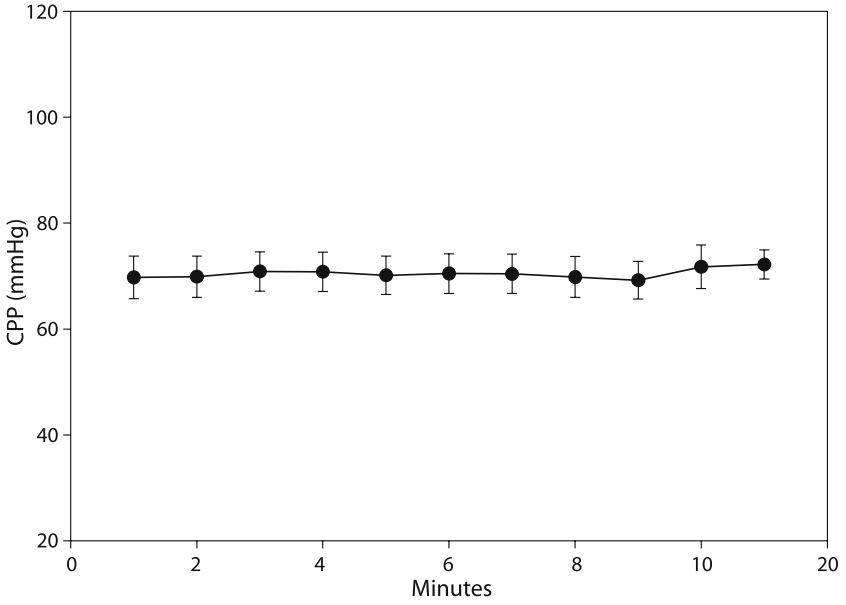

Fig. 15.2 Changes in CPP in the supine position and during a 10-min period of 10° rTp. Means and SE are indicated

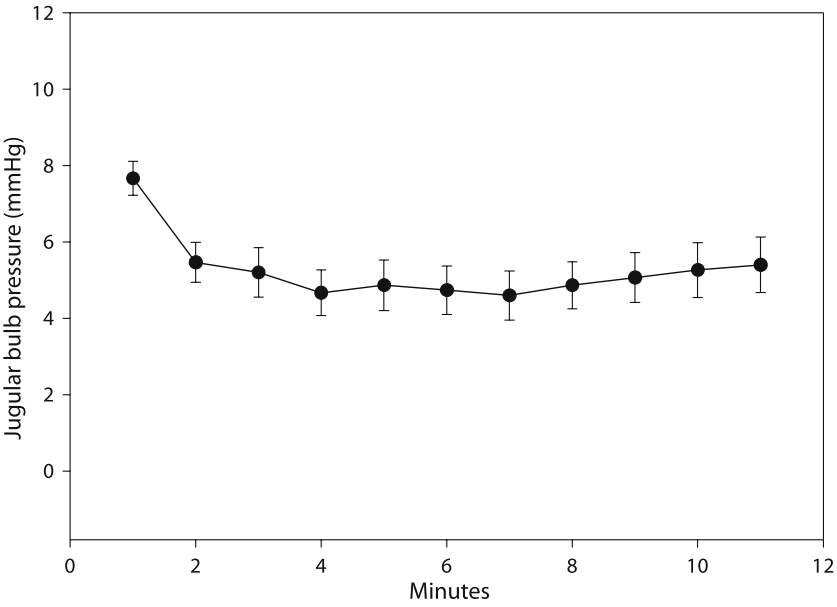

Fig. 15.3 Changes in JBP in the supine position and during a 10-min period of 10° rTp. Means and SE are indicated

Table 15.1 Degrees of dural tension in 15 patients evaluated before and repeatedly up to 10 min after change in position form supine to 10° rTp. Number of patients is indicated

	Dura very slack	Normal tension of dura	Increased tension of dura	Pronounced increased tension
Before tilting	1	5	8	1
One minute after tilting	3	8	4	0
Five minutes after tilting	3	9	3	0
Ten minutes after tilting	3	9	3	0

A significant decrease in JBP was also demonstrated (Fig. 15.3). The degree of dural tension as estimated by the neurosurgeon is indicated in Table 15.1. One minute after change in position the tension of dura decreased significantly, $P<0.05$. The degree of dural tension thereafter remained unchanged. Neither the correlation between subdural ICP and JBP, nor the correlation between change in subdural ICP and change in JBP following tilting of the table were significant.

Conclusion During craniotomy 10° rTp reduces subdural ICP and MABP significantly, while CPP is unchanged. These changes occur within 1 min after change in position, and during the next 9 min subdural ICP and CPP remain stable. The change in position is accompanied by a decrease in dural tension.

Study 2: Effect of 10 Degrees Reverse Trendelenburg Position on Intracranial Pressure and Cerebral Perfusion Pressure in Prone-Positioned Patients Subjected to Craniotomy for Occipital or Cerebellar Tumours

Aim The aim of the study is to evaluate the effect of 10° rTp on subdural ICP, CPP, MABP and JBP in prone-positioned patients subjected to craniotomy for occipital or cerebellar tumours.

Method Twelve patients with occipital tumour and 14 patients with cerebellar tumour underwent propofol-fentanyl anaesthesia in the prone position. The patients were moderately hyperventilated, with attempted $PaCO_2$ levels between 4.0 and 5.0 kPa, and PaO_2 > 13 kPa. After induction of anaesthesia 500 ml of 6% hydroxyethyl starch was infused. Catheters were inserted in the radial artery and jugular vein. MABP, subdural ICP and JBP were measured in the neutral position and in 10° rTp. CPP was calculated as MABP – subdural ICP. Measurements were performed in the neutral position and after change in position to 10° rTp. Changes in subdural ICP and JBP were calculated. Tension of dura was estimated in the neutral position and again at 10° rTp by the neurosurgeon. Dural tension was graded as: normal, increased tension and pronounced increased tension (for details, see Chapter 3).

Statistical analysis Mean±SD were calculated. Between groups and within groups Student's *t*-test and paired *t*-test were used for analyses, respectively. When the normality test failed the Mann-Whitney rank sum test and the Wilcoxon test were used.

Results In patients with occipital tumours subdural ICP decreased from 21.0 to 15.6 mmHg ($P<0.05$) after change in position. In 7 of 12 patients the decrease in ICP was ≥ 5 mmHg. MABP and JBP also decreased significantly from 87.9 to 83.3 mmHg and from 14.3 to 7.7 mmHg, respectively. CPP did not change significantly (Table 15.2). In patients with cerebellar tumours a significant decrease in subdural ICP from 18.3 to 14.2 mmHg was found. In 6 of 14 patients the decrease in ICP was ≥ 5 mmHg. MABP and JBP decreased significantly as well, but CPP did not change significantly (Table 15.3). In Table 15.4 the tactile estimations of dural tension are indicated before and after change in position. Both occipital and cerebellar tumours are included. The

Table 15.2 MABP, subdural ICP, CPP and JBP in the neutral position and after change in position to 10° rTp. Twelve patients with occipital tumours are included. Mean±SD are indicated

Position	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	JBP(mmHg)
Neutral	87.9±16.4	21.0±4.6	66.9±16.9	14.3±5.5
10° rTp	83.3±16.0*	15.6±5.6*	67.7±16.5	7.7±5.3*

*$P<0.05$

Table 15.3 MABP, subdural ICP, CPP and JBP in the neutral position and after change in position to 10° rTp. Fourteen patients with cerebellar tumours are included. Mean±SD are indicated

Position	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	JBP (mmHg)
Neutral	93.8±13.4	18.3±6.1	75.5±14.3	12.1±6.3
10° rTp	90.5±13.7*	14.2±5.9*	76.4±15.2	5.0±4.6*

*$P<0.05$

Table 15.4 Estimation of tension of dura in prone-positioned patients with the operating table in the neutral position and after change to 10° rTp. Numbers of patients are indicated

Tension of dura	Neutral position	10° rTp
Normal	1	7
Increased	15	10
Pronounced increased	10	9

number of patients with normal tension of dura increased from 1 to 7. When patients with cerebellar and occipital tumours were compared, no significant differences between MABP, subdural ICP, CPP and JBP were disclosed. Neither did the changes in subdural ICP, MABP, CPP and JBP differ between occipital and cerebellar tumours.

Conclusion In prone-positioned patients 10° rTp significantly decreases subdural ICP, MABP and JBP, while CPP is unchanged.

Study 3: Optimal Reverse Trendelenburg Position in Patients Undergoing Craniotomy for Cerebral Tumours

Aims 1: Investigation of the effects of the neutral position and 5°, 10° and 15° rTp on subdural pressure, MABP, CPP and JBP in supine-positioned patients undergoing craniotomy for cerebral tumour. 2: To determine the optimal rTp, defined as the position at which subdural ICP is as low as possible and CPP ≥ 60 mmHg. 3: On the basis of subdural ICP measurements during neutral position and 5°, 10° and 15° rTp, to define risk groups for development of cerebral swelling.

Method Fifty-three patients underwent craniotomy in propofol-fentanyl anaesthesia in the supine position. The patients were moderately hyperventilated, the aim being a $PaCO_2$ level between 4.0 and 5.0 kPa and $PaO_2 \geq 13$ kPa. After induction of anaesthesia 500 ml of 6% hydroxyethyl starch was infused. Catheters were inserted in the radial artery and jugular vein. MABP, subdural ICP and JBP were measured in the neutral position. These measurements were repeated after change in position to 5°, 10° and 15° rTp. The pressure measurements were performed about 1 min after change in position, imme-

diately after readjustment of the transducer position, the reference point being the horizontal level of dura perforation for subdural ICP measurement. CPP was calculated as MABP – subdural ICP. Measurements were performed in the neutral position and after change in position to 10° rTp. Changes in subdural ICP, MABP, CPP and JBP were calculated for each 5° step in position. Tension of dura was estimated at the neutral position and again at 10° rTp by the neurosurgeon. Dural tension was graded as: normal, increased tension and pronounced increased tension. The optimal position was defined as the position at which subdural ICP was as low as possible and CPP ≥ 60 mmHg. Tension of dura was estimated by the surgeon as slack, normal tension, increased tension, and pronounced increased tension (for details, see Chapter 3). The distribution of optimal positions was divided into three groups of patients at the neutral position. Group 1 consisted of 15 patients with subdural ICP < 5 mmHg, group 2 included 29 patients with subdural ICP ranging from 5 to 13 mmHg and group 3 contained 9 patients with subdural ICP > 13 mmHg.

Statistical analysis Mean±SD are presented. Comparisons of pressure within the group were performed using analysis of variance for repeated studies. Comparisons between groups were performed using an independent *t*-test. The chi-square test was used for comparisons of demographic data, the degree of dural tension and distributions of optimal positions. $P<0.05$ was considered significant.

Results Subdural ICP, MABP and JBP decreased significantly after each 5° change in position compared with the preceding position. In contrast CPP remained unchanged at 5° rTp, but decreased significantly at 10° and 15° rTp compared with the neutral position (Table 15.5). At the neutral position, 9 patients were at high risk of cerebral swelling, defined as subdural ICP > 13 mmHg, compared with only 1 patient at 15° rTp. The number of patients with low risk of cerebral swelling (subdural ICP < 5 mmHg) increased from 15 to 39 at 10° rTp, and from 39 to 42 when the position was changed from 10° to 15° rTp (Table 15.6).

The optimal position was the neutral position in 5 patients, 5° rTp in 5 patients, 10° rTp in 10 patients and 15° rTp in 33 patients (Table 15.7). No significant intergroup differences as regards the distribution of the optimal posi-

Table 15.5 Subdural ICP, MABP, CPP and JBP in the neutral position and after 5°, 10° and 15° rTp. Fifty-three supine-positioned patients with cerebral tumours were included

Variable	Neutral position	5° rTp	10° rTp	15° rTp
MABP (mmHg)	82.9±15.8	79.9±15.6*	76.9±15.2*	73.6±15.4*
ICP (mmHg)	7.6±5.1	5.1±5.3*	3.2±5.1*	1.8±5.0*
CPP (mmHg)	75.3±15.5	74.7±15.3	73.7±14.8*	71.8±15.2*
JBP (mmHg)	2.5±3.1	0.6±2.8*	−1.3±2.7*	−2.9±2.7*

*Significant change compared with the preceding position

Table 15.6 Distribution of number of patients in three risk groups related to the occurrence of brain swelling after opening of dura

ICP risk group	Neutral position	5° rTp	10° rTp	15° rTp
Group 1 (ICP < 5 mmHg)	15	26	39	42
Group 2 (ICP 5–13 mm Hg)	29	22	12	10
Group 3 (ICP > 13 mmHg)	9	5	2	1

Table 15.7 Number (%) of patients with optimal position related to risk groups for the occurrence of cerebral swelling after opening of the dura: group 1 (subdural ICP < 5 mmHg), group 2 (subdural ICP 5–13 mmHg) and group 3 (subdural ICP > 13 mmHg). The distributions of patients into the optimal position are independent of the level of ICP measured in the neutral position

Optimal position	All patients (n=53)	Group 1 (n=15)	Group 2 (n=29)	Group 3 (n=9)
Neutral position	5 (9.4%)	1 (6.7%)	3 (10.3%)	1 (11.1%)
5° rTp	5 (9.4%)	2 (13.3%)	2 (6.9%)	1 (11.1%)
10° rTp	10 (18.9%)	4 (26.7%)	5 (17.2%)	1 (11.1%)
15° rTp	33 (62.3%)	8 (53.3%)	19 (65.5%)	6 (66.7%)

tion were found. At the neutral position, 23 patients had increased tension of dura. The number of patients with increased tension of dura decreased to 17 at 5° rTp, to 10 at 10° rTp and to 9 patients at 15° rTp. Compared with the neutral position the degree of dural tension decreased significantly at 5° and 10° rTp, but the changes in tension from 10° to 15° rTp were not significant.

Conclusion Before opening the dura mater for craniotomy, repeated measurements of ICP and CPP in the neutral position and at 5°, 10° and 15° rTp provide valuable information regarding the optimal level of ICP and CPP.

Study 4: Effect of Reverse Trendelenburg Position on Intracranial Pressure and Cerebral Perfusion Pressure in Patients with Cerebral Tumours. A Comparative Study of Propofol-Fentanyl and Propofol-Remifentanil Anaesthesia

Aim To investigate whether the effect of 10° rTp on ICP, CPP and JBP differed in propofol-fentanyl- and propofol-remifentanil-anaesthetized patients.

Method Patients scheduled for elective craniotomy for supratentorial cerebral tumours were included. Fifty-eight patients were anaesthetized with propofol-fentanyl and 52 patients with propofol-remifentanil. As regards principles for monitoring and anaesthetic procedures, see Chapter 3. Subdural ICP, MABP and JBP were measured in the neutral position and thereafter during tilting of the table to 5°, 10° and 15° rTp. CPP was calculated as MABP – subdural ICP. Optimal position was defined as the position where

CPP was ≥ 60 mmHg, or as high as possible, and ICP was as low as possible. The level of ICP and CPP and the distributions of optimal positions were compared.

Statistical analysis With data from another study, including patients with cerebral tumours, and where SD of ICP was 5 mmHg (Petersen et al. 2003), the sample size was calculated to be 44 and it provided a minimum detectable difference of 3 mmHg, power 0.8 and a significance level of $P<0.05$. Data were tested with normality and equal variance tests. One-way analysis of variance was used when these tests were passed and the Tukey test was used for pair-wise multiple comparison. Otherwise the Kruskall-Wallis test of variance on ranks was used. The Bonferroni test was applied. The chi-square test was used for analysis of demographics. For correlation studies Pearson's product moment correlation was performed. Mean±SD are indicated for normal distributions and median (range) for non-normal distributions. $P<0.05$ was considered significant.

Results No significant difference was found in the neuroradiological data and histopathology. The ages of the patients were significantly higher in the propofol-fentanyl group. Likewise, the propofol maintenance doses were significantly higher in the propofol-fentanyl group (8.0±2.2 mg/kg/h) compared with the propofol-remifentanil group (5.6±1.4 mg/kg/h) (Table 15.8). In the neutral position ICP averaged 7.5±5.0 and 7.8±5.3 mmHg in the propofol-fentanyl- and propofol-remifentanil-anaesthetized patients, respectively. At each 5° step of rTp, subdural ICP decreased significantly in both groups. In the neutral position and at all steps of rTp, MABP and CPP were significantly lower in the propofol-remifentanil group. In both groups CPP was unchanged during 5° rTp, but a significant decrease was disclosed in each group when tilting of the table was forced to 10° and 15° rTp (Table 15.9). The medians of JBP decreased significantly during each step of rTp (Table 15.10). Although the median values were highest in the propofol-fentanyl group, the difference in JBP never reached significant levels. In all positions, the correlation coefficients r between JBP and subdural ICP were significant in the propofol-fentanyl group, but not in the propofol-remifentanil group (Table 15.11). No significant differences as regards the distribution of number of patients in positions at which ICP and CPP were optimal were found. In the majority of patients the optimal position was 15° rTp in both groups (Table 15.12). In this position, however, the operation could not proceed because the steepness of the table prevented surgical access.

Conclusion In this non-randomized study, rTp reduces subdural ICP to the same level whether propofol-fentanyl or propofol-remifentanil were used for anaesthesia. Although CPP is significantly lower during propofol-remifentanil compared with propofol-fentanyl anaesthesia, the distribution of optimal position as defined in this study was independent of choice of anaesthesia. A randomized study seems justified to verify these findings.

Table 15.8 Demographics, neuroradiological data, histopathology, maintenance dose of anaesthesia and data obtained immediately before subdural ICP measurements with the patients in the neutral position

	Propofol-fentanyl	Propofol-remifentanil
Preoperative values		
Number	58	52
Men/women	26/32	28/24
Age (years)	56.0±12.0	49.0±15.0*
Weight (kg)	76.0±17.0	74.0±17.0
Steriods (+/−)	31.0/27.0	29.0/23.0
Serum Na^+ (mmol/L)	137.0±5.0	138.0±4.0
MABP before anaesthesia (mmHg)	103.0±16.0	103.0±12.0
Tumour area (cm^2)	15.0±12.0	15.0±17.0
Midline shift	7.5±7.2	5.9±6.6
Localization of tumour		
Frontal	20	17
Parietal	15	6
Temporal	14	13
Occipital	2	7
Hemispheric	4	4
Basal	3	5
Histopathology		
Glioblastoma	15	12
Meningioma	14	14
Metastasis	12	5
Glioma	15	13
Other	2	8
Maintenance of anaesthesia		
Propofol (mg/kg/h)	8.0±2.2	5.6±1.4*
Fentanyl (μg/kg/h)	1.8±0.4	0
Remifentanil (μg/kg/h)	0	29.0±10.0
Data in neutral position		
Temperature (°C)	35.8±0.5	35.8±0.4
$PaCO_2$ (kPa)	4.6±0.5	4.6±0.5
PaO_2 (kPa)	27.0±9.6	24.0±7.9
SjO_2 (%)	53.0±9.3	51.0±9.6
$AVDO_2$ (mmol/L)	3.4±0.7	3.5±0.7

*$P<0.01$

Table 15.9 MABP, subdural ICP and CPP in propofol-fentanyl (P/F)- and propofol-remifentanil (P/R)-anaesthetized patients. Mean±SD is indicated in the neutral position and during 5°, 10° and 15° rTp position

	Neutral	5° rTp	10° rTp	15° rTp
MABP (P/F) (mmHg)	83.0±15.0	79.0±14.0*	77.0±15.0*	74.0±15.0*
MABP (P/R) (mmHg)	75.0±13.0**	71.0±13.0*,**	68.0±12.0*,**	66.0±12.0*,**
ICP (P/F) (mmHg)	7.5±5.0	5.0±5.2*	3.0±5.0*	1.6±5.0*
ICP (P/R) (mmHg)	7.8±5.3	5.4±5.2*	3.1±5.0*	1.3±5.4*
CPP (P/F) (mmHg)	75.0±14.0	75.0±14.0	74.0±14.0*	72.0±15.0*
CPP (P/R) (mmHg)	67.0±14.0**	66.0±13.0**	65.0±12.0*,**	64.0±12.0*,**

*P<0.05 intragroup difference
**P<0.05 intergroup difference

Table 15.10 Median and range of JBP in propofol-fentanyl (P/F)- and propofol-remifentanil (P/R)-anaesthetized patients. The measurements were performed in the neutral position and during 5°, 10° and 15° rTp

	Neutral	5° rTp	10° rTp	15° rTp
JBP (P/F) (mmHg)	3 (−4 to 13)	1 (−5 to 7)*	−1 (−7 to 4)*	−3 (−8 to 3)*
JBP (P/R) (mmHg)	2 (−2 to 13)	0 (−6 to 10)*	−2 (−8 to 8)*	−4 (−7 to 6)*

**P*<0.05 significant difference from the preceding value

Table 15.11 Correlation coefficient (*r*) for the relationship between JBP and subdural ICP in the neutral position and during 5°, 10° and 15° rTp. The patients were anaesthetized with propofol-fentanyl (P/F) or propofol-remifentanil (P/R)

	Neutral	5° rTp	10° rTp	15° rTp
Correlation coefficient(*r*) for JBP related to ICP (P/F)	0.2878	0.1304	0.1746	0.3176
Correlation coefficient(*r*) for JBP related to ICP (P/R)	0.4044*	0.4512*,#	0.4067*	0.3437*

**P*<0.05
#Power > 0.8

Table 15.12 Number of patients at which optimal position was found. Optimal position had the following criteria: CPP ≥ 60 mmHg, or as high as possible, and subdural ICP as low as possible. The patients were anaesthetized with propofol-fentanyl or propofol-remifentanil, and the measurement of subdural ICP and CPP was performed in the neutral position and during 5°, 10° and 15° rTp. The distribution did not differ significantly. Chi-square (*P*=0.526)

	Neutral	5° rTp	10° rTp	15° rTp
Propofol-fentanyl (*n*)	4	5	8	41
Propofol-remifentanil (*n*)	8	3	7	34

Discussion

Intracranial pressure is not the only important physiological factor during elevation of the head and trunk. A decrease in MABP and CPP can have important consequences, partly because of a decline in CBF, if cerebral autoregulation is impaired or CPP is below the lower point of autoregulation, and partly because a fall in CPP provokes an increase in ICP if cerebral autoregulation is intact (Rosner and Coley 1986). Therefore, either the neutral position (Rosner and Coley 1986; Schwarz et al. 2002) or 15–30° head-trunk elevation are recommended to optimize the therapy of increased ICP (Davenport et al. 1990; Feldman et al. 1992; Schneider et al. 1993; Meixensberger et al. 1997).

In patients with severe head injury, routine nursing at 30° semi-sitting position has been recommended. A decrease in ICP and unchanged CPP, SjO_2, and partial tissue oxygen tension ($PtiO_2$) were reported during 30° elevation (Ng et al. 2004). Moraine et al. recommended that, when the ICP is high and CBF is normal, the head-up position should not exceed 30° because greater head elevation increased ICP (Moraine et al. 2000). Meixensberger et al. (1997) reported a decrease in ICP and unchanged cerebral brain tissue-PaO_2 during 30° head-trunk elevation in patients with acute brain injury. In patients with fulminant hepatic-renal failure after acetaminophen self-poisoning, ICP decreased and CPP was unchanged during 20° semi-sitting position. Elevations to 40–60° increased ICP in some patients (Davenport et al. 1990). In awake patients with cerebral tumours, 20° head-trunk elevation reduced ICP (Hung et al. 2000). In summary, in the clinical setting it is possible to define an "optimal position" at which the ICP-reducing effect is pronounced or maximal (Kenning et al. 1981; Ropper et al. 1982) without compromising CPP and CBF (Yoshida et al. 1993; Schneider et al. 1993).

In one study, the effects of supine, prone and sitting positions on epidural ICP were investigated during posterior fossa procedures in patients anaesthetized with fentanyl, thiopental and nitrous oxide/oxygen. ICP, measured by means of an epidural sensor, was lowest at the lateral 45° sitting position, with only minimal change in CPP compared to the neutral position. Furthermore, MABP, mean pulmonary artery/wedge pressure, cardiac output, CVP and lung compliance did not change in this position (Calliauw et al. 1987).

In propofol-fentanyl-anaesthetized patients with intracranial tumours or cerebral aneurysms, a decrease in lumbar cerebrospinal pressure averaging 1.8 mmHg and unchanged MABP/CPP with 30° table head-up position has been demonstrated during craniotomy. A non-significant decrease in CVP averaging 1 mmHg was also apparent in this position. In contrast, during 30° head-down position, mean ICP increased significantly from 8.8±2.5 to 13.3±2.9 mmHg and mean CVP increased from 3.9±2.3 to 8.4±2.4 mmHg ($P<0.05$) (Mavrocordatos et al. 2000). In nitrous oxide/oxygen isoflurane-alfentanil-anaesthetized patients with cerebral tumours, a decrease in ICP (Camino fiberoptic monitor) averaging 5.0±5.9 mmHg was reported during 20° head-up position combined with flexion at the hips (Hung et al. 2000).

Rolighed Larsen et al. (2002) studied the effect of 10° rTp on ICP and CPP in 40 supine-positioned patients with space-occupying lesions. The subdural ICP decreased significantly from 9.5 to 6.0 mmHg within 1 min after change in position, and CPP was unchanged. The number of patients with increased tension of the dura, as estimated by the neurosurgeon, decreased from 24 to 8 at 10° rTp. The correlation between the ICP at the neutral position and the decrease in ICP (ΔICP) at 10° rTp was positive and significant. In another study including supine-positioned patients with cerebral tumours, the effect of 10° rTp were analysed during a 10-min period. One minute after change in position subdural ICP, JBP and MABP decreased but remained stable during the subsequent 9 min. The subdural ICP was 10.9±5.7 mmHg at the neutral position and decreased to 7.3±5.2 mm Hg at 10° rTp (Fig 15.1). During the 10-min study period, CPP, heart rate, $AVDO_2$ and arterial and venous oxygen saturation did not change. The degree of dural tension as estimated by the neurosurgeon also decreased within 1 min after assumption of the rTp position (Haure et al. 2003).

In a recent study ICP was the strongest predicting factor of cerebral swelling after opening of dura during craniotomy (Rasmussen et al. 2004). However, maintenance of CPP is essential during intracranial surgery because falling CPP may decrease CBF below the ischaemic threshold. Furthermore, in patients with intact cerebral autoregulation, a fall in CPP may precipitate an increase in ICP (Rosner and Coley 1986). Consequently, measurements of both ICP and MABP (CPP) have been performed at the neutral position and again at 5°, 10° and 15° rTp in a series of 53 supine-positioned patients anaesthetized with propofol-fentanyl-air during operation for cerebral tumours. The optimal position was defined as the position at which subdural ICP was as low as possible, with CPP remaining greater than 60 mmHg, or as high as possible. There was considerable individual variation in the optimal position, which was the neutral position in 5 patients (9.4%), 5° rTp in 5 patients (9.4%), 10° rTp in 10 patients (18.9%) and 15° rTp in 33 patients (62.3%). The lowest ICP was disclosed in 1 patient (2%) in the neutral position, 2 patients (4%) in 5° rTp, 10 patients (19%) in 10° rTp and 40 patients (75%) in 15° rTp. The number of the patients with increased dural tension decreased from 23 to 10 during 10° rTp and 9 during 15° rTp. During 5° and 10° rTp, the tension of dura decreased significantly compared to the neutral position. There was no significant change in the tension of dura when the position was changed from 10° to 15° rTp (Tankisi and Cold 2007).

