White Coat Hypertension

An Unresolved Diagnostic and Therapeutic Problem

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White Coat Hypertension: Definition, Terminology and Prevalence

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Gianfranco Parati, Juan Eugenio Ochoa, Carolina Lombardi, and Grzegorz Bilo

1.1 Introduction

The medical visit, or more in general the situation of being in a clinical environment, often leads the patient to experience an alerting reaction and a transient increase in blood pressure (BP) levels [1–3], known as the "white coat effect" [4]. This represents a major problem associated with BP measurement in clinical practice, as it prevents BP measures obtained in the clinic from accurately reflecting the "true" subject's blood pressure values. Although the first description of this phenomenon was performed by the end of the nineteenth century [5], it was thanks to the observations made by studies implementing sophisticated systems for continuous BP monitoring in ambulatory conditions that the nature and mechanisms responsible for the pressor response to the medical visit could be better understood [1, 3]. These pioneering studies not only provided direct and precise quantitative assessment of the BP rise associated with the doctor's visit but also indicated that it is the alerting reaction and not the cuff inflation at the moment of BP measurement that causes this pressor response [1, 6].

Following the introduction of techniques for intermittent ambulatory BP monitoring in clinical practice, and the observation that in most cases office BP values are higher than ambulatory BP [7], the difference between clinic and daytime ambulatory BP values was proposed as an alternative, indirect measure of the pressor response to the doctor's visit, and indicated as a means to assess the "white coat

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effect" (WCE). This difference was also indicated as a possible basic mechanism for the condition characterized by persistently elevated BP levels in the medical environment and normal ambulatory BP during daily life, which was referred to as "white coat hypertension" [4, 8].

Despite the complex pathophysiology underlying the so-called WCE and WCH phenomena, these conditions have been often treated rather simplistically, ignoring important and still unresolved problems associated with their measurement and identification. Although the use of these terms has become widespread in clinical practice, there are still concerns on whether they are appropriate and comprehensive enough to reflect potentially different phenomena such as the acute pressor response triggered by the alerting reaction during the medical visit and the difference between office and daytime or 24-h ambulatory BP levels. However, even if somehow arbitrary, current definitions of the WCE and WCH based on the clinic-ambulatory BP difference were intended to help the practicing physician in clinical decision making, i.e., in deciding whether or not antihypertensive treatment should or should not be administered to a given patient.

This chapter will provide a critical appraisal of the definitions currently employed when referring to WCE and WCH, also addressing the terminology that should be used when assessing discrepancies between office and ambulatory BP levels in treated hypertensive patients, in whom the white coat effect may continue to be present with a higher than expected frequency, and a difference between office and ambulatory BP levels may thus indicate a different response to treatment, with out-of-office BP levels being reduced by antihypertensive drugs and office BP levels remaining elevated because of a persisting emotional reaction, a condition which could be better defined as "white coat resistant hypertension" [9].

1.2 The "Real" White Coat Effect as Directly Measured with Beat-to-Beat BP Recordings During the Doctor's Visit

As mentioned above, a major problem associated with conventional auscultatory BP measurement in the clinic is the alerting reaction and BP rise that is often induced in the patient at the time of consultation, which has been commonly referred to as the "white coat effect" (WCE) [4]. The term "white coat" comes from the observation made at the end of the nineteenth century [5] that clinic BP measurement elicits an alerting reaction that may elevate BP, sometimes to a marked degree. However, it was, thanks to the observations, made by studies implementing sophisticated systems for continuous BP recording in ambulatory conditions that the nature of the WCE could be better understood. These pioneering studies not only provided direct and precise quantitative assessment of the BP rise associated with the doctor's visit but also provided significant insight into the pathophysiology of the WCE.

By using continuous intra-arterial ambulatory BP recordings over 24 h (i.e., through a percutaneous catheter inserted into the radial artery), these studies clearly showed that the BP rise during a physician's visit starts with the beginning of the visit, even before the time of the actual BP measurement, persisting until the last minutes of a visit of about 10–15 min duration (Fig. 1.1).

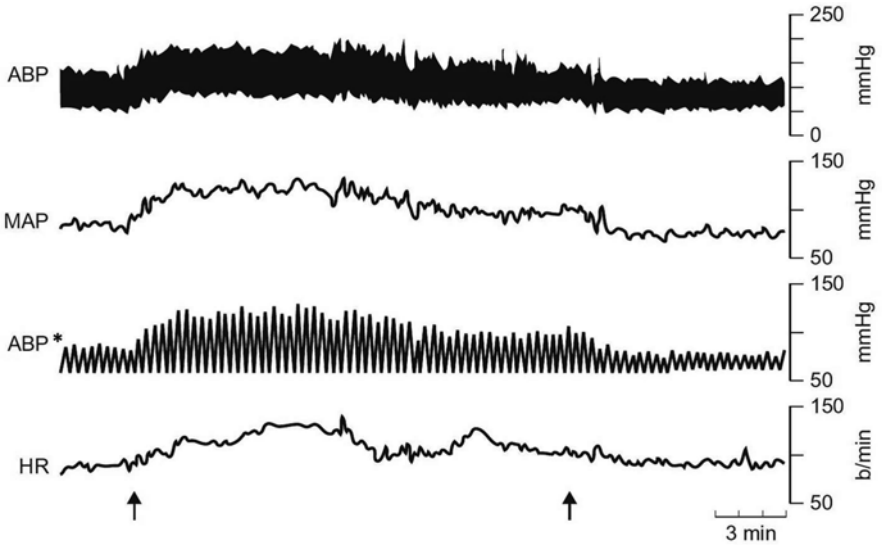

Fig. 1.1 Original intra-arterial blood pressure recording performed in a patient before, during, and after a 15 min visit by a physician unknown to the patient. *Arrows* indicate the beginning and the end of a 15 min doctor's visit. *ABP* pulsatile arterial BP, *MAP* mean BP, *ABP** BP values integrated every 10 min, *HR* heart rate (Taken from Mancia et al. [54] with permission)

Remarkably, the increase in BP levels during the clinical visit was shown to be of considerable magnitude amounting on average to +27/+14 mmHg for SBP/DBP in a group of 48 hypertensive patients within the first 2–4 min of the visit and being accompanied by a parallel increase in heart rate as shown in (Fig. 1.2) [1–3].

This phenomenon was correctly interpreted as the hemodynamic response associated with patients' alerting reaction to the physician's visit. These findings were further confirmed by means of noninvasive continuous BP monitoring at the finger level showing that WCE, rather than being a research artifact, corresponds to a reproducible phenomenon [10, 11].

These studies also provided evidence that the WCE may characterize not only the period when the patient actually sees the physician but also the entire period spent in a clinic setting.

1.3 Clinic-Ambulatory BP Difference: An Indirect Estimate of the White Coat Effect?

A direct and precise quantification of the pressor reaction to the medical visit is only possible through implementation of beat-to-beat BP recordings in a clinic environment. However, the ethical concerns associated with the invasive nature of intra-arterial BP monitoring and the costs and technical difficulties of noninvasive systems for continuous BP recording at the finger level have prevented their routine use either in a clinical setting or in epidemiological studies.

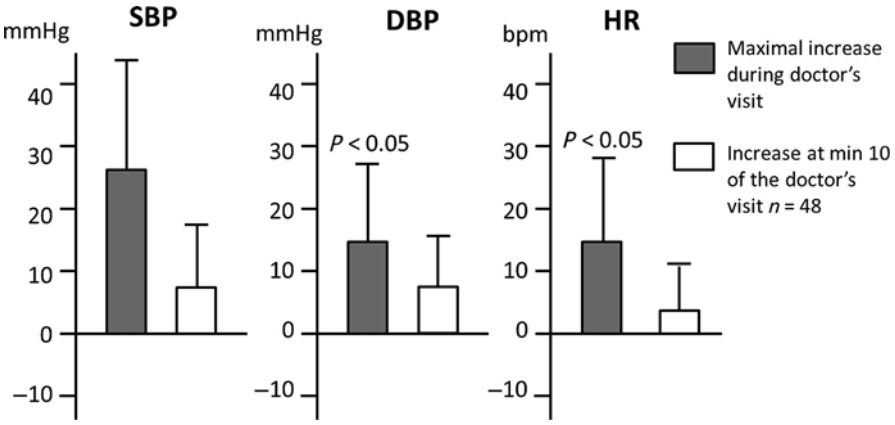

Fig. 1.2 Peak increases in systolic blood pressure (*SBP*), diastolic blood pressure (*DBP*), and heart rate (*HR*) during the doctor's visit. Data are shown as average values for a group of 48 hypertensive patients (Taken from Mancia et al. [3] with permission)

The introduction of noninvasive techniques for intermittent ambulatory or home BP monitoring in clinical practice and the observation that, in general, office BP levels are higher than BP measured out of the office [1] led to the suggestion that the difference between clinic and mean daytime ambulatory or home blood pressure values might provide an easier, although indirect, assessment of the pressor reaction to the medical visit [4]. This concept was also based on the assumption that out-of-office BP is not influenced by the stressful conditions present in the medical environment and on the evidence provided by previous studies showing that intermittent automated cuff inflations during noninvasive ambulatory BP monitoring do not trigger the alerting reaction and pressure rise induced by a physician's visit and thus do not overestimate daytime BP values [6]. The difference between clinic and ambulatory BP values was later taken by some authors as a measure of the "white coat effect" (WCE) [4]. This difference was regarded as a possible explanation for the finding of persistently elevated BP levels in the medical environment associated with normal ambulatory BP during daily life, a condition which was thus defined as "white coat hypertension" [4, 8].

Although the use of the clinic-ambulatory BP difference as a measure of the so-called WCE gained popularity in clinical practice, studies comparing direct measures of the "real" WCE (i.e., as assessed by means of continuous, noninvasive BP recordings during a doctor's visit) with the clinic-ambulatory BP difference have shown limited [12] or even lack of correlation between these measures [10, 13]. Significant discrepancies between these measures were shown in one of these studies, in which clinic-ambulatory BP difference corresponded to less than 30 % of the peak finger beat-by-beat blood pressure increases during the physician's visit [10], which is in line with the finding of an inverse relationship between [14] the

clinic-ambulatory BP difference and the real white coat effect. These reports have raised important concerns regarding the ability of the clinic-ambulatory BP difference to reasonably reflect the patient's pressor response associated with the alerting reaction during the clinical visit. It is likely that the clinic-ambulatory BP difference may represent a different physiological phenomenon, influenced also by mechanisms other than the alarm reaction to the medical environment. In support of this, the observations from several studies have raised the possibility that variables known to affect daytime BP levels, such as psychosocial, behavioral factors, varying degrees of physical activity, variable wake and sleep time periods, and stressful conditions occurring in daily life, may be more important determinants of the clinic-ambulatory daytime BP difference than the office BP rise due to an alerting reaction triggered by the medical visit [10, 15, 16].

Even from a technical point of view, the discrepancies between direct (real WCE) and indirect (surrogate WCE) measures of the WCE are not at all surprising if we consider that, at variance from continuous BP recordings in a clinic setting, intermittent ambulatory BP measures are not performed in concomitance with the medical visit. Indeed, when the WCE is directly assessed by measures taken before, during, and after the visit of a doctor or a nurse in charge of measuring the BP, the WCE appears to be characterized not only by an increase in BP levels but also by a tachycardic response [1, 3, 17]. In contrast, the clinic-daytime ambulatory BP difference is often not accompanied by any similar difference in heart rate [18]. Furthermore, the real (i.e., directly assessed) WCE has been shown to be independent of the patients age and average clinic BP values [1, 19]; in contrast, the clinic-daytime ambulatory BP difference increases progressively with age and clinic BP values [18, 20] (Fig. 1.3).

The considerations mentioned above and the poor correlation between measures of the "real" white coat effect (i.e., the BP increase in response to the alerting reaction triggered by the presence of a physician) and its surrogate assessment (i.e., the clinic-ambulatory BP difference) make the term "WCE" inappropriate when referring to the clinic-daytime average BP difference. However, even despite the lack of consistent evidence to support the use of the difference between clinic and daytime blood pressure as a reliable quantitative index of the "real" white coat effect, this difference is currently the most commonly used approach to indirectly quantify the WCE, largely because of the simplicity and feasibility of this approach in clinical practice. Another proposed approach to the indirect assessment of the white coat effect is the quantification of BP levels during the so-called white coat window during 24-h ABPM, i.e., the BP levels recorded during the first and/or last hour of a 24-h ABPM when a subject is in the clinic environment to have to ABPM device applied or removed, respectively [21].

Use of the difference between office and ambulatory BP as an indirect measure of the white coat effect, however, should be considered on the background of its important limitations, mentioned above. The same caution should also apply to the interpretation of the difference between clinic and home BP levels [8].

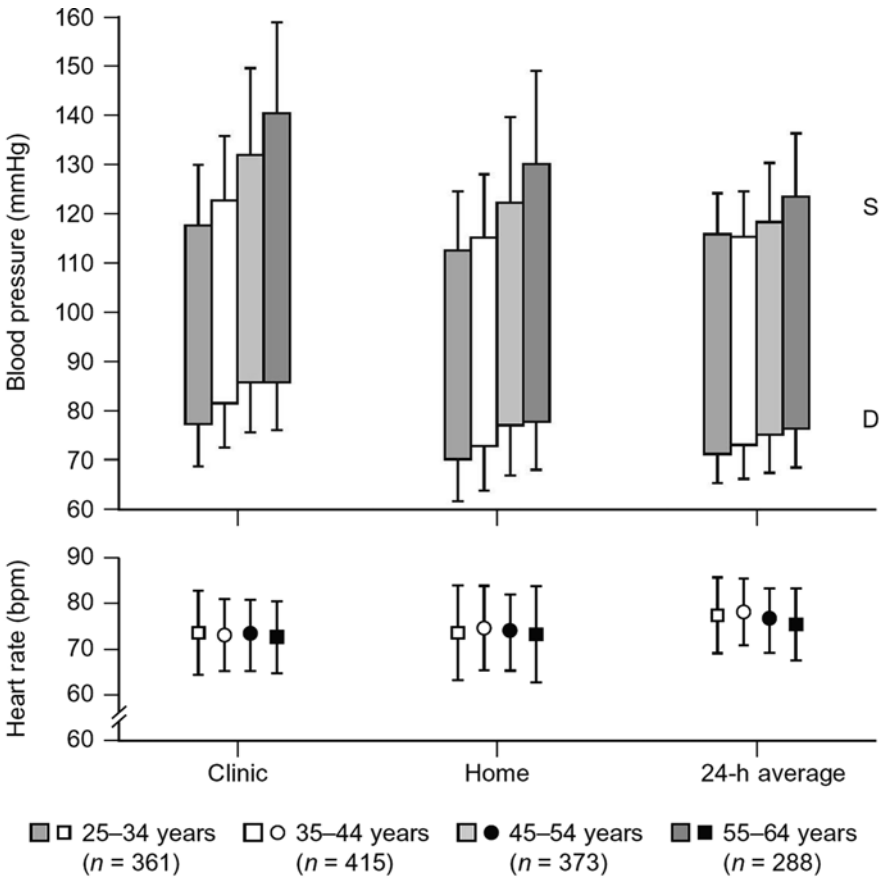

Fig. 1.3 Clinic, home, and 24-h average blood pressure and heart rate values in normotensive and untreated hypertensive subjects included in the PAMELA study. Data are shown as average values ± SEM separately for different age decades. *S* systolic blood pressure, *D* diastolic blood pressure (Taken from Mancia et al. [18] with permission)

1.4 White Coat Hypertension (Isolated Clinic Hypertension): Its Assessment from Intermittent ABPM Recordings

The widespread, although somehow improper, adoption of the difference between clinic and mean daytime ambulatory or home blood pressure values as an indirect measure of the "white coat effect" [4] has led to consider the condition characterized by a persistently high BP in the clinic environment associated with a persistently normal BP in daily life as to reflect the persistence over time of an alerting reaction to the physician's visit. This condition was therefore referred to as "white coat hypertension" [4, 22].

The term WCH was coined under the assumption that the difference between the higher BP values measured in the clinic and the lower values monitored automatically during daytime reflects a pronounced pressor response to the clinic visit and BP measurement procedure in individuals with a normal BP during daily life activities [4, 23]. Indeed, while clinic BP is often affected by the alerting reaction to its measurement by a doctor or a nurse, ambulatory BP data are not influenced by any substantial alerting component in response to automatic or semiautomatic cuff inflations [6]. An exception is represented by the abovementioned reports showing a pronounced rise in BP occurring during the first and/or the last hour of a 24-h ambulatory BP monitoring, when patients are in the hospital environment for fitting or removal of the BP recorder [21, 24].

More in general, use of the term WCH to describe the finding of persistently elevated clinic BP and normal out-of-office BP is inaccurate, because a difference between clinic and ambulatory BP does not necessarily reflect only a white coat effect (as suggested by the reported limited relationship between clinic-ambulatory BP difference and the "real" WCE). It is likely that a high clinic and a normal out-of-office BP may also be generated by factors that lower ambulatory or home BP, such as physical activity or orthostatic hypotension, and not necessarily only by the increase in-office BP due to an alerting reaction to the medical environment.

Besides, the increase in BP levels in response to the medical environment may not be high enough to reach the hypertensive range, so that a given subject may present considerable increase in BP levels during the medical visit without yet being in the hypertensive range. Conversely, hypertensive patients may continue to present a WCE at the time of a doctor's visit, even if their BP levels are persistently elevated.

The occurrence of the WCE regardless of the presence of hypertension is the reason why WCH should be clearly distinguished from the WCE. While the WCE represents an increase in BP levels during the doctor's visit, regardless of the usual BP levels of subjects and the administration of antihypertensive treatment, the term "white coat hypertension" should be used to address the condition characterized by persistently elevated BP in the medical environment and by persistently normal daytime ambulatory BP values during daily life in a patient not yet receiving antihypertensive medication [4], although office BP values higher than ambulatory BP may occur independently of a white coat effect [10].

In consideration of all the conceptual concerns mentioned above, the World Health Organization/International Society of Hypertension (WHO/ISH) Guidelines [25, 26] recommended that the condition characterized by persistently elevated clinic or office BP and by persistently normal daytime ambulatory or home BP values should be named "isolated office hypertension" (IOH) or "isolated clinic hypertension" instead of using the appealing, but sometimes misleading, term "white coat hypertension" (Table 1.1).

Despite of this, the term WCH has become the most commonly used term for describing patients with elevated BP in the clinic or office but not in other settings [4, 27]. Moreover, current hypertension guidelines recommend that the term "white coat hypertension" should be reserved to define untreated individuals [9, 27].

Table 1.1 Definitions

Alerting reaction	A complex, stereotypical reaction to an emotional, potentially threatening stimulus, characterized in the circulatory system by an increase in blood pressure and heart rate accompanied by vasoconstriction in the skin, splanchnic, and renal circulation and by vasodilation in the skeletal muscle
White coat effect, direct, "real" (=white coat phenomenon)	Alerting reaction and pressor response of the patient to the measurement of blood pressure in the clinic environment; can be quantified by continuous blood pressure monitoring (invasive or noninvasive) before and during the physician's visit
White coat effect, surrogate	Difference between cuff blood pressure measured in physician's office (clinic blood pressure) and a measurement of blood pressure outside the physician's office (daytime ambulatory blood pressure, home blood pressure); see the text for its relationship with the direct white coat effect
Isolated office hypertension (also known as white coat hypertension)	A condition characterized by persistently elevated clinic blood pressure in a patient with normal daytime ambulatory or home blood pressure values; the 1999 WHO/ISH Guidelines suggest using the term "isolated office hypertension" instead of "white coat hypertension" because of a limited or absent correlation of office-daytime or office-home blood pressure differences with the "real" white coat effect

Taken from Parati et al. [53] by permission

WHO/ISH World Health Organization/International Society of Hypertension

When using ABPM or home BP monitoring, white coat hypertension has traditionally been defined as BP levels measured in the office, clinic, or surgery persistently ≥140 mmHg systolic and/or ≥90 mmHg diastolic and persistently normal mean daytime BP levels (i.e., <135/85 mmHg), either on ambulatory or in home BP monitoring [28] (Fig. 1.4).

In consideration of the prevailing prognostic relevance of nighttime blood pressure levels over other components of ABPM, current ESH/ESC guidelines for hypertension management [27] and guidelines for ABPM [9] have expanded the definition of white coat hypertension, requiring normality not only in awake BP values but also in 24-h (i.e., <130/80 mmHg) and sleep BP levels (i.e., <120/70 mmHg) (see Box 1.1).

1.5 Prevalence of WCH

Although WCH (or IOH) has been shown to be reasonably reproducible when properly studied with OBP measurements along with real-life ABPM [29], the prevalence reported in literature for WCH has been widely variable and inconsistent, ranging from less than 10 % [18] to more than 60 % [30] with several intermediate values [9, 31, 32].

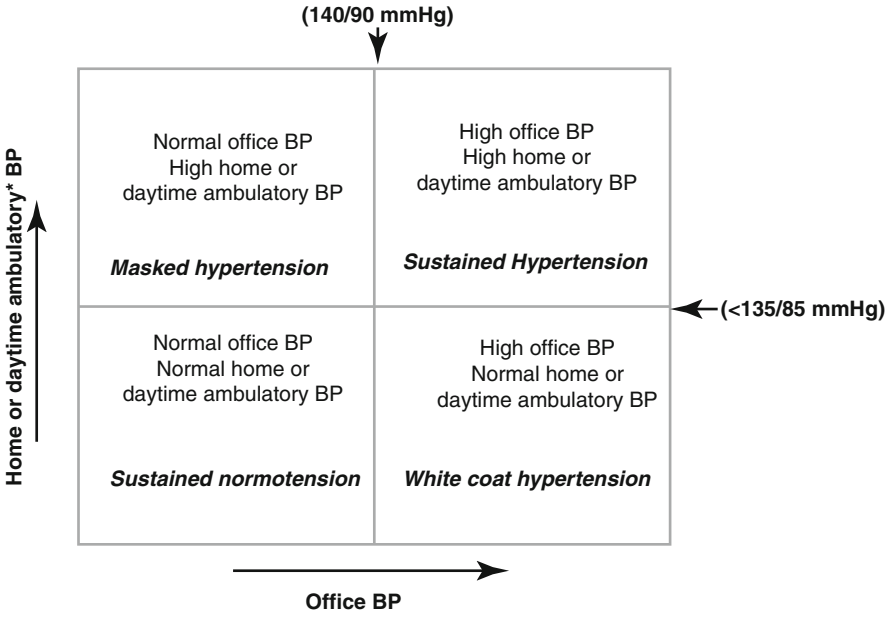

Fig. 1.4 Schematic relationship between office and home or daytime ambulatory *BP* in untreated subjects (Adapted from Parati et al. [52] with permission). *Recent *ABPM* guidelines [9] recommend to compare office *BP* with 24h rather than with daytime ambulatory blood pressure, when considering these different *BP* phenotypes, in order not to exclude the role of differences in night-time *BP*

Box 1.1. Defining Criteria for White Coat Hypertension

Untreated patients with elevated office blood pressure ≥140/90 mmHg[a]
24-h ambulatory blood pressure measurement <130/80 mmHg
Awake ambulatory blood pressure measurement <135/85 mmHg
Sleep measurement <120/70 mmHg or
Home blood pressure <135/85 mmHg

Taken from O'Brien et al. [9] with permission
Diagnoses require confirmation by repeating ambulatory blood pressure monitoring or home blood pressure monitoring within 3–6 months, depending on the individual's total cardiovascular risk
[a]Ambulatory blood pressure values obtained in the clinic during the first or last hour of a 24-h recording may also partly reflect the white coat effect

These important discrepancies might have been the result of the varying demographic features of the populations being surveyed as well as the different threshold values employed for the definition of white coat hypertension in these studies [9, 31, 32]. The first reports on the frequency of white coat hypertension, considering a threshold value of 140/90 mmHg as the upper limit of normality for both office

and daytime ambulatory BP levels, found WCH to be present in as much as 60 % of the overall hypertensive population [30, 33]. However, after the evidence provided by the PAMELA study [18] and other population studies [34, 35] and meta-analyses [36] supporting a threshold value <130/85 mmHg as the upper limit of daytime ambulatory BP normality, the frequency of this phenomenon was found to be significantly lower. Indeed, the prevalence of white coat hypertension in subsequent studies was reported to range from 9 to 16 % in the general population (average 13 %) and from 25 to 46 % (average about 32 %) among hypertensive subjects [9, 18, 31, 32, 37].

Although the prevalence of WCH continues to be widely variable in different studies, available reports strongly emphasize that this condition is rather common, irrespective of whether out-of-office BP is measured by home or ambulatory BP criteria [38].

Many of the studies addressing the prevalence of WCH have also comparatively explored demographic and clinical characteristics of patients with WCH vs. those of patients with sustained hypertension and of normotensive controls, in an attempt to identify potential predictive factors for this condition.

In these studies, the frequency of WCH has been shown to increase in the presence of certain clinical characteristics, such as office systolic (S)BP in the range of 140–159 mmHg or diastolic (D)BP in the range of 90–99 mmHg, female sex, increasing age, non-smoking status, hypertension of recent diagnosis, limited number of BP measurements in the doctor's office, and normal left ventricular mass at echocardiography [4, 32, 39]. The prevalence has been shown to be lower in the case of documented target organ damage or when office BP is based on repeated measurements or when measured by a nurse or another healthcare provider [32].

Regarding demographic variables, age has been shown to be a stronger predictor of WCH than either gender or ethnicity, based on the fact that the relationship of age with clinic BP is much steeper than with ambulatory or home readings [40].

In relation to BP levels, the prevalence of WCH has been shown to be more common among patients with the mildest hypertension (i.e., SBP/DBP 140/90–159/99 mmHg) and virtually nonexistent among those with the most severe hypertension (i.e., above 210/120 mmHg) [22, 23, 41–43]. The analysis of a large international database including performance of ABPM in 7,069 subjects who were initially diagnosed as either normotensive or hypertensive based on conventional office BP measurements showed the prevalence of WCH to be inversely correlated to the level of office BP. While the percentage of white coat hypertension amounted to about 55 % in grade 1 hypertension, it may correspond to only 10 % in grade 3 hypertensive subjects [43]. Similar results were reported in an analysis of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study in 1,333 untreated subjects with essential hypertension in whom the prevalence of WCH markedly decreased with increasing severity of hypertension. When classifying subjects according to the Joint National Committee V classification criteria, the prevalence of white coat hypertension was 33.3 % in stage I (systolic 140–159 mmHg or diastolic BP 90–99 mmHg), 11.8 % in stage

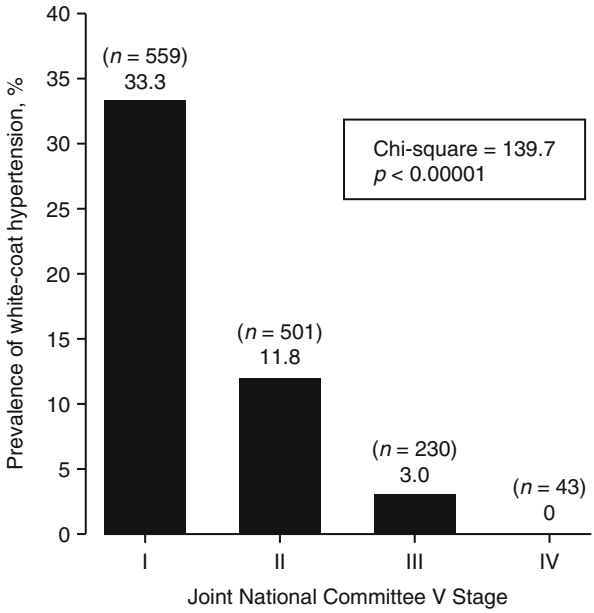

Fig. 1.5 *Bar graph* showing that the prevalence of white coat hypertension decreased with increasing severity of hypertension according to the Joint National Committee V stage of classification (Taken from Verdecchia et al. [22] with permission)

II (systolic 160–179 mmHg or diastolic BP 100–109 mmHg), and 3 % in stage III hypertension (systolic ≥180 mmHg or diastolic BP ≥110 mmHg) [22] (Fig. 1.5).