Anaesthetic agents have different effects on cardiovascular and cerebrovascular physiology. In study 4, the effect of rTp on subdural ICP, CPP and JBP were analysed in supine-positioned patients with supratentorial cerebral tumours. The patients were anaesthetized with either propofol-fentanyl (n=58) or propofol-remifentanil-air (n=52). The distribution of optimal positions was analysed in positions extending from neutral up to 15° rTp. In patients scheduled for propofol-fentanyl anaesthesia, a significantly higher maintenance dose of propofol was disclosed. A significant fall in ICP and JBP during

increasing rTp was observed in both groups without significant intergroup ICP differences. At each 5° step of increasing rTp subdural ICP decreased significantly in each group, averaging 1.6 and 1.3 mmHg at 15° rTp in the propofol-fentanyl and propofol-remifentanil groups, respectively. Thus, rTp reduced subdural ICP to the same level, whether anaesthesia was maintained with propofol-fentanyl or propofol-remifentanil. The levels of CPP and MABP, however, were significantly lower during propofol-remifentanil anaesthesia. In both groups, CPP was unchanged during 5° rTp, but there was a significant decrease in CPP when tilting was forced to 10° and 15° rTp. JBP decreased significantly during each successive step of rTp. In the majority of patients, the optimal position was 15° rTp for both types of anaesthesia. No significant intergroup difference in the distribution of optimal position was found. In supine-positioned patients with cerebral aneurysm, 10° rTp reduces the ICP and dural tension significantly compared to the neutral position ($P<0.05$) (for details see Chapter 19 or Tankisi et al. (2006)). In prone-positioned patients, ICP decreased significantly from 21.0±4.6 to 15.6±5.6 mmHg in patients with occipital tumours and from 18.3±6.1 to 14.2±5.9 mmHg in patients with cerebellar tumours ($P<0.05$). CPP remained unchanged during 10° rTp compared to the neutral position. In the neutral position JBP was 14.3±5.5 and 12.1±6.3 mmHg in patients with occipital and cerebellar tumours, respectively (Tankisi et al. 2002).

According to the Monro-Kellie doctrine, the intracranial volume consist of a sphere of bone (rigid cranium) that is exactly filled by its contents (Lundberg 1983):

$$\begin{aligned} &\text{ICP}_{\text{Monro-Kellie Doct}} \\ &V_{\text{Cerebrum}}\ (80\text{–}85\%) + V_{\text{Blood}}\ (5\text{–}8\%) + V_{\text{CSF}}\ (7\text{–}10\%) + V_{\text{Pathology}}\ (?\%) \\ &= \text{Constant}\ (100\%) \end{aligned}$$

According to the doctrine, a decrease in the volume of one of the intracranial contents decreases ICP. As 70–80% of the CBV is located in cerebral veins, this compartment, together with the CSF volume are the most important volumes, as regards the possibilities for changing the total volume of the intracranial content. This model therefore predicts that, during head elevation, a decrease in CBV and/or CSF displacement from the intracranial compartment to the spinal compartment may decrease ICP. A decrease in CBV during elevation of the head has been reported (Lovell et al. 2000; Pichler et al. 2004). In anaesthetized subjects, the reduction of CBV was less compared to the change found in awake patients, probably because the CBV was already reduced by propofol anaesthesia (Lovell et al. 2000).

In neutral positioned, propofol-anaesthetized patients with unruptured aneurysm, the ICP was 2.9±2.6 mmHg (Tankisi et al. 2006). In contrast, the ICP in supine-positioned, propofol-anaesthetized patients with cerebral tu-

mours averaged between 7.5±5.0 and 7.8±5.3 mmHg. The ICP in awake patients without space-occupying lesions was between 7 and 11 mmHg (Albeck et al. 1991). The difference in ICP is supposed to be caused by propofol, which decreases CBF, CBV and ICP (Lagerkranser et al. 1997; Kaisti et al. 2002; Petersen et al. 2003).

In several studies, a decrease in JBP is accompanied by a decrease in ICP during rTp (Rolighed Larsen et al. 2002; Tankisi et al. 2002, 2006; Haure et al. 2003; Tankisi and Cold 2007), presumably because an increase in cerebral venous outflow reduces ICP (Toole 1968; Marmarou et al. 1975; Magnaes 1976a, b; Davenport et al. 1990; Yoshida et al. 1993). Rotating the head to the right/left and neck flexion increases ICP compared to baseline neutral neck position (Hulme and Cooper 1976; Williams and Coyne 1993; Hung et al. 2000; Mavrocordatos et al. 2000). Furthermore, application of a rigid cervical collar has been associated with elevated ICP due to impaired venous drainage (Craig and Nielsen 1991; Davies et al. 1996; Kolb et al. 1999; Hunt et al. 2001; Ho et al. 2002; Mobbs et al. 2002). In contrast, the elevation of the head above the heart level decreases the increased ICP associated with head position (Hung et al. 2000; Mavrocordatos et al. 2000). A significant correlation between the decrease in JBP (ΔJBP) and the decrease in ICP (ΔICP) was expected in those studies during rTp, but could not be detected.

A Starling resistor is defined as any collapsible vein/vessel surrounded in its middle section by an external pressure that is higher than the outlet pressure (Holt 1941). The cerebral bridging veins, which drain blood from the cerebral cortex into the superior sagittal sinus, may collapse and act as a Starling resistor (Huseby et al. 1981). During intracranial hypertension, for example, the veins connecting cortical veins and the superior sagittal sinus collapse and prevent the superior sagittal sinus pressure from affecting the pressure and volume in cortical veins (Huseby et al. 1981; Luce et al. 1982a, b). In dogs, the decrease in dorsal sagittal sinus pressure is small when the superior vena cava pressure decreases during adoption of the upright position, and maintenance of CBV caused by a decrease in venous outflow (or increased arterial flow) is the "key factor" in increasing ICP in this model (Luce et al. 1982a, b). Thus, studies in experimental animals may explain the observation that JBP decreases but ICP is unaffected in some patients during rTp (Tankisi et al. 2002, 2006; Tankisi and Cold 2007). Furthermore, during rTp the collapse of cerebral bridging veins may explain the insignificant correlation between ΔJBP and ΔICP.

Another potential resistor for cerebral venous outflow is the jugular veins. Postural changes lead to a gradual collapse of the internal jugular veins, caused mainly by the external pressure. Postural dependency of the cerebral venous outflow was evaluated in 23 young healthy adults by colour-coded duplex sonography. The measurements were performed with the body at 0°, 15°, 30°, 45° and 90° elevation. During body elevation internal jugular vein flow decreased from 700±270 ml/min at the neutral position to 70 ml/min at 90° body elevation, whereas the vertebral venous blood flow increased from

40±20 ml/min at the neutral position to 210±120 ml/min. The largest decrease in internal jugular venous flow, from 700±270 to 150±130 ml/min, was observed between 0° and 15° elevation of the body. Results of this study indicate that an increase in vertebral venous blood flow was not sufficient to compensate for the drop in jugular flow. The spinal epidural veins are the most probable additional drainage pathway in the upright position (Valdueza et al. 2000). The above findings from colour-coded duplex sonography studies are supported by studies of cerebral venous blood flow measurements using MR technology (Alperin 2004). In healthy upright-positioned volunteers venous drainage shifted from the jugular vein to the epidural and the deep neck veins. An increase in intracranial compliance and a decrease in ICP were also documented (Alperin 2004).

In another study cerebral venous drainage patterns were studied in healthy adult volunteers. Three types of venous drainage patterns were defined as follows: A total jugular flow of more than 2/3, between 1/3 and 2/3 and less than 1/3 of the global arterial blood flow. In 72% of the individuals jugular venous drainage was predominant in the supine position, whereas the jugular drainage was equal to extrajugular drainage in 22% (Doepp et al. 2004). Extrajugular pathways of cerebral venous blood drainage were also investigated. Total venous blood flow at rest was 766±226 ml/min (internal jugular vein 720±232 ml/min; vertebral vein 47±33 ml/min) in supine-positioned volunteers. During circular neck compression, vertebral vein flow increased to 186±70 ml/min. However, this flow increase did not compensate for the fall in internal jugular vein flow, and the authors concluded the existence of additional alternative drainage pathways, including the intraspinal epidural veins and the deep cervical veins (Schreiber et al. 2003).

The existence of a Starling resistor-type mechanism in the jugular veins has also been investigated during positive end-expiratory pressure (PEEP) application in human. An increase in PEEP did not increase cerebral venous pressure when the head was elevated in dogs (Toung et al. 2000). In sitting and standing humans, the veins above the heart level collapse. However, this collapse can be prevented with sufficiently high positive pressure breathing (Cirovic et al. 2003), and a marked increase in CVP in the standing position completely re-opens the jugular vein (Gisolf et al. 2004). Moreover, venous collapse prevents venous pressure variations inside the cranium during head elevation (Asgeirsson and Grände 1996; Kongstad and Grände 1999). Our results are in agreement with the existence of venous outflow Starling resistors. During rTp the jugular veins collapse due to a decrease in JBP, and the collapse of the jugular veins prevents a large decreases in ICP. As a consequence the correlation between ΔICP and ΔJBP is insignificant (Tankisi et al. 2002, 2006; Tankisi and Cold 2007). Thus, extra jugular pathways influence changes in JBP during rTp (Doepp et al. 2004).

According to Moraine et al. (2000) the difference between arterial blood pressure at the level of the foramen of Monro and JBP is the major determinant of CBF during head elevation. In a recent study it was documented that

a siphon mechanism in human does not support CBF in the standing position (Dawson et al. 2004). During 10° rTp the decrease in MABP in counteracted by the decrease in jugular venous pressure, leaving CPP unchanged in the majority of patients (Tankisi et al. 2002, 2006; Tankisi and Cold 2007) and CBF is therefore unchanged.

In experimental (Halverson et al. 1998; Rosenthal et al. 1998a, b) and human studies (Hering et al. 2001), the prone position increases intraabdominal pressure, and ICP is higher in prone-positioned patients (Calliauw et al. 1987; Lee 1989; Tankisi et al. 2002). An increase in intraabdominal pressure causes a significant rise in ICP in head trauma patients with ICP less than 20 mmHg. Any rise in intraabdominal pressure causes a concomitant and rapid significant increase in CVP from 6.2±2.4 to 10.4±2.9 mmHg, while internal jugular pressure increases from 11.9±3.2 to 14.3±2.4 mmHg, and ICP increases from 12.0±4.2 to 15.5±4.4 mmHg (Citerio et al. 2001). In prone-positioned patients undergoing to craniotomy (Tankisi et al. 2002) the ICP at the neutral position averaged 21.0 mmHg in occipital tumours and 18.3 mmHg in cerebellar tumours, while the JBP averaged 14.3 mmHg in occipital tumours and 12.1 mmHg in cerebellar tumours. These values were significantly higher than those reported in supine-positioned patients (Rolighed Larsen 2002; Haure et al. 2003; Tankisi and Cold 2007), where mean ICP and JBP levels below 10 mmHg were recorded. Thus, an elevated ICP is more likely to occur in prone-positioned patients, due in part to the occurrence of increased jugular venous pressure. The Monro-Kellie doctrine predicts that any reduction in volume of the intracranial compartment should decrease ICP. Hydrodynamic forces in CSF pressure may decrease ICP during elevation of the head by displacement of CSF into the spinal segment. Displacement of relatively small volumes of intracranial CSF produces a prompt decrease in ICP, provided that the volumetric limit of the spinal sac capacity is not exceeded (Kenning et al. 1981). Studies of CSF volume and dislocation of CSF to the spinal compartment during rTp are not available and so the part they play in reducing ICP during head elevation or rTp is unanswered.

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Chapter 16
Effect of Evacuation of Cerebral Cysts on Subdural Intracranial Pressure and Cerebral Perfusion Pressure

Niels Juul and Georg Emil Cold

Abstract
Patients with intracerebral cysts are frequently presented to the neurosurgical team. Cerebral cysts can either be part of a tumour process or a parasitic disease, such as neurocysticercosis, or present as an arachnoid cyst. The presence of a cerebral cyst can give rise to classic symptoms of increased ICP, and during intracranial surgery a cyst can jeopardize surgical access to deep brain structures and increase the risk of cerebral ischaemia with possible worsening of the outcome. When fluid is removed from a cystic process in the cranial vault the pressure in the cyst will decrease. We have not found any literature addressing this subject. In this chapter unpublished data concerning subdural ICP monitoring in patients with intercerebral cysts and the pressure/volume relationship during emptying are discussed.

Patients with intracerebral cysts are frequently presented to the neurosurgical team. Cerebral cysts can either be part of a tumour process or a parasitic disease, such as neurocysticercosis, or present itself as an arachnoid cyst. Arachnoid cysts are CSF-filled sacs localized either in the brain or the spinal cord. They are divided into primary cysts, present at birth and the result of development abnormalities that arise in the early weeks of gestation, and secondary cysts, which are not as common as primary cysts and developed as a result of head injury, meningitis or as a complication to previous brain surgery. The presence of a cerebral cyst can give rise to classic symptoms of increased ICP, and during intracranial surgery a cyst can jeopardize surgical access to deep brain structures and increase the risk of cerebral ischaemia with possible worsening of the outcome.

When fluid is removed from a cystic process in the cranial vault the pressure in the cyst will decrease. We have not found any literature addressing this subject. In this chapter unpublished data concerning subdural ICP monitoring in patients with intercerebral cysts and the pressure/volume relationship during emptying are discussed.

Study Outline

Aim To study the changes in subdural pressure and CPP after evacuation of cerebral cysts.

Method Data from the perioperative ICP database were used (Chapter 2). Thirty-eight patients, 26 with supratentorial and 12 with infratentorial cysts, were included. Subdural ICP and CPP were measured before opening of dura and immediately after evacuation of the cystic process. In 4 patients with supratentorial cysts and 5 patients with infratentorial cysts the volume of drainage from the cysts was correlated to changes in subdural ICP. The degree of dural tension and degree of cerebral swelling after opening of dura was evaluated by the surgeon.

Statistical analysis Mann-Whitney's test and Wilcoxon's test were used to compare data within and between groups. Median and range are indicated. $P<0.05$ was considered significant.

Results In patients with supratentorial cerebral cysts subdural ICP decreased from 14 to 0 mmHg ($P<0.05$). MABP was unchanged, while CPP increased from 61 to 75 mmHg ($P<0.05$). In patients with infratentorial cysts the subdural ICP decreased from 20 to 1 mmHg ($P<0.05$). MABP was unchanged, while CPP increased from 67 to 86 mmHg (Tables 16.1 and 16.2). The amounts of removed fluid were registered in 13 patients. This volume was plotted against the reduction in ICP (Fig. 16.1). With a Z of −1.266 (Wilcoxon's signed ranks test) we did not find any correlation between volume of fluid removed and reduction in ICP. The relationship between volume of drained fluid and decrease in subdural ICP are indicated for supra- and infratentorial cysts in Figs. 16.2 and 16.3. The slope of the individual curves differed considerably in both groups without any significant differences between the two groups. In both groups the decrease in subdural ICP was accompanied by a significant decrease in dural tension. Cerebral swelling after opening of dura was not registered in any of the patients (Table 16.2).

Conclusion Perioperative evacuation of cerebral cystic processes before opening of dura reduces subdural ICP substantially, and reduces the tactile estimation of dural tension considerably.

Table 16.1 Demographic data, level of $PaCO_2$ and drainage volume. Median and range are indicated

	Localization of cysts	
	Supratentorial	Infratentorial
Age (years)	45 (9–71)	52 (3–68)
Men/women	14/12	5/7
$PaCO_2$ (kPa)	4.2 (3–6)	4.3 (3.7–5.4)
Drainage volume (ml)	20 (9–30)	11 (5–27)

Table 16.2 Values of MABP, subdural ICP and CPP before and immediately after evacuation of cystic processes in patients with supratentorial and infratentorial tumours. Median and range are indicated

Localization of cysts	Supratentorial		Infratentorial	
	Before evacuation	After evacuation	Before evacuation	After evacuation
MABP (mmHg)	79 (60–122)	77 (52–122)	90 (65–123)	91 (65–120)
ICP (mmHg)	14 (4–32)	0 (−2 to 5)*	20 (13–33)	1 (0–11)*
CPP (mmHg)	61 (38–112)	75 (52–122)*	67 (46–108)	86 (65–118)*

*$P<0.05$ significant intragroup difference

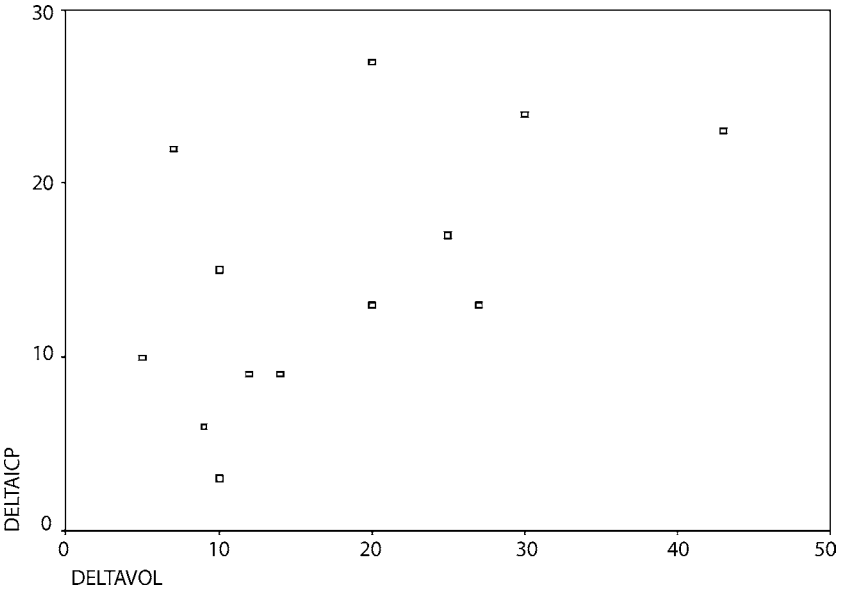

Fig. 16.1 Relationship between reduction in volume and reduction in ICP in 13 patients (deltavol in ml, deltaICP in mmHg)

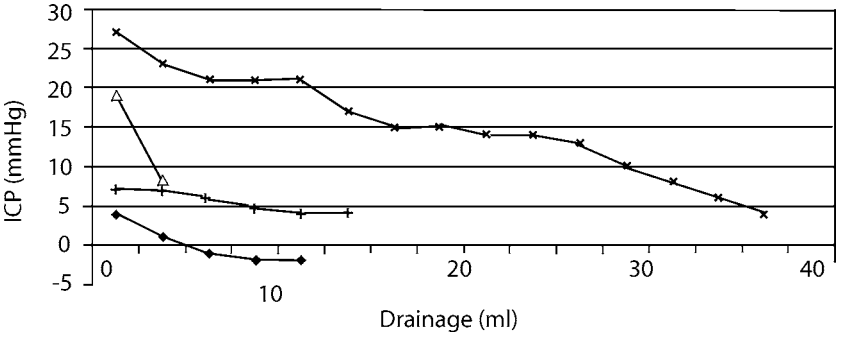

Fig. 16.2 Relationship between drainage volume and subdural ICP before and during gradual evacuation of cystic supratentorial processes in four patients

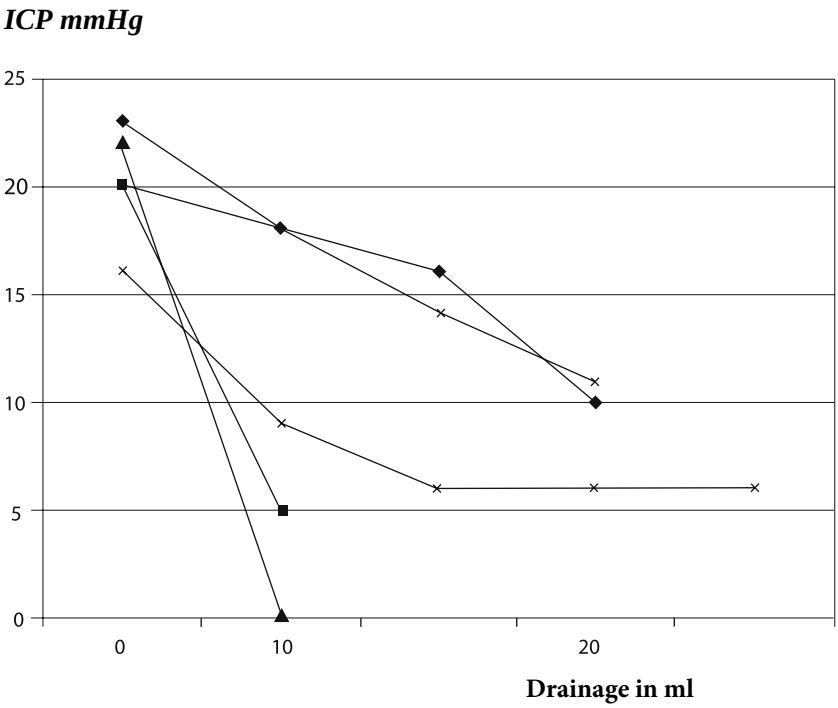

Fig. 16.3 Relationship between drainage volume and subdural ICP before and during gradual evacuation of cystic infratentorial processes in five patients

Discussion

Cystic processes in the cranial vault result in either direct pressure on adjacent structures or universally increased ICP. The net result will eventually be pressure on brain structures, where the clinical impact depends on the speed of growth of the process and its anatomical localization. One must assume that when you subtract fluid from a cystic process in a vault with limited volume, the pressure will decrease, but we were not able to find any correlation between the amount of fluid removed and the reduction in subdural pressure recorded.

Intercerebral cysts can be treated in different ways depending on the anatomical localization, size of the cyst, rate of growth, age of the patient and last but not least the patients symptoms. Treatment can be craniotomy (Yan and Yu 2004), ventriculoperitoneal shunting (Boltshauser et al. 2002) or endoscopic opening of the process to the normal CSF-containing system (Tirakotai et al. 2004). Outcome after treatment varies depending on age of the patient, anatomical localization of the process and chosen treatment (Colli et al. 1994).

We have not been able to identify any studies in the literature which have addressed the issue of volume reduction of cerebral cysts during continuous

ICP monitoring. In a study of prolonged ICP monitoring of Sylvian arachnoid cysts, Di Rocco et al. (2003) found patients with increased ICP but without any clinical symptoms. In contrast, normal ICP recordings were found in three children, despite the fact that two of them were apparently symptomatic; one complained of recurrent headaches and one had epileptic seizures. It was not possible in this study to elucidate any correlation between cystic volume, anatomical localization and ICP.

A graphic evaluation of cyst reduction in millilitres of fluid removed and reduction in ICP is presented in Fig. 16.1. It was not possible to define a significant correlation between the ICP reduction and volume reduction, in the group. When you consider each patient the ICP reduction concurrently with the volume reduction is evident, but we only had data on volume reduction in 13 patients, and that could explain the lack of statistical significance. In 4 patients with supratentorial (Fig. 16.2) and 5 patients with infratentorial cysts (Fig. 16.3) we measured the gradual pressure reduction when fluid was removed from the intracranial cysts. As with the overall fluid removal, it was impossible to find a regression line that in any way connected the amount of removed fluid with the reduction in pressure measured. The missing statistical significance in our material may have several reasons. One reason may be a small sample size; 38 patients might seem sufficient, but the ages of the patients spanned over 68 years, from 3 to 71 years. It is reasonable to assume that the pressure/volume relationship is dependent on the size of the cranial vault. Different anatomical localizations of cysts may also influence the pressure/volume relationship. A small cystic process in the posterior fossa might exert more pressure on adjacent structures and cause hydrocephalus and an increase in ICP. In comparison, a similar-sized cystic process in the supratentorial compartment might be asymptomatic or show symptoms not directly related to high ICP.

In recent studies of patients subjected to craniotomy in the prone position ICP averaged 18.3 mmHg for patients with occipital tumours and 21.0 mmHg for infratentorial tumours (Tankisi et al. 2002). These levels of ICP were identical with the ICP levels observed in another study of infratentorial tumours (Jørgensen et al. 1999). Concerning the difference in pressure in the different cranial compartments, a previous study (Chapter 5) indicates that between compartments of the neuroaxis differences in pressure exist, with the smallest differences within the supratentorial compartment and higher differences between the supra- and infratentorial compartments. In addition, there might be a difference in the pressure/volume relationship when a cystic process with a thin wall is evacuated compared to a process with a thicker wall, since the thin-walled structure will be more collapsible and hence the pressure/volume curve will be much steeper. Moreover, will there be differences in the pressure/volume relationship between patients with slowly growing processes with a thick wall and faster-growing cystic processes with a thin wall. The pathology of the cyst may play an important role since different pathologies will give rise to different macroscopic structures of the cyst and thus a variation in the pressure/volume relationship.

Volume changes in the cranial vault are being used as a novel way to describe the pressure/volume relationship. Intracranial compliance is defined as the pressure reaction to a change in intracranial volume ($\Delta V/\Delta P$). The exponential nature of the pressure/volume curve indicates that a similar volume increment at different points of the curve results in different pressure responses. The pressure/volume index is defined as the volume necessary to raise the ICP by a factor of 10. The pressure/volume relationship in the cranial vault has been investigated in recent years by use of the Spiegelberg intracranial compliance monitor which calculates intracranial compliance ($C = \Delta V/\Delta P$) from a moving average of small ICP perturbations (ΔP) resulting from a sequence of up to 200 pulses of added volume ($\Delta V = 0.1$ ml, total $V = 0.2$ ml) made into a double lumen intraventricular balloon catheter (Abdullah et al. 2005). This method has been used to monitor intracranial compliance in different patient categories. In a study of patients with severe head injury it was found that at ICP > 20 mmHg compliance was linearly correlated to CPP suggesting failure of autoregulatory mechanisms (Portella et al. 2000). In another study of patients with closed head injury it was found that at similar values of ICP, intracranial compliance depends on the age of the patient (Kiening et al. 2000).

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Chapter 17
Comparative Studies of Therapeutic Measures to Reduce Subdural Intracranial Pressure During Craniotomy

Mads Rasmussen and Georg Emil Cold

Abstract

The level of ICP is of importance in the surgical management of space-occupying cerebral lesions. For many years hyperventilation-induced reduction of cerebral blood volume and mannitol treatment based on osmotic withdrawal of brain tissue water have been used to reduce dural tension before opening of dura mater. Other therapeutic measures to reduce ICP during craniotomy include intravenous administration of indomethacin, placing the patient in the reverse Trendelenburg position and decompression by puncture of cystic tumours.

In this chapter three studies are presented. The ICP-reducing effects of hyperventilation, 10 degrees reverse Trendelenburg position, mannitol treatment, indomethacin or surgical decompression in patients subjected to craniotomy in the supine and prone positions in either propofol-fentanyl or propofol-remifentanil anaesthesia are discussed.

The level of ICP is of importance in the surgical management of space-occupying cerebral lesions. At high ICP surgical access to deep cerebral structures is impeded, and pressure by self-retaining specula may decrease cerebral perfusion regionally (Hongo et al. 1987; Rosenørn 1987). Likewise, swelling/herniation of cerebral tissue through the opening of dura mater may be deleterious by preventing venous outflow from the affected brain tissue. A vicious circle may develop with increasing cerebral oedema and ischaemia. Surgical decompression by ventricular drainage reduces ICP effectively, but insertion of a ventricular catheter can be difficult during surgery, either because of the position of the patient or because the ventricular system is compressed. For decades, hyperventilation-induced reduction of CBV and mannitol treatment based on osmotic withdrawal of brain tissue water have been used to reduce dural tension before opening of dura mater. Other therapeutic measures to reduce ICP during craniotomy include intravenous administration of indomethacin

(Bundgaard et al. 1996), placing the patient in rTp (Rolighed Larsen et al. 2002; Tankisi et al. 2002, 2006; Haure et al. 2003; Tankisi and Cold 2007) and decompression by puncture of cystic tumours. Comparable clinical studies of ICP-reducing management are not available in patients subjected to craniotomy for supratentorial cerebral tumours. Both hyperventilation (Petersen et al. 2003) and rTp (Rolighed Larsen 2002; Tankisi et al. 2002; Haure et al. 2003) reduce ICP during craniotomy. To our knowledge studies comparing the effects on ICP and CPP of hyperventilation or rTp are not available.