Remarkably, at variance from white coat hypertension, the study clearly showed an increase in the magnitude of the surrogate measure of the white coat effect (based on the difference between office and ambulatory BP), which was directly related with the JNC V stage of severity of hypertension (7/4 mmHg in the 559 subjects in stage I, 16/6 mmHg in the 501 subjects in stage II, 23/8 mmHg in the 230 subjects in stage III, 29/12 mmHg in the 43 subjects in stage IV). Besides, the white coat effect increased with the JNC V stage both in the group with white coat hypertension (15/11 mmHg in stage I, 31/17 mmHg in stage II, 42/19 mmHg in stage III) and in that with ambulatory hypertension (3/1 mmHg in stage I, 13/5 mmHg in stage II, 22/8 mmHg in stage III, 28/12 mmHg in stage IV) [22] (Fig. 1.6).

Despite having normal home and ambulatory BP, subjects with WCH have nevertheless slightly higher out-of-office BP levels than normotensive controls [38] (Fig. 1.7).

In addition, subjects with WCH have also been shown in the PAMELA study to exhibit a greater prevalence and severity of metabolic risk factors (blood glucose, serum cholesterol, prevalence of an impaired fasting glucose or DM, etc.), albeit less than in patients with true hypertension (Fig. 1.8).

Despite the evidence provided by the above studies suggesting that the likelihood of identifying WCH increases in the presence of certain clinical characteristics, neither pathognomonic diagnostic features nor a cluster of clinical predictors highly specific for diagnosing this condition have so far been identified.

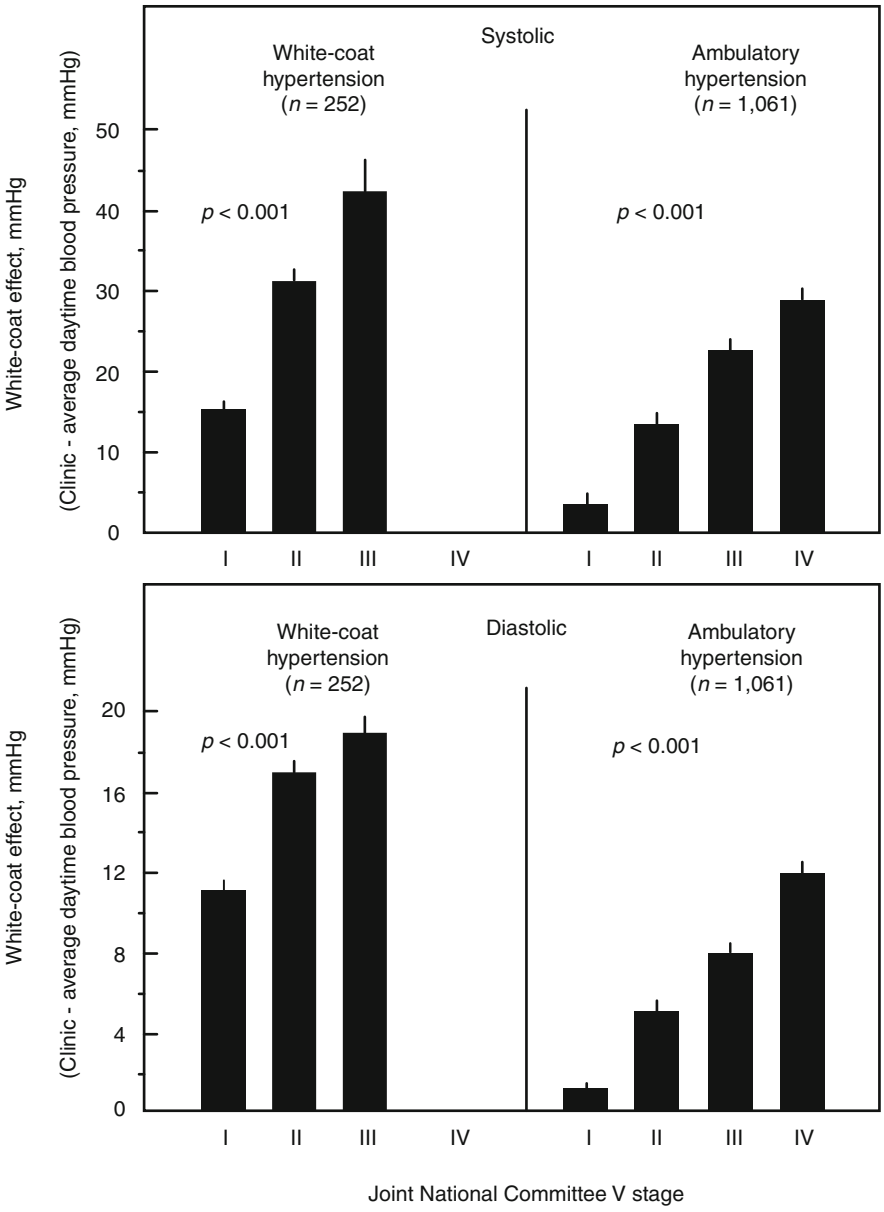

Fig. 1.6 *Bar graph* showing that the magnitude of the white coat effect increased with increasing severity of hypertension according to the Joint National Committee V stage of classification both in the group with white coat hypertension and in that with ambulatory hypertension (Taken from Verdecchia et al. [22] with permission)

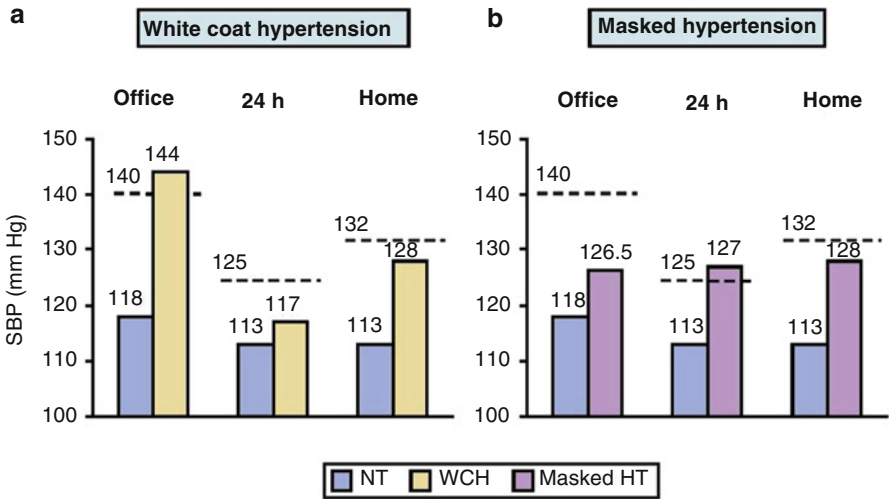

Fig. 1.7 Office, home, and 24-h systolic blood pressure (*SBP*) values in subjects with white coat hypertension (*WCH*) vs. normotensive (*NT*) subjects (**a**) or in patients with masked hypertension (Masked HT) vs. normotensive (*NT*) subjects (**b**). Data are shown as means (Modified from Mancia et al. [38] with permission)

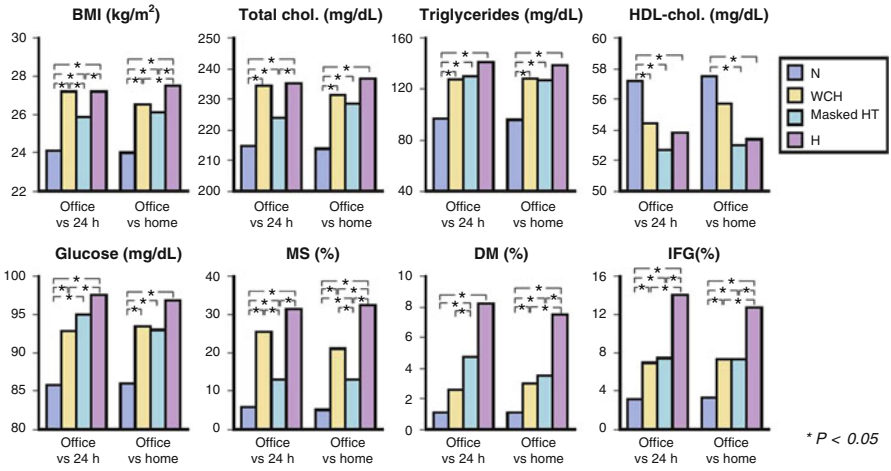

Fig. 1.8 Anthropometric and metabolic variables in normotensive (*N*) subjects and in patients with white coat and masked hypertension. Groups are classified according to office vs. 24-h and office vs. home blood pressure (*BP*) differences. Asterisks refer to the statistical significance to between-group differences (*, $P<0.05$). *H* hypertension, *Masked HT* masked hypertension, *WCH* white coat hypertension (Modified from Mancia et al. [38] with permission)

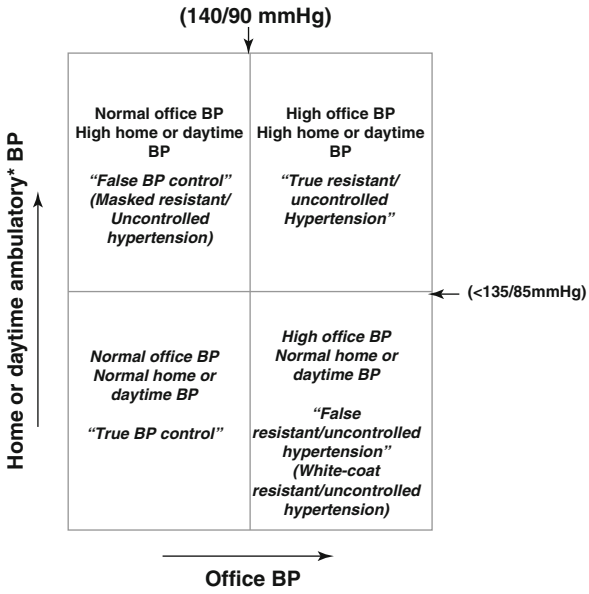

Fig. 1.9 Schematic relationship between office and home or daytime ambulatory *BP* in treated hypertensive subjects. Classification of patients based on the comparison of office and home or daytime ambulatory blood pressure (*BP*) (Modified from Parati et al. [52] with permission). *Recent *ABPM* guidelines [9] recommend to compare office *BP* with 24h rather than with daytime ambulatory blood pressure, when considering these different *BP* phenotypes, in order not to exclude the role of differences in night-time *BP*

1.6 White Coat Resistant Hypertension (False Resistant Hypertension): Definition and Associated Terminology

Current guidelines for the management of resistant hypertension still define resistance to antihypertensive treatment based on OBP measurements.

Indeed, when combining office BP readings either with ambulatory or home BP monitoring in treated patients, and when considering the threshold values to assess lack of BP control, using in-office (OBP ≥140/90 mmHg) and out-of-office techniques (HBP or daytime ABP ≥135/85 mmHg), a treated hypertensive patient initially identified as having resistant hypertension based on office BP values may fall into one of four categories: (1) true BP control (normal in-office and out-of-office BP levels); (2) true resistant hypertension (elevated in-office and out-of-office BP levels); (3) false resistant/uncontrolled hypertension (elevated in-office but normal out-of-office BP levels) also known as white coat resistant/uncontrolled hypertension (WCRH); and (4) false BP control (normal in-office but elevated out-of-office BP levels) also known as masked resistant/uncontrolled hypertension (MRH) (Fig. 1.9).

A proper assessment of BP control and classification of treated hypertensive patients with the combined use of office, ambulatory, and ideally home BP measurements is of upmost relevance for defining the need of performing additional diagnostic procedures (i.e., screening tests for secondary causes of resistant hypertension) and/or implementing more aggressive pharmacological or interventional strategies for the management of resistant hypertension.

1.7 Prevalence of White Coat Resistant Hypertension

Analyses of large databases of observational and interventional studies in hypertension implementing ABPM and HBPM in addition to OBP have overwhelmingly shown that a substantial and sometimes larger than expected number of subjects initially diagnosed with resistant hypertension or with BP control based on OBP actually correspond either to false resistant hypertension (white coat resistant hypertension, WCRH) or false BP control (masked resistant hypertension, MRH), respectively.

In the absence of definitive large prospective trials specifically designed to assess the prevalence of this phenomenon, data from large community-based observational studies and clinical trials suggest that about 10–30 % of subjects within the overall hypertensive population may be resistant to antihypertensive treatment [44–47]. The prevalence of resistant hypertension may considerably increase when applying lower BP cutoff limits for defining BP control (i.e., OBP <130/80 mmHg for hypertensive subjects with diabetes mellitus, renal insufficiency, or high/very high CV risk as recommended by guidelines). It may also falsely increase due to the presence of the "white coat" effect, inadequate doses of antihypertensive therapy, improper use of diuretics, and poor adherence to medical treatment after increases in dosing or number of drugs [47, 48].

Of relevance, in a significant proportion of subjects with resistant hypertension, the persistent elevation in OBP has been shown to correspond to WCRH (false resistant hypertension) as indicated by the analysis of observational studies and clinical trials in hypertension [46, 47]. A report of the Spanish Ambulatory Blood Pressure Monitoring Registry provided relevant data on the prevalence and clinical features of resistant hypertension in a large sample of about 68.000 hypertensive patients from Spain who had 24-h ABPM performed and were recruited from primary care and specialty clinics since 2004 [46]. Overall, a total of 8,295 subjects, corresponding to 12.2 % of the study population, had resistant hypertension, i.e., OBP ≥140/90 mmHg, while taking three antihypertensive drugs. Interestingly, about 37.5 % of these subjects had relatively normal 24-h ABP (24-h systolic/diastolic ambulatory BP <130/80 mmHg) so that their elevated OBP could be explained by the "white coat" effect. This high prevalence of false resistant hypertension exceeds previously reported estimates (18–33 %) of this phenomenon in the general hypertensive population [49]. The remaining 62.5 % of resistant hypertensive subjects in this study had "true resistant hypertension" (i.e., 24-h ABP ≥130/80 mmHg). More recently, a subsequent report of the Spanish database showed that the prevalence of MRH (false BP control), i.e., 24-h ambulatory SBP >130 and/or DBP >80 mmHg, was present in 31 % of treated hypertensive patients apparently controlled based on OBP measures [50]. A previous report in a large sample of Japanese subjects in the frame of the J-HOME Study using cutoff values of 140/90 and 135/85 mmHg for office and home BP, respectively [51], reported a prevalence of WCRH (false resistant hypertension) and true resistant hypertension among patients with resistant hypertension based on office readings of 27.4 and 72.6 % respectively. Conversely, among patients with controlled OBP, the prevalence of true BP control and MRH (false BP control) were 43.1 and 56.9 %, respectively [51].