In this chapter three studies are presented which compare the various treatments for ICP reduction under various conditions.

Study 1: A Comparative Study of the Intracranial Pressure-Reducing Effect of Hyperventilation, 10 Degrees Reverse Trendelenburg Position, Mannitol Treatment, Indomethacin or Surgical Decompression in Patients with Intracranial Hypertension Subjected to Craniotomy for Supratentorial Cerebral Tumours in Propofol-Fentanyl Anaesthesia

Aim To compare the ICP-reducing effect of hyperventilation, 10° rTp, mannitol treatment, indomethacin or surgical decompression in patients with intracranial hypertension undergoing craniotomy for supratentorial cerebral tumours in propofol-fentanyl anaesthesia.

Method We included 93 patients undergoing craniotomy for supratentorial tumours in propofol-fentanyl anaesthesia. All patients had a subdural ICP ≥ 10 mmHg. Data were consecutively collected between 1997 and 2005 and subjected to a retrospective analysis. The following ICP-reducing managements were analysed: 5 min of hyperventilation (n=30), 10° rTp (n=16), mannitol treatment 0.5–1.0 g/kg (n=19), surgical decompression 17±9 ml (n=13) and indomethacin 0.5 mg/kg (n=15). Subdural ICP was measured before opening of dura. The changes in ICP, MABP and CPP were calculated. The effect of mannitol on ICP was measured 5 min after termination of the infusion. The effects on ICP of rTp, drainage and indomethacin were recorded after 1 min. Concerning methodological data, maintenance doses of anaesthesia and neuroradiological data, see Chapter 3.

Statistical analysis Data within groups were tested for normal distribution. The normality test and equal variance test were applied. One-way ANOVA was used for analysis if these tests were passed and the Tukey test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis one-way analysis of variance on ranks and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. The chi-square test was used for statistical analysis of demographic data, localization, size and histopathological diagnosis

of the tumours, preoperative steroid administration and position of the head between the groups. The difference in tension of dura and the degree of cerebral swelling were tested by the chi-square test in 2×4 or 2×3 tables. Mean±SD were calculated. $P<0.05$ was considered statistically significant.

Results No significant differences were disclosed as regards demographic data or data obtained before the ICP-reducing management, including PaO_2, rectal temperature, ICP, MABP or CPP (Table 17.1). The level of $PaCO_2$ was significantly lower in patients treated with mannitol compared with other groups, except drainage (Table 17.1). The maintenance dosages of propofol and fentanyl did not show any significant intergroup difference (Table 17.2). Neither did the neuroradiological findings, including the distribution of localization of tumour, maximal area of the tumours or midline shift differ significantly between the groups (Table 17.1 and 17.2). The average dose of mannitol and indomethacin are indicated in Table 17.2. Indomethacin induced an increase in MABP averaging 9.1 mmHg. This increase was significantly greater that that obtained by hyperventilation (0.3 mmHg), surgical decompression (−0.6 mmHg), 10° rTp (−6.4 mmHg), but not significantly different from mannitol treatment (2.4 mmHg). A significant difference was also found between mannitol treatment and rTp, and between rTp and hyperventilation (Table 17.3). The ICP-reducing effect of surgical decompression averaged 16.2 mmHg. This value was significantly higher than the values obtained by hyperventilation (3.2 mmHg), 10° rTp (5.0 mmHg), mannitol treatment (6.0 mmHg) and indomethacin treatment (6.9 mmHg). Moreover, the ICP-reducing effect of indomethacin treatment was significantly greater than that

Table 17.1 Demographic data, gas analyses, temperature, ICP, MABP, CPP and neuroradiological data in patients subjected to ICP-reducing therapy including hyperventilation, 10° rTp, mannitol treatment, drainage of cystic tumours or indomethacin treatment. Mean±SD are indicated. Data were obtained before the ICP-reducing therapy

	Hyperventilation	Reverse Trendelenburg position	Mannitol	Drainage	Indomethacin
Number	30	16	19	13	15
Men/women	16/14	5/11	11/8	7/6	7/8
Age (years)	52.0±14.0	53.0±10.0	54.0±14.0	50.0±15.0	59.0±14.0
Weight (kg)	77.0±13.0	78.0±20.	76.0±14.0	80.0±19.0	79.0±17.0
$PaCO_2$ (kPa)	4.7±0.5#	4.7±0.6#	4.1±0.4	4.4±0.5	4.6±0.4#
PaO_2 (kPa)	25.0±8.0	27.0±11.0	29.0±10.0	27.0±9.0	21.0±6.0
Temperature (°C)	35.9±0.5	35.9±0.6	36.2±0.4	35.9±0.4	35.9±0.4
Tumour area (cm^2)	16.0±8.0	18.0±9.0	17.0±10.0	23.0±11.0	22.0±13.0
Midline shift (mm)	6.5±7.0	9.3±8.0	9.5±7.8	9.5±6.7	8.5±6.2
ICP (mmHg)	15.1±4.2	14.0±3.8	15.8±4.6	17.5±5.7	16.9±7.2
MABP (mmHg)	85.0±18.0	91.0±15.0	88.0±16.0	79.0±12.0	82.0±13.0
CPP (mmHg)	70.0±17.0	77.0±15.0	72.0±15.0	61.0±14.0	65.0±16.0

#Significantly different from mannitol

Table 17.2 Localization of tumour, histopathology and maintenance doses of propofol and fentanyl in patients with supratentorial tumours undergoing ICP-reducing therapy, including hyperventilation, 10° rTp, mannitol treatment, drainage of cystic tumours or indomethacin treatment. Number±SD are indicated

	Hyperventilation	Reverse Trendelenburg position	Mannitol	Drainage	Indomethacin
Localization					
Frontal	14	5	8	7	4
Parietal	4	2	3	1	5
Temporal	6	5	3	3	2
Occipital	5	1	4	1	2
Hemispheric	1	2	1	0	0
Basal	0	1	0	1	1
Histopathology					
Glioblastoma	16	5	11	5	7
Meningioma	2	4	0	0	4
Metastasis	6	4	5	3	3
Glioma	5	1	5	4	1
Other	1	2	0	1	0
Anaesthesia					
Propofol (mg/h)	707.0±150.0	706.0±217.0	816.0±212.0	642.0±215.0	700.0±180.0
Fentanyl (μg/h)	166.0±49.0	142.0±270.0	148.0±32.0	138.0±38.0	133.0±26.0
Mannitol (g/kg)			0.8±0.2		
Indomethacin (mg/kg)					0.5±0.0
Drainage (ml)				20.0±8.0	

obtained by hyperventilation (Table 17.3). The increase in CPP during surgical drainage (16.0 mmHg) and indomethacin treatment (16.7 mmHg) was not significantly different, but was significantly greater than that found with hyperventilation (3.4 mmHg), rTp (−1.7 mmHg) or mannitol treatment (8.0 mmHg). Moreover the increase in CPP during mannitol treatment was significantly greater than that obtained by rTp (Table 17.3). In Table 17.4, the changes in $AVDO_2$ and SjO_2 are shown. Hyperventilation, as well as indomethacin, was followed by a significant fall in SjO_2 and an increase in $AVDO_2$. During mannitol treatment no significant changes were observed.

In Table 17.5 the degree of dural tension as estimated by the neurosurgeon is registered. During treatment of intracranial hypertension, the percentage number of patients with increased dural tension decreased in all groups, most pronounced, however, in patients subjected to surgical decompression. In the group of surgical decompression no swelling/herniation of the cerebral tissue was observed after opening of dura. In contrast some degree of cerebral swelling was observed in all other groups. The swelling was most pronounced in

Table 17.3 Differences in $PaCO_2$, ICP, MABP and CPP measured before and after ICP-reducing therapy including hyperventilation, 10° rTp, mannitol treatment, drainage of cystic tumours or indomethacin treatment. Number±SD are indicated

	Hyper-ventilation	Reverse Trendelenburg position	Mannitol	Drainage	Indomethacin
Decrease in $PaCO_2$ (kPa)	0.8±0.2	0.0±0.0*	0.1±0.1*	0.0±0.0*	0.1±0.1*
Decrease in ICP (mmHg)	3.2±2.2#	5.0±2.2#	6.0±3.9#	16.2±6.1	6.9±3.7*#
Increase in MABP (mmHg)	0.3±3.8	−6.4±4.0*#	2.4±6.3°	−0.6±1.5	9.1±9.4*#°
Increase in CPP (mmHg)	3.4±3.8#	−1.7±3.6#	8.0±7.2°	16.0±6.7	16.7±8.8*°

*Significant difference from hyperventilation
#Significant difference from drainage
°Significant difference from rTp

Table 17.4 SjO_2 and $AVDO_2$ measured before and after treatment with hyperventilation, mannitol or indomethacin, and before rTp and surgical drainage

	Hyper-ventilation	Reverse Trendelenburg	Mannitol	Drainage	Indomethacin
Number	21	7	7	2	12
Venous saturation before (%)	57.9±9.3	48.8±4.4	66.4±16.0	48.9±4.4	52.8±7.4
Venous saturation after (%)	52.3±9.2*		64.9±		43.4±6.5*
Percent change in venous saturation	−9.7		−2.3		−17.8
$AVDO_2$ (mmol/L) before	3.1±0.8		2.8±0.8		3.5±0.4
$AVDO_2$ (mmol/L) after	3.5±0.8*		2.8±0.5		4.1±0.4*
% change in $AVDO_2$	−12.9		0.0		−17.1

*$P<0.05$ paired comparison

hyperventilated patients (77%) followed by mannitol treatment (68%), indomethacin treatment (60%) and rTp (56%). In patients subjected to surgical decompression swelling did not occur (Table 17.6).

Table 17.5 Degree of dural tension before treatment and after/during treatment with hyperventilation, 10° rTp, mannitol treatment, surgical drainage or indomethacin treatment. Number of patients and percentage of patients are indicated

Dural tension	Before hyper-ventilation	After hyper-ventilation	Before 10° rTp	After 10° rTp	Before mannitol	After mannitol	Before drainage	After drainage	Before indo-methacin	After indo-methacin
No tension	7	11	1	7	0	8	0	13	1	7
Moderate tension	16	14	12	8	16	10	8	0	8	6
Pronounced tension	7	5	3	1	3	1	5	0	6	2
Percentage of patients with increased tension	77	63	94	56	100	58	100	0	93	53

Table 17.6 The degree of brain swelling/herniation after opening of dura in patients subjected to hyperventilation, 10° rTp, mannitol treatment, surgical decompression (drainage of cerebral cysts) or indomethacin treatment. Number of patients and percentage with cerebral swelling are indicated

	Hyper ventilation	Reverse Trendelenburg	Mannitol	Drainage	Indomethacin
No swelling	7 (23)	7 (44)	6 (32)	13(100)	6 (40)
Moderate swelling	17 (57)	8 (50)	9 (47)	0 (0)	8 (53)
Pronounced swelling	6 (20)	1 (6)	4 (21)	0 (0)	1 (7)
Percentage of patients with swelling	77	56	68	0	60

Conclusion The ICP-reducing effect of surgical decompression is superior to hyperventilation, 10° rTp, mannitol treatment or indomethacin, and the effect of indomethacin is superior to 5 min of hyperventilation. The increase in CPP was greater during drainage or indomethacin compared with hyperventilation and rTp.

Study 2: A Comparative Clinical Study of the Intracranial Pressure-Reducing Effect of 10 Degrees Reverse Trendelenburg Position and Hyperventilation in Patients Subjected to Supratentorial Craniotomy for Cerebral Tumours in Propofol-Remifentanil Anaesthesia

Aim Comparative studies of ICP-reducing management are not available in propofol-remifentanil-anaesthetized patients subjected to craniotomy for supratentorial cerebral tumours. In this observational study we analysed the ICP-reducing effect of hyperventilation and 10° rTp in patients with cerebral tumours subjected to propofol-remifentanil anaesthesia.

Method From our database concerning subdural ICP measurement we collected consecutive data from 45 patients subjected to supratentorial tumour surgery in propofol-remifentanil anaesthesia. The following ICP-reducing managements were analysed. Five minutes of hyperventilation (n=15) and 10° rTp (n=15). Patients, in whom therapeutic intervention was not performed, served as control (n=15). Subdural ICP was measured before opening of dura. The changes in ICP (ΔICP), $PaCO_2$ ($\Delta PaCO_2$) and CPP (ΔCPP) were calculated. The effect of hyperventilation were estimated during a 5-min period and the effect of rTp after 1 min. For details concerning methodology including neuroradiological data, histopathology, perioperative fluid management and monitoring and maintenance of anaesthesia, see Chapter 3.

Table 17.7 Demographics, parameters from blood gas analysis, ICP, MABP, CPP, rectal temperature, neuroradiological findings (tumour size, localization), histopathology and maintenance doses of propofol and remifentanil are presented. Three groups were studied including a control group, a group subjected to 5 min of hyperventilation and a group where 10° rTp was applied

	Control group	Hyperventilation	Reverse Trendelenburg
Number	15	15	15
Men/women	9/6	10/5	8/7
Age (years)	44.0±15.0	52.0±16.0	53.0±14.0
Weight (kg)	79.0±17.0	71.0±14.0	73.0±16.0
Height (cm)	174.0±8.0	173.0±8.0	173.0±8.0
$PaCO_2$ (kPa)	4.5±0.3	4.6±0.4	4.6±0.4
PaO_2 (kPa)	25.0±7.0	24.0±9.0	20.0±8.0
Temperature (°C)	35.7±0.4	35.8±0.3	35.8±0.4
ICP (mmHg)	9.5±6.2	7.1±4.0	8.9±5.3
MABP (mmHg)	77.0±15.0	78.0±14.0	72.0±12.0
CPP (mmHg)	68.0±15.0	71.0±14.0	63.0±12.0
Tumour area (cm^2)	11.0±7.0	13.0±9.0	13.0±8.0
Midline shift (mm)	4.2±6.6	5.6±5.9	6.8±7.9
Localization (number)			
Frontal	2	7	7
Parietal	3	2	2
Temporal	4	1	2
Occipital	1	2	2
Hemispheric	1	0	1
Basal	4	3	1
Histopathology			
Glioblastoma	3	4	4
Meningioma	4	4	6
Metastasis	0	2	2
Glioma	5	4	0
Other	3	1	3
Anaesthesia			
Propofol (mg/h)	460.0±115.0	403.0±79.0	383.0±94.0
Remifentanil (ml/h)	48.0±18.0	43.0±12.0	42.0±14.0

Statistical analysis Data within groups were tested for normal distribution. The normality test and equal variance test were applied. One-way ANOVA was used for analysis if these tests were passed, and Tukey's test was used for pair-wise multiple comparison procedures. The Kruskal-Wallis one-way analysis of variance on ranks and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. The chi-square test was used for statistical analysis of demographic data, tumour localization, size and histopathological diagnosis of the tumours, preoperative steroid administration and position of the head. Difference in tension of dura and the degree of cerebral swelling were tested by the chi-square test. Mean±SD were calculated. $P<0.05$ was considered statistically significant.

Results No significant intergroup differences as regards demographic data, neuroradiological findings (tumour size, tumour volume, midline shift, localization of tumour) or histopathology were found. Neither did parameters of cerebral haemodynamics including ICP, CPP, SjO_2 and $AVDO_2$ show any significant intergroup differences. The same applies to levels of $PaCO_2$, PaO_2 and rectal temperature (Table 17.7).

During the 5-min observation period no significant changes in $PaCO_2$, ICP, MABP or CPP were found in the control group. Hyperventilation and rTp induced a significant decrease in ICP averaging 2.3 and 4.3 mmHg, respectively (Table 17.8). The decrease in ICP was significant after 1 min in the group subjected to rTp, and after 2 min in the hyperventilation group. The ICP-reducing effect of rTp was significantly greater compared with that induced by hyperventilation (Tables 17.8 and 17.9). The rTp induced a significant increase in CPP averaging 2.1 mmHg. CPP was unchanged during hyperventilation (Table 17.8). During hyperventilation SjO_2 decreased significantly from 52.3% to 48.1%, and a significant increase in $AVDO_2$ from 3.3 to 3.7 mmol/L was disclosed. No significant difference in SjO_2 or $AVDO_2$ was found after rTp (Table 17.10).

Table 17.8 Changes in $PaCO_2$ ($\Delta PaCO_2$), MABP (ΔMABP), ICP (ΔICP) and CPP (ΔCPP) in the control group, during 5 min hyperventilation and 1 min after 10° rTp

	Control group	Hyperventilation	Reverse Trendelenburg
$\Delta PaCO_2$ (kPa)	0.0±0.1	0.6±0.2*	0.0±0.1
ΔMABP (mmHg)	0.0±1.4	1.4±2.0	5.8±2.8°
ΔICP (mmHg)	0.1±0.5	2.3±1.2*	4.3±2.9*#
ΔCPP (mmHg)	−0.5±1.1	−0.2±	2.1±3.8*

*Significant difference from control
#Significant difference from hyperventilation
°Significant difference from the other groups

Table 17.9 MABP, ICP and CPP recorded at time zero and up to 5 min during hyperventilation in 15 patients. Mean values are indicated

	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)
0	78.3	7.1	71.3
1 min	77.6	6.3	71.4
2 min	77.1	5.5*	71.4
3 min	76.6*	5.0*	71.7
4 min	76.4*	4.8*	71.4
5 min	76.2*	4.7*	71.6

*$P \leq 0.01$ significant difference from zero

Table 17.10 SjO_2, $AVDO_2$ and $PaCO_2$ before and at 5 min in the control group and in patients subjected to 5 min of hyperventilation

	Control			Hyperventilation		
	SjO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)	SjO_2 (%)	$AVDO_2$ (mmol/L)	$PaCO_2$ (kPa)
0	49.8±8.7	3.6±0.8	4.4±0.3	52.3±11.6	3.3±0.8	4.6±0.4
5 min	49.7±8.4	3.6±0.8	4.5±0.3	48.1±11.6*	3.7±0.8*	4.0±0.4*

*$P<0.05$

In comparison with the control group, 10° rTp as well as hyperventilation decreased ICP significantly. The decrease in ICP during rTp was more pronounced compared with hyperventilation, and rTp decreased both MABP and CPP significantly.

Conclusion Compared with the control group rTp and hyperventilation caused a significant decrease in ICP. Reverse Trendelenburg position was associated with a significant increase in CPP.

Study 3: A Comparative Study of the Intracranial Pressure-Reducing Effect of 10 Degrees Reverse Trendelenburg Position, Hyperventilation, Indomethacin and Surgical Drainage in Patients Undergoing Fossa Posterior Surgery in the Prone Position

Aim To compare the ICP-reducing effect of 10° rTp, hyperventilation, surgical draining and indomethacin in patients undergoing fossa posterior surgery in the prone position.

Method Fifty-three patients with space-occupying processes in the posterior fossa participated in the study. Eleven patients were subjected to 10° rTp, 12 patients underwent hyperventilation for 5 min, 12 patients received intravenous indomethacin (0.5 mg/kg) as a bolus and 18 patients were subjected to drainage of cystic processes. Propofol-remifentanil was used for maintenance

of anaesthesia. All patients had a subdural ICP ≥ 10 mmHg measured before any intervention to reduce ICP. The effects of rTp, drainage and indomethacin were recorded after 1 min. Concerning methodological data, maintenance doses of anaesthesia and neuroradiological data, see Chapter 3.

Statistical analysis As study 1; mean±SD are indicated.

Results No significant differences were disclosed as regards demographic data or data obtained before the ICP-reducing management, including PaO_2, rectal temperature, ICP, MABP, CPP and maintenance dose of anaesthesia. Neither did the neuroradiological findings, including the maximal area of the process, differ significantly between the groups (Table 17.11). In all treatment groups subdural ICP decreased significantly. The decrease in subdural ICP in the drainage group was significantly greater than in the other groups, in which the decrease in ICP did not differ significantly. The increase in CPP was significantly higher in the indomethacin group and in patients subjected to drainage compared with the other two groups (Table 17.12).

Conclusion In all four groups subdural ICP decreased significantly, but the decrease in ICP was substantially greater in patients subjected to drainage. In the indomethacin and drainage groups an increase in CPP was significantly greater than the changes observed during rTp and during hyperventilation.

Table 17.11 Demographic data, gas analyses, temperature, ICP, MABP, CPP and neuroradiological data in patients subjected to ICP-reducing therapy including 10° rTp, 5 min of hyperventilation, indomethacin bolus (0.5 mg/kg) and drainage of cystic processes. Mean±SD are indicated. Data were obtained before the ICP-reducing therapy. No significant intergroup differences were found

	Reverse Trendelenburg	Hyper-ventilation	Indomethacin	Drainage
Number	11	12	12	18
Men/women	6/5	5/7	6/6	7/11
Age (years)	42.0±20.0	43.0±19.0	56.0±9.0	48.0±16.0
Weight (kg)	73.0±23.0	74.0±22.0	77.0±17.0	74.0±18.0
$PaCO_2$ (kPa)	4.4±0.4	4.6±0.5	4.5±0.4	4.2±0.5
PaO_2 (kPa)	31.0±5.0	25.0±6.0	24.0±5.0	29.0±9.0
Temperature (°C)	35.9±0.5	35.9±0.6	36.2±0.4	35.9±0.4
ICP (mmHg)	19.9±5.8	19.8±11.1	17.8±5.3	18.8±6.7
MABP (mmHg)	84.0±16.0	78.0±17.0	79.0±20.0	87.0±15.0
CPP (mmHg)	64.0±15.0	51.0±16.0	61.0±20.0	68.0±16.0
Tumour area (cm^2)	7.5±5.3	13.0±6.0	9.0±6.0	10.0±8.0
Midline shift (mm)	0.6±1.6	0.3±0.9	1.4±2.6	0.9±2.1

Table 17.12 Differences in $PaCO_2$, ICP, MABP and CPP measured before and after ICP-reducing therapy including 10° rTp, 5 min hyperventilation, indomethacin treatment (0.5 mg/kg) and drainage of a cystic process. Number±SD are indicated

	Reverse Trendelenburg	Hyper-ventilation	Indomethacin	Drainage
Decrease in $PaCO_2$ (kPa)	0.1±0.1	0.7±0.1*	0.1±0.1	−0.1±0.1
Decrease in ICP (mmHg)	5.6±1.9	2.6±2.6	4.4±2.0	16.6±6.8*
Increase in MABP (mmHg)	−5.1±2.0*	0.0±6.3	13.8±5.1*	1.1±0.5
Increase in CPP (mmHg)	−0.5±2.0	−3.1±4.6	18.0±4.8°	17.7±8.2°

*Significant difference compared with the other groups
°Significant difference from both rTp and hyperventilation

Discussion

In studies 1 and 3 the inclusion criterion was a subdural ICP ≥ 10 mmHg. This threshold is in accordance with recent studies in patients subjected to supratentorial craniotomy where cerebral swelling is rare if ICP is below 5–7 mmHg, while subdural ICP above 10–13 mmHg is accompanied by moderate cerebral swelling and ICP above 15 mmHg is associated with pronounced cerebral swelling (Cold et al. 1996; Bundgaard et al. 1998; Rasmussen et al. 2004). These thresholds are independent of $PaCO_2$ level, choice of anaesthesia and diagnosis (tumour contra aneurysm surgery) (Bundgaard et al. 1998). The tension of dura was not used as an inclusion criterion because it is a based on a subjective evaluation and because the degree of cerebral swelling is better correlated to subdural ICP compared with degree of dural tension (Bundgaard et al. 1998). In the present study, the degree of swelling after opening of dura is semiquantitative and subjective as well. Nevertheless, we used this estimate because the presence of brain swelling increases retractor pressure resulting in low regional perfusion pressure (Hongo et al. 1987; Rosenørn 1987), thereby increasing the risk for development of cerebral ischaemia. Furthermore, brain swelling makes surgical access difficult.

The three studies were based on prospective continuous data collected between the years 1997 and 2005. During that period, subdural ICP monitoring was performed in 289 patients with supratentorial tumours anaesthetized with propofol-fentanyl, indicating that ICP ≥ 10 mmHg occurred in 32% of the patients. Demographic data, histopathological data, neuroradiological data and levels of ICP, MABP and CPP, however, did not show any intergroup difference. A difference in $PaCO_2$ between the mannitol group and the other treatment groups, except patients subjected to surgical decompression, seems of minor importance because the effect of mannitol is based on osmotic activ-

ity independent of the level of $PaCO_2$. The ICP-reducing effect used in the present study is elicited by different mechanisms. In the second study the ICP-decreasing effect of rTp was superior to hyperventilation, and in the third study drainage was followed by a substantially greater decrease in subdural ICP compared with rTp, indomethacin treatment and hyperventilation.

Hyperventilation and indomethacin increase cerebrovascular resistance, and thereby decreases CBF and CBV, and as a consequence a decrease in ICP is observed. The decrease in blood volume by hyperventilation is dependent on the change in $PaCO_2$. For the awake normal human the change in CBV is 0.049 ml/100 g/mmHg $PaCO_2$ (Greenberg et al. 1978), meaning that the decrease in blood volume should average 3.8 ml by a 0.8-kPa reduction in $PaCO_2$. Similar studies during indomethacin treatment are not available, but taking the more pronounced decrease in ICP during indomethacin administration into account, the decrease in blood volume must be higher. This is supported by the findings in the present study that the % changes in venous oxygen tension and $AVDO_2$ were higher during indomethacin treatment compared with hyperventilation. At least the decrease in intracranial compartment effected by both hyperventilation and indomethacin is substantially lower compared with the averaged drainage volume of 20 ml found in the group subjected to surgical decompression.

In awake humans a dose-related decrease in CBF has been documented after indomethacin (Jensen et al. 1996). According to previous studies in patients with severe head injury (Jensen et al. 1991; Biestro et al. 1995; Dahl et al. 1996; Imberti et al. 2005) and patients with cerebral tumours (Bundgaard et al. 1996), a 0.5-mg/kg i.v. dose of indomethacin was used in the present study. Although, an experimental study in pigs suggests that indomethacin might cause ischaemic changes (Nilsson et al. 1995), a recent diffusion-weighted MRI study indicates that indomethacin does not cause ischaemic damage in propofol-fentanyl-anaesthetized patients with cerebral tumours (Rasmussen et al. 2004), and in the present study indomethacin did cause unexpected prolonged recovery or neurological changes. In a recent review this issue has been discussed (Rasmussen 2005).

In contrast to hyperventilation and indomethacin the ICP-reducing effect of rTp is based on drainage of CBV primarily from the venous compartment. The decrease in ICP averaging 5.0 mmHg is greater compared with other studies in our clinic where a decrease averaging 3.6 and 3.5 mmHg in supine-positioned patients with cerebral tumours was found (Rolighed Larsen et al. 2002; Haure et al. 2003). The higher level of ICP before intervention in the present study, although not significant, can explain the differences in ICP decrease, because the volume/pressure curves are steeper at the given higher ICP level. According to other studies in our clinic (Rolighed et al. 2002; Tankisi et al. 2002, 2006; Haure et al. 2003) 10° rTp did not change CPP, because the decrease in MABP was similar to the reduction in ICP. According to a recent study a 1-min observation period after the change to 10° rTp, was used. Within this period MABP, ICP and CPP are stabilized (Haure et al. 2003).

In patients with intracranial hypertension, fast intravenous mannitol infusion of 0.5–1 g/kg is followed by a decrease in ICP within 2–5 min. The ICP-reducing effect is of hours duration, dependent on the dose and the infusion rate (James 1980). The faster the concentration difference of mannitol occurs between plasma and extracellular fluid, the stronger and the longer the reduction in ICP (Takagi et al. 1993). The decrease in ICP is correlated to the decrease in the water content in brain tissue (Nath and Galbraith 1986). Following mannitol infusion blood viscosity decreases for at least 2 h, suggesting an enhancement of cerebral microcirculation (Burke et al. 1981). An increase in CBV a few minutes after mannitol infusion has been demonstrated experimentally (Lin et al. 1997) and in human studies (Ravussin et al. 1986a). Accordingly, studies of cerebral circulation indicate an increase in CBF occurring after 10–20 min and lasting for up to 24 h, and a variable increase in $CMRO_2$ (Jafar et al. 1986). The effect of mannitol on ICP has been studied in patients with cerebral tumours and aneurysms. In patients with normal ICP a transient but significant increase in ICP followed by a steady decrease towards values below control were found. In contrast, patients with intracranial hypertension showed no increase in ICP, which decreased immediately after mannitol infusion (Ravussin et al. 1986b). In the present study mannitol (20% solution) was administered in doses ranging from 0.5 to 1.0 g/kg (average 0.8 g/kg). These dosages were given through a fast running i.v. infusion over 5–10 min, and subdural ICP was monitored before and until 5 min after discontinuation of administration. An initial increase in subdural ICP, as demonstrated elsewhere, was not observed (Ravussin et al. 1986b). On the one hand, it can be argued that during the relatively short observation period the maximal ICP-reducing effect was not observed. On the other hand, a prolongation of the observation period, more than 10 min, would produce an unacceptable delay of the surgical procedure.

In the present study all patients were anaesthetized with propofol-fentanyl, which is known to produce a substantial decrease in CBF and cerebral metabolism (Stephan et al. 1987; Vandesteene et al. 1988;). In a randomized study in patients undergoing supratentorial tumour surgery, the level of ICP was lower, the level of $AVDO_2$ higher, and the ICP-reducing effect by hyperventilation was more pronounced in propofol-fentanyl-anaesthetized patients compared with isoflurane-fentanyl- or sevoflurane-fentanyl-anaesthetized patients (Petersen et al. 2003). Although the level of ICP differed from the present study, it cannot be excluded that the ICP-reducing effect of both hyperventilation and indomethacin in patients with intracranial hypertension would be more pronounced if the patients were anaesthetized with one of these volatile agents. This is substantiated in a previous study where indomethacin was highly effective in reducing ICP in isoflurane-anaesthetized patients with a high level of ICP (Bundgaard et al. 1996). A possible explanation is that the CO_2 reactivity is higher during isoflurane-fentanyl or sevoflurane-fentanyl anaesthesia compared with propofol-fentanyl-anaesthetized patients (Petersen et al. 2003), and/or the steeper course of the volume/pressure curve at higher ICP levels.

Limitations of the study include the condition that hyperventilation was only used for a 5-min period. As the ICP-reducing effect during hyperventilation is maximal after 10–15 min, it can be argued that a longer period would elicit a more pronounced decrease in ICP. Nevertheless, the decrease in ICP during hyperventilation starts precipitously, with the greatest fall in ICP within the first few minutes, and the decrease in ICP follows the decrease in end-tidal CO_2, which only decreases little after the first 5 min. Moreover, the decrease in $PaCO_2$ averaged 0.8 kPa, a value which is comparable with other studies where the ICP-reducing effect of hyperventilation has been investigated (Petersen et al. 2003). Another limitation is that ICP was measured 5 min after finishing the mannitol infusion. A prolonged observation period of 15–30 min certainly would reveal a more pronounced decrease in ICP. Nevertheless, the rapid ICP-reducing effects of rTp, indomethacin and surgical decompression, taking place within few minutes, are in sharp contrast to the effects of hyperventilation and mannitol treatment where the maximal effect should be expected after approximately 15 and 45 min, respectively. Accordingly, the operation time would be prolonged and the patience of the neurosurgeon challenged. A randomized study in order to confirm the findings in the present study seems justified. Taking into account that in our clinic data collection spanned over 7 years, such a study should be a designed as a multicentre trial.

Clinical significance The present study demonstrates that surgical decompression, either by withdrawal of CSF via a ventricular catheter or evacuation of cystic processes, is superior in controlling intracranial hypertension and preserving CPP when compared with 5 min of hyperventilation, 10° rTp and mannitol treatment extending 5 min after conclusion of infusion. The ICP-reducing effect of indomethacin is pronounced and is accompanied by a substantial increase in CPP. These observations should be confirmed in a randomized study.

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Chapter 18
Effect of Positive End-Expiratory Pressure on Subdural Intracranial Pressure in Patients Undergoing Supratentorial Craniotomy

Birgitte Duch and Georg Emil Cold

Abstract

Adult respiratory distress syndrome develops in up to 20% of patients with severe head injury. Positive end-expiratory pressure (PEEP) is often required to support oxygenation. It is well known that PEEP might increase ICP in intensive care patients through decreased cerebral venous outflow as well as an effect on venous return and subsequent reduced mean arterial blood pressure. The effect of PEEP on ICP have been the focus of several experimental and clinical studies, and the results and their interpretation remain controversial. All studies were performed at intensive care units in trauma patients and patients with subarachnoid haemorrhage, but the effect of PEEP, however, have not been investigated during craniotomy.

In this chapter the effects of 5 and 10 cmH_2O PEEP on subdural ICP, cerebral perfusion pressure and jugular bulb pressure were studied during craniotomy for cerebral tumours or cerebral aneurysms.

Positive end-expiratory pressure has been shown to be an effective means for optimizing alveolar recruitment and improves oxygenation in patients with acute lung injury. However, it may worsen or trigger elevated ICP through decreased cerebral venous outflow as well as have an effect on venous return and subsequently reduce MABP. The effect of PEEP on ICP have been the focus of several experimental and clinical studies, and the results and their interpretation remain controversial. All studies were performed at intensive care units in trauma patients and patients with SAH. Shapiro and Marshall (1978) showed an increase in ICP of up to 10 mmHg after applying 4–8 cmH_2O of PEEP. A decrease of CPP was also shown. In contrast Frost (1977) did not see any change in ICP after applying up to 40 cmH_2O of PEEP. More recently Mascia et al. (2005) elevated PEEP to 5 and 10 cmH_2O and showed that patients who achieved lung recruitment showed no increase in $PaCO_2$ and ICP remained stable. However, in non-recruiters alveolar hyperinflation occurred,

and $PaCO_2$ increased with the consequence of an increase in ICP. It is well known that during anaesthesia lung atelectasis is present in most humans and is the major cause of impaired oxygenation in fragile patients. Hedenstierna and Rothen (2000) showed that by applying PEEP, atelectasis could be avoided.

In neuroanaesthesia PEEP has not routinely been applied to the respirator during operations as controversy exists as to whether a rise in ICP would be the consequence. According to the existing literature obtained in intensive care units, it seems safe to apply PEEP without the risk of raising ICP as long as the PEEP is kept below the ICP and the PEEP results in recruitment and not hyperinflation of the lungs. In this chapter two studies are presented that evaluate the safety of applying PEEP during supratentorial craniotomy.

Study 1: Effect of 5 cmH_2O Positive End-Expiratory Pressure on Subdural Intracranial Pressure, Cerebral Perfusion Pressure and Jugular Bulb Pressure

Aim To study the effect of 5 cmH_2O PEEP on subdural ICP and CPP during craniotomy.

Method Twenty-five patients without pulmonary disease participated in the study. All patients underwent craniotomy for cerebral tumours (n=22) or cerebral aneurysm (n=3) in the supine position and were anaesthetized with propofol-remifentanil. Before and 3 min after PEEP application subdural ICP and MABP were measured and CPP was calculated. These parameters were recorded every minute for a period of 3 min. In 21 patients a catheter was inserted in the jugular vein and JBP was monitored before and after PEEP application. $PaCO_2$ was measured at time zero, and end-tidal CO_2 was monitored continuously during the study period. As regards perioperative fluid therapy, see Chapter 3.

Statistical analysis Mean±SD are indicated. Intragroup differences were tested with Wilcoxon's test.

Results During 5 cmH_2O PEEP the maximal pressure of the respirator increased from 15.6 to 21.8 cmH_2O. End-tidal CO_2 remained stable. Three minutes after application of 5 cmH_2O PEEP a significant decrease in MABP from 70.9 to 68.2 mmHg was found. Within the same time interval subdural ICP increased significantly from 5.7 to 6.7 mmHg and CPP decreased from 65.4 to 61.5 mmHg (all changes at P<0.001 level). An increase in JBP from 4.6 to 5.5 mmHg was observed following 5 cmH_2O PEEP (Table 18.1). At time zero $PaCO_2$ averaged 4.61±0.33 kPa. A significant correlation was found between the changes in subdural ICP and changes in bulb pressure during 5 cmH_2O PEEP, $\Delta ICP = 0.0373 + (0.8734 \times \Delta JBP)$, r=0.8377, P<0.001.

Conclusion Application of 5 cmH_2O PEEP reduces blood pressure and CPP and increases subdural ICP and bulb pressure. A positive significant correla-

Table 18.1 Changes in MABP, subdural ICP, CPP and JBP during a 3-min period, after application of 5 cmH_2O PEEP

Minutes	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	JBP (mmHg)
0	70.9±10.2	5.7±4.0	65.4±10.5	4.6±3.2
1	69.3±10.0	6.2±4.1	63.0±9.8	5.1±3.2
2	68.6±9.5	6.6±4.0	62.0±9.1	5.4±3.0
3	68.2±9.7*	6.7±4.0*	61.5±9.3*	5.5±3.0*
Difference 0–3	2.7±3.0	1.0±1.2	3.9±3.7	1.1±1.1

*$P<0.01$ significant intragroup difference from time 0

tion between change in bulb pressure and change in subdural ICP suggests that the increase in ICP is secondary to an increase in bulb pressure.

Study 2: Effect of 10 cmH_2O Positive End-Expiratory Pressure on Subdural Intracranial Pressure, Cerebral Perfusion Pressure and Jugular Bulb Pressure

Aim To study the effect of 10 cmH_2O PEEP on subdural ICP and CPP during craniotomy.

Method Twelve patients without pulmonary disease participated in the study. All patients underwent craniotomy for cerebral tumours (n=11) or cerebral aneurysm (n=1) in the supine position and were anaesthetized with propofol-fentanyl. Before and 3 min after PEEP application subdural ICP and MABP were measured and CPP was calculated. These parameters were recorded every minute for a period of 3 min. A catheter was inserted in the jugular vein and JBP was monitored before and after PEEP application. HAES, as a volume expander, was only used in 4 of 12 patients.

Statistical analysis Mean±SD are indicated. Intragroup differences were tested with Wilcoxon's test, and Mann-Whitney's test was used for intergroup differences (comparison with data from the first study).

Results During PEEP application the respirator pressure increased from 15.8 to 25.0 cmH_2O. End-tidal CO_2 remained stable. The increase in respirator pressure was significantly greater during 10 cmH_2O PEEP compared with 5 cmH_2O PEEP (first study). Application of 10 cmH_2O resulted in the following changes: MABP decreased from 75.3 to 72.3 mmHg, ICP increased from 5.1 to 8.2 mmHg and CPP decreased from 70.2 to 65.1 mmHg (all changes at $P<0.01$ level). An increase in JBP from −0.8 to 2.4 mmHg followed the application of 10 cmH_2O PEEP (Table 18.2). $PaCO_2$ averaged 4.53±0.30 kPa. With 10 cmH_2O PEEP the correlation between changes in JBP and changes in subdural ICP was significant: $\Delta ICP = 0.2283 + 0.7913 \times \Delta JBP$, r=0.9008, $P<0.001$.

Table 18.2 Changes in MABP, subdural ICP, CPP and JBP during a 3-min period, after application of 10 cmH_2O PEEP

Minutes	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	JBP (mmHg)
0	85.3±16	5.1±3.0	80.2±16	−0.83±2.4
1	82.8±17	6.2±4.1	75.3±17	1.80±3.9
2	82.8±17	6.6±4.0	75.5±16	2.30±4.0
3	82.3±17*	6.7±4.0*	75.1±16*	2.40±3.9*
Difference 0–3	2.9±3.7	3.3±2.3**	5.1±4.5	3.20±2.1**

*$P<0.01$ significant intragroup difference from time 0
**$P<0.01$ significant intergroup difference compared with the first study

The changes in subdural ICP and changes in JBP were significantly greater in the 10 cmH_2O PEEP study compared with the 5 cmH_2O PEEP study. Thus, the change in ICP averaged 1.0 mmHg during the 5 cmH_2O PEEP study against 3.3 mmHg in the 10 cmH_2O PEEP study ($P<0.01$). Likewise a significant increase in maximal respirator pressure was observed ($P<0.01$) and the increase in JBP from 1.1 to 3.2 mmHg was also disclosed ($P<0.01$).

Conclusion Application of 10 cmH_2O PEEP reduces blood pressure and CPP and increases subdural ICP and bulb pressure. A positive significant correlation between change in bulb pressure and change in subdural ICP suggests that the increase in ICP is secondary to an increase in bulb pressure. Comparison between the two studies with 5 and 10 cmH_2O PEEP suggests a dose relation because the changes in both subdural ICP and JBP were significantly greater during 10 cmH_2O PEEP compared with 5 cmH_2O PEEP.

Discussion

The physiological consequences of the application of PEEP depend on its effects on systemic haemodynamics and gas exchange. The haemodynamic mechanism may alter cerebral circulation both on the arterial side by reducing the arterial pressure and on the venous side by reducing cerebral venous drainage. The gas exchange mechanism may change the cerebral circulation by a CO_2-mediated vasodilatation resulting in an increase in CBV.

A positive significant correlation was disclosed between changes in bulb pressure and changes in subdural ICP, suggesting that the increase in bulb pressure elicits an increase in subdural ICP. This relationship is further strengthened by the fact that the changes in subdural ICP, as well as bulb pressure, were significantly greater during 10 cmH_2O PEEP than during 5 cmH_2O PEEP. In patients McGuier et al. (1997) showed that PEEP increased ICP when the applied PEEP was higher than the baseline ICP, but had less effect if the applied PEEP was lower than the ICP. In our study the baseline ICP was 5.7 and

5.1 mmHg in the two groups. So in the group where 10 cmH_2O PEEP was applied the PEEP was higher than the ICP and this may explain why the change in ICP in this group was more pronounced.

Caricato et al. (2005) investigated the relationship between PEEP and ICP in patients with SAH. The patients were divided into groups based on their respiratory system compliance. ICP was unchanged in both groups with an increase of PEEP from 0 to 12 cmH_2O. The haemodynamic effects of PEEP, including a reduced MABP, were only observed in patients with normal respiratory compliance. Those with a reduced compliance were protected.

Mascia et al. (2005) demonstrated in head-injury patients that those who achieved significant alveolar recruitment with PEEP showed no increase in ICP. In contrast, patients who showed no increase in lung volumes had an increase in $PaCO_2$, resulting in a rise in cerebral blood flow and elevated ICP.

In both studies a decrease in both MABP and CPP was seen. Our patients had no lung disease and, therefore, they were expected to have normal compliance. So according to Caricato et al. (2005) the decrease in MABP should be expected. We did not measure the compliance, nor did we measure the lung volumes. At time zero, the $PaCO_2$ in the two studies did not differ significantly, and the end-tidal CO_2 concentration did not change after application of PEEP, which otherwise could explain why ICP increased in both studies.

Suggestions based on comparison between the two studies, however, are not convincing because it is based on non-controlled conditions. Between the two studies several differences exist. In study 1 propofol-remifentanil was used, while propofol-fentanyl was used in study 2. The higher MABP and CPP in study 1 are reasonably explained by different principles for maintenance of anaesthesia. In contrast, the level of subdural ICP was lower in propofol-fentanyl-anaesthetized patients. The reason for this difference might be explained by the difference in MABP because a higher blood pressure elicits a vasoconstrictor effect, provided that cerebral autoregulation is intact.

The difference in JBP between the two studies also calls for considerations. One explanation is that all patients in study 1 received i.v. volume expanders (HAES 500 ml) before the measurements, while in study 2 only 4 of 12 patients received similar volume-expanding solutions. Using a 2×2 table and Fisher's exact test the difference was significant ($P<0.001$). Georgiadis et al. (2001) found a significant reduction in CPP after PEEP only in patients with low CVP, suggesting a deleterious effect of hypovolaemia during ventilation with PEEP. Interestingly, Doblar et al. (1981) found that volume loading just before the application of PEEP failed to show any protective action, causing a further increase in ICP.

Although the increase in ICP was significantly greater during 10 cmH_2O PEEP compared with 5 cmH_2O PEEP, conclusions regarding dose-dependent changes in subdural ICP as well as JBP are uncertain. Only a blinded, controlled crossover study might resolve this question.

The main finding in this study was that, in patients undergoing surgery for supratentorial tumours or aneurysm of the brain, applying low levels of PEEP resulted in an increase of ICP and JBP.

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Chapter 19
Subdural Intracranial Pressure and Cerebral Haemodynamics During General Anaesthesia for Craniotomy in Patients with Cerebral Aneurysm

Alp Tankisi and Georg Emil Cold

Abstract

Patients with cerebral aneurisms are frequently presented to the neuroanaesthesiologist, although the number is decreasing due to intravascular coiling. In the intensive care setting a significant correlation between ICP and Hunt & Hess gradation has been described in patients with subarachnoid haemorrhage. The relationship between H&H gradation and perioperative ICP is an important issue because measures to decrease ICP may prevent brain swelling and improve surgical access. It therefore seems reasonable to investigate this issue, taking both patient positioning and anaesthetic technique into consideration.

In this chapter two studies are presented. In the first study we investigated the subdural ICP and cerebral perfusion pressure in patients with cerebral aneurysm anaesthetized with either propofol-fentanyl or isoflurane-fentanyl. In the second study the effect of 10 degrees reverse Trendelenburg position on subdural ICP and cerebral perfusion pressure in patients subjected to craniotomy for cerebral aneurysm were investigated.

In a previous study no relationship was found between H&H gradation and perioperative ICP (Auer and Mokry 1990). In the intensive care setting, however, a significant correlation between ICP and H&H gradation has been described in patients with SAH (Hayashi et al. 1977; Hase et al. 1978; Hartmann 1980; Voldby and Enevoldsen 1982). The relationship between H&H gradation and perioperative ICP is an important issue because measures to decrease ICP may prevent brain swelling and improve surgical access. It therefore seems reasonable to re-investigate this issue. However, other questions arise, including comparison of the effects of volatile anaesthetics and intravenous anaesthetics, and the effect of rTp on ICP and CPP.

Two properties are common for inhalation anaesthetics: a dose-related decrease in $CMRO_2$ and a dose-related decrease in CVR. Intravenous anaesthetic agents have the same ability to reduce $CMRO_2$ but CVR is changed somewhat less. This will be discussed in depth later in this chapter. In addition to the anaesthetic technique used, patient position plays an important role. In supine-positioned patients subjected to craniotomy for cerebral tumours a significant decrease in ICP from 9.5 to 6.0 mmHg with unchanged CPP was observed after change in position to 10° rTp (Rolighed Larsen et al. 2002). Likewise, 10° rTp resulted in a significant decrease in subdural ICP averaging 3 mmHg from a median value of 10 mmHg in supine-positioned patients with cerebral tumours (Haure et al. 2003). In patients subjected to craniotomy in the prone position for occipital or fossa posterior tumours a significant decrease in subdural ICP from 21 to 15.6 mmHg and 18.3 to 14.2 mmHg was recorded, respectively (Tankisi et al. 2002). As a consequence of these studies, we found it of interest also to study the effect of rTp on ICP in patients with SAH.

This chapter is based on two studies, the second of which is based on data presented by Tankisi et al. in J Neurosurg Anesthesiol (2006) 18:11–17.

Study 1: Comparative Study of Subdural Intracranial Pressure and Cerebral Perfusion Pressure in Patients with Cerebral Aneurysm Anaesthetized with Either Propofol-Fentanyl or Isoflurane-Fentanyl

Aim Comparison of subdural ICP and CPP in patients with cerebral aneurysm anaesthetized with either propofol-fentanyl or isoflurane-fentanyl.

Method One hundred and ten patients with cerebral aneurysm, including 33 patients anaesthetized with isoflurane-fentanyl and 77 patients anaesthetized with propofol-fentanyl participated in the study. All patients with SAH were in treatment with nimodipine. Within 1 h of anaesthesia for craniotomy H&H gradation was performed. Before opening of dura subdural ICP and CPP were measured, and the degree of dural tension and cerebral swelling after opening of dura were estimated.

Statistical analysis Within groups the paired *t*-test was used for the analyses of normally distributed data. Between groups, analysis of variance was used. The chi-square test was used to estimate the difference in proportion. Mean±SD are indicated. $P<0.05$ was considered significant.

Results No significant differences as regards demographics, localization of the aneurysms or distributions of numbers of patients in the respective H&H groups were found between the two anaesthetic groups. The maintenance doses of anaesthetics are indicated in Table 19.1. The level of $PaCO_2$, PaO_2, rectal temperature, MABP and CPP did not differ between the two anaesthetic groups (Table 19.2). In H&H 0 and H&H I patients ICP was low, averaging 6.2 and

5.1 mmHg in the isoflurane group, and 3.8 and 3.9 mmHg in the propofol group, respectively. In H&H II and H&H III patients a gradual increase in subdural ICP was found in both groups, with subdural ICP in the H&H III averaging 18.3 mmHg in the isoflurane group against 17.2 mmHg in the propofol group. In the H&H III patients a significant decrease in CPP was also found in both anaesthetic groups. Compared with the isoflurane group, subdural ICP was lower in all H&H groups in propofol-fentanyl-anaesthetized patients, but the differences in subdural ICP in the respective H&H groups were not significant (Table 19.2). Neither did the degree of dural tension before opening of dura nor the degree of brain swelling after opening of the dura differ significantly between the two anaesthetic groups, but with increasing H&H classification the proportion between normal/increased tension and no swelling/swelling changed significantly (Table 19.3).

Table 19.1 Maintenance dosages of anaesthetics in the isoflurane-fentanyl group and the propofol-fentanyl group

Doses	Isoflurane-fentanyl	Propofol-fentanyl
Isoflurane (MAC)	1.0±0.2	0
Propofol (mg/kg/h)	0	9.0±1.7
Fentanyl (μg/kg/h)	2.2±0.5	2.3±0.6

Table 19.2 Number of patients and physiological variables in patients anaesthetized with isoflurane-fentanyl or propofol-fentanyl. The respective H&H gradations are indicated. Mean±SD are indicated

	H&H 0	H&H I	H&H II	H&H III
Isoflurane-fentanyl				
Number	6	7	12	8
Temperature (°C)	35.9±0.4	36.1±0.8	36.5±0.7	36.2±0.8
$PaCO_2$ (kPa)	4.6±0.5	4.3±0.6	4.1±0.8	4.4±0.6
PaO_2 (kPa)	22.0±6.0	24.0±6.0	27.0±10.0	22.0±10.0
MABP (mmHg)	88.0±12.0	77.0±10.0	80.0±6.0	78.0±10.0
ICP (mmHg)	6.2±4.9	5.1±3.5	9.6±3.2	18.3±4.4*,**
CPP (mmHg)	82.0±12.0	71.0±12.0	70.0±5.0	58.0±11.0**
Propofol-fentanyl				
Number	17	16	27	17
Temperature (°C)	35.9±0.6	36.6±0.8	36.4±0.6	36.7±0.9
$PaCO_2$ (kPa)	4.5±0.3	4.3±0.4	4.5±0.4	4.3±0.5
PaO_2 (kPa)	30.0±7.0	29.0±9.0	25.0±12.0	23.0±11.0
MABP (mmHg)	84.0±10.0	79.0±17.0	83.0±13.0	80.0±9.0
ICP (mmHg)	3.8±3.2	3.8±3.2	9.4±3.4*,**	17.2±4.6*,**
CPP (mmHg)	81.0±9.0	75.0±16.0	74.0±12.0	62.0±10.0*,**

*$P<0.05$ compared with the preceding H&H group
**$P<0.05$ compared with H&H 0

Table 19.3 Degree of dural tension and degree of brain swelling after opening of dura. Number of patients is indicated

	Isoflurane-fentanyl		Propofol-fentanyl	
Degree of dural tension	Normal tension	Increased tension	Normal tension	Increased tension
H&H 0	5	1	17	0
H&H I	6	1	15	1
H&H II	5	7	11	16*,**
H&H III	0	8**	0	17*,**
Degree of brain swelling	No swelling	Swelling present	No swelling	Swelling present
H&H 0	5	1	17	0
H&H I	5	2	15	1
H&H II	4	8	9	18*,**
H&H III	0	8**	0	17*,**

*$P<0.05$ compared with the preceding H&H grade
**$P<0.05$ compared with H&H 0

Conclusion Independent of anaesthetic agent (propofol contra isoflurane), subdural ICP increases with higher H&H gradation, but although the mean values of subdural ICP in all H&H groups were higher during isoflurane anaesthesia, these differences never reached significance.

Study 2: Effect of 10 Degrees Reverse Trendelenburg Position on Subdural Intracranial Pressure and Cerebral Perfusion Pressure in Patients Subjected to Craniotomy for Cerebral Aneurysm

Aims 1: To examine the effect of 10° rTp position on subdural ICP, CPP and dural tension during craniotomy in patients with cerebral aneurysm. 2: To analyse the relationship between subdural ICP in the neutral position and changes in subdural ICP (ΔICP) after change in position to 10° rTp in different H&H groups. 3: To investigate the relationship between preoperative H&H grade and ICP in the neutral position.

Method Twenty-eight patients with cerebral aneurysm were subjected to craniotomy in propofol-fentanyl (n=15) or propofol-remifentanil (n=13) maintenance anaesthesia, respectively. During anaesthesia the level of $PaCO_2$ was between 4.0 and 5.0 kPa, and PaO_2 was > 13 kPa. All patients were in treatment with oral nimodipine. The localization of the aneurysm was classified with preoperative four-vessel angiography. The localization was as follows: middle cerebral artery, 13 patients; anterior communicans artery, 7 patients; internal carotid artery, 6 patients; and posterior communicans artery, 2 patients. H&H grade was determined just before induction of anaesthesia. Twelve patients were classified as H&H 0, 8 patients as H&H I and 8 patients as H&H II. Intu-

bated patients, patients with ventricular catheters and patients in treatment with mannitol were not included in the statistical analysis. These patients were classified separately as H&H III.

Catheters were inserted into the radial artery and into the jugular vein. After reference measurement of MABP, subdural ICP and JBP in the neutral position the operating table was adjusted to 10° rTp. All transducers were readjusted to the same level (point of the needle perforating the dura) and the measurements of MABP, subdural ICP and JBP were repeated after 1 min of stabilization. CPP was calculated as the difference between MABP and subdural ICP. Changes in subdural ICP (ΔICP) and changes in JBP (ΔJBP) were calculated as well. Tension of dura was estimated by the surgeon and graded as follows: low tension; normal tension; increased tension; and pronounced increased tension. These estimations were performed in the neutral position as well as in 10° rTp.

Statistical analysis Within groups the paired *t*-test was used for the analyses of normally distributed data. Between groups, analysis of variance was used. The chi-square test was used to estimate the difference in proportion. Mean±SD are indicated. $P<0.05$ was considered significant.

Results No significant differences between the anaesthetic groups with regards $PaCO_2$, PaO_2, subdural ICP, MABP, CPP, JBP, H&H classification, localization of aneurysms or demographic data were disclosed. Including all patients ($n=28$), 10° rTp was accompanied by a significant decrease in subdural ICP, MABP and JBP, whereas CPP remained unchanged (Table 19.4). In Table 19.5 the values of subdural ICP, MABP, CPP, JBP and ΔICP are related to the respective H&H groups. A progressive significant increase in subdural ICP was found with increasing H&H classification. Compared with H&H 0 (unruptured aneurysm), ΔICP was significantly higher in H&H II patients.