Conclusions

The transient BP rise ("white coat effect") associated with the alarm reaction during the medical visit leads to significant overestimation and misclassification of BP levels in a substantial number of subjects (whether or not hypertensive and whether or not receiving antihypertensive treatment).

Although WCH might be a consequence of the WCE, they represent different conditions: while the first corresponds to a categorical definition based on the presence of elevated BP levels during the medical visit, accompanied by normality in ambulatory or home BP levels, the WCE represents a quantitative measure of the magnitude of BP rise occurring immediately before and during the medical visit (which may be expected to occur in the majority of subjects and regardless of the presence of hypertension) [1].

A direct and precise quantification of the pressor reaction to the medical visit is only possible through implementation of continuous BP recordings in such condition. However, the ethical difficulties and costs associated with this approach limit its routine use in clinical practice. Another suggested approach is based on the quantification of BP levels in the so-called white coat windows of a 24-h ABPM. Conversely, the clinic-ambulatory BP difference, currently the most commonly employed method to indirectly estimate the WCE in clinical practice, has been shown to be a rather imprecise approach which may not necessarily reflect the pressor response to the alerting reaction during the medical visit. Over the years, different definitions for the WCE and threshold values for identification WCH have been proposed. Of remark, in recognition of the prevailing prognostic value of nighttime BP levels over other components of the 24-h ABPM, current guidelines for hypertension management [9, 27] have expanded the definition of WCH requiring not only the presence of persistently elevated BP levels in the medical office and normality in daytime BP but also normality in nighttime and 24-h ambulatory BP levels.

In the future, studies are required in order to determine the prevalence of WCH according to this new definition, as well as for better defining outcome-driven thresholds for out-of-the-office BP measurement, the diurnal intervals (24-h versus daytime versus nighttime) or the number of self-measurements to be considered to quantify the white coat effect using home BP monitoring.

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Diagnostic Approach to White Coat Effect and White Coat Hypertension

2

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2.1 Introduction

An accurate measurement of blood pressure (BP) levels has important implications for clinical decision making, as it is the basis for a reliable diagnosis of hypertension and for assessment of BP control in treated subjects. The BP rise associated with the alerting reaction during the medical visit, the so-called white coat effect (WCE), represents a major problem associated with conventional BP measurement as it may lead to overestimation of initial BP levels in the absence of treatment and/or to underestimation of the effect of antihypertensive drugs in treated subjects. As a consequence of this, there will be a significant number of subjects with elevated BP levels in the office but with persistently normal out-of-office BP levels (a condition defined as "white coat" hypertension, WCH, or "isolated office" hypertension). Likewise, a considerable number of treated subjects will have apparent resistant hypertension in the office, despite achieving adequate out-of-office BP control with antihypertensive drugs (a condition defined as white coat resistant hypertension, WCRH). From a practical standpoint, the quantification of the magnitude of the

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WCE would allow estimating subjects' actual BP levels, thus reducing misclassification of hypertension and providing a better assessment of BP control. However, an accurate and direct estimation of the WCE requires implementation of complex and sophisticated BP measurement techniques (i.e., beat-to-beat BP recordings) before, during, and after the medical visit [1, 2] which prevents it to be obtained routinely either in a clinical setting or in population studies. To overcome these difficulties, alternative, indirect approaches for estimation of the alarm reaction to the medical visit, based on discontinuous ambulatory BP recordings, have been proposed. The most popular of these indirect methods for the assessment of the WCE consists in the straightforward estimation of the difference between clinic BP and average daytime ambulatory BP levels (measured either with ambulatory or home BP monitoring) [3, 4]. By using this methodology, it is also possible to identify WCH (elevated in-office but normal out-of-office blood pressure levels) as well as WCRH (apparent resistant hypertension based on the finding of persisting elevated OBP measures accompanied by adequate control of out-of-office BP levels) in treated subjects. Since both of these conditions occur with a relatively high frequency in clinical practice, current hypertension guidelines [5, 6] have included suspicion of WCH in untreated patients among the clinical indications for out-of-office BP monitoring. Along the same line, guidelines for the management of resistant hypertension request as a mandatory step the exclusion of WCRH by means of a 24-h ambulatory BP monitoring, before proceeding with any interventional therapy of this condition [7].

Identification of WCH would allow avoiding implementation of unnecessary treatment in subjects who have otherwise normal BP levels in daily life conditions, thus preserving them from the possible adverse effects associated with an inappropriate long-term drug administration, improving subject's quality of life, and reducing the healthcare costs. In treated subjects, identification of false resistant hypertension would allow avoiding performing unnecessary and costly diagnostic tests for identification of secondary causes of hypertension and/or would prevent introducing unnecessary changes in current antihypertensive treatment regimens, thus also preventing the possible occurrence of adverse effects associated with inappropriate multidrug therapy.

The first part of this chapter will review the different methods for assessment of the WCE in clinical practice: addressing both those based on continuous BP recordings for its direct quantification during the medical visit as well as the more indirect approaches based on intermittent ambulatory BP recordings (i.e., the office-ambulatory BP difference and the "ambulatory WCE"). In the second part of this chapter, the initial diagnostic approach to the patient who is found with elevated BP levels in the medical office is addressed, focusing on the role of ABPM and HBPM for defining whether an office BP elevation actually corresponds to true sustained hypertension. Attention is also given to the problems associated with OBP measurement for assessment of BP control in treated hypertensive patients, discussing a practical diagnostic approach for differentiating between true and white coat resistant hypertension.

2.2 Direct Assessment of the WCE from Beat-to-Beat BP Recordings: The "True" WCE

The occurrence of a transient pressor response when BP is measured in the clinical environment, commonly known as the "white coat effect," was first described by Riva Rocci at the end of the nineteenth century [8]. A further report in 1940 by Ayman and Goldshine in a group of hypertensive subjects showed that BP values recorded by the patient at home could be as much as 30 mmHg lower than the readings taken by physicians in their office [9]. Remarkably, this study showed that these differences were not transient but could persist over observation periods of several months [9].

However, a better understanding of the nature of the WCE was only possible, thanks to the information provided by pioneering studies implementing intra-arterial beat-to-beat BP recordings in ambulatory conditions and in concomitance of (i.e., before, during, and after) a medical visit [2, 1]. The first of these studies, performing intra-arterial 24-h BP recordings in a group of hospitalized subjects, showed that the doctor's appearance in the patient's room is accompanied by an immediate rise in patient's BP and heart rate, presumably elicited by an alerting reaction. Remarkably, the BP rise reached its maximum at 2–4 min after the start of the doctor's visit, with a subsequent decline during the remaining 10 min of a 15 min visit, but without disappearing until the end of the medical visit [1]. Translated into recommendations for clinical practice, this finding clearly emphasizes that taking BP readings in a hurry only during the first few minutes of a consultation by a physician should be carefully avoided to prevent an important overestimation of patient's actual BP levels (Fig. 2.1).

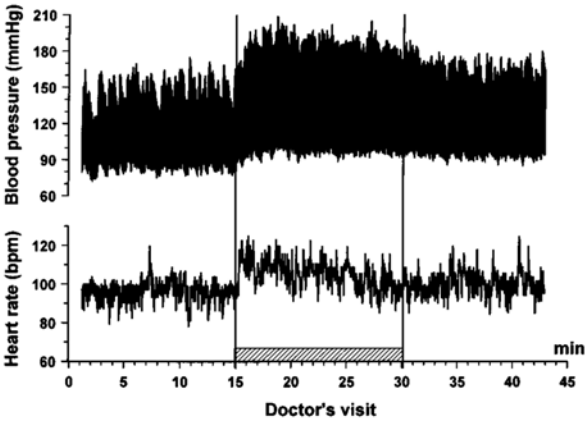

Fig. 2.1 Original finger blood pressure and heart rate tracing showing the pressor and tachycardic effects of the physician's visit in a representative subject. The segment of blood pressure and heart rate tracing between vertical bars corresponds to the time of physician's visit (Taken from Parati et al. [25] with permission)

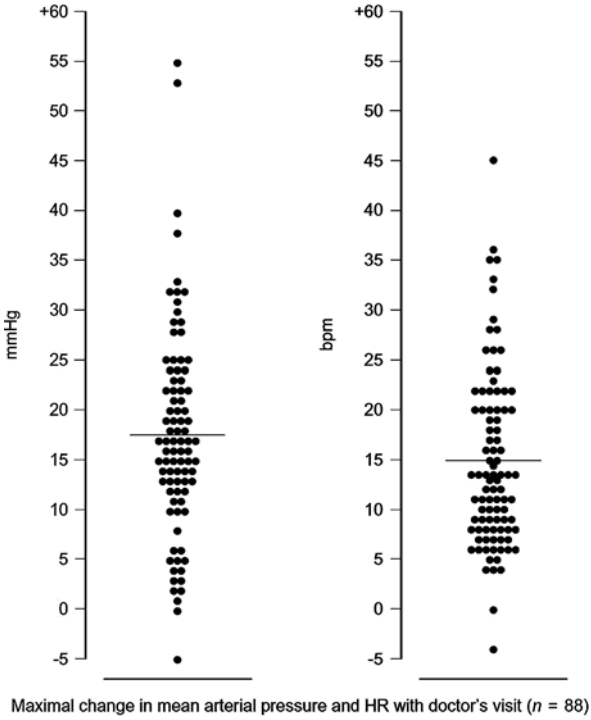

Fig. 2.2 Peak increase in intra-arterial mean arterial pressure (*MAP, left*) and heart rate (*HR, right*) in 88 patients during a visit by a physician measuring blood pressure with a sphygmomanometer. The intra-arterial blood pressure and heart rate values observed during the physician's visit were compared with those observed 4 min before the visit. Data are shown for individual patients (*points*) and as average changes for the group as a whole (*horizontal lines*) (Taken from Mancia et al. [1] with permission)

This study also provided direct and precise quantification of the magnitude of the WCE showing on average a peak increase in systolic and diastolic intra-arterial BP during the physician's visit of 27 and 14 mmHg in a group of hypertensive patients. The magnitude of this WCE phenomenon also showed a high degree of interindividual variations (ranging from 4 to 75 mmHg in SBP and from to 1 to 36 mmHg for DBP) [1]. See Fig. 2.2.

This wide between-subject variability in the size of the WCE was not entirely explained by differences in demographic characteristics of recruited subjects (i.e., age, sex) nor by differences in average 24-h BP levels or in the degree of spontaneous 24-h BP variability, indicating that the degree of BP response to the medical visit is largely unpredictable in the individual subject [1].

A further study, exploring the effects on intra-arterial BP and heart rate of four repeated visits performed by the same physician over a 48-h period, showed no significant differences in the average BP peaks observed during the four visits. The absence of a consistent attenuation in the magnitude of the WCE when the patient was repeatedly visited by the same doctor seems to suggest that no reduction in the error of overestimation of OBP can be expected with the simple repetition of the physician's visit, at least within relatively short time windows [2] (see Fig. 2.3).

However, in the same report, the peak BP and heart rate increases observed during the visit were significantly less if a nurse, rather than a physician, was in charge of BP measurement (Fig. 2.4).

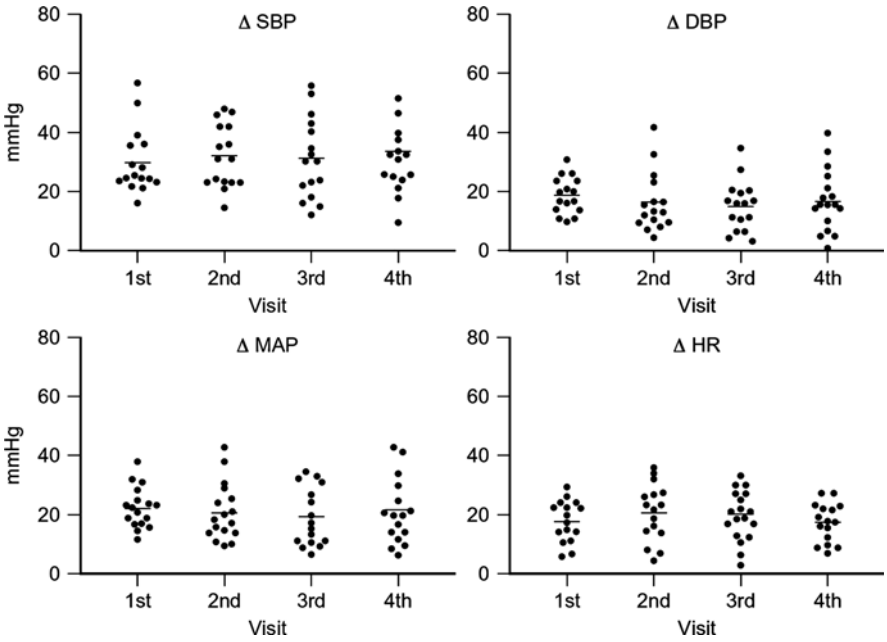

Fig. 2.3 Peak changes in intra-arterial systolic blood pressure (**Δ***SBP*) diastolic blood pressures (*ΔDBP*), mean arterial pressure (*ΔMAP*), and heart rate (**Δ***HR*) during a physician's visit in 46 hypertensive patients. Data are separately shown for four consecutive visits by the same physician performed over a 48-h period (Modified from Mancia, et al. [2] with permission)