The relationship between subdural ICP in the neutral position and ΔICP was significant (ΔICP = 0.3661 ICP + 1.347; $r=0.627$, $P<0.001$). The relationship between ΔCPP and ΔICP was significant as well (ΔICP = 0.376 ΔCPP + 4.059; $r=0.596$; $P=0.001$). Change in position to 10° rTp was accompanied by a significant decrease in dural tension. The number of patients with increased tension of dura decreased from 10 to 4 patients. Additionally, a significant relationship between tension of dura and H&H grade was observed (Table 19.6).

Table 19.4 The effect of 10° rTp on MABP, subdural ICP, CPP, and JBP in 28 patients with cerebral aneurysm. Δ Values indicate change in pressure during rTp

Variable	Neutral position	10° rTp	Δ Value
MABP (mmHg)	77.0±14.0	72.0±14.0*	4.6±3.4
ICP (mmHg)	6.6±4.6	2.8±3.6*	3.7±2.7
CPP (mmHg)	70.0±14.0	70.0±14.0	0.8±4.2
JBP (mmHg)	4.6±4.1	0.5±4.1*	4.2±1.6

*Significant change compared with neutral position

Table 19.5 Effect of 10° rTp on MABP, subdural ICP, CPP and JBP in different H&H gradations

H&H grade	Position	MABP (mmHg)	ICP (mmHg)	CPP (mmHg)	JBP (mmHg)	ΔICP (mmHg)
H&H 0	Neutral	75.0.±13.0	2.9±2.6	72.0±13.0	2.1±2.0	
(*n*=12)	10° rTp	70.0±14.0*	0.4±2.2*	70.0±14.0	−1.6±2.8*	2.5±1.4
H&H I	Neutral	81.0±14.0	6.8±3.3º	74.0±15.0	8.8±4.9º	
(*n*=8)	10° rTp	76.0±13.0*	2.9±2.4*	74.0±14.0	3.8±5.4*	3.9±2.6
H&H II	Neutral	78.0±17.0	11.9±2.0º#	66.0±17.0	4.5±2.4	
(*n*=16)	10° rTp	73.0±15.0*	6.3±3.3*º#	67.0±15.0	0.5±1.9*	5.5±3.4º
H&H I+II	Neutral	79.0±15.0	9.3±3.8º	70.0±16.0	6.9±4.4º	
(*n*=16)	10° rTp	75.0±14.0*	4.6±3.3*º	70.0±14.0	2.3±4.3*	4.7±3.0º
H&H III	Neutral	85.0±10.0	8.5±4.9	76.0±13.0	9.5±0.7	
(*n*=4)	10° rTp	77.0±9.0	3.7±5.1	73.0±13.0	3.0±1.4	4.7±1.3

*Significant difference from neutral position
ºSignificant difference from H&H 0
#H&H II data are significantly different from H&H I data

Table 19.6 Estimation of dural tension in the neutral position related to the H&H gradation. Number of patients is indicated. Pearson $\chi^2 = 15.750$, $P<0.003$

Tension of dura	H&H 0	H&H I	H&H II
Low or normal	1	2	0
Increased tension	10	4	1
Pronounced increased	1	2	7

Conclusion Subdural ICP in the neutral position is related to H&H gradation. Thus, the more severely injured patients with a high H&H gradation had a higher subdural ICP. Ten degrees rTp reduces subdural ICP, MABP and dural tension significantly, whereas CPP is unchanged.

Discussion

In study 1 it was documented that independent of anaesthetic agent (propofol contra isoflurane) subdural ICP increases with higher H&H gradation, but although the mean values of subdural ICP in all H&H groups were higher during isoflurane anaesthesia, these differences never reached significance.

Two properties are common for inhalation anaesthetics: a dose-related decrease in $CMRO_2$ and a dose-related decrease in CVR. As regards isoflurane experimental studies have demonstrated this (Cucchiara et al. 1974; Stullken et al. 1977; Newberg and Michenfelder 1983; Gelman et al. 1984; Todd and Drummond 1984). Comparative clinical studies in patients without cerebral lesions (Murphy et al. 1974; Algotsson et al. 1988; Olsen et al. 1994) and studies in patients with mass-expanding cerebral lesions (Eintrei et al. 1985; Madsen

et al. 1987) have shown that the increase in CBF is dose dependent. Simultaneously, isoflurane induces a decrease in $CMRO_2$ (Murkin et al. 1986; Madsen et al. 1987; Algotsson et al. 1988; Olsen et al. 1994). The decrease in CVR is accompanied by an increase in CBF and CBV (Archer et al. 1987), an effect that increases ICP. Todd and Weeks (1996), however, made a comparative study of the effects of propofol, pentobarbital and isoflurane on CBF and CBV. They found that CBF in isoflurane-anaesthetized animals was 2.0–2.6 times greater than with propofol or pentobarbital. Nevertheless, although CBV was greater in the isoflurane group than in the propofol and pentobarbital groups, the magnitudes of the intergroup differences were much smaller (about 20%). In another experimental study, rabbits with brain tumour had a higher CBF and CBV when anaesthetized with isoflurane compared with propofol (Cenic et al. 2002). In comparison, in experimental studies, propofol is known to reduce both CBF and $CMRO_2$ (Werner et al. 1992). A dose-related decrease in CBF and $CMRO_2$ under conditions where blood pressure is maintained has been found (Ramani et al. 1992). However, in the same study a direct drug-related cerebral vasodilation cannot be excluded at excessive propofol concentrations. In dogs, a low and moderate dose of propofol decreases EEG activity and $CMRO_2$, and an associated decrease of CBF and CSF pressure were observed (Artru et al. 1992). Clinical studies support this. In other human studies propofol given as a bolus injection suppresses CBF and $CMRO_2$ (Stephan et al. 1987, 1988). Similar changes in CBF and $CMRO_2$ have been observed during continuous infusion with propofol (Vandesteene et al. 1988). Other clinical studies, including patients with cerebral tumours, indicate that subdural ICP is lower during propofol-fentanyl anaesthesia compared with isoflurane-fentanyl (Petersen et al. 2003). In children, however, a significant difference in subdural ICP between propofol and isoflurane anaesthesia was not found (Stilling et al. 2005).

Taking experimental and clinical evidence into consideration, all indicating that CBF and CBV are higher during isoflurane anaesthesia than during propofol anaesthesia, two conclusions concerning the effect of anaesthetic agents on ICP might be drawn from the first study:

1. The number of patients in the respective H&H groups was not sufficient. This combined with high standard deviations in the H&H groups makes statements concerning significant difference in subdural ICP invalid.
2. Although the mean values of subdural ICP were higher during isoflurane compared with propofol anaesthesia, the differences in the H&H II and III groups, where the highest levels of subdural ICP were recorded, only averaged 0.2 and 1.1 mmHg, indicating that this small difference hardly had clinical significance. In unruptured aneurysms, however, the difference was 2.4 mmHg, but the levels of subdural ICP in this group were far below the threshold for brain swelling of 10 and 13 mmHg, found in patients with cerebral aneurysm (Bundgaard et al. 1998) and patients with brain tumours (Rasmussen et al. 2004), respectively, and therefore also without

clinical significance as regards risk of cerebral swelling and impaired surgical access.

It is important to emphasize that the first study was not randomized. Thus, the clinical implication may be drawn with reservation. However, both experimental and human studies support the view that subdural ICP is higher during isoflurane compared with propofol anaesthesia. The first study does not deny this conclusion, but only a randomized study in children might settle this issue.

In a previous study no relationship was found between H&H gradation and perioperative ICP (Auer and Mokry 1990). In the intensive care setting, however, a significant correlation between ICP and H&H gradation has been described in patients with SAH (Hayashi et al. 1977; Hase et al. 1978; Hartmann 1980; Voldby and Enevoldsen 1982). This finding is in agreement with the result of the present study where a significant correlation between H&H gradation and ICP before and after tilting of the operating table was observed. The levels of ICP in H&H I and H&H II patients are identical with the values observed in awake patients where ICP in H&H I–II patients averaged 10.3 mmHg (Voldby and Enevoldsen 1982) or ranged between 10 and 13 mmHg (Hartmann 1982).

In the second study it was demonstrated that subdural ICP in the neutral position is related to H&H gradation. Thus, the more severely injured patients with a high H&H gradation had a higher subdural ICP. Furthermore, 10° rTp reduces subdural ICP, MABP and dural tension significantly, whereas CPP is unchanged.

Remifentanil and fentanyl have similar effects on cerebral haemodynamics, ICP and CO_2 reactivity (Guy et al. 1997; Ostapkovich et al. 1998; Balakrishnan et al. 2000). The present non-randomized study suggests that propofol-remifentanil and propofol-fentanyl have similar effects on MABP, ICP, ΔICP, CPP and JBP. These findings are in contrast to the study presented in Chapter 8, study 3, where subdural ICP and JBP were significantly lower in patients with supratentorial cerebral tumours during propofol-remifentanil compared with propofol-fentanyl anaesthesia. Only a randomized controlled study comparing subdural ICP and cerebral haemodynamics will settle this question, and seem justified.

Recently, we studied the effect of 10° rTp in patients with cerebral tumours in the supine and prone positions and found a significant decrease in subdural ICP as well as JBP (Rolighed Larsen et al. 2002; Tankisi et al. 2002; Haure et al. 2003). The results of the second study confirm these findings. In all H&H groups, expect H&H III, both subdural ICP and JBP decreased significantly. The lack of significant difference in the H&H III group is explained by the fact that only four patients were included.

In patients with head injury a positive correlation between the ICP level in the horizontal position and ΔICP during 30° head-up position has been dis-

closed (Feldman et al. 1992; Schneider et al. 1993). In the present study tilting of the operating table resulted in a significantly greater decrease in ICP in patients classified as H&H I–II compared with patients classified as unruptured aneurysm, and the correlation between ICP in the neutral position and ΔICP was positive and significant. These observations are in agreement with the ICP/volume concept, indicating that the decrease in ICP, effected by volume displacement, is reduced at low values of ICP, compared to the change in ICP observed during a high level of ICP (Langfitt et al. 1964). Difference in cerebral compliance between unruptured aneurysm patients and patients with SAH, however, may also explain the difference in ΔICP found in the present study.

In patients with head injury a decrease in mean ICP ranging from 4.5 to 11 mmHg with unchanged CPP during head-up position has been documented (Durward et al. 1983; Feldman et al. 1992; Schneider et al. 1993; Meixensberger et al. 1997; Moraine et al. 2000). An increase in ICP, however, secondary to a decrease in CPP has been described in patients with severe head injury. Thus, cerebral vasodilatation elicited by the autoregulatory mechanism might provoke an increase in ICP caused by a fall in CPP (Rosner and Coley 1986). In experimental studies (Hauerberg et al. 1993; Ma et al. 2000) as well as clinical studies (Voldby et al. 1985) of SAH cerebral autoregulation is disturbed. In the present study a significant relationship between the increase in CPP and decrease in ICP during rTp was found, suggesting that the autoregulatory mechanism influences the change in ICP, and that cerebral autoregulation, even in patients with ruptured aneurysm, predominantly was intact. Nevertheless, CPP did not differ between unruptured and ruptured aneurysm, and it is therefore unlikely that the level of CPP had any influence when ICP in unruptured and ruptured aneurysms was compared.

In a recent study, including 692 patients with cerebral tumour, cerebral swelling rarely occurred at subdural ICP < 5 mmHg (Rasmussen et al. 2004). Likewise, in patients with cerebral aneurysm cerebral swelling after opening of dura rarely occurred at subdural ICP < 7 mmHg, while cerebral swelling occurred with high probability at ICP ≥ 10 mmHg (Bundgaard et al. 1998). In the present study, the lowest ICP in H&H II patients was 9 mmHg, and 3 mmHg in H&H I patients. The highest ICP in patients without SAH was 6 mmHg. In all H&H groups 10° rTp significantly reduced ICP and dural tension. No cerebral swelling after dural incision occurred in patients (including all H&H 0 patients) with ICP ≤ 7 mmHg.

In awake patients without cerebral pathology ICP averages 11±2 mmHg (range 7–15 mmHg) (Albeck et al. 1991). In the present study the level of ICP in unruptured aneurysm, representing patients without intracranial mass-expanding lesion, averaged 2.9±2.6 mmHg. The difference in ICP level is supposed to be caused by propofol. In experimental studies (Ramani et al. 1992; Watts et al. 1998) and clinical studies (Stephan et al. 1987; Madsen 1991) reduces cerebral oxygen uptake and ICP. Furthermore, the low ICP may also be caused by hypocapnia (Petersen et al. 2003).

Lovell et al. (2000) examined changes in CBV before and after head elevation in awake and anaesthetized subjects. In awake subjects the decrease in CBV was more pronounced compared with subjects anaesthetized with propofol, probably because the CBV was already reduced by propofol anaesthesia. The ICP-reducing effect of head elevation was accompanied by a reduction in the cerebral venous blood volume and the capillary blood volume. In a recent study we found that the decrease in ICP was stable within 1 min after change in position, and the decrease in ICP was accompanied by a decrease in JBP (Haure et al. 2003). These findings indicate that the ICP-reducing effect of 10° rTp is secondary to mobilization of intracranial blood volume, but may also be caused by mobilization of intracranial CSF to the spinal segments.

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Chapter 20
Subdural Intracranial Pressure in Children

Alp Tankisi, Etienne Karatasi and Georg Emil Cold

Abstract

Studies of ICP in adult supine-positioned patients with supratentorial tumours or prone-positioned patients with infratentorial tumours suggest a dependency of both tactile estimate of dural tension and the degree of brain swelling after opening of dura on subdural ICP monitored immediately before opening of dura. However, comparative studies of ICP and the degree of cerebral swelling during craniotomy for space-occupying lesions in children are not available. The pressure/volume relationship in children is different from that in adults because of the smaller intracranial volume and the compliancy of the cranial vault.

In this chapter data on children in supine and prone positions during surgery are discussed, the influence of the anaesthetic technique, either propofol-fentanyl or isoflurane-nitrous oxide 50%-fentanyl, is disclosed and the ICP-lowering effect of reverse Trendelenburg position are presented.

The pressure/volume relationship in children is different from adults because of the smaller intracranial volume and the compliancy of the cranial vault. As a consequence, the effects of anaesthetics on ICP may differ from that observed in adults. Likewise, the cerebral haemodynamic effect of change in position on ICP might differ from adults because cerebral as well as central circulation is age dependent.

Studies of ICP in adult supine-positioned patients with supratentorial tumours (Cold et al. 1996; Bundgaard et al. 1998; Rasmussen et al. 2004) or prone-positioned patients with infratentorial tumours (Jørgensen et al. 1999; Tankisi et al. 2002) suggest a dependency of both tactile estimate of dural tension and the degree of brain swelling after opening of dura on subdural ICP monitored immediately before opening of dura. However, comparative studies of ICP and the degree of cerebral swelling during craniotomy for space-occupying lesions in children are not available.

In this chapter two studies of subdural ICP in children will be presented. The first study was presented by Stilling et al. in Acta Neurochir Suppl (2005) 95:133–136; the second study has not been presented before.

Study 1: Subdural Intracranial Pressure, Cerebral Perfusion Pressure and Degree of Cerebral Swelling in Supra- and Infratentorial Space-Occupying Lesions in Children

Aim To gather information on the degree of cerebral swelling, ICP and CPP in a group of children subjected to craniotomy.

Patients Forty-eight children with space-occupying tumours were subjected either to isoflurane-nitrous oxide 50%-fentanyl (n=22) or propofol-fentanyl (n=26) anaesthesia, Twenty-five children were operated on supratentorially in the supine position, while 23 patients were operated on infratentorially in the prone position. Subdural ICP, CPP, estimation of dural tension and degree of cerebral swelling after opening of dura were monitored in accordance with the procedure described in detail in Chapter 3.

Statistical analysis The data are presented as mean±SD. Intergroup differences were analysed with a one-way ANOVA model. The chi-square test was used for analyses of difference in distribution. *Post hoc* tests using Bonferroni corrections were performed. $P<0.05$ was considered significant.

Results The age and weight of the children anaesthetized with isoflurane in the prone position were significantly lower than the propofol-anaesthetized children. No significant intergroup differences as regards tumour size, midline

Table 20.1 Demographic data, neuroradiological data and data related to anaesthesia. Mean±SD are indicated

	Isoflurane/ supine	Isoflurane/ prone	Propofol/ supine	Propofol/ prone
Number	14	8	11	15
Male/female	8/6	4/4	8/3	11/4
Age (years)	6.1±4.4	3.6±2.1	9.3±2.1*	8.3±4.3*
Weight (kg)	24.0±15.0	17.0±4.5	34.0±11.0*	29.0±11.0
Steroid therapy +/−	5.0/9.0	2.0/6.0	2.0/9.0	3.0/12.0
Neuroradiology				
Tumour area (cm^2)	10.4±10.0	9.5±4.7	10.4±9.7	9.4±8.5
Midline shift (mm)	0.7±2.7	1.0±1.9	1.4±3.2	3.3±6.4
Anaesthesia				
Propofol (mg/kg/h)	0	0	10.5±3.8	12.7±5.1
Fentanyl (μg/kg/h)	1.8±1.3	1.2±0.6	2.2±1.1	2.3±0.8
Isoflurane (% expiratory)	1.3±0.5	1.2±0.2	0	0

*$P<0.05$ significant difference from isoflurane prone position

shift, pathology, rectal temperature, mean blood pressure, PaO_2 and $PaCO_2$ were disclosed (Table 20.1). Subdural ICP in prone-positioned children averaged 16.9 mmHg against 9.0 mmHg in supine-positioned children ($P<0.001$). In prone-positioned patients the tension of dura and the degree of brain swelling were significantly more pronounced (Table 20.2). No significant difference as regard ICP was disclosed when isoflurane-nitrous oxide and propofol-fentanyl were compared. Mean blood pressure and CPP, however, were significantly lower in children anaesthetized with isoflurane-nitrous oxide than in the children anaesthetized with propofol. No significant difference between isoflurane-nitrous oxide- and propofol-fentanyl-anaesthetized children as regards tension of dura and the degree of brain swelling after opening of dura were disclosed (Tables 20.3 and 20.4).

Table 20.2 Data related to cerebral circulation, tension of dura and degree of cerebral swelling. Anaesthesia and positioning are indicated. Mean±SD are indicated

	Isoflurane	Propofol	Supine	Prone
$PaCO_2$ (kPa)	3.9±0.6	4.2±0.4	4.0±0.5	4.1±0.6
PaO_2 (kPa)	33.0±12.0	36.0±10.0	36.0±14.0	36.0±9.0
Temperature (°C)	36.8±0.9	36.4±0.7	36.3±0.0	36.4±0.7
ICP (mmHg)	12.5±9.1	13.0±7.6	9.0±6.9	16.9±7.6*
MABP (mmHg)	66.0±11.0	739.0±*	68.0±8.0	70.0±9.0
CPP (mmHg)	52.0±10.0	59.0±10.0*	59.0±10.0	52.0±11.0*
Tension of dura				
Normal	10	14	17	7
Increased	8	7	6	9
Pronounced increased	4	5	2	7
Degree of swelling				
No swelling	9	11	15	5
Moderate swelling	6	10	6	10
Pronounced swelling	7	5	4	8

*$P<0.05$ significant difference between isoflurane and propofol anaesthesia and supine and prone positioning

Table 20.3 Data related to cerebral circulation. Anaesthesia and positioning are indicated. Mean±SD are indicated

	Isoflurane/ supine	Isoflurane/ prone	Propofol/ supine	Propofol/ prone
$PaCO_2$ (kPa)	3.9±0.6	3.9±0.7	4.1±0.4	4.2±0.5
PaO_2 (kPa)	33.0±12.0	33.0±12.0	39.0±17.0	39.0±9.0
Temperature (°C)	36.7±0.9	36.9±1.1	36.1±0.9	36.0±0.6
ICP (mmHg)	9.5±6.8	17.6±10.8*#	8.3±7.3	16.5±5.7*
CPP (mmHg)	55.0±9.0	48.0±10.0	63.0±8.0	55.0±11.0*

*$P<0.05$ significant difference from propofol, supine position
#Significant difference from isoflurane, supine position

Table 20.4 Tension of dura and degree of cerebral swelling. Anaesthesia and position are indicated

	Isoflurane/ supine	Isoflurane/ prone	Propofol/ supine	Propofol/ prone
Tension of dura				
Normal	8	2	9	5
Increased	4	3	2	6
Pronounced increased	2	3	0	4
Degree of swelling				
No swelling	8	2	9	3
Moderate swelling	4	2	2	7
Pronounced swelling	2	4	1	4

Conclusion In children with space-occupying lesions subdural ICP is significantly higher and the degree of cerebral swelling after opening of dura significantly more pronounced in the prone-positioned compared with the supine-positioned children. In this study choice of anaesthesia did not significantly influence the level of ICP, but CPP was significantly lower in isoflurane-nitrous oxide-anaesthetized children.

Study 2: Effect of Reverse Trendelenburg Position on Subdural Intracranial Pressure in Children During Craniotomy

Aim To study the effects of 5° and 10° rTp in children subjected to craniotomy.

Method In 9 children, with cerebral tumour (n=8) or cerebral abscess (n=1), subdural ICP was measured in the neutral supine position, 5° rTp and 10° rTp.

Table 20.5 Subdural ICP and CPP during change in position from neutral to 5° rTp and 10° rTp

Patient number	Age (years)	ICP			CPP		
		Neutral (mmHg)	5° rTp (mmHg)	10° rTp (mmHg)	Neutral (mmHg)	5° rTp (mmHg)	10° rTp (mmHg)
1	2	2	1	1	54	59	51
2	2	9	7	6	52	51	52
3	8	2	0	−2	58	55	59
4	1	4	3	2	55	55	54
5	14	17	13	11	68	68	70
6	10	40	26	25	18	34	34
7	6	14	11	9	58	53	51
8	12	8	5	4	70	69	69
Median	7	8.5	6.0*	5.0*	56.5	55	53
Range	1–14	2–40	0–26	−2 to 25	18–70	34–69	34–70

*P<0.05 significant change compared with the preceding values

The time interval between each measurement was 1–2 min. Simultaneously, MABP was monitored and CPP was calculated as the difference between MABP and subdural ICP.

Statistical analysis Median and range were calculated. Wilcoxon's test was used to assess difference in values. $P<0.05$ was considered significant.

Results The median values decreased significantly between each change in position from neutral via 5° rTp to 10° rTp, the three values being 8.5, 6.0 and 5.0 mmHg. The changes in CPP were not significant (Table 20.5).

Conclusions In children with cerebral tumours, reverse Trendelenburg effectively reduces subdural ICP without significant change in CPP.

Discussion

In the first study it was demonstrated that subdural ICP and the degree of cerebral swelling after opening of dura were significantly more pronounced in children subjected to infratentorial surgery in the prone position, compared with children operated on in the supine position for supratentorial lesions. The difference in subdural ICP was not related to the level of $PaCO_2$, blood pressure or tumour size.

The volume of the infratentorial compartment is considerably smaller than the supratentorial compartment. As a consequence, space-occupying lesions in the posterior fossa might increase ICP more, compared with supratentorial space-occupying lesions of the same size. To our knowledge studies of ICP and CPP during infra- and supratentorial craniotomy are few. In adult patients with cerebral tumours subdural ICP was significantly higher in prone-positioned patients with infratentorial lesions (Tankisi et al. 2002) compared with supine-positioned patients with supratentorial lesions (Tankisi and Cold 2007), and a higher ICP in the prone position compared with the supine position has also been demonstrated in patients with severe head injury (Lee 1989). In the prone-positioned patients the head is rotated downwards in order to gain acceptable surgical access. As a consequence the pressure in the intracerebral venous system is increased, the reason being the hydrostatic difference between the central and the cerebral venous system. Moreover, in the adult patient with acute lung injury the prone position results in an increase in abdominal pressure (Hering et al. 2001), and in experimental studies it has been demonstrated that an increase in intraabdominal pressure during insufflation augments ICP (Halverson et al. 1998; Rosenthal et al. 1998).

In the adult patient with supratentorial cerebral tumours subdural ICP is significantly higher with isoflurane-propofol compared with propofol-fentanyl (Petersen et al. 2003). This finding is supported by studies in rabbits with brain tumour, indicating that CBF as well as CBV are significantly greater during isoflurane than with propofol anaesthesia (Cenic et al. 2002). To our

knowledge comparative studies of ICP in isoflurane-fentanyl- compared with propofol-fentanyl-anaesthetized children are not available. A dose-related increase in ICP, however, has been demonstrated in children when isoflurane concentration was changed from 0.5 to 1.0 MAC, and in the same study ICP averaged 6 and 7 mm Hg, respectively (Sponheim et al. 2003). In contrast, increasing propofol infusion rates stabilize flow velocity at a low level in children (Karsli et al. 2002). Nitrous oxide also contributes to changes in ICP. Thus, addition of nitrous oxide to inhalation anaesthetics increases flow velocity in children (Sponheim et al. 2003) and increases ICP in patients with intracranial disorders (Henriksen et al. 1973). Other differences between the two anaesthetic regimes include preserved CO_2 reactivity in children during isoflurane and sevoflurane anaesthesia (Rowney et al. 2004), while the CO_2 reactivity is decreased during hypocapnic propofol anaesthesia (Leon and Bissonnette 1991). In the present study the mean values of subdural ICP were lower during propofol anaesthesia, compared with isoflurane anaesthesia, but the difference in pressures did not reach a significant level. This finding is surprising, the reasons being that the sample sizes were too small, combined with the small differences in subdural ICP and the relatively high SD. However, another reason might be that the pressure/volume relationship in children is different from adults because of the smaller intracranial volume and the compliancy of the cranial vault. Thus, changes in cerebral vascular resistance caused by anaesthetics might give rise to smaller changes in subdural ICP. Moreover, the present study was not controlled and randomized to the two anaesthetic procedures. Only a randomized controlled study might resolve this issue.

In many patients relatively low CPP values were observed in the present studies. In some patients the low CPP were related to the size of the space-occupying lesions. It is important, however, to emphasize that MABP is age and gender dependent, with relatively low values compared with adults (Jackson et al. 2007; Haque and Zaritsky 2007).

In the second study it was demonstrated that 5° and 10° rTp significantly reduced subdural ICP without significant change in CPP. These findings are in agreement with studies in adult patients with cerebral tumour in the supine (Haure et al. 2003, Tankisi and Cold 2007) and the prone positions (Tankisi et al. 2002), and in patients with cerebral aneurysm (Tankisi et al. 2006).

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Chapter 21
Subdural Spinal Pressure During Surgery for Intradural Tumours and Surgery for Tethered Cord

Georg Emil Cold, Claus Mosdal and Niels Juul

Abstract
To our knowledge studies of subdural spinal pressure during spinal surgery have never been performed. Knowledge of the spinal subdural pressure could be of importance for the surgeon when resecting intradural tumour masses from the spine. Additionally it could be of interest for the team treating the patient with a spinal mass to gain knowledge of the pressure both cranial and caudal to the tumour.

In this chapter a study of the measurements of spinal subdural pressure was performed before opening of dura in patients subjected to spinal surgery for intradural tumour or tethered cord. Measurements were performed cranially and caudally to the tumour (if present) and the effect of hyperventilation and positive end-expiratory pressure on spinal subdural pressure studied.

To our knowledge studies of subdural spinal pressure during spinal surgery have never been performed. Knowledge of the spinal subdural pressure could be of importance for the surgeon when resecting intradural tumour masses from the spine. Additionally could it be of interest for the team treating the patient with a spinal mass to gain knowledge of the pressure both cranial and caudal to the tumour. In this study measurements of spinal subdural pressure (SSP) were performed before opening of dura in patients subjected to spinal surgery for intradural tumour or tethered cord.

Study Outline

Aims 1: To measure SSP and spinal perfusion pressure (SPP) in patients subjected to spinal surgery. 2: To study the effect of hyperventilation on SSP. 3: To study the effect of PEEP on SSP.