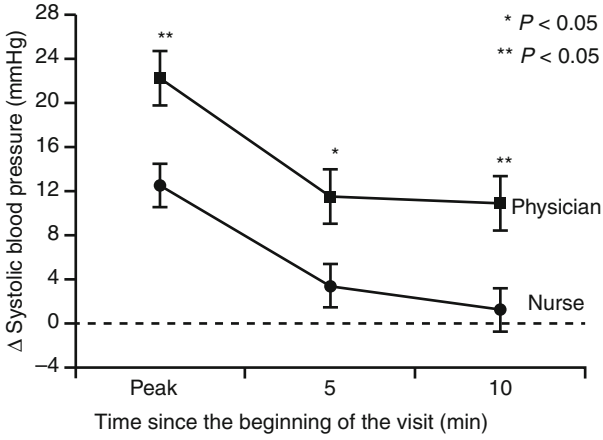

Fig. 2.4 Intra-arterial systolic (S) blood pressure changes induced during the visit by a doctor and a nurse. Data are shown as average values ± SE from 35 patients. Values obtained at the time of maximal changes (peak), after 5 and 10 min since the beginning of the visit, are separately shown (Taken from Mancia et al. [2] with permission)

Further studies also provided important evidence to better characterize the nature of the WCE, showing that intermittent automated or semiautomated (i.e., triggered by the subject) cuff inflations do not trigger an alerting reaction and pressure rise, at variance from what is induced by a physician's visit, and thus do not overestimate

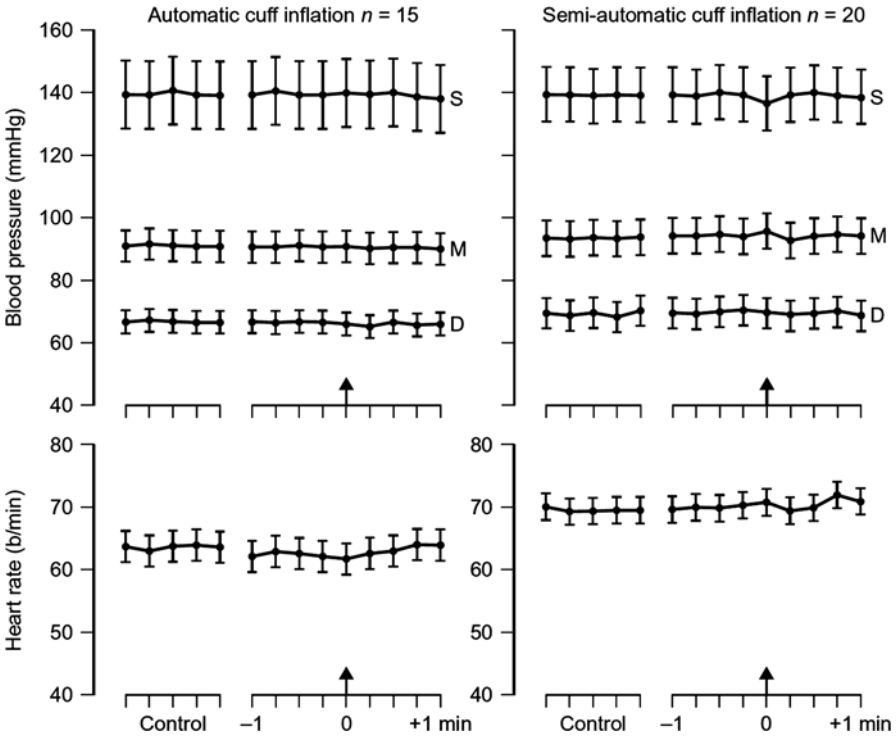

Fig. 2.5 Intra-arterial blood pressure and heart rate values obtained in 15 patients at the time of automatic blood pressure measurements and in 20 patients when the cuff inflation was triggered by the patient himself. Data are shown as average values ± SEM for 10-s segments of the intra-arterial tracing taken 5 min before cuff inflation and during the 1-min period immediately preceding and following cuff inflation. *Arrows* refer to the time of cuff inflation. *S* systolic blood pressure, *D* diastolic blood pressure, *M* mean arterial pressure (Taken from Parati et al. [10] with permission)

actual subject's BP values [10]. This was elegantly demonstrated in a study performing intra-arterial continuous BP recordings in a group of hypertensive patients in whom BP levels were concomitantly measured automatically by a noninvasive oscillometric BP monitoring device programmed to measure BP levels every 10 min during 2 h, after which semiautomated BP measures were performed for other 2 h (i.e., cuff inflations were triggered by patient's command at 10-min intervals). As shown in Figs. 2.5 and 2.6, cuff inflations, either automated or semiautomated, were not associated with an increment in intra-arterial BP levels neither before, during, nor after oscillometric BP measurements, except perhaps for the first few measurements only. This finding was evident not only when data were averaged but also when individual measurements were considered separately, showing that the WCE is not due to arm cuff inflation per se, but to the presence of a physician performing the measurement. This demonstration provides important information to exclude any increase in BP levels during noninvasive ambulatory BP monitoring, in response to repeated cuff inflations.

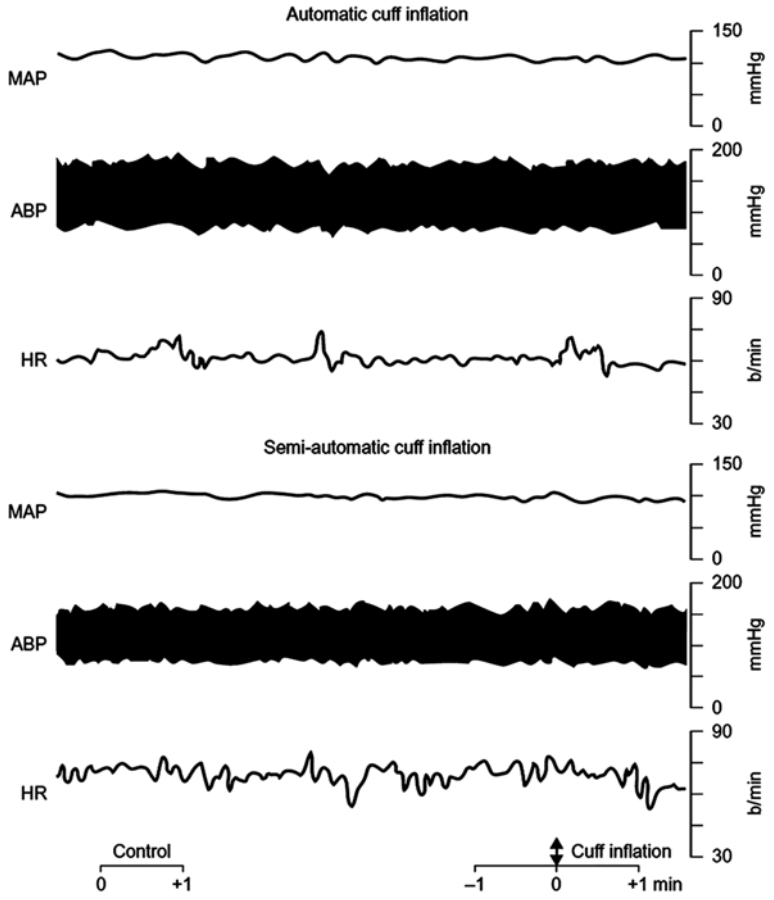

Fig. 2.6 Original intra-arterial blood pressure recordings performed in a representative subject at the time of noninvasive blood pressure measurements in which cuff inflation was started automatically (*upper panel*) or was self-triggered by the patient (semiautomatic measurement, *lower panel*). *Arrows* refer to the time of cuff inflation (Taken from Parati et al. [10] with permission)

Subsequent studies, although employing different BP measurement techniques (i.e., discontinuous ambulatory BP monitoring), provided additional evidence that the WCE may characterize not only the period when the patient actually sees the physician but also the entire period spent in a clinic environment [11, 12], indicating that the setting where BP is measured may be a more important contributor to the BP response during a doctor's visit than the subject who is in charge of the measurement.

Although a direct and precise quantitative estimation of the magnitude of the WCE was originally performed by implementing intra-arterial beat-to-beat BP recordings, the ethical concerns associated with the invasive character of this approach (risks and inconveniences to the patients) prevented its routine implementation for large-scale human research or for use in clinical practice.

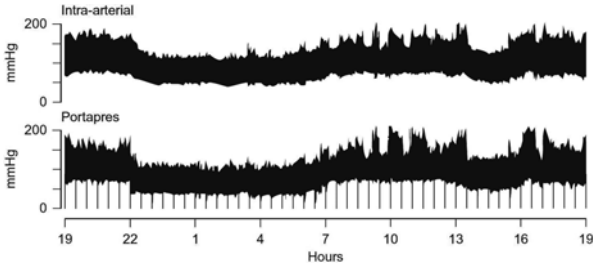

Fig. 2.7 Original ambulatory blood pressure recordings simultaneously obtained in the same subjects with the intra-arterial method (*upper tracing*) and with the Portapres device (*lower tracing*). *Vertical bars* at the bottom of Portapres tracing refer to between-finger shifts at 30-min intervals (Taken from Imholz et al. [16] with permission)

In the early 1970s, new approaches for noninvasive beat-to-beat BP monitoring were developed based on the principle of vascular unloading. This approach, originally described by Penaz [13], makes use of a small cuff wrapped around a finger of the hand, which contains an infrared photoplethysmograph and is connected to a computer-operated proportional pneumatic valve, a source of compressed air and an electropneumatic transducer. This device was later improved by Wesseling and coworkers in Amsterdam, resulting in a BP monitor called Finapres (from Finger Arterial PRESsure, Ohmeda, CO) [14]. In a number of validation studies, this device was shown to provide BP values close to those simultaneously obtained through intra-arterial recordings, during anesthesia as well as at rest or under laboratory tests known to induce rapid and often marked BP changes [15].

A portable version of this device is now also available, named Portapres (TNO, Amsterdam), which allows continuous noninvasive BP monitoring in ambulant subjects, all over 24 h, with acceptable accuracy [16] (Fig. 2.7).

Although several studies implementing noninvasive, beat-to-beat BP recordings at the finger level before, during, and after the medical visit showed the ability of this approach to provide a direct and reliable measure of the WCE [17–19], the costs and technical complexity of these systems prevented their routine use in clinical practice, confining them to a research setting.

2.3 Indirect Assessment of the WCE from Intermittent Ambulatory BP Recordings

All the limitations associated with direct assessment of the WCE based on beat-to-beat BP recordings (either invasive or non invasive) stimulated the development of alternative, noninvasive, and simpler approaches for obtaining at least an indirect estimation of the WCE. Following the introduction of ABPM in clinical practice, some authors proposed the straightforward calculation of the difference between BP levels measured in the office and average daytime ambulatory BP values measured

out of the clinic environment [20] as a means to estimate the magnitude of the WCE ("surrogate" WCE). Alternative methods based on ABPM only were also proposed which define the WCE as the difference between the average of all daytime readings (reflecting awake BP outside the medical setting) and the average of BP measures performed during the first or last hour of the ABPM recording (reflecting BP levels in the office, at the time of device application or removal, respectively) ("ambulatory" WCE) [21].

2.3.1 Assessing the WCE from the Combined Use of Office and Ambulatory BP Measures: The "Surrogate" WCE

The idea that the pressor response to the medical environment could be measured by means of ABPM without necessarily implementing continuous BP recordings was based on the abovementioned evidence provided by several studies showing that intermittent cuff inflations during noninvasive ambulatory BP monitoring do not trigger the alerting reaction and pressure rise induced by a physician's visit and thus do not overestimate subject's actual BP values [10]. This was further supported by the observation that in general BP measurements obtained out of the office during patient's daily life are significantly lower than those measured in the clinic or office environment [11]. However, while in the case of its direct assessment, BP reactivity to the physician's presence is precisely quantified both in size and duration, taking the BP levels recorded under the standardized resting conditions preceding the physician's visit as a reference; in the case of the surrogate approach, based on the clinic-ambulatory daytime BP difference, important methodological problems are to be anticipated. On one hand, clinic BP is quantified from the average of a limited number of readings (usually 1–3), with the risk of poor reproducibility of the values obtained. On the other hand, ambulatory BP measures are not performed at the moment of the clinical visit and cannot precisely reflect either the basal BP levels immediately before the start of the visit or the BP changes occurring during the medical visit. In addition while, at variance from OBP, ambulatory BP levels are not influenced by the alerting reaction (excepting the first or last hour of the recording when the patient is in the clinical environment for fitting and removing the ABPM device respectively), they are instead importantly influenced by different factors modulating blood pressure values in daily life, such as the degree of physical activity [22, 23] and other environmental stimuli. These factors affecting ambulatory BP may indeed be largely responsible for the office-daytime BP difference, more than the effects on OBP by the alerting reaction to the doctor's visit. In view of the important methodological differences between direct and indirect methods for estimation of the WCE, it is thus not surprising that large discrepancies were reported in literature between these methods for estimating the WCE [24–26].

Indeed, studies comparing direct measures of the "real" WCE (i.e., as assessed by means of continuous, noninvasive BP recordings during a doctor's visit) with the clinic-ambulatory BP difference have shown limited [19] or even lack of correlation between these estimates [25, 17]. Significant discrepancies between these measures

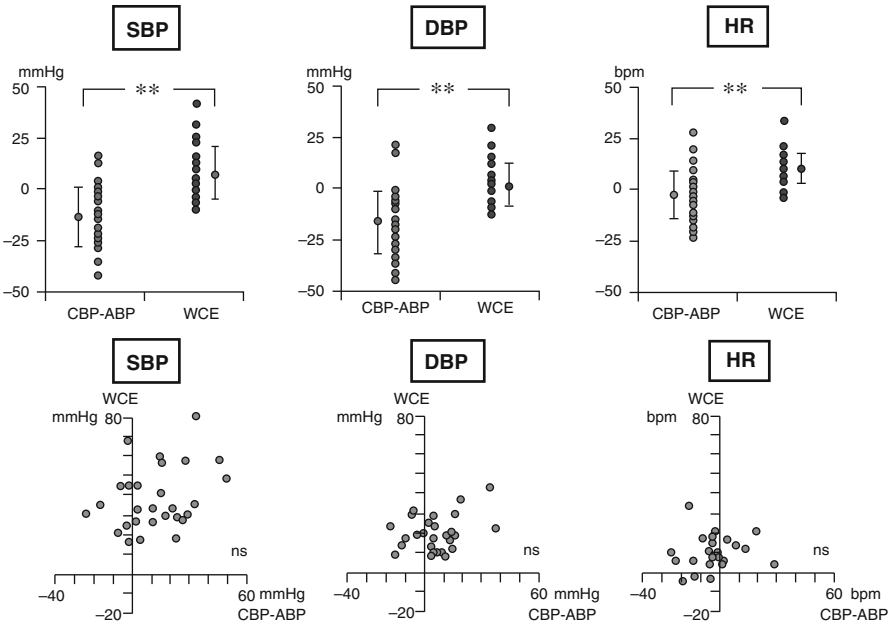

Fig. 2.8 *Upper panels* show the individual values of directly assessed white coat effect (*WCE*), obtained by beat-to-beat noninvasive blood pressure monitoring during a physician's visit (*black dots*) and the surrogate quantification of this phenomenon based on the difference between clinic and ambulatory daytime average BP values (CBP-ABP) (*open circles*), as well as the average values of each parameter (±SE) for the group as a whole (*dots* with *vertical bars*), separately for systolic blood pressure (*SBP*), diastolic blood pressure (*DBP*), and heart rate (*HR*). Lower panels show the lack of correlation between direct measures of WCE (*vertical axis*) and the surrogate measure of this phenomenon (computed as the difference of CBP-ABP, *horizontal axis*). Individual data are separately shown for SBP, DBP, and HR. $^{**}p < 0.01$ for the difference between WCE and CBP-ABP; *bpm* beats per minute (Taken from Parati et al. [25] with permission)

were shown in one of these studies, in which clinic-ambulatory BP difference corresponded to less than 30 % of the peak finger beat-to-beat BP increases directly recorded during the physician's visit [25]. Moreover, this difference has been shown to correlate directly with baseline clinic BP, but inversely with baseline ambulatory BP [26], while no significant correlation has been reported between the clinic-ambulatory BP difference and the "real" WCE [24] (Fig. 2.8).

Despite all the above limitations and the lack of consistent evidence to support the use of the difference between clinic and daytime BP as a reliable quantitative index of the "real" WCE [25], this difference has gained popularity and is currently the most commonly used approach to indirectly quantify the WCE, largely because of the simplicity and feasibility of this approach, as well as because of the availability of techniques for intermittent out-of-office BP monitoring in clinical practice. However, the difference between office and ambulatory BP as a surrogate measure of the WCE should be interpreted on the background of its important limitations (see Table 2.1).

Table 2.1 Comparison of different methods for assessment of the WCE

Feature	Direct measurement of the WCE (real WCE)	Indirect measurement of the WCE (clinic-ambulatory or clinic-home BP difference)	Indirect measurement of the WCE based on ABPM data only
BP measurement technique	Continuous BP recordings performed under ambulatory conditions over 24-h and/or in concomitance with the medical visit (before, during, and after the medical visit)	Intermittent ABPM or HBPM	Intermittent ABPM only
		The medical visit and ambulatory or home BP measures are generally performed in separate days	
BP measurement intervals	Beat-to-beat BP recordings over 24 h and in concomitance of the medical visit	ABPM: every 15–20 min over the 24 h preceding or following the medical visit	ABPM: every 15–20 min over the 24 h preceding or following the medical visit
		HBPM: duplicate measures obtained in the morning and in the evening during the 7 days preceding the medical visit, discarding the first day [50]	
Quantification of the WCE	The magnitude of the WCE is precisely quantified both in its size and duration, taking the blood pressure levels recorded under the standardized resting condition preceding the physician's visit as reference	OBP is quantified from the average of a few number of readings (usually 1–3). Ambulatory or home BP measures are obtained in different days with regard to the medical visit	The WCE is calculated by subtracting the average of all daytime readings (reflecting awake BP outside the medical setting), from the average of BP measures performed during the first or last hour of the ABPM recording (reflecting BP levels in the office)
		The WCE is calculated by subtracting the average of all ambulatory daytime or of the 6-day home BP readings (reflecting awake BP outside the medical setting), from OBP	
Definition of the WCE	Difference between the average of beat-to-beat BP values recorded at the time of the maximum BP increase during the medical visit (during which a doctor repeatedly measures BP by the cuff method) and the average of the beat-to-beat values recorded at rest in 5 min preceding the doctor's visit	Difference between clinic and ambulatory average daytime or home blood pressures	Difference between the average BP values obtained during the first or last hour of ABPM and the remaining daytime or 24-h BP average

(continued)

Table 2.1 (continued)

Feature	Direct measurement of the WCE (real WCE)	Indirect measurement of the WCE (clinic-ambulatory or clinic-home BP difference)	Indirect measurement of the WCE based on ABPM data only
Terminology for the WCE	"Real" WCE	"Surrogate" WCE	"Ambulatory" WCE
Advantages	Direct and precise quantification of the magnitude and time course of the real WCE	Ease of implementation in clinical practice	Requires performance of ABPM only
		ABPM: extensive information on day and nighttime BP and 24-h BP profiles	
		HBPM is cheap and available	
Disadvantages	Ethical concerns regarding use of invasive intra-arterial BP monitoring	ABPM is not always available	ABPM is not always available
	Noninvasive devices for beat-to-beat BP monitoring are costly, and the stability of measurements outside the laboratory setting needs to be checked	HBPM requires patient training and involvement	Current software for analysis of ABPM does not yet incorporate separate calculation of average BP values obtained during the first or last hour of ABPM, from the remaining daytime or 24-h BP average
		OBP is quantified from the average of a limited number of readings (usually 1–3), with the risk of poor reproducibility of the values obtained	
		Out-of-office BP measures (either with ABPM or HBPM) are not performed at the moment of the clinical visit and thus cannot precisely reflect the basal BP levels immediately before and then in concomitance to the medical visit	

Abbreviations: *BP* blood pressure, *ABPM* ambulatory blood pressure monitoring, *HBPM* home blood pressure monitoring, *OBP* office blood pressure

2.3.2 Assessment of the WCE Using ABPM Only: "Ambulatory" WCE

It is well accepted that ambulatory BP measures collected outside the medical office are not affected by the alerting reaction to the medical visit. However, several reports have indicated that ambulatory BP recordings are not entirely free from the WCE and that the first or final measurements of ABPM are characteristically higher than the mean value for the daytime ambulatory BP values (although yet smaller compared to OBP) [27]. This transient elevation in BP levels in the initial and final portions of ambulatory BP recordings has been interpreted as a consequence of the alerting reaction to the clinical environment when the patient attends the clinic for device placement and removal [21, 28] (Fig. 2.9), and these subperiods of the 24-h ambulatory BP recording have been commonly addressed as the "white coat windows," i.e., the periods of time during an ambulatory BP recording in which it is still possible to at least partly appreciate the pressor response to the medical visit.

On the basis of this evidence, the question was raised on whether BP values monitored during the first or last hour of a 24-h ABPM recording, when the subject is usually in a clinic environment, might be used in replacement of conventional

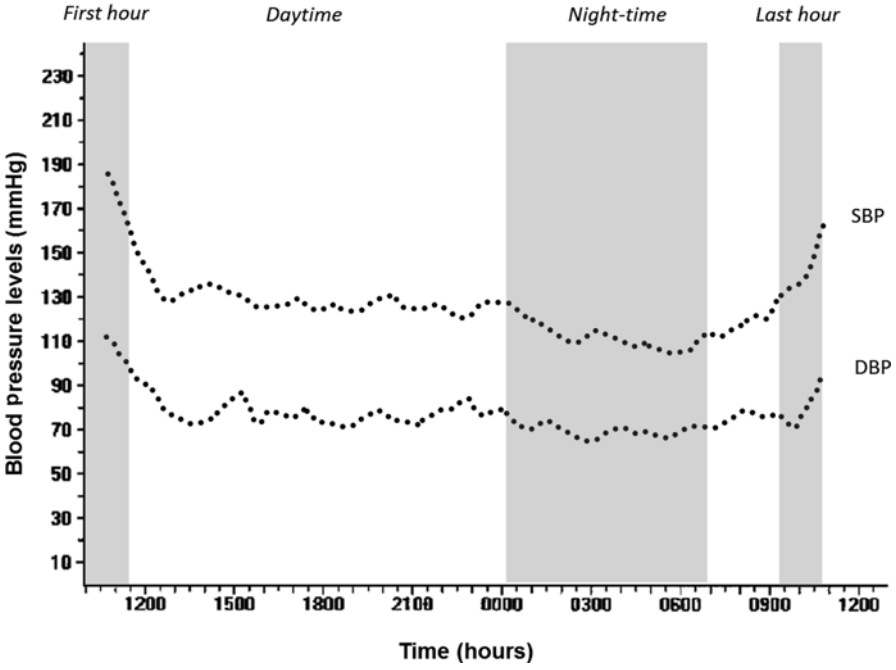

Fig. 2.9 Typical ambulatory blood pressure recording showing transient elevation in *BP* levels in the initial (first hour) and final portions (last hour) when the patient attends the clinic for device placement and removal, respectively. Modified from Owens P, et al. [21] with permission. *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure

office BP measurements to identify the presence of the white coat phenomenon. Based on the assumption that the same stressful situation that is responsible for a WCE on OBP might affect also the initial portion of a 24-h ABPM (when the patient is still in the clinic setting for fitting the ABPM device), and possibly also its final segment (at the time when subjects go back to the clinic for device removal), it was suggested that the first and last hours of a 24-h ABPM might be taken to reflect the patient's alarm reaction to a clinic visit, more than the effects of usual daily activities on ABP. Consequently, some authors have proposed separately to consider the readings obtained during the first and last hour of a 24-h ABPM (the so-called white coat window), taking them out from the calculation of the mean awake ambulatory BP levels [21]. According to this approach, the difference between the average BP values obtained during the first or last hour of an ABPM and the average of the remaining daytime or 24-h BP values would provide an indirect measure of the WCE (defined as "ambulatory" WCE) [21]. An indirect validation of this approach was provided in the frame of a large cohort study in non-treated hypertensive patients referred for ambulatory BP monitoring, by exploring the relationship between measures of the WCE obtained by applying the clinic-ambulatory BP difference and other measures obtained by considering the "white coat window" approach [21].

Overall, this study showed that measures of the WCE obtained by the "white coat window" approach were highly correlated with traditional measures of the WCE based on the clinic-ambulatory BP difference [21], although it should be acknowledged that the latter cannot be taken as a reference measure of the WCE, given its own intrinsic limitations, as discussed in the previous paragraphs of this chapter [23]. In spite of the fact that the agreement between this approach and the traditional although limited method for assessing the WCE was not perfect, their close correlation led authors to make a further step and to suggest that the finding of an elevated average BP in the first or last hour of a 24-h ABPM measurement (systolic BP $\geq$140 mmHg and/or diastolic BP $\geq$90 mmHg), when the average of the remaining ambulatory daytime BP values is normal (i.e., <135/85 mmHg), is to be taken as indicating a white coat hypertension condition, defined by the authors as "ambulatory white coat hypertension" [21]. According to this approach, both WCE and WCH could be, although indirectly, assessed from ABPM data only, independently of BP measures performed by the physician during the medical visit [21], an interesting proposal which however would need further validation with proper methodology (see Table 2.1).

2.4 Diagnosis of WCH from the Combined Use of Office and Ambulatory BP Monitoring (ABPM)

Consistent evidence has been provided that BP levels measured in the clinical setting are in general higher than ambulatory BP measurements performed out of the clinic environment [29]. This is considered a major explanation for the frequently

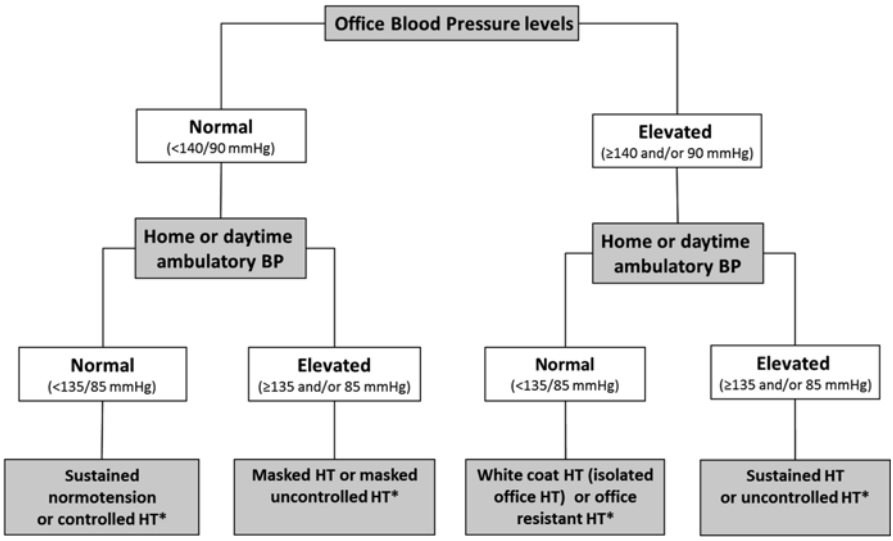

Fig. 2.10 Schematic relationship between office and home or daytime ambulatory blood pressure. *BP* blood pressure, *HT* hypertension, In treated hypertensive subjects (*asterisk*)

observed disagreements between OBP and out-of-office BP measurements when classifying hypertensive subjects [30] (Fig. 2.10).

Based on this evidence and assuming that the discrepancies between office and out-of-office BP levels might be the result of the alerting reaction to the physician's visit, the condition characterized by a persistently high BP in the physician's office and a persistently normal BP away from the clinical environment was referred to as "white coat hypertension" [20].