Method In 18 patients, 12 patients with spinal tumour and 6 patients with tethered cord, SSP and MABP were measured. SPP was calculated as the dif-

ference between MABP and SSP. Simultaneously, arterial blood was analysed for $PaCO_2$, PaO_2 and pH. The measurements were performed during general anaesthesia with the patient in the prone position. In 10 patients with spinal cord tumour SSP was measured cranially and caudally to the tumour. None of the patients had a complete block of CSF flow. The effect of 5 min hyperventilation on SSP and SPP were studied in 17 patients (12 patients with spinal tumour and 5 patients with tethered cord). In 11 patients with spinal tumour and 6 patients with tethered cord, 10 cm PEEP was applied for a period of 2 min.

Statistical analysis Medians and ranges are indicated. Wilcoxon's test was used for analysing intragroup differences, and the Mann-Whitney test was used for intergroup statistics. $P<0.05$ was considered significant.

Results In the neutral position of the operating table median SSP was 10 (4–17) mmHg in patients with spinal tumour and 8 (0–10) mmHg in patients with tethered cord. In 7 patients with spinal tumour, regional differences between cranial and caudal SSP were recorded with a difference in median of 5.5 (3–15) mmHg. A tendency was observed, indicating that the difference between pressures measured cranially and caudally to the tumour was positive when the tumour was placed cranially in the neuroaxis, and vice versa (Table 21.1). During hyperventilation $PaCO_2$ decreased from median 4.5 to 3.8 kPa. No significant change in SSP or SPP was observed (Table 21.2). In all groups, 10 cm PEEP increased SSP, and in the total number of patients PEEP increased SSP significantly from median 10 to 11 mmHg. Simultaneously, a significant decrease in SPP from median 57 to 52 mmHg was observed, $P<0.001$ (Table 21.3).

Table 21.1 Patients in whom SSP was measured cranially as well as caudally to the tumour. Tumour localization is indicated. Difference in SSP is calculated as the difference between SSP cranial and caudal to the tumour

Patient number	Tumour localization	Cranial spinal pressure (mmHg)	Caudal spinal pressure (mmHg)	Difference in pressure (mmHg)
1	C3–4	17	10	7
2	C6–7	9	12	−3
3	C7–T1	12	6	6
4	T3–4	9	4	5
5	T8	14	11	3
6	T10–11	15	8	7
7	T10	3	8	−5
8	T11–L1	2	6	−4
9	T12	4	19	−15
10	L2	9	15	−6
Median		9	9	5.5
Range		(2–17)	(4–19)	(−15 to 7)

Table 21.2 The effect of 5 min hyperventilation on $PaCO_2$, SSP and SPP in patients with spinal tumour and tethered cord. Median and range are indicated. Group 1: spinal tumour, SSP measured cranial to tumour (n=6). Group 2: spinal tumour, SSP measured caudal to tumour (n=6). Group 3: tethered cord (n=5). Group 4: tumour and tethered cord (n=17)

Group	$PaCO_2$ before (kPa)	$PaCO_2$ after (kPa)	SSP before (mmHg)	SSP after (mmHg)	SPP before (mmHg)	SPP after (mmHg)
1	4.6 (4.3–5.4)	3.9* (3.7–4.4)	6.0 (2.0–8.0)	4.0 (1.0–10.0)	68.5 (37.0–89.0)	69.0 (36.0–89.0.)
2	4.6 (4.2–5.4)	3.8* (3.5–4.4)	7.0 (4.0–21.0)	6.0 (3.0–19.0)	62.0 (54.0–86.0)	64.0 (50.0–84.0)
3	4.3 (4.1–4.7)	3.7* (3.5–4.0)	10.0 (0.0–12.0)	10.0 (−1.0 to 10.0)	50.0 (47.0–57.0)	54.0 (46.0–67.0)
4	4.5 (4.1–5.4)	3.8* (3.5–4.4)	8.0 (0.0–21.0)	7.0 (−1.0 to 19.0)	59.0 (37.0–89.0)	64.0 (36.0–89.0)

*P<0.05

Table 21.3 The effect of 10 cm PEEP on $PaCO_2$, SSP and SPP in patients with spinal tumour or tethered cord. The measurements are recorded immediately before and 2 min after 10 cmH_2O PEEP application. Median and range are indicated. Group 1: spinal tumour, SSP measured cranial to tumour (n=7). Group 2: spinal tumour, SSP measured caudal to tumour (n=4). Group 3: tethered cord (n=6). Group 4: tumour and tethered cord (n=17)

Group	$PaCO_2$ before PEEP (kPa)	$PaCO_2$ after PEEP (kPa)	SSP before PEEP (mmHg)	SSP after PEEP (mmHg)	SPP before PEEP (mmHg)	SPP after PEEP (mmHg)
1	4.4 (4.1–4.6)	4.40 (4.1–4.6)	10.0 (0.0–15.0)	11.0* (5.0–15.0)	59.0 (37.0–76.0)	58.0 (38.0–75.0)
2	4.3 (4.1–4.5)	4.30 (4.1–4.5)	14.0 (6.0–19.0)	15.5 (8.0–22.0)	61.5 (38.0–79.0)	58.0 (39.0–78.0)
3	4.4 (4.1–4.8)	4.45 (4.1–4.8)	8.5 (0.0–12.0)	10.0* (1.0–13.0)	51.0 (37.0–61.0)	49.0 (38.0–56.0)
4	4.4 (4.1–4.8)	4.40 (4.1–4.8)	10.0 (0.0–19.0)	11.0* (1.0–22.0)	57.0 (37.0–79.0)	52.0* (38.0–78.0)

*P<0.05

Conclusion During surgery SSP can be measured accurately. PEEP application significantly increases spinal pressure and reduces SPP. Hyperventilation decreases spinal pressure and increases SPP, but these changes are small. Regional differences in SSP were observed in patients with intradural spinal cord tumour.

Discussion

In the study on the effect of hyperventilation it was demonstrated that hyperventilation did not change SSP significantly. As the effect of hyperventilation is based on vasoconstriction, this finding must be related to experimental and clinical studies of spinal cord blood flow (SBF) and metabolism and its regulation, and the loss of an SSP-reducing effect might be discussed in relation to experimental and clinical data.

In the rat $CMRO_2$ averaged 3.5 ml/100 g/min in the grey matter and 1.0 ml/100 g/min in the white matter. These values are independent of spinal level (Hayashi 1984). With the hydrogen method SBF averages 64.5 and 20.4 ml/100 g/min in the rat grey and white matter, respectively. This difference corresponds to the increased density of the vascular bed in the grey matter (Jellinger 1974). While the blood flow in the white matter differs very little, the blood flow in the grey matter ranges from 39.6 to 79.4 ml. SBF, however, is independent of whether it is measured in the cervical, thoracic or lumbar segment (Hayashi 1984). Immediately after spinal cord injury a marked reduction of blood flow in the lesioned region occurs (Bingham et al. 1975; Kobrine et al. 1975; Griffiths 1976; Senter and Venes 1978; Fehlings et al. 1989; Tator and Fehlings 1991). Thoracic spinal cord ischaemia was induced by inflation of a balloon in aorta in cats. After spinal ischaemia regional SBF increased as much as 2 times the control values and decreased gradually thereafter. After 10 min of balloon occlusion, regional SBF returned to control value. After 30 min of occlusion hypoperfusion after recirculation correlated with irreversible amplitude changes in evoked spinal cord potential, and postischaemic paraparesis and pathological ischaemic changes in the spinal segments were recognized (Yamada et al. 1998).

In experimental studies autoregulation of SBF has been demonstrated (Flohr et al. 1971; Kindt 1971; Kindt et al. 1971; Kobrine and Doyle 1975; Kobrine et al. 1976a, b; Marcus et al. 1977; Hickey et al. 1986). Intact autoregulation has also been confirmed in human studies (Wullenweber 1967). In the monkey regional SBF remains constant in the normal range of MABP of 50 to 135 mmHg. Above MABP of 135 mmHg vasodilatation occurs, resulting in breakthrough of autoregulation (Kobrine et al. 1976b).

Spinal cord blood flow increases with hypercapnia and hypoxaemia, and it decreases with hypocapnia (Wullenweber 1967). When SBF and CBF are compared, the absolute change in SBF per unit CO_2 change is less than the

change in CBF, but because SBF is lower the percentage changes in SBF and CBF are the same.

After reversible spinal cord ischaemia in the rat, marked hyperaemia was seen for the first 15 min, followed by hypoperfusion at 60 min. The CO_2 reactivity was completely absent at 60 min (Marsala et al. 1994).

In the present study, the loss of SSP-reducing effect was not related to autoregulatory mechanisms, because the period with hyperventilation was not accompanied by significant changes in blood pressure or SPP. Although it has been demonstrated that the CO_2 reactivity may be absent following trauma or ischaemia of the spinal cord, this explanation for the absent SSP-reducing effect seems unlikely because the tumour process in the majority of patients was localized to a few segments, leaving the intracranial as well as the functioning part of spinal cord compartments without pathological changes. In four patients a convincing ICP-reducing effect was found. ICP was unchanged in seven patients, while an increase in pressure was observed in three patients. This pattern was not related to the level of spinal pressure measured before hyperventilation, which otherwise might influence an expected SSP-reducing effect caused by the volume/pressure relationship. However, in contrast to the intracranial volume/pressure relationship, where a small reduction in volume elicits a considerably greater ICP reduction at high levels of ICP compared with low levels of ICP, experimental or clinical studies concerning the volume/pressure relationship in the spinal compartment are not available. However, it seems reasonable to hypothesize that the volume/pressure relationship obtained from spinal segments during operation, if present at all, is flat. The operative decompression of the spinal channel also is supposed to constrain any effect of volume-elicited pressure change. Furthermore, it is supposed that the high respirator peak and mean pressures during hyperventilation might impede venous return, increase intraabdominal pressure, dilate the epidural venous vessels and counteract any pressure-reducing effect of hyperventilation. Taking these factors into consideration, changes in spinal blood volume caused by hyperventilation-induced spinal vasoconstriction is not supposed to have a significant effect on SSP.

It has been demonstrated that the application of PEEP prevents the development of pulmonary atelectasis (Hedenstierna et al. 2000). As regards the effect of PEEP on the ICP, Mascia et al. (2005) elevated PEEP to 5 and 10 cmH_2O in patients with head injury, and showed that patients who achieved lung recruitment showed no increase in $PaCO_2$ and ICP remained stable. However, in non-recruiters alveolar hyperinflation occurred, and $PaCO_2$ increased with the consequence of an increase in ICP. These findings are in accordance with studies in patients with SAH (Caricato et al. 2005). McGuire et al. (1997) showed, in patients, that PEEP increased ICP when the applied PEEP was higher than the baseline ICP, but had less effect if the applied PEEP was lower than the ICP. In our study the baseline ICP was 5.7 and 5.1 mmHg in the two groups. So in the group where 10 cmH_2O PEEP was applied the PEEP was higher than the ICP and this may explain why the change in ICP in this group

was more pronounced. Thus, it can be concluded that in the intensive care setting ICP is not affected by PEEP when a significant alveolar recruitment is achieved with PEEP, while patients who showed no increase in lung volumes had an increase in $PaCO_2$ resulting in a rise in CBF and an elevated ICP.

In the present study 10 cmH_2O PEEP application resulted in a significant increase in spinal pressure from 10 to 11 mmHg. The increase in SSP was not related to changes in $PaCO_2$, but a decrease in SPP averaging 5 mmHg was found when all studies were included. In cannot be excluded that autoregulatory vasodilatation occurred caused by the decrease in perfusion pressure, resulting in the detectable increase in SSP. Furthermore, it is supposed that the high respirator peak and mean pressures during PEEP application impedes venous return, increases intraabdominal pressure and dilates the epidural venous vessels, resulting in an increase in SSP.

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Chapter 23
Differences in PCO_2, pH, Lactate, K^+ and Na^+ Between Arterial Blood and Jugular Bulb Blood in Patients Subjected to Craniotomy in Either Propofol-Fentanyl or Propofol-Remifentanil Anaesthesia

Georg Emil Cold and Niels Juul

Abstract

Studies of intensive care patients indicate that the arteriovenous difference (AVD) of PCO_2 in the systemic circulation increases during critical hypoperfusion. As regards the cerebral circulation, studies in pigs indicate that the AVD-PCO_2 increases with CBF reduction. In patients subjected to craniotomy for supratentorial cerebral tumours the AVD-PCO_2 or AVD-pH has not been studied. It has repeatedly been documented that low values of jugular bulb oxygen saturation (SjO_2) and high values of $AVDO_2$ occur during anaesthesia with propofol-fentanyl or propofol-alfentanil, and in a comparative study of propofol-fentanyl or propofol-remifentanil anaesthesia SjO_2 is even lower during the latter.

In this chapter, the results of a database study of AVD of physiological parameters are reported and discussed. We investigated the relationships between $AVDO_2$, AVD-PCO_2, AVD-pH, AVD of the electrolytes Na^+, K^+ and Ca^{++}, SjO_2, jugular oxygen content and jugular oxygen tension during maintenance anaesthesia with propofol-fentanyl and propofol-remifentanil.

Studies of intensive care patients indicate that the AVD of PCO_2 in the systemic circulation increases during critical hypoperfusion (Zhang and Vincent 1993; Mekontso-Dessap et al. 2002). As regards the cerebral circulation, studies in pigs indicate that the AVD-PCO_2 increases with CBF reduction (Rossi et al. 2002). In a case study, this finding has been documented in a patient with severe head injury (Chieregato et al. 1997) and in a series of 12 patients with severe cerebral damage, it was found that the relationship between the $AVDO_2$ and

AVD-PCO_2 was coupled, until severe cerebral ischaemia occurred, at which time the ratio of AVD-PCO_2 to $AVDO_2$ increases (Stocchetti et al. 2005).

In patients subjected to craniotomy for supratentorial cerebral tumours the AVD-PCO_2 or AVD-pH has not been studied. It has repeatedly been documented that low values of SjO_2/high values of $AVDO_2$ occur during anaesthesia with propofol-fentanyl (Jansen et al. 1999; Nandate et al. 2000; Petersen et al. 2003; Kuwano et al. 2004) or propofol-alfentanil (Moss et al. 1995), and in a comparative study of propofol-fentanyl or propofol-remifentanil anaesthesia SjO_2 is even lower during the latter (Schlünzen and Cold; Chapter 8). The threshold of SjO_2 at which cerebral ischaemia occurs, however, has not been defined. Until now, only $AVDO_2$ has been related to AVD-PCO_2, while the correlations between SjO_2, jugular venous oxygen tension (PvO_2) or cerebral venous oxygen content (O_2Ct) as dependent variables have not been studied. As cerebral ischaemia triggers ion dysfunction with movement of water and sodium into the cell, and lactate, potassium and calcium in the opposite direction (Stiefel et al. 2005), membrane failure of cerebral cells theoretically should be accompanied by an increase in the AVD of lactate, K^+ and Ca^{++} and a decrease in AVD-Na^+.

In this chapter, the results of a database study of AVD of physiological parameters are reported and discussed.

Study Outline

Aim To investigate the relationships between $AVDO_2$, AVD-PCO_2, AVD-pH, AVD of the electrolytes Na^+, K^+ and Ca^{++}, SjO_2, jugular O_2Ct, and PvO_2 during maintenance anaesthesia with propofol-fentanyl and propofol-remifentanil.

Patients In total 88 patients were included in the study, 38 patients were anaesthetized with propofol-fentanyl and 50 patients with propofol-remifentanil (see Chapter 3).

Method During craniotomy, paired samples of arterial and jugular venous blood were analysed in 38 patients subjected to propofol-fentanyl and 50 patients subjected to propofol-remifentanil anaesthesia for supratentorial cerebral tumours. Immediately after induction of anaesthesia a jugular bulb catheter and an arterial line were inserted. At the time of opening of dura arterial and jugular blood were analysed for pH, PCO_2, PvO_2, SjO_2, PvO_2, jugular O_2Ct, lactate, K^+, Na^+ and Ca^{++}. The AVD of O_2, PCO_2, pH, lactate, K^+, Na^+ and Ca^{++} were calculated.

Statistical analysis Sigma Stat and Sigma Plot programs were used for linear correlation, significance and power estimation. Data within anaesthetic groups were tested for normal distribution. Within groups the paired *t*-test or Wilcoxon's signed rank test were used. Between groups the normality test and equal variance test were applied. Intergroup analyses included one-way analysis of variance. Tukey's test was used for pair-wise multiple comparison pro-

cedures. The Kruskal-Wallis analysis of variance on ranks, and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. The chi-square test was used for statistical analysis of proportions of observation within neuroradiological, histopathological findings and the degrees of dura tension and brain swelling. Medians (ranges) are indicated. $P<0.05$ was considered statistically significant.

Results of comparison between anaesthetic groups The demographic data (age, weight, height, sex), arterial Na^+, arterial K^+, arterial Ca^{++}, arterial lactate, $PaCO_2$, PaO_2 or rectal temperature were comparable (Table 23.1). The propofol maintenance dose was significantly lower in propofol-remifentanil-anaesthetized patients compared to patients anaesthetized with propofol-fentanyl (Table 23.1).

Table 23.1 Demographic, neuroradiological findings, data concerning maintenance doses of anaesthesia, data from arterial and jugular venous blood and data of MABP, subdural ICP and CPP are presented. Mean±SD are indicated

	Propofol-fentanyl	Propofol-remifentanil
Number	38	50
Men/women	29/21	25/13
Age (years)	53.00±9.0	53.00±11.0
Weight (kg)	72.00±16.0	71.00±13.0
Neuroradiological findings		
Maximal area of the tumour (cm^2)	14.00±11.0	13.00±8.2
Volume of the tumour (cm^3)	27.00±26.0	26.00±31.0
Midline shift (mm)	5.00±6.3	5.50±6.7
Data concerning anaesthesia		
Propofol maintenance dose (mg/h)	509.00±113.0	386.00±105.0*
Fentanyl maintenance dose (μg/h)	128.00±25.0	
Remifentanil maintenance dose (μg/h)		1.80±0.59
Data from arterial and venous samples		
Arterial Na^+ (mmol/L)	138.00±3.0	138.00±3.0
Arterial K^+ (mmol/L)	3.50±0.4	3.70±0.4
Arterial lactate (mmol/L)	1.17±0.53	1.18±0.7
Arterial Ca^{++}(mmol/L)	1.16±0.05	1.14±0.05
$PaCO_2$ (kPa)	4.70±0.3	4.50±0.3
PaO_2 (kPa)	20.00±6.5	24.00±5.7
$AVDO_2$ (mmol/L)	3.33±0.66	3.22±0.70
SjO_2 (%)	53.30±9.1	54.00±8.8
Temperature, MABP, subdural ICP and CPP		
Temperature (°C)	35.80±0.3	35.80±0.3
MABP (mmHg)	87.00±13.0	74.00±11.0*
Subdural ICP (mmHg)	8.70±5.7	7.70±5.7
CPP (mmHg)	78.00±15.0	66.00±13.0*

*$P<0.05$

The neuroradiological data, including midline shift, area and volume of the tumours did not differ significantly between propofol-fentanyl- and propofol-remifentanil-anaesthetized patients (Table 23.1). During propofol-fentanyl anaesthesia the mean±SD of MABP (87±13 mmHg) and CPP (78±15 mmHg) were significantly higher than the values obtained during propofol-remifentanil: MABP (74±11 mmHg) and CPP (66±13 mmHg). No significant difference was found as regards $AVDO_2$ or SjO_2.

Results of correlation studies with AVD-pH and AVD-PCO_2 as independent variables The highest values of correlation coefficients were found when the dependent variables were SjO_2 or $AVDO_2$ (Table 23.2). However, all correlations were highly significant with $P<0.001$ and powers of 1.000, or close to 1 (Table 23.3). The linear correlation of the relationship between propofol-

Table 23.2 Correlation coefficients between SjO_2, $AVDO_2$, PvO_2 and O_2Ct as abscissa, and the AVD-PCO_2 and AVD-pH as ordinate. The patients had supratentorial cerebral tumours and were anaesthetized with propofol-fentanyl or propofol-remifentanil

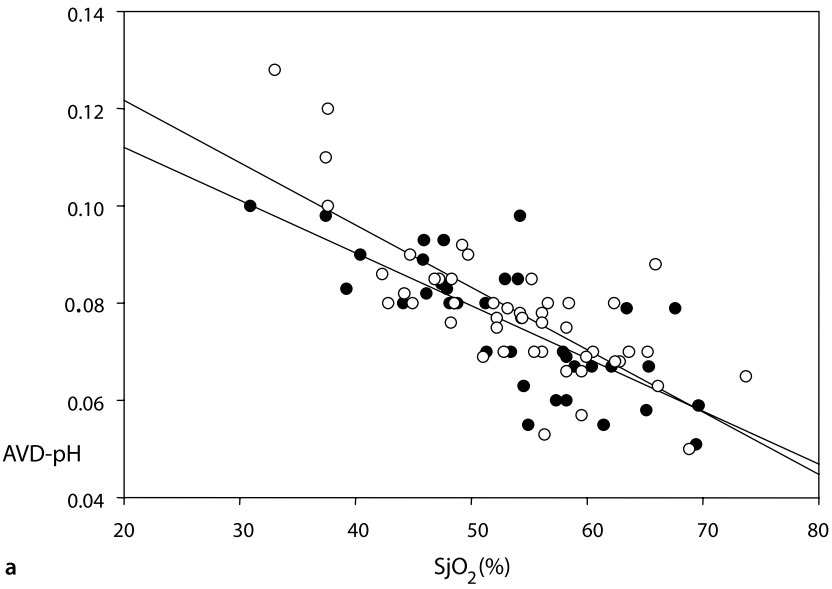
	Correlation coefficient (*r*) AVD-PCO_2 (kPa)	Correlation coefficient (*r*) AVD-pH
Propofol-fentanyl		
SjO_2 (%)	0.7970	0.7499
$AVDO_2$ (mmol/L)	0.8112	0.7463
(PvO_2) (kPa)	0.6672	0.6839
Jugular O_2Ct (mmol/L)	0.5517	0.4974
Propofol-remifentanil		
SjO_2 (%)	0.7943	0.7694
$AVDO_2$ (mmol/L)	0.7623	0.6373
PvO_2 (kPa)	0.6856	0.7035
Jugular O_2Ct (mmol/L)	0.5722	0.6867

Table 23.3 Power and statistical significance (*P* value) of the relationships between SjO_2, $AVDO_2$, PvO_2 and O_2Ct as abscissa, and the AVD-PCO_2 and AVD-pH as ordinate. The patients had supratentorial cerebral tumours and were anaesthetized with propofol-fentanyl or propofol-remifentanil

	AVD-PCO_2 (kPa)		AVD-pH	
	Power	*P* value	Power	*P* value
Propofol-fentanyl				
SjO_2 (%)	1.000	<0.001	1.000	<0.001
$AVDO_2$ (mmol/L)	1.000	<0.001	1.000	<0.001
PvO_2 (kPa)	0.997	<0.001	0.998	<0.001
Jugular O_2Ct (mmol/L)	0.952	<0.001	0.889	<0.001
Propofol-remifentanil				
SjO_2 (%)	1.000	<0.001	1.000	<0.001
$AVDO_2$ (mmol/L)	1.000	<0.001	1.000	<0.001
PvO_2 (kPa)	1.000	<0.001	1.000	<0.001
Jugular O_2Ct (mmol/L)	0.993	<0.001	1.000	<0.001

Table 23.4 Linear regressions of the relationships between SjO_2, $AVDO_2$, PvO_2 and O_2Ct as abscissa, and the AVD-PCO_2 and AVD-pH as ordinate. The patients had supratentorial cerebral tumours and were anaesthetized with propofol-fentanyl or propofol-remifentanil

	Linear regression AVD-PCO_2 (kPa)	Linear regression AVD-pH
Propofol-fentanyl		
SjO_2 (%)	$AVD\text{-}PCO_2 = 2.9720 - 0.0270 \times SjO_2$	$AVD\text{-}pH = 0.1337 - 0.00109 \times SjO_2$
$AVDO_2$ (mmol/L)	$AVD\text{-}PCO_2 = 0.2774 + 0.3765 \times AVDO_2$	$AVD\text{-}pH = 0.0266 + 0.01478 \times AVDO_2$
PvO_2 (kPa)	$AVD\text{-}PCO_2 = 2.7910 - 0.3183 \times PvO_2$	$AVD\text{-}pH = 0.1310 - 0.01390 \times PvO_2$
Jugular O_2Ct (mmol/L)	$AVD\text{-}PCO_2 = 2.3210 - 0.2073 \times O_2Ct$	$AVD\text{-}pH = 0.1060 - 0.00798 \times O_2Ct$
Propofol-remifentanil		
SjO_2 (%)	$AVD\text{-}PCO_2 = 2.9150 - 0.0252 \times SjO_2$	$AVD\text{-}pH = 0.1473 - 0.00128 \times SjO_2$
$AVDO_2$ (mmol/L)	$AVD\text{-}PCO_2 = 0.5634 + 0.3072 \times AVDO_2$	$AVD\text{-}pH = 0.0349 + 0.01342 \times AVDO_2$
PvO_2 (kPa)	$AVD\text{-}PCO_2 = 2.8520 - 0.3386 \times PvO_2$	$AVD\text{-}pH = 0.1474 - 0.01800 \times PvO_2$
Jugular O_2Ct (mmol/L)	$AVD\text{-}PCO_2 = 2.4110 - 0.2342 \times O_2Ct$	$AVD\text{-}pH = 0.1321 - 0.01470 \times O_2Ct$



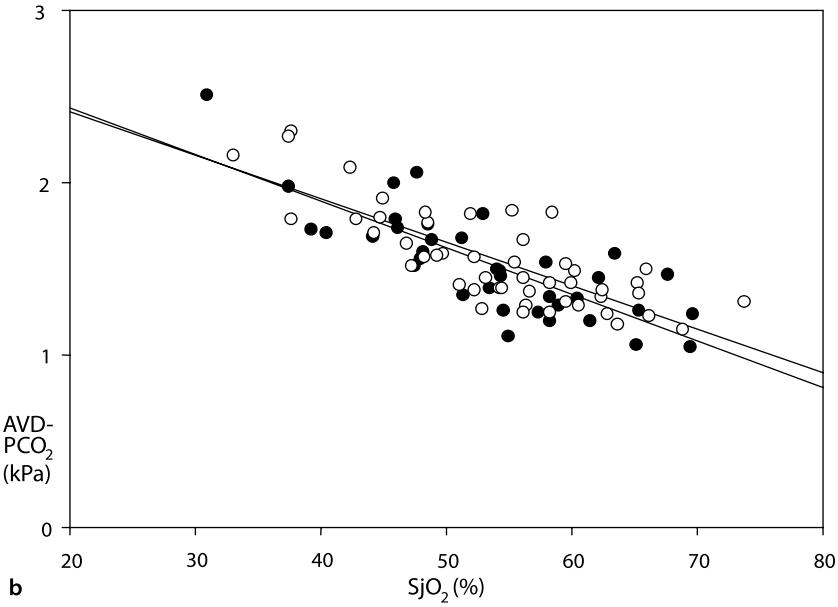
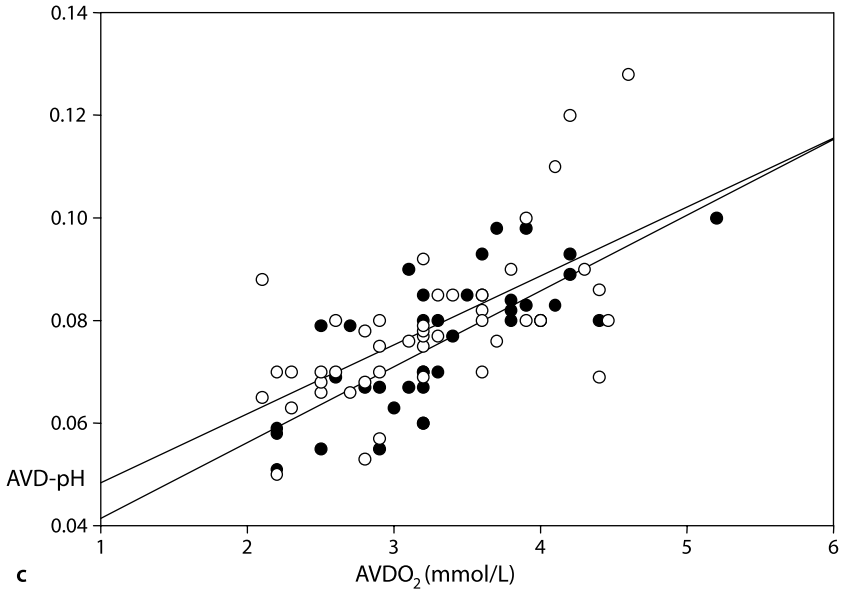


Fig. 23.1 Relationships between SjO_2 and AVD-pH (**a**), SjO_2 and AVD-PCO_2 (**b**), $AVDO_2$ and AVD-pH



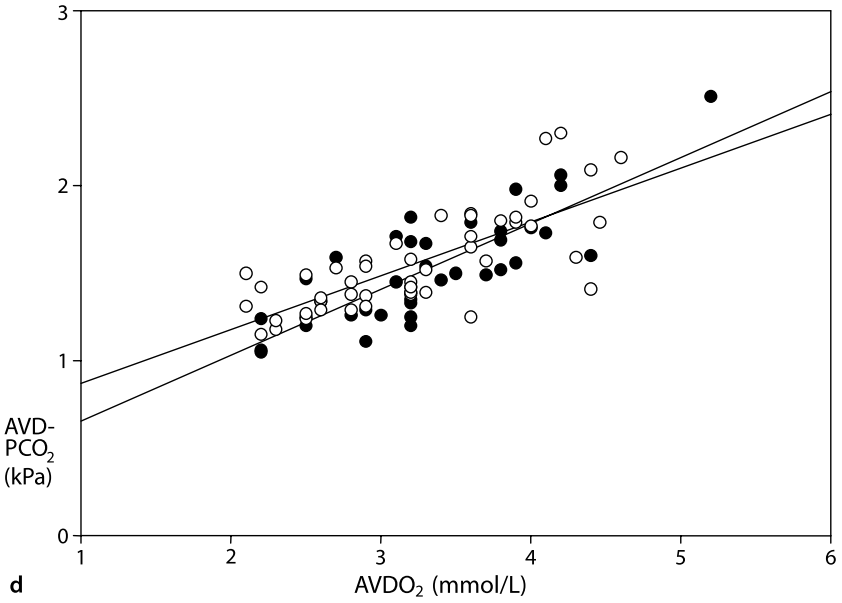


Fig. 23.1 *(continued)* (**c**) and $AVDO_2$ and AVD-PCO_2 (**d**) are indicated. Data were obtained during craniotomy in either propofol-fentanyl (*closed circle*) or propofol-remifentanil (*open circle*). The regression lines are indicated

fentanyl- and propofol-remifentanil-anaesthetized patients did not differ significantly (Table 23.4). The linear regressions between SjO_2 $AVDO_2$ as dependent variable and AVD-pH and AVD-PCO_2 as independent variable, respectively, are indicated in Fig. 23.1a–d.