Although WCH is a consequence of the white coat effect, the presence of a significant WCE in a given subject may not necessarily be accompanied by WCH, unless the rise in BP levels during the medical visit is high enough to reach the hypertensive range. That is why some subjects even despite having a marked WCE (i.e., a substantial difference between office and out-of-office BP levels), but with office BP levels still in the normal range, cannot be considered as having WCH; conversely, subjects with a small WCE, but with office BP levels in the hypertensive range, may fall in the category of WCH if their ambulatory BP levels are persistently normal. Relevant evidence in this regard was provided by a report of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) conducted in a large population of 1,333 untreated subjects with essential hypertension in which the severity of hypertension (according to the JNC V stage) was inversely correlated with the prevalence of WCH (i.e., the more severe the hypertension, the lower the prevalence of WCH), but directly correlated with the magnitude of the WCE (i.e., as estimated by the difference between clinic BP and average daytime

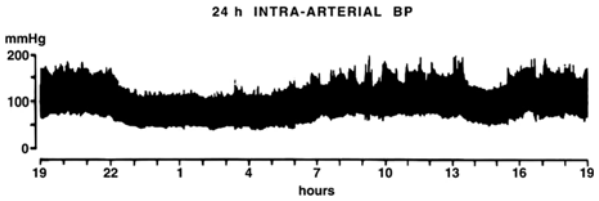

Fig. 2.11 Beat-to-beat blood pressure (*BP*) tracing obtained in an ambulant subject over the 24-h period through the Oxford technique, based on insertion of a catheter in a peripheral artery (Taken from Mancia et al. [72] with permission)

ambulatory BP). The results of this study raised important concerns regarding the clinical relevance of the clinic-ambulatory BP difference as an index of the WCE, as this difference cannot reliably predict WCH nor normalcy in ambulatory BP levels.

A critical condition for the diagnosis of WCH or isolated office hypertension is the occurrence of a persistent BP elevation at the time of consultation and of normal out-of office BP levels over time. Thus, isolated elevations in OBP levels that can be found only at the beginning of the first few visits, and that later disappear, should be regarded as temporary BP increases [31] and should not lead to the diagnosis of WCH. Indeed, the inclusion of subjects with a temporary rather than a persistent office hypertension could have contributed to the inflated prevalence of WCH (i.e., 60 %) reported in some population studies [32].

In some subjects, rather than representing a real pressor response to the doctor's presence, these transient, non-sustained increases in BP levels may be just the result of an increased BP variability, i.e., a phenomenon that characterizes BP levels in daily life. As clearly shown by studies carried out by means of 24-h intra-arterial ambulatory BP monitoring techniques [33], both fast and slow fluctuations occur continuously over the day and night, in response to different behavioral challenges, the magnitude of which is greater among hypertensive subjects (Fig. 2.11).

Although, in general, WCH has been shown to be a reasonably reproducible phenomenon, the ABPM levels in subjects defined as having WCH might represent, by chance, a sample taken at the low extreme of their random distribution. Consequently, day-to-day reproducibility of WCH might be impaired by a regression-to-the-mean phenomenon. In one study, in a group of mild hypertensive subjects who underwent duplicate ABPM 3 months apart, diagnosis of WCH was not reproducible in as many as 50 % of subjects (likely as a consequence of the regression toward the mean), indicating that the current diagnosis of WCH is also subject to selection bias [34]. Based on the above observations, an argument sometimes raised against the concept of WCH is that if patients are seen a sufficient number of times in the clinic, BP will return to normal. However, while this may be true in a subset of patients (by effect of an increased BPV or the regression to the mean phenomenon) in many subjects, clinic BP will remain high indefinitely, despite persistently normal ambulatory BP levels.

Finally, also the criteria considered for defining normalcy of BP levels during daytime may lead to over- or underestimation of the frequency of WCH. The first reports on the frequency of white coat hypertension, considering a threshold value of 140/90 mmHg as the upper limit of normality for both office and daytime ambulatory BP levels, found WCH to be present in as much as 60 % of the overall hypertensive population [32, 35]. However, after the evidence provided by the PAMELA study [36] and other population studies [37, 38] and meta-analyses [39] supporting a threshold value of <130–135/85 mmHg as the upper limit of daytime ambulatory BP normality, the frequency of this phenomenon was found to be significantly lower. Indeed, the prevalence of white coat hypertension in subsequent studies was reported to range from 9 to 16 % in the general population and from 25 to 46 % among hypertensive subjects [40, 36, 41, 42, 6]. While the conventional cutoff value for hypertension is an office BP value of ≥140/90 mmHg, most studies in WCH have used a cutoff value of ≥135/85 mmHg for out-of-office daytime or home BP and ≥130/80 mmHg for 24-h BP. Following the demonstration by several prospective population studies of the superiority of nighttime BP levels over other components of ABPM in predicting cardiovascular outcomes [43, 44] and in consideration that a subset of subjects with WCH present elevation in BP levels during nighttime (i.e., nighttime hypertension) and/or during the 24 h, current hypertension guidelines [5, 6] have expanded the definition of white coat hypertension, requiring normality not only in awake BP values but also in 24-h (i.e., <130/80 mmHg) and sleep (i.e., <120/70 mmHg) BP levels.

A recent position paper on ABPM of the European Society of Hypertension [6] recommends performing 24-h ABPM and/or HBPM for discarding the presence of WCH in all patients with uncomplicated, stage 1 and 2 essential hypertension before starting antihypertensive drug therapy. Once the initial diagnosis of white coat hypertension has been made, patients should have their BP status monitored more carefully, preferably with home BP or automated office BP. If a trend toward higher BP readings is noted, then ABPM should be repeated in order to detect the development of sustained hypertension [45, 6] (Box 2.1).

Box 2.1. Defining Criteria for White Coat Hypertension

Untreated patients with elevated office blood pressure ≥140/90 mmHg[a]
24-h ambulatory blood pressure measurement <130/80 mmHg
Awake ambulatory blood pressure measurement <135/85 mmHg
Sleep measurement <120/70 mmHg or
Home blood pressure <135/85 mmHg

Taken from O'Brien et al. [6] by permission

Diagnoses require confirmation by repeating ambulatory blood pressure monitoring or home blood pressure monitoring within 3–6 months, depending on the individual's total cardiovascular risk

[a]Ambulatory blood pressure values obtained in the clinic during the first or last hour of a 24-h recording may also partly reflect the white coat effect

Based on the evidence provided by several studies on the clinical value of ABPM either for selecting patients for treatment or for assessing the effects of antihypertensive drug therapy, ABPM is currently considered the standard method for identifying white coat hypertension and thus to confirm the diagnosis of hypertension in clinical practice [6].

Although the recent British National Institute for Health and Clinical Excellence (NICE) guidelines advocate that every person with elevated office BP aged >18 years should undergo ABPM to rule out a diagnosis of white coat hypertension with the potential for savings in healthcare costs by virtue of avoiding unnecessary treatment with antihypertensive drugs [46], performing ABPM deliberately in all subjects presenting with elevated BP levels in the medical office is hardly possible in clinical practice and is not recommended by recent ESH/ESC Guidelines [5]. Besides, despite the acknowledged clinical value of ABPM, its use in clinical practice is still highly regulated and the reimbursement rates kept low [6, 5]. The cost of performing ABPM in clinical practice could be offset by the savings resulting from avoiding healthcare expenditures (i.e., unnecessary drug treatment in patients identified as having white coat hypertension and reducing physician visits and adverse effects due to inappropriate treatment) [47]. Cost-effectiveness studies in general clinical practice have shown that on the basis of the prevailing costs of antihypertensive drug treatment and the prevalence of WCH, the break-even cost for performing ABPM in newly diagnosed hypertensives could be much lower than the actual cost of a single recording [48].

2.5 Diagnosis of WCH from the Combined Use of Office and Home BP Monitoring (HBPM)

Ambulatory BP monitoring is currently considered the standard method for the diagnosis of hypertension [49] and for assessing BP control in treated hypertensive patients [5, 6, 46]. However, it is not easily available everywhere and requires trained clinic staff and specialized equipment and software for its analysis [50]. When performed on a regular basis and following standardized protocols [50], repeated BP measures obtained by patients at home offer the possibility to perform accurate and frequent out-of-office BP measurements not only during a single day but also over several days, weeks, or months in a usual life setting, thus providing more reliable measures not only on the degree but also on the consistency of BP control over time [50]. Besides, recent studies have indicated that HBPM is as reliable as ABPM in identifying WCH [51] being as useful as ABPM in identifying "truly" hypertensive patients, likely to benefit from implementation of antihypertensive therapy from those with WCH in whom antihypertensive treatment is not necessary [52]. This suggestion has been made in spite of the fact that, as in the case of ABPM, home BP measures are not performed immediately before, during, or after the medical visit and thus cannot provide a precise estimate of the WCE.

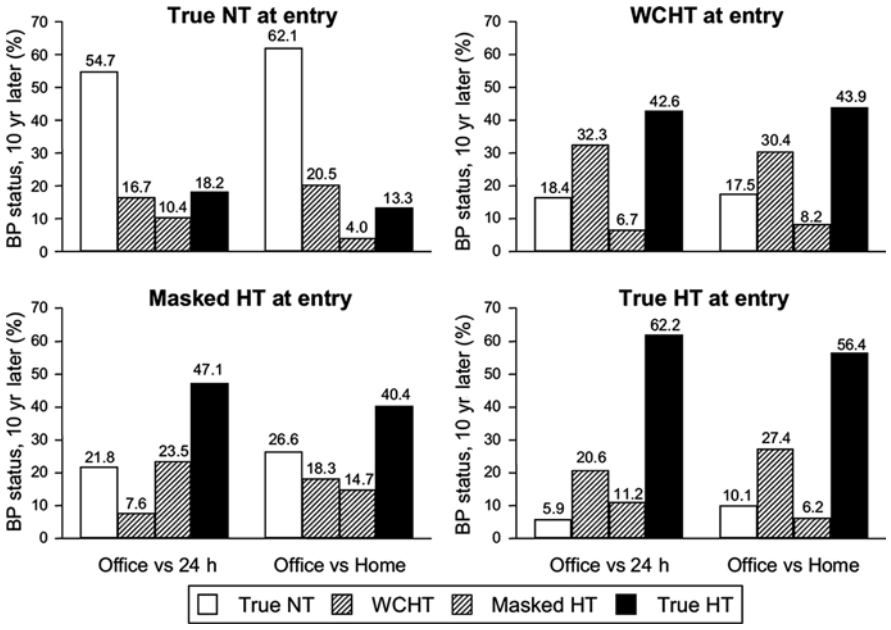

Fig. 2.12 Mean percentage changes in BP status among normotension (*NT*), white coat hypertension (*WCHT*), and masked hypertension (*MHT*) over the 10-year period of the study. Data referring to true hypertension (true HT) are shown for comparison (Taken from Mancia et al. [54] with permission)

Based on the abovementioned important advantages, HBPM was thus proposed as an additional useful method for assessment of WCH, which according to this methodology is defined as the presence office systolic/diastolic BP levels persistently ≥140/90 mmHg and home daytime BP levels persistently normal, i.e., <135/85 mmHg [6, 5].

Regarding its ability to identify WCH, population studies implementing office, ambulatory, and home BP measures have provided evidence that HBPM and ABPM may result similarly effective for identifying white coat hypertension [53, 54]. In particular, a report of the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study in which the initial diagnosis of WCH (i.e., identified as office BP >140/90 mmHg and 24-h BP mean <125/79 mmHg or home BP <132/82 mmHg) was reassessed 10 years later showed similar results in the ability of HBPM and ABPM for identifying WCH, sustained hypertension, true normotension, and masked hypertension, even if a substantial percentage of subjects changed from one category to another, including progression to sustained hypertension (true hypertension) (Fig. 2.12).

In the light of the available evidence supporting the clinical advantages of HBPM as well as the superior prognostic value of home vs. office BP levels, current hypertension guidelines recommend the extensive use of HBPM not only for the initial diagnostic approach to hypertension but also for the long-term

follow-up of treated hypertensive patients [50, 5, 55]. However, although HBPM shares many of the advantages of ABPM, resulting more cost-effective for the diagnosis of WCH, it cannot be considered as a substitute but a complement to ABPM, as these methods are likely to pick up different moments of BP behavior in a subject's daily life.

2.5.1 Assessing WCH from Automated BP Measures Performed by Patients Alone

Studies implementing intra-arterial, continuous BP recordings simultaneously with self-BP measurements performed by patients at home showed that the alerting reaction is absent when it is the patient who triggers cuff inflation [10]. Other reports implementing intermittent 24-h ABPM have suggested that even if the patient is alone and records BP by activating an automated sphygmomanometer, there may still be some alerting reaction although lower than that triggered by the physician or the nurse [56]. Based on this evidence, some authors have proposed an alternative method to replace manual BP measures with sphygmomanometers, with fully automated blood pressure measuring devices. This approach, which has been named automated office (AO) BP, requires taking multiple automated BP readings with the patient resting quietly alone, in order to eliminate conversation between the patient and the observer (known to induce an important pressor response). Using a BP cutoff value of 135/85 mmHg for AOBP (i.e., the same cutoff point currently recommended for defining hypertension based on awake ambulatory BP and home BP), use of this approach has been suggested to reduce the white coat response while reducing the need to monitor patients with ambulatory BP and home BP after initiation of antihypertensive therapy [57]. Despite its simplicity and potential for extensive use in clinical practice, the diagnostic value of this method should still be validated by further studies.

2.6 Do Subjects with WCH Need Further Diagnostic Testing?

Population studies have indicated that WCH may evolve into sustained hypertension with a higher than expected frequency [54], leading to consider WCH as a prehypertensive state [58]. In a report of the PAMELA study, regardless of whether the definition of white coat hypertension was based on ambulatory or home BP values, subjects with WCH had a significantly higher incidence of sustained hypertension after 10 years of follow-up compared to true normotensive individuals (Fig. 2.13).

Even when accounting for age and sex, the risks of developing sustained hypertension were significantly increased and almost doubled in subjects with WCH, regardless of the method employed for its assessments (i.e., office vs. ABPM or office vs. HBPM) (Fig. 2.14).