Results of correlation studies with AVD of lactate, Na^+, K^+ and Ca^{++} as independent variables In Fig. 23.2a–d the correlations between SjO_2 as dependent variable and the AVD of lactate, Na^+, K^+ and Ca^{++} as independent variables are indicated. All correlations were insignificant. In comparison with high values of SjO_2 low values were not associated with any significant changes in the AVD of lactate, Na^+, K^+ or Ca^{++}. As regards AVD-PCO_2 and AVD-pH, the correlation coefficients were highest for the relationships with SjO_2 or $AVDO_2$ as the dependent variable, followed by PvO_2 and O_2Ct, and the data concerning the correlations were close to the regression lines with both anaesthetic regimes, and without significant differences. Although high values of AVD-PCO_2 and AVD-pH were found at low SjO_2 and high $AVDO_2$ values, no signs of increased lactate, K^+ or Ca^{++} liberation from cerebral tissue suggesting impeding cerebral ischaemia were disclosed.

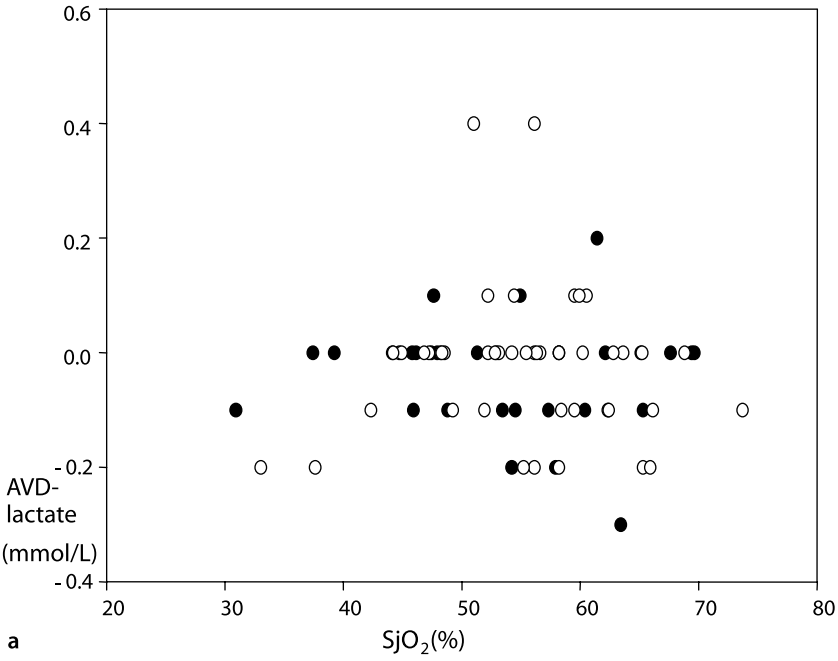
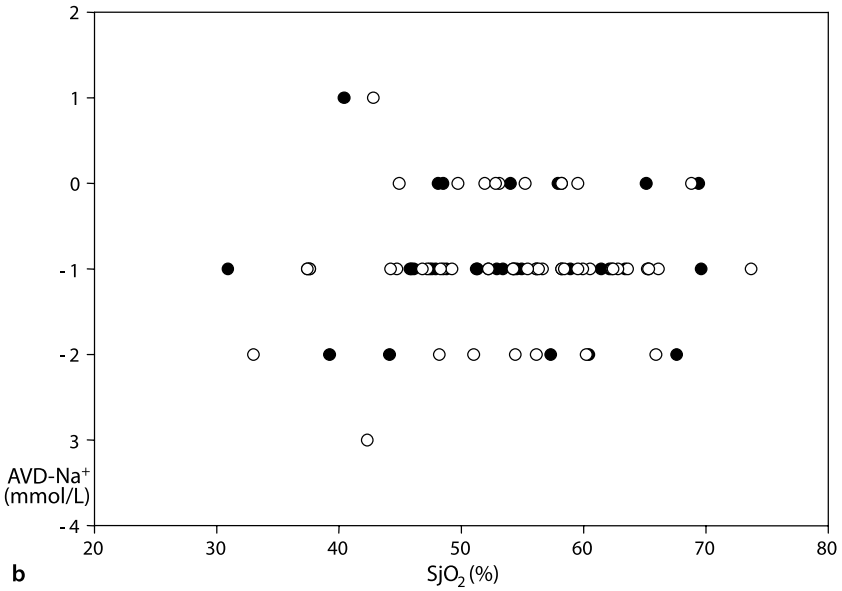


Fig. 23.2 Relationships between SjO_2 and AVD-lactate (**a**), SjO_2 and AVD-Na^+



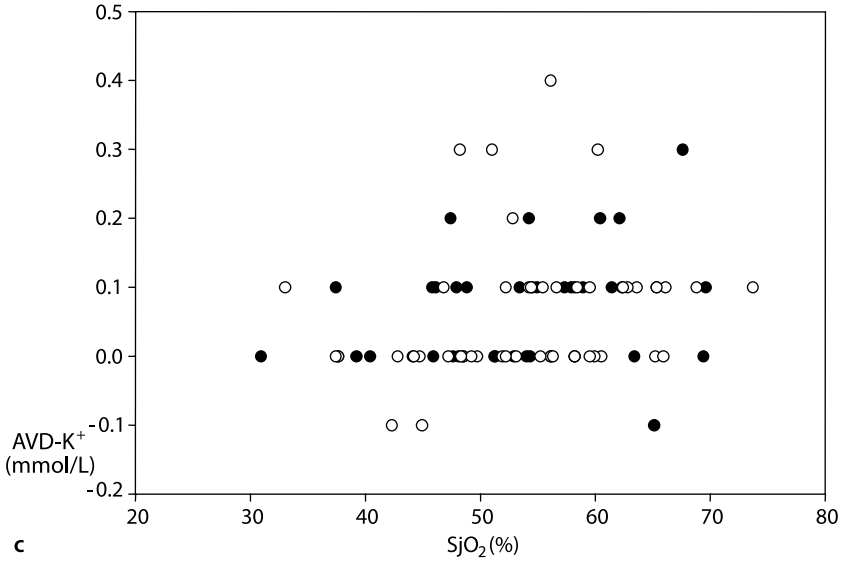


Fig. 23.2 *(continued)* (**b**), SjO_2 and AVD-K^+ (**c**) and SjO_2 and AVD-Ca^{++}

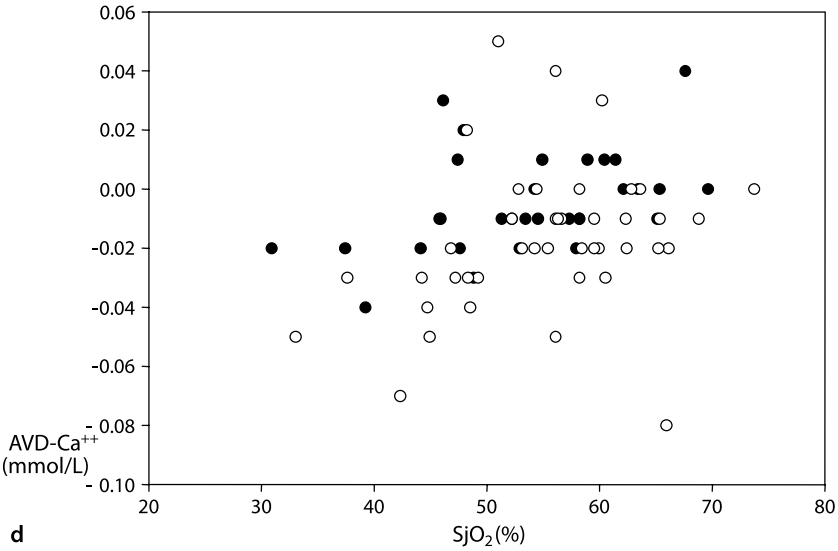


Fig. 23.2 *(continued)* (**d**) are indicated. Data were obtained during craniotomy in either propofol-fentanyl (*closed circle*) or propofol-remifentanil (*open circle*). No significant correlations were found

Conclusion Although an increase in AVD-pH and AVD-PCO_2 is found with low values of SjO_2 and high values of $AVDO_2$, it is not accompanied by significant changes in AVD-lactate, AVD-K+, AVD-Na^+ or AVD-Ca^{++} suggesting cerebral ischaemia.

Discussion

In the present study, patients scheduled for elective supratentorial tumour craniotomy were anaesthetized with either propofol-fentanyl or propofol-remifentanil. Blood from arterial and jugular venous catheters were analysed for oxygen tension, oxygen saturation, electrolytes (K^+, Na^+ and Ca^{++}) and lactate. The aims of the study were as follows: (1) to investigate the relationship between $AVDO_2$, SjO_2, PvO_2 or O_2Ct as dependent factor related to AVD-PCO_2 or AVD-pH; (2) to investigate whether the relationship between $AVDO_2$ with respect to SjO_2 and AVD-PCO_2 with respect to AVD-pH differed between propofol-fentanyl- and propofol-remifentanil-anaesthetized patients; and (3) to study the levels of AVD of lactate K^+, Na^+ and Ca^{++} at low values of SjO_2 with respect to high values of $AVDO_2$.

The results of the study indicate that fairly good correlations were found between $AVDO_2$, SjO_2, PvO_2 or O_2Ct as dependent factor when related to

AVD-PCO_2 or AVD-pH as independent factors. The correlations between these factors were not significantly influenced by choice of anaesthesia, and low values of SjO_2 with respect to high values of $AVDO_2$ were not associated with signs of increased venous influx of lactate/Ca^{++}/Na^+ or venous efflux of K^+.

According to early clinical studies the lower limits of SjO_2 in conscious subjects without cerebral disease are 54.6% and 55.0% (Gibbs et al. 1942; Datsur et al. 1963). In a recent study, however, the lower limit of SjO_2 in patients without cerebral disease was 44.7% with confidence limits 36.5–53% (Chieregato et al. 2003). The authors suggest that contamination by extracerebral blood of the facial veins and the inferior petrosal sinuses is responsible for the higher values found in earlier studies. In accordance with a clinical study indicating that avoidance of extracerebral contamination is prevented when the tip of the catheter is placed within 2 cm of the base of the skull (Jakobsen and Enevoldsen 1989) we introduced the guide wire until resistance was obtained by the base of the skull, and introduced the jugular catheter with the guide wire in this position. Furthermore, we performed moderate neck compression cranial to the catheter to secure cranial direction of the catheter.

Experimental studies have shown that severe cerebral ischaemia is accompanied by flux of K^+ and lactate from the intracellular to the extracellular space, and movement of Na^+ in the opposite direction (Stiefel et al. 2005). Ca^{++} follows K^+, the result being an increased concentration in the extracellular space. In the present study we hypothesized that the AVD of K^+, Ca^{++} and lactate would increase and the AVD of Na+ decrease during cerebral ischaemia. $AVDO_2$, however, is dependent on CBF. If CBF is high, the $AVDO_2$ decreases, while $AVDO_2$ increases at low values of CBF. In several studies it has been observed that during propofol anaesthesia the reduction of CBF is larger than the reduction of $CMRO_2$, resulting in a decrease of the CBF/$CMRO_2$ ratio (Manohar 1986; Scheller et al. 1988, 1990; Mielck et al. 1999). Accordingly, relatively high values of $AVDO_2$ during both anaesthetic procedures were found in the present study, and the correlation between $AVDO_2$ and AVD-PCO_2 and AVD-pH was positive and highly significant, indicating prevention of efflux of CO_2 and H^+ caused by low CBF. During high $AVDO_2$/low SjO_2, however, the AVD of K^+, Ca^{++} and lactate did not increase, and the AVD-Na^+ did not fall, suggesting that cerebral ischaemia, giving rise to disturbed ion homeostasis and increased cerebral lactate efflux, did not occur. These findings support that, although high values of $AVDO_2$ were observed, the threshold of severe global cerebral ischaemia was not exceeded. However, as the AVD data are a global estimate, it does not exclude that regional ischaemia might occur.

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Chapter 23
Differences in PCO_2, pH, Lactate, K^+ and Na^+ Between Arterial Blood and Jugular Bulb Blood in Patients Subjected to Craniotomy in Either Propofol-Fentanyl or Propofol-Remifentanil Anaesthesia

Georg Emil Cold and Niels Juul

Abstract

Studies of intensive care patients indicate that the arteriovenous difference (AVD) of PCO_2 in the systemic circulation increases during critical hypoperfusion. As regards the cerebral circulation, studies in pigs indicate that the AVD-PCO_2 increases with CBF reduction. In patients subjected to craniotomy for supratentorial cerebral tumours the AVD-PCO_2 or AVD-pH has not been studied. It has repeatedly been documented that low values of jugular bulb oxygen saturation (SjO_2) and high values of $AVDO_2$ occur during anaesthesia with propofol-fentanyl or propofol-alfentanil, and in a comparative study of propofol-fentanyl or propofol-remifentanil anaesthesia SjO_2 is even lower during the latter.

In this chapter, the results of a database study of AVD of physiological parameters are reported and discussed. We investigated the relationships between $AVDO_2$, AVD-PCO_2, AVD-pH, AVD of the electrolytes Na^+, K^+ and Ca^{++}, SjO_2, jugular oxygen content and jugular oxygen tension during maintenance anaesthesia with propofol-fentanyl and propofol-remifentanil.

Studies of intensive care patients indicate that the AVD of PCO_2 in the systemic circulation increases during critical hypoperfusion (Zhang and Vincent 1993; Mekontso-Dessap et al. 2002). As regards the cerebral circulation, studies in pigs indicate that the AVD-PCO_2 increases with CBF reduction (Rossi et al. 2002). In a case study, this finding has been documented in a patient with severe head injury (Chieregato et al. 1997) and in a series of 12 patients with severe cerebral damage, it was found that the relationship between the $AVDO_2$ and

AVD-PCO_2 was coupled, until severe cerebral ischaemia occurred, at which time the ratio of AVD-PCO_2 to $AVDO_2$ increases (Stocchetti et al. 2005).

In patients subjected to craniotomy for supratentorial cerebral tumours the AVD-PCO_2 or AVD-pH has not been studied. It has repeatedly been documented that low values of SjO_2/high values of $AVDO_2$ occur during anaesthesia with propofol-fentanyl (Jansen et al. 1999; Nandate et al. 2000; Petersen et al. 2003; Kuwano et al. 2004) or propofol-alfentanil (Moss et al. 1995), and in a comparative study of propofol-fentanyl or propofol-remifentanil anaesthesia SjO_2 is even lower during the latter (Schlünzen and Cold; Chapter 8). The threshold of SjO_2 at which cerebral ischaemia occurs, however, has not been defined. Until now, only $AVDO_2$ has been related to AVD-PCO_2, while the correlations between SjO_2, jugular venous oxygen tension (PvO_2) or cerebral venous oxygen content (O_2Ct) as dependent variables have not been studied. As cerebral ischaemia triggers ion dysfunction with movement of water and sodium into the cell, and lactate, potassium and calcium in the opposite direction (Stiefel et al. 2005), membrane failure of cerebral cells theoretically should be accompanied by an increase in the AVD of lactate, K^+ and Ca^{++} and a decrease in AVD-Na^+.

In this chapter, the results of a database study of AVD of physiological parameters are reported and discussed.

Study Outline

Aim To investigate the relationships between $AVDO_2$, AVD-PCO_2, AVD-pH, AVD of the electrolytes Na^+, K^+ and Ca^{++}, SjO_2, jugular O_2Ct, and PvO_2 during maintenance anaesthesia with propofol-fentanyl and propofol-remifentanil.

Patients In total 88 patients were included in the study, 38 patients were anaesthetized with propofol-fentanyl and 50 patients with propofol-remifentanil (see Chapter 3).

Method During craniotomy, paired samples of arterial and jugular venous blood were analysed in 38 patients subjected to propofol-fentanyl and 50 patients subjected to propofol-remifentanil anaesthesia for supratentorial cerebral tumours. Immediately after induction of anaesthesia a jugular bulb catheter and an arterial line were inserted. At the time of opening of dura arterial and jugular blood were analysed for pH, PCO_2, PvO_2, SjO_2, PvO_2, jugular O_2Ct, lactate, K^+, Na^+ and Ca^{++}. The AVD of O_2, PCO_2, pH, lactate, K^+, Na^+ and Ca^{++} were calculated.

Statistical analysis Sigma Stat and Sigma Plot programs were used for linear correlation, significance and power estimation. Data within anaesthetic groups were tested for normal distribution. Within groups the paired *t*-test or Wilcoxon's signed rank test were used. Between groups the normality test and equal variance test were applied. Intergroup analyses included one-way analysis of variance. Tukey's test was used for pair-wise multiple comparison pro-

cedures. The Kruskal-Wallis analysis of variance on ranks, and multiple comparisons versus control groups (Dunn's method) were used for statistical analysis when the normality test or equal variance test were not passed. The chi-square test was used for statistical analysis of proportions of observation within neuroradiological, histopathological findings and the degrees of dura tension and brain swelling. Medians (ranges) are indicated. $P<0.05$ was considered statistically significant.

Results of comparison between anaesthetic groups The demographic data (age, weight, height, sex), arterial Na^+, arterial K^+, arterial Ca^{++}, arterial lactate, $PaCO_2$, PaO_2 or rectal temperature were comparable (Table 23.1). The propofol maintenance dose was significantly lower in propofol-remifentanil-anaesthetized patients compared to patients anaesthetized with propofol-fentanyl (Table 23.1).

Table 23.1 Demographic, neuroradiological findings, data concerning maintenance doses of anaesthesia, data from arterial and jugular venous blood and data of MABP, subdural ICP and CPP are presented. Mean±SD are indicated

	Propofol-fentanyl	Propofol-remifentanil
Number	38	50
Men/women	29/21	25/13
Age (years)	53.00±9.0	53.00±11.0
Weight (kg)	72.00±16.0	71.00±13.0
Neuroradiological findings		
Maximal area of the tumour (cm^2)	14.00±11.0	13.00±8.2
Volume of the tumour (cm^3)	27.00±26.0	26.00±31.0
Midline shift (mm)	5.00±6.3	5.50±6.7
Data concerning anaesthesia		
Propofol maintenance dose (mg/h)	509.00±113.0	386.00±105.0*
Fentanyl maintenance dose (μg/h)	128.00±25.0	
Remifentanil maintenance dose (μg/h)		1.80±0.59
Data from arterial and venous samples		
Arterial Na^+ (mmol/L)	138.00±3.0	138.00±3.0
Arterial K^+ (mmol/L)	3.50±0.4	3.70±0.4
Arterial lactate (mmol/L)	1.17±0.53	1.18±0.7
Arterial Ca^{++}(mmol/L)	1.16±0.05	1.14±0.05
$PaCO_2$ (kPa)	4.70±0.3	4.50±0.3
PaO_2 (kPa)	20.00±6.5	24.00±5.7
$AVDO_2$ (mmol/L)	3.33±0.66	3.22±0.70
SjO_2 (%)	53.30±9.1	54.00±8.8
Temperature, MABP, subdural ICP and CPP		
Temperature (°C)	35.80±0.3	35.80±0.3
MABP (mmHg)	87.00±13.0	74.00±11.0*
Subdural ICP (mmHg)	8.70±5.7	7.70±5.7
CPP (mmHg)	78.00±15.0	66.00±13.0*

*$P<0.05$

The neuroradiological data, including midline shift, area and volume of the tumours did not differ significantly between propofol-fentanyl- and propofol-remifentanil-anaesthetized patients (Table 23.1). During propofol-fentanyl anaesthesia the mean±SD of MABP (87±13 mmHg) and CPP (78±15 mmHg) were significantly higher than the values obtained during propofol-remifentanil: MABP (74±11 mmHg) and CPP (66±13 mmHg). No significant difference was found as regards $AVDO_2$ or SjO_2.

Results of correlation studies with AVD-pH and AVD-PCO_2 as independent variables The highest values of correlation coefficients were found when the dependent variables were SjO_2 or $AVDO_2$ (Table 23.2). However, all correlations were highly significant with $P<0.001$ and powers of 1.000, or close to 1 (Table 23.3). The linear correlation of the relationship between propofol-

Table 23.2 Correlation coefficients between SjO_2, $AVDO_2$, PvO_2 and O_2Ct as abscissa, and the AVD-PCO_2 and AVD-pH as ordinate. The patients had supratentorial cerebral tumours and were anaesthetized with propofol-fentanyl or propofol-remifentanil

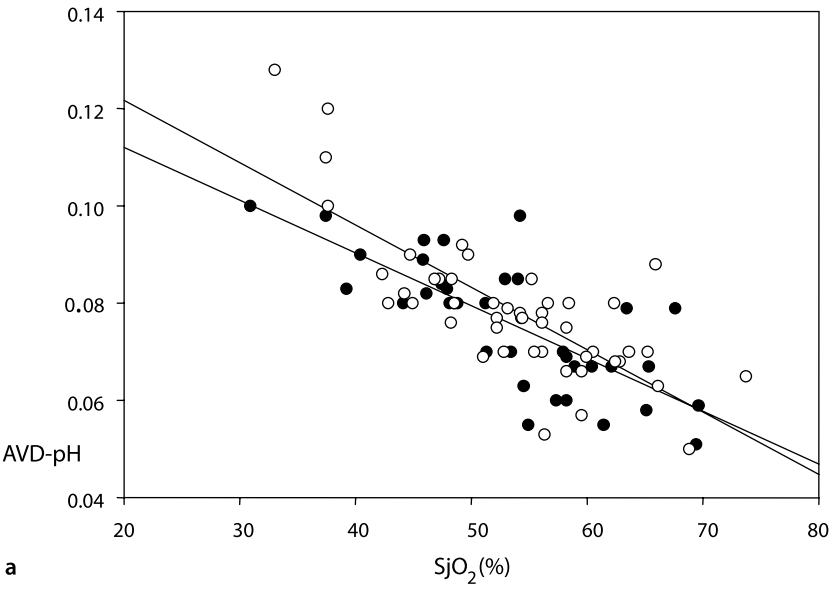
	Correlation coefficient (*r*) AVD-PCO_2 (kPa)	Correlation coefficient (*r*) AVD-pH
Propofol-fentanyl		
SjO_2 (%)	0.7970	0.7499
$AVDO_2$ (mmol/L)	0.8112	0.7463
(PvO_2) (kPa)	0.6672	0.6839
Jugular O_2Ct (mmol/L)	0.5517	0.4974
Propofol-remifentanil		
SjO_2 (%)	0.7943	0.7694
$AVDO_2$ (mmol/L)	0.7623	0.6373
PvO_2 (kPa)	0.6856	0.7035
Jugular O_2Ct (mmol/L)	0.5722	0.6867

Table 23.3 Power and statistical significance (*P* value) of the relationships between SjO_2, $AVDO_2$, PvO_2 and O_2Ct as abscissa, and the AVD-PCO_2 and AVD-pH as ordinate. The patients had supratentorial cerebral tumours and were anaesthetized with propofol-fentanyl or propofol-remifentanil

	AVD-PCO_2 (kPa)		AVD-pH	
	Power	*P* value	Power	*P* value
Propofol-fentanyl				
SjO_2 (%)	1.000	<0.001	1.000	<0.001
$AVDO_2$ (mmol/L)	1.000	<0.001	1.000	<0.001
PvO_2 (kPa)	0.997	<0.001	0.998	<0.001
Jugular O_2Ct (mmol/L)	0.952	<0.001	0.889	<0.001
Propofol-remifentanil				
SjO_2 (%)	1.000	<0.001	1.000	<0.001
$AVDO_2$ (mmol/L)	1.000	<0.001	1.000	<0.001
PvO_2 (kPa)	1.000	<0.001	1.000	<0.001
Jugular O_2Ct (mmol/L)	0.993	<0.001	1.000	<0.001

Table 23.4 Linear regressions of the relationships between SjO_2, $AVDO_2$, PvO_2 and O_2Ct as abscissa, and the AVD-PCO_2 and AVD-pH as ordinate. The patients had supratentorial cerebral tumours and were anaesthetized with propofol-fentanyl or propofol-remifentanil

	Linear regression AVD-PCO_2 (kPa)	Linear regression AVD-pH
Propofol-fentanyl		
SjO_2 (%)	$AVD\text{-}PCO_2 = 2.9720 - 0.0270 \times SjO_2$	$AVD\text{-}pH = 0.1337 - 0.00109 \times SjO_2$
$AVDO_2$ (mmol/L)	$AVD\text{-}PCO_2 = 0.2774 + 0.3765 \times AVDO_2$	$AVD\text{-}pH = 0.0266 + 0.01478 \times AVDO_2$
PvO_2 (kPa)	$AVD\text{-}PCO_2 = 2.7910 - 0.3183 \times PvO_2$	$AVD\text{-}pH = 0.1310 - 0.01390 \times PvO_2$
Jugular O_2Ct (mmol/L)	$AVD\text{-}PCO_2 = 2.3210 - 0.2073 \times O_2Ct$	$AVD\text{-}pH = 0.1060 - 0.00798 \times O_2Ct$
Propofol-remifentanil		
SjO_2 (%)	$AVD\text{-}PCO_2 = 2.9150 - 0.0252 \times SjO_2$	$AVD\text{-}pH = 0.1473 - 0.00128 \times SjO_2$
$AVDO_2$ (mmol/L)	$AVD\text{-}PCO_2 = 0.5634 + 0.3072 \times AVDO_2$	$AVD\text{-}pH = 0.0349 + 0.01342 \times AVDO_2$
PvO_2 (kPa)	$AVD\text{-}PCO_2 = 2.8520 - 0.3386 \times PvO_2$	$AVD\text{-}pH = 0.1474 - 0.01800 \times PvO_2$
Jugular O_2Ct (mmol/L)	$AVD\text{-}PCO_2 = 2.4110 - 0.2342 \times O_2Ct$	$AVD\text{-}pH = 0.1321 - 0.01470 \times O_2Ct$



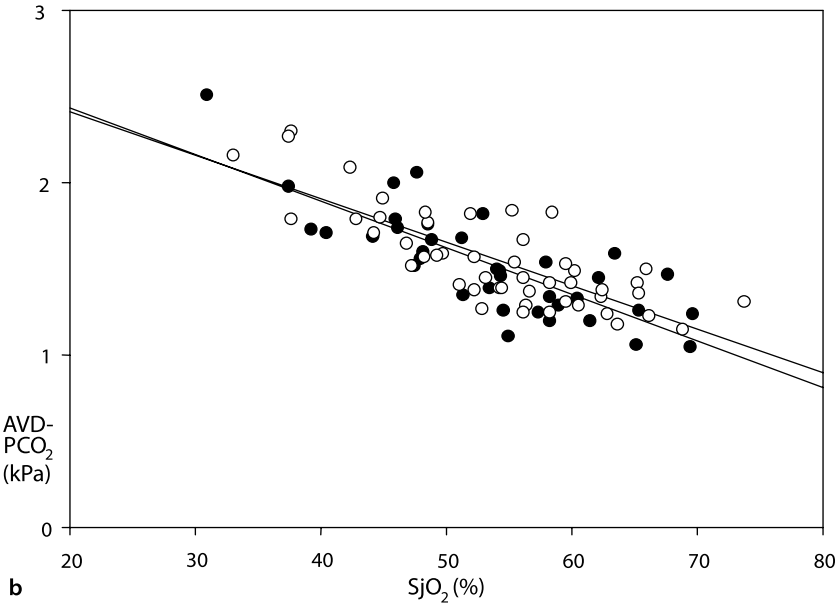
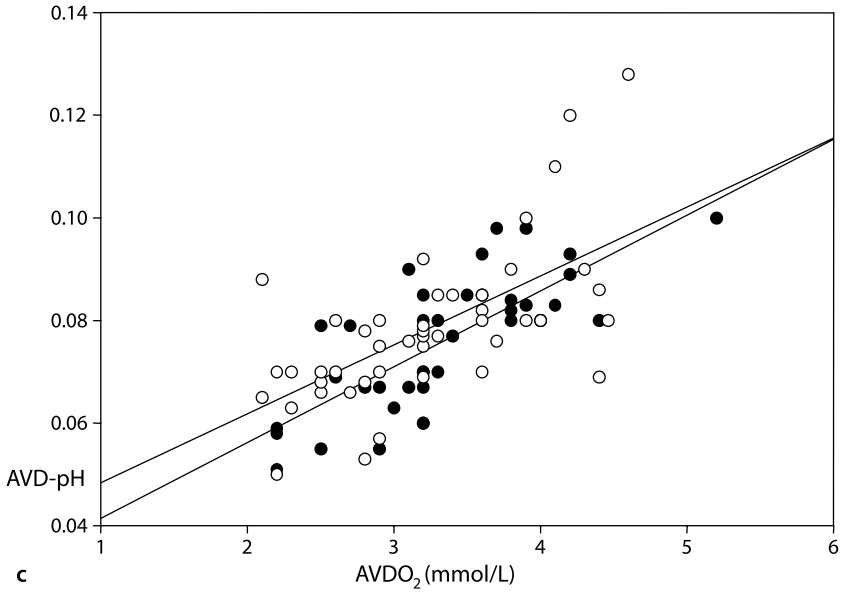


Fig. 23.1 Relationships between SjO_2 and AVD-pH (**a**), SjO_2 and AVD-PCO_2 (**b**), $AVDO_2$ and AVD-pH



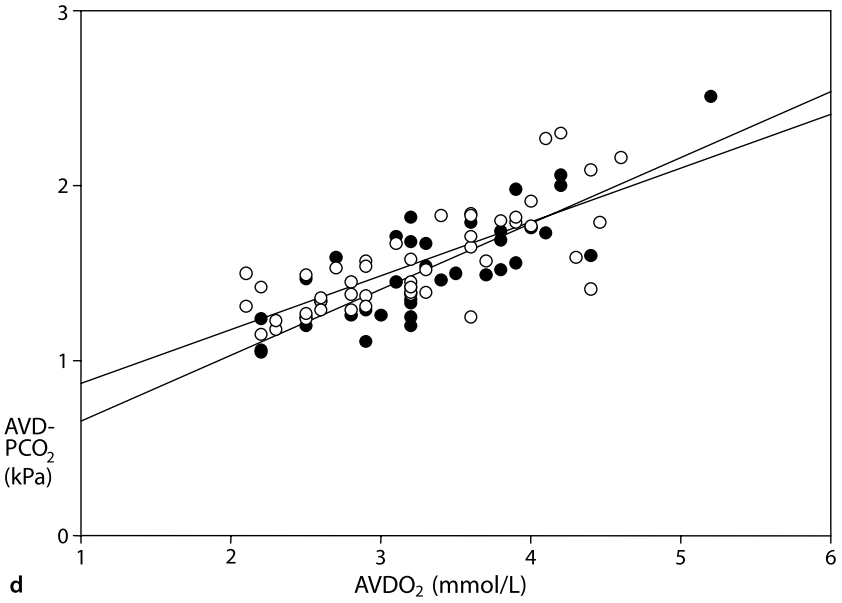


Fig. 23.1 *(continued)* (**c**) and $AVDO_2$ and AVD-PCO_2 (**d**) are indicated. Data were obtained during craniotomy in either propofol-fentanyl (*closed circle*) or propofol-remifentanil (*open circle*). The regression lines are indicated

fentanyl- and propofol-remifentanil-anaesthetized patients did not differ significantly (Table 23.4). The linear regressions between SjO_2 $AVDO_2$ as dependent variable and AVD-pH and AVD-PCO_2 as independent variable, respectively, are indicated in Fig. 23.1a–d.

Results of correlation studies with AVD of lactate, Na^+, K^+ and Ca^{++} as independent variables In Fig. 23.2a–d the correlations between SjO_2 as dependent variable and the AVD of lactate, Na^+, K^+ and Ca^{++} as independent variables are indicated. All correlations were insignificant. In comparison with high values of SjO_2 low values were not associated with any significant changes in the AVD of lactate, Na^+, K^+ or Ca^{++}. As regards AVD-PCO_2 and AVD-pH, the correlation coefficients were highest for the relationships with SjO_2 or $AVDO_2$ as the dependent variable, followed by PvO_2 and O_2Ct, and the data concerning the correlations were close to the regression lines with both anaesthetic regimes, and without significant differences. Although high values of AVD-PCO_2 and AVD-pH were found at low SjO_2 and high $AVDO_2$ values, no signs of increased lactate, K^+ or Ca^{++} liberation from cerebral tissue suggesting impeding cerebral ischaemia were disclosed.

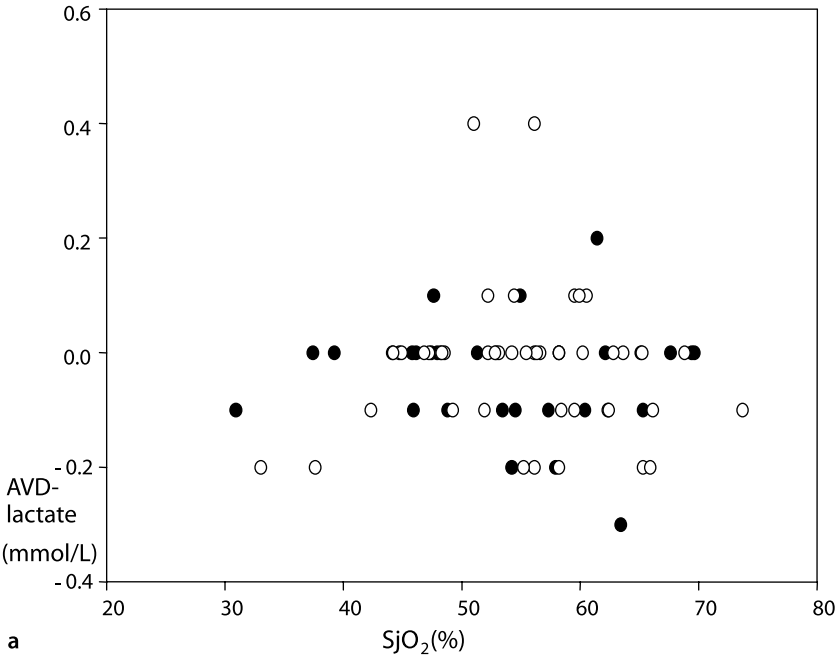
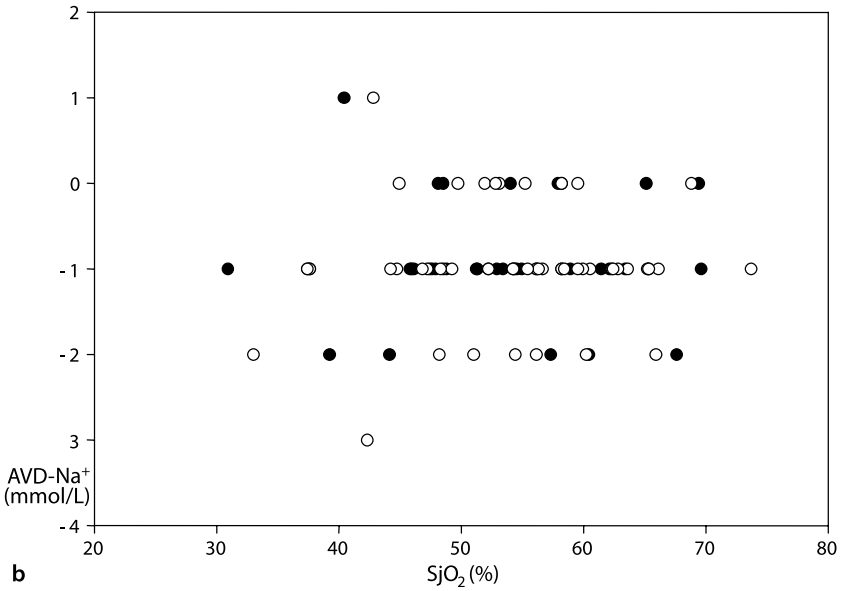


Fig. 23.2 Relationships between SjO_2 and AVD-lactate (**a**), SjO_2 and AVD-Na^+



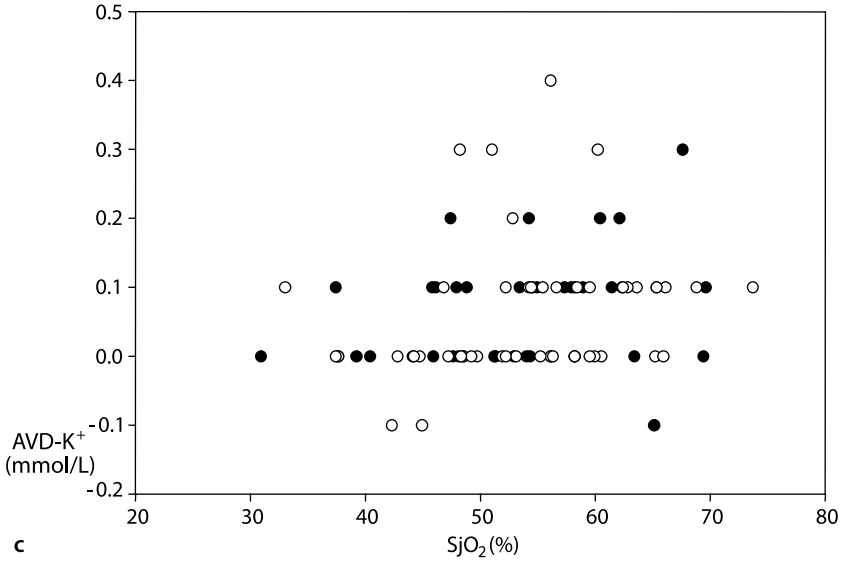


Fig. 23.2 *(continued)* (**b**), SjO_2 and AVD-K^+ (**c**) and SjO_2 and AVD-Ca^{++}

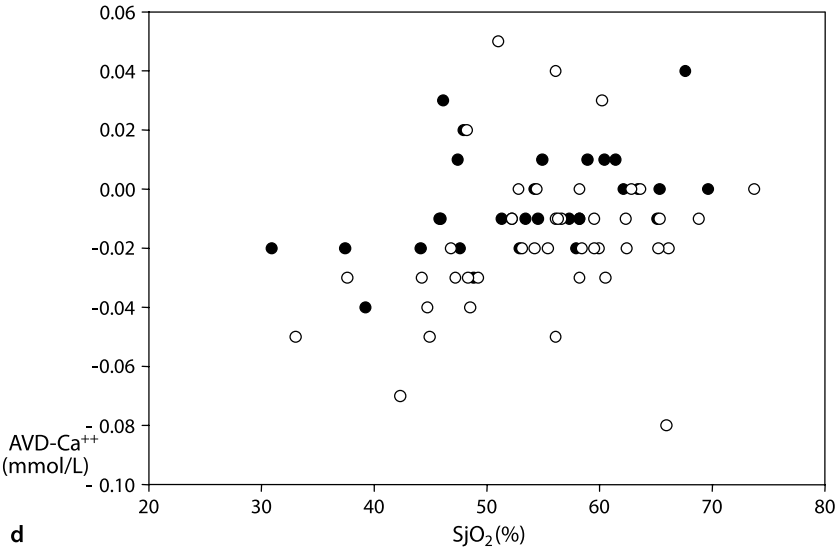


Fig. 23.2 *(continued)* (**d**) are indicated. Data were obtained during craniotomy in either propofol-fentanyl (*closed circle*) or propofol-remifentanil (*open circle*). No significant correlations were found

Conclusion Although an increase in AVD-pH and AVD-PCO_2 is found with low values of SjO_2 and high values of $AVDO_2$, it is not accompanied by significant changes in AVD-lactate, AVD-K+, AVD-Na^+ or AVD-Ca^{++} suggesting cerebral ischaemia.

Discussion

In the present study, patients scheduled for elective supratentorial tumour craniotomy were anaesthetized with either propofol-fentanyl or propofol-remifentanil. Blood from arterial and jugular venous catheters were analysed for oxygen tension, oxygen saturation, electrolytes (K^+, Na^+ and Ca^{++}) and lactate. The aims of the study were as follows: (1) to investigate the relationship between $AVDO_2$, SjO_2, PvO_2 or O_2Ct as dependent factor related to AVD-PCO_2 or AVD-pH; (2) to investigate whether the relationship between $AVDO_2$ with respect to SjO_2 and AVD-PCO_2 with respect to AVD-pH differed between propofol-fentanyl- and propofol-remifentanil-anaesthetized patients; and (3) to study the levels of AVD of lactate K^+, Na^+ and Ca^{++} at low values of SjO_2 with respect to high values of $AVDO_2$.

The results of the study indicate that fairly good correlations were found between $AVDO_2$, SjO_2, PvO_2 or O_2Ct as dependent factor when related to

AVD-PCO_2 or AVD-pH as independent factors. The correlations between these factors were not significantly influenced by choice of anaesthesia, and low values of SjO_2 with respect to high values of $AVDO_2$ were not associated with signs of increased venous influx of lactate/Ca^{++}/Na^+ or venous efflux of K^+.

According to early clinical studies the lower limits of SjO_2 in conscious subjects without cerebral disease are 54.6% and 55.0% (Gibbs et al. 1942; Datsur et al. 1963). In a recent study, however, the lower limit of SjO_2 in patients without cerebral disease was 44.7% with confidence limits 36.5–53% (Chieregato et al. 2003). The authors suggest that contamination by extracerebral blood of the facial veins and the inferior petrosal sinuses is responsible for the higher values found in earlier studies. In accordance with a clinical study indicating that avoidance of extracerebral contamination is prevented when the tip of the catheter is placed within 2 cm of the base of the skull (Jakobsen and Enevoldsen 1989) we introduced the guide wire until resistance was obtained by the base of the skull, and introduced the jugular catheter with the guide wire in this position. Furthermore, we performed moderate neck compression cranial to the catheter to secure cranial direction of the catheter.

Experimental studies have shown that severe cerebral ischaemia is accompanied by flux of K^+ and lactate from the intracellular to the extracellular space, and movement of Na^+ in the opposite direction (Stiefel et al. 2005). Ca^{++} follows K^+, the result being an increased concentration in the extracellular space. In the present study we hypothesized that the AVD of K^+, Ca^{++} and lactate would increase and the AVD of Na+ decrease during cerebral ischaemia. $AVDO_2$, however, is dependent on CBF. If CBF is high, the $AVDO_2$ decreases, while $AVDO_2$ increases at low values of CBF. In several studies it has been observed that during propofol anaesthesia the reduction of CBF is larger than the reduction of $CMRO_2$, resulting in a decrease of the CBF/$CMRO_2$ ratio (Manohar 1986; Scheller et al. 1988, 1990; Mielck et al. 1999). Accordingly, relatively high values of $AVDO_2$ during both anaesthetic procedures were found in the present study, and the correlation between $AVDO_2$ and AVD-PCO_2 and AVD-pH was positive and highly significant, indicating prevention of efflux of CO_2 and H^+ caused by low CBF. During high $AVDO_2$/low SjO_2, however, the AVD of K^+, Ca^{++} and lactate did not increase, and the AVD-Na^+ did not fall, suggesting that cerebral ischaemia, giving rise to disturbed ion homeostasis and increased cerebral lactate efflux, did not occur. These findings support that, although high values of $AVDO_2$ were observed, the threshold of severe global cerebral ischaemia was not exceeded. However, as the AVD data are a global estimate, it does not exclude that regional ischaemia might occur.

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Chapter 24
Limitations and Complications Connected with Monitoring of Subdural Intracranial Pressure and Insertion of Jugular Catheter

Georg Emil Cold and Niels Juul

Abstract

With any invasive monitoring procedure the risk of adverse events is present. The incidence of dural tears during opening of the surgical field has previously been reported in the literature. Predisposing factors for accidental dural tears occurring during supratentorial craniotomy have been reported. Predisposing factors included extracerebral pathology (meningioma), age of the patients, thickness of the cranial vault, the presence of hyperostosis frontalis and a frontal or pterional location. In elderly patients adhesions between the dura and the skull are increased, leaving dura more vulnerable during craniotomy. Moreover, with respect to the auxiliary surgical tools, the use of the drill was associated significantly with dural tears.

In this chapter the adverse effects of subdural monitoring are disclosed. In addition the potential dangers of jugular venous puncture and wound infection are discussed.

Since 1994 we have performed perioperative measurement of subdural ICP combined with arterial pressure, JBP and gas analysis in primarily elective patients subjected to craniotomy. ICP was measured with a 22G needle connected to a pressure transducer via a polyethylene catheter. Until May 2006 1,833 patients have been investigated, and in 989 patients insertion of a jugular bulb catheter was performed. The data have been collected in a database. The techniques used for subdural ICP measurement and insertion of a jugular bulb catheter are described in Chapter 3.

Study Outline

Aim In this study, the incidence of dural lesions, which in some cases may prevent subdural ICP measurement, the incidence of traumatic SAH due to

needle insertion for ICP measurement, and the incidence of wound infection are analysed.

Method After removal of the skull the dura was inspected. If lesion of dura occurred it was registered. If a dural lesion greater than 2 cm was found subdural ICP measurement was omitted. After opening of dura the surface of the brain was inspected. Traumatic SAH was registered.

The occurrence of failed jugular catheter insertion and puncture of the internal carotid artery were registered as well. Via the records, skull wound infection was registered retrospectively for the year 2004. All patients were treated with i.v. cefuroxime (1.5 g for adults) administered shortly after induction of anaesthesia.

Table 24.1 Age of the patients related to number and percentage of patients with dural lesion where it was impossible to measure subdural ICP

Age (years)	Number of patients	Number of dural lesions	Percent of total
0–10	50	0	0.0
11–20	53	0	0.0
21–30	106	2	1.9
31–40	217	8	3.7
41–50	377	19	5.0
51–60	514	30	5.8
61–70	397	36	9.1
71–80	111	21	18.9
81–90	8	2	25.0
Total	1,833	117	6.4

Table 24.2 The incidence of failed subdural ICP monitoring due to large lesion of dura is indicated in different cerebral disorders. Patients undergoing supratentorial craniotomy are included

Pathology	Number	Percent	Total
SAH	19	8.4	225
Arteriovenous malformation	2	7.1	28
Head injury	0	0.0	15
Glioblastoma	21	4.5	467
Meningioma	40	11.6	345
Metastasis	20	7.3	275
Oligodendroglioma	7	6.3	111
Craniopharangioma	1	7.1	14
Glioma	6	7.0	86
Other tumours	1	6.1	21
Other disorders	0	0.0	63
Total	117	7.1	1,657

Results In 10 patients it was impossible to measure subdural ICP because of technical reasons (cable or transducer defect (n=4), bleeding (n=2) or unstable ICP (n=4)). In 293 patents (16%) dural lesion occurred, and in 117 patients (6.4%) ICP measurement was impossible because of dural lesion exceeding 2 cm. The occurrence of dural lesions increased with the age of the patients (Table 24.1) and in patients undergoing supratentorial craniotomy. Dural lesion was frequently found in patients with convexity meningioma and patients with cerebral aneurysm where the pterion approach was used (Table 24.2). In infratentorial surgery the incidence was highest in patients with angioma (9.8%) (Table 24.3). Traumatic SAH occurred in 16 patients (0.87%) (Table 24.4).

In 13 of 989 patients (1.3%) it was impossible to locate the jugular vein. Also, puncture of the carotid artery occurred in 12 cases (1.2%) and, in these

Table 24.3 The incidence of failed subdural ICP monitoring due to large lesion of dura is indicated in different cerebral disorders. Patients undergoing infratentorial craniectomy are included

Pathology	Number	Percent	Total
Angioma	4	9.8	41
Metastasis	4	5.8	69
Astrocytoma	1	6.7	15
Meningioma	2	8.0	25
Trigeminus	2	7.7	26
Total	13	7.4	176

Table 24.4 The occurrence of fresh traumatic SAH in 1,833 patients (10 male, 6 female), mean age 57.6 years (15–68 years)

	Number	Percent
Diagnosis		
Glioblastoma	6	
Oligodendroglioma	2	
Glioma	3	
Meningioma	1	
Astrocytoma	1	
Metastasis	1	
Ependynoma	1	
Intracerebral haematoma	1	
Total	16	0.87
Localization		
Frontal	4	
Parietal	2	
Temporal	7	
Occipital	3	
Total	16	0.87

cases, further attempts to insert a catheter were avoided. No further adverse events were reported as regards insertion of the jugular catheters. For a period of 12 months (year 2004) the incidence of wound infection was registered. During this period wound infections were not disclosed. In comparison, among the 143 patients subjected to acute craniotomy without ICP monitoring 4 patients (2.8%) suffered from deep skull wound infection.

Conclusion Perioperative subdural ICP measurement gives valuable information about ICP, and in addition information concerning the effects of ICP-reducing managements. Due to large dural lesions subdural ICP measurement could not be performed in 5.3% of patients. Traumatic SAH occurs rarely, and wound infections were not registered in the present study.

Discussion

The incidence of dural tears during opening in the present study is in accordance with the literature. Predisposing factors for accidental dural tears occurring during supratentorial craniotomy were studied by Engelhardt et al. (2005). They found an incidence of 26%. Predisposing factors included extracerebral pathology (meningioma), age of the patients, thickness of the cranial vault, the presence of hyperostosis frontalis and a frontal or pterional location. In elderly patients adhesions between the dura and the skull are increased, leaving dura more vulnerable during craniotomy. Moreover, with respect to the auxiliary surgical tools, the use of the drill was associated significantly with dural tears.

One reason for the relatively high incidence of lesion of dura in patients with meningioma is that meningioma generally is attached to dura, whereas meningioma without dural attachment is extremely rare (Zhang et al. 2007). Thus, in some meningioma opening of dura inevitably results in lesion of dura.

In the present study, the incidence of fresh SAH discovered after opening of dura was 0.87%. In all cases dura was intact after removal of the bone flap. The low incidence made estimation of risk factors futile. In three patients (0.17%) it was possible to locate the source of bleeding to cerebral veins, located just under the needle used for subdural ICP measurement. In the other cases the source of bleeding was undetectable. In these cases the source of bleeding might also be caused by incision of dura, and by the sewing of dura to the bone. If SAH was present some degree of brain swelling occurred, but in none of the cases did the presence of haemorrhage prevent the surgical procedure. Literature concerning the incidence of SAH after opening of dura is not available.

In order to avoid puncture of the carotid artery, catheterization of the jugular vein was performed with the head in the neutral position (Sulek et al. 1996) and with the patient positioned in 5–10° rTp. This position dilates the jugular vein (Clenaghan et al. 2006). Only the right jugular vein was used. Ultrasound guide in order to localize the jugular vein was not used in the present study,

although the success rate is higher with this technique and complications are fewer (Hayashi and Amano 2002; Cajozza et al. 2004). Nevertheless, puncture of the carotid artery occurred in 12 patients (1.2%), and in 13 of 989 patients (1.3%) it was impossible to locate the jugular vein. Data concerning the incidence of carotid puncture are not available for jugular catheterization in the cranial direction. The incidence during central placement of jugular catheters varies between zero in children (Sheridan and Weber 2006) and 2.9% in critically ill patients (Schummer et al. 2007). Thus, the incidence in the present material seems acceptable. Infections localized to the jugular catheter were not observed, probably because the catheter was removed before extubation of the patients.

In the present study the incidence of wound infection was surprisingly low in the year 2004, and meningitis did not occur. One reason may be that the incidence was registered retrospectively. Moreover, in the present study, surgical site infections were not classified according to the guidelines of the Center for Disease Control (Barker 1994). An infection rate as high as 17.6% has been found (Idali et al. 2004). More seriously, postcraniotomy meningitis has been recorded in 5.5% of patients (Kourbeti et al. 2007). In a prospective study, where antibiotic prophylaxis was used, an incidence of 6.6% has been documented (Korinek et al. 2005). In the same study CSF leak, male gender, surgical diagnosis (glial tumours, meningioma, metastasis), early re-operation and surgical duration were independent risk factors, and it was documented that antibiotic prophylaxis decreased rates of infection significantly. That surgery for meningioma and metastasis is a risk factor for infection has also been documented in other studies (Blomstedt 1985; Tenney et al. 1985; Gaillard and Gilsbach 1991). Presence of diabetes mellitus, presence of foreign body and ICP monitoring were risk factors in a study by Erman et al. (2005), and the surgeon was found to be the most important risk factor influencing the infection rate (George et al. 1979; Blomstedt 1985). Taking the retrospective analysis of infection rate in the present study into consideration, it must be concluded that subdural ICP monitoring as such does not increase the rate of postcraniotomy infection.

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Subject Index

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