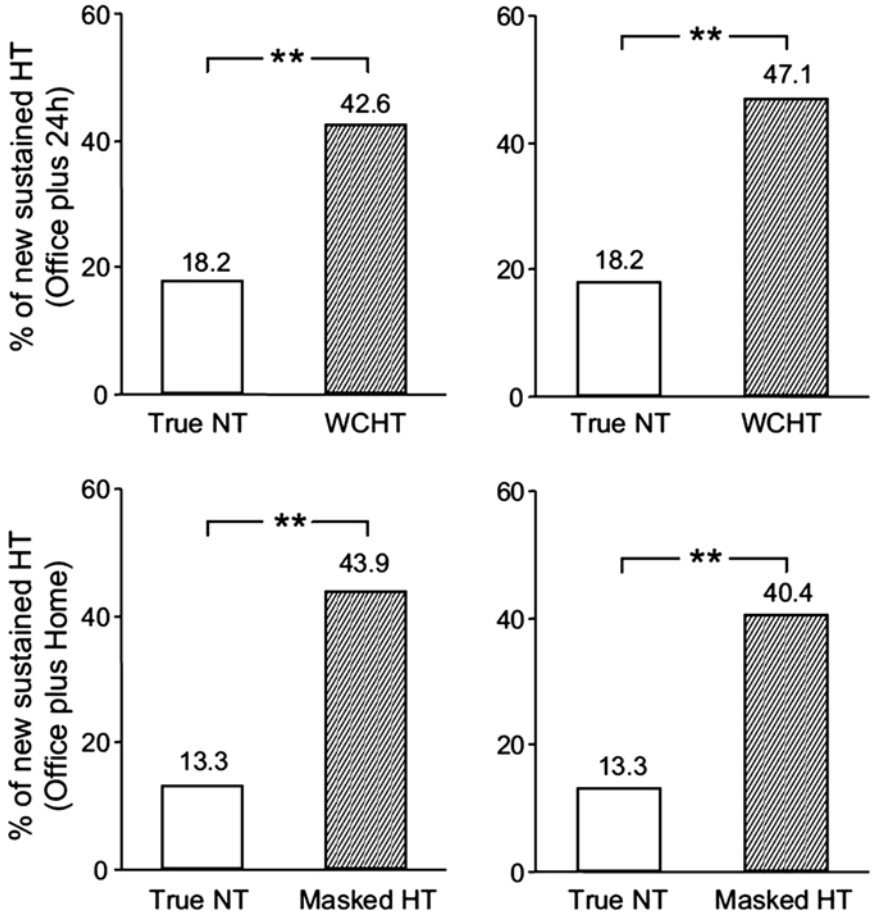

Fig. 2.13 Mean percentage of individuals developing sustained HT, i.e., a combined office and ambulatory HT (*top*) or office and home HT (*bottom*) in subjects with WCHT, MHT, and true normotension (*NT*) at entry. $^{**}p<0.0001$ refers to the statistical significance between groups (Taken from Mancia, et al. [54] with permission)

Remarkably, this study showed that the percentage of subjects who developed a sustained hypertensive state over a relatively long time interval is greater in individuals who originally had WCH than in true normotensive subjects (i.e., those in whom both in-office and out-of-office BP are within the normal range) [54].

Although WCH has been reported to have a benign prognosis and may not need to be treated, the increased risk of evolving into sustained hypertension (which in turn is associated with an increased cardiovascular risk) justifies a conservative approach for subjects presenting with this condition.

In consideration of this, current hypertension guidelines recommend confirming the diagnosis of WCH within 3–6 months along with close follow-up visits at yearly intervals with out-of-office BP measurements (i.e., ABPM or home BP

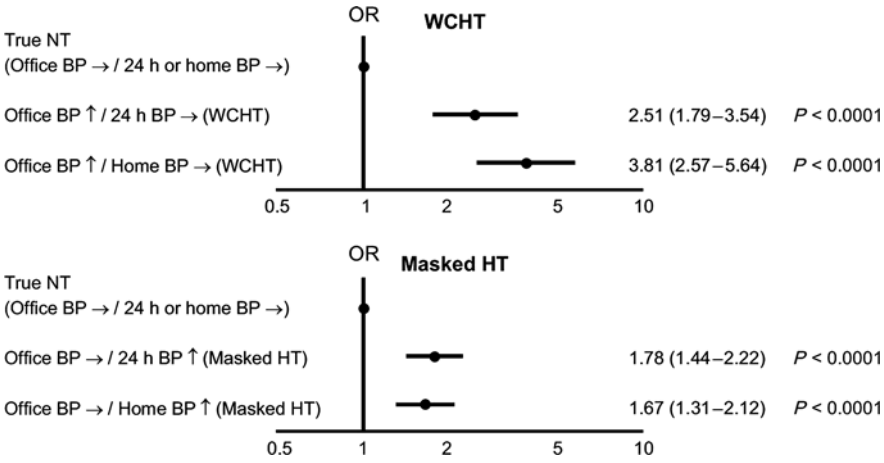

Fig. 2.14 Ten-year age- and sex-adjusted odds ratios (*ORs*) of new-onset SHT in WCHT and MHT vs. true normotension (*NT*) at entry (Taken from Mancia et al. [54] with permission)

monitoring), so as to detect whether and when sustained hypertension occurs [5, 6]. Even subjects who exhibit a substantial white coat effect (without yet presenting WCH) may need to be followed with out-of-office BP readings (i.e., automated office BP at home or repeat ABPM), especially if a trend to higher BP readings is observed [6].

An additional question, of conceptual and terminological relevance, concerns the relationship between WCH and the so-called borderline hypertension. While the first condition regards subjects with persistently elevated OBP and normal out-of-office BP levels, borderline hypertension is a term used in the past to denote those subjects whose clinic BP values are sometimes above and sometimes below 140/90 mmHg and who often present high-normal blood pressure levels (i.e., SBP 120–139 and/or DBP 80–89 mmHg). However, as in the case of WCH, subjects with high-normal blood pressure have a higher chance of developing sustained hypertension [59, 60] and should also be properly identified and followed.

2.7 Assessing the White Coat Effect and White Coat Resistant Hypertension (WCRH) in Treated Hypertensive Patients

The alerting reaction to the medical visit may continue to be present in anyone treated for hypertension, regardless of the number of drugs being taken [61]. Although limited information is available on the effects of antihypertensive treatment on the magnitude of the "real" WCE, it is well known that in treated patients the clinic-ambulatory daytime BP difference tends to decrease [24, 62]. Despite of this, it is not uncommon to find subjects with mild hypertension based on ABPM

who yet appear to have severe hypertension due to a white coat effect on office BP [25] or treated subjects who, despite achieving adequate out-of-office BP control with antihypertensive drugs, continue to present elevation in-office BP levels because of a persisting emotional reaction to the medical visit. This phenomenon, which is equivalent to WCH in non-treated subjects, has been addressed as "white coat resistant hypertension" (WCRH) in order to emphasize its occurrence in subjects receiving antihypertensive treatment [6]. Of remark, observational and interventional studies in treated hypertensives implementing office BP measures along with ambulatory or home BP monitoring have overwhelmingly shown that up to one third of treated hypertensives may be mistakenly classified as having resistant hypertension, while on the contrary they are only affected by WCRH (white coat resistant hypertension, i.e., false resistant hypertension due to a persisting white coat effect) [63]. An even worse condition has been also reported, i.e., the finding that another 30 % of treated subjects may be mistakenly classified as having BP controlled based on OBP only, while their out-of-office BP levels actually remain elevated (masked resistant hypertension or false BP control) [64, 65].

The high prevalence of WCRH (false resistant hypertension) further reinforces the clinical relevance of identifying this condition. On one hand, it would prevent unnecessary modifications of antihypertensive treatment, i.e., a not required increase in dosing or number of antihypertensive drugs, thus reducing the chance of adverse effects associated with improperly prescribed multidrug therapy that often interferes with patients' quality of life, leading in the end to poor compliance with treatment. On the other hand, it would reduce the expenditures associated with a not necessary additional pharmacological treatment and/or interventional device-based strategies (i.e., carotid baroreceptor activation [66] and renal denervation [67]) for the management of resistant hypertension. Indeed, given the elevated costs and invasive character of these approaches, as well as their potential adverse effects when not properly indicated, discarding WCRH based on out-of-office BP measures is currently considered among the eligibility criteria before proceeding with interventional treatment of resistant hypertension [7].

In view of the important limitations of office BP measurements for assessing BP control, a first step in the diagnostic approach of the patient who presents with apparently resistant hypertension consists in defining whether resistance to antihypertensive treatment is true or whether the persisting BP elevation is just the result of an emotional reaction to the doctor's visit ("white coat effect") corresponding to WCRH.

Although demonstration of elevation in both office and out-of-office BP levels is an essential step for the diagnosis of true resistant hypertension, several interfering factors other than the "white coat effect" may contribute to increase BP levels in treated subjects during the medical visit and should thus be also discarded before confirming the diagnosis of true resistant hypertension. These include inappropriate drug choices or doses, concurrent use of drugs that may interfere with prescribed antihypertensive agents, or failure of the patient to adhere to the prescribed treatment regimen. With regard to this latter issue, several factors may further contribute to discontinuation of antihypertensive treatment by patients, increasing the

prevalence of WCRH, such as side effects of multidrug therapy and cost of medications, lack of consistent and continuous primary care, absence of strong physician motivation, poor understanding of instructions related to treatment, and social and cultural fences. Indeed, recent analyses of several interventional trials have shown that administration of multidrug regimens by clinical staff to subjects who had been previously uncontrolled by antihypertensive treatment resulted in optimal BP control [68] suggesting that in addition to the WCE and inaccuracies of OBP measuring techniques, a poor adherence to recommended lifestyle measures and/or to prescribed drug treatment may be major contributing factors to the apparent resistance to antihypertensive treatment. In some instances, also physicians' inertia may increase the prevalence of WCRH as indicated by several surveys showing that many physicians not only fail to perform a proper BP measurement in the office accompanied by out-of-office BPM but also fail to increase the number or doses of antihypertensive medications as recommended by guidelines when BP levels are out of control.

2.8 Diagnostic Approach for Identifying White Coat Resistant Hypertension in Treated Hypertensives Through ABPM and HBPM

In view of the limitations characterizing OBP measurements, it becomes clear that an adequate assessment of BP control and a proper diagnosis of resistant hypertension cannot be based on isolated OBP readings only. Considering the high prevalence of WCRH (false resistant hypertension) among subjects with resistant hypertension, a first step in the evaluation of the patient with a diagnosis of resistant hypertension (performed on the basis of OBP measurements only) consists in classifying patients into two wide categories: true resistant and false resistant hypertension (WCRH) through the combined use of office and out-of-office BP measurement techniques. As mentioned above, ABPM and HBPM provide out-of-office BP measurements detecting BP changes in real-life conditions, without interference by the alarm reaction associated with OBP [30], i.e., by avoiding a reaction which is considered a major contributor to the frequently observed disagreement between OBP and out-of-office BP measurements.

By providing accurate and frequent BP measurements at regular time intervals over several days, weeks, or months, within a real-life setting, HBPM is able to accurately track changes in BP levels induced by antihypertensive treatment, thus representing a useful solution for a better assessment of BP control in treated hypertensive subjects when combined with conventional OBP measurements [30].

This would allow differentiating WCRH from true resistant hypertension, avoiding unnecessary costly screening tests for investigation of secondary causes of hypertension or the inappropriate implementation of more aggressive pharmacological or interventional strategies (i.e., carotid baroreceptor activation or radiofrequency catheter-based renal denervation).

Although ABPM remains the standard method for the diagnosis of WCRH in treated hypertensive subjects, evidence on the diagnostic value of HBPM for discriminating between true and false resistant hypertension has also been provided. In a recent study conducted in a group of subjects on stable treatment with ≥3 antihypertensive drugs using ABPM as reference method [69] in which resistant hypertension was defined as elevated OBP (≥140/90 mmHg) and true resistant hypertension as concomitant elevation in-office and out-of-office BP (SBP and/or DBP ≥135/85 mmHg for HBP or awake ABP), there was agreement between ABP and HBP in diagnosing clinic or "white coat" resistant hypertension in 82 % of the cases (59 % with and 23 % without clinic resistant hypertension; kappa 0.59). Regarding the diagnosis of true resistant hypertension, there was agreement between ABP and HBP in 74 % of the cases (49 % with and 25 % without true resistant hypertension; kappa 0.46). The sensitivity, specificity, and positive and negative predictive values for HBP in detecting white coat resistant hypertension were 93 %, 63 %, and 81 % and 83 %, respectively. The respective values for HBP in detecting true resistant hypertension were 90 %, 55 %, and 71 %, and 82 %, indicating that HBP may be a useful tool in the evaluation of false and true resistant hypertension [69].

Based on the above data, it may be concluded that a proper assessment of BP control and classification of treated hypertensive patients with the combined use of office, ambulatory, and ideally home BP measurements are essential for defining the need of performing additional diagnostic procedures (i.e., screening tests for secondary causes of resistant hypertension) and/or implementing more aggressive pharmacological or interventional strategies (Fig. 2.15) [70].

Conclusion

The WCE may characterize not only the period when the patient actually sees the physician but also the entire period spent in a clinic environment [11, 12]. Thus, any improvement of the methods for measuring BP in the physician's office is unlikely to completely remove the confounding influence of the WCE on conventional BP measurements, which in due course is responsible for the substantial disagreements between office and 24-h or daytime ambulatory BP measures. Not unexpectedly there will be a significant number of subjects with elevated BP levels in the office, accompanied by persistently normal out-of-office BP levels (white coat hypertension).

Therefore, a proper diagnostic approach to the patient who presents with elevated BP levels in the medical office should include implementation of out-of-office BP monitoring for defining whether elevation in BP levels is true or is just the result of the "white coat effect" (white coat hypertension). This also applies for treated hypertensive subjects, in whom the alerting reaction to the medical visit continues to be present being responsible for the so-called false resistant hypertension, i.e., persistency of elevated BP levels in the office despite achieving adequate out-of-office BP control with antihypertensive drugs.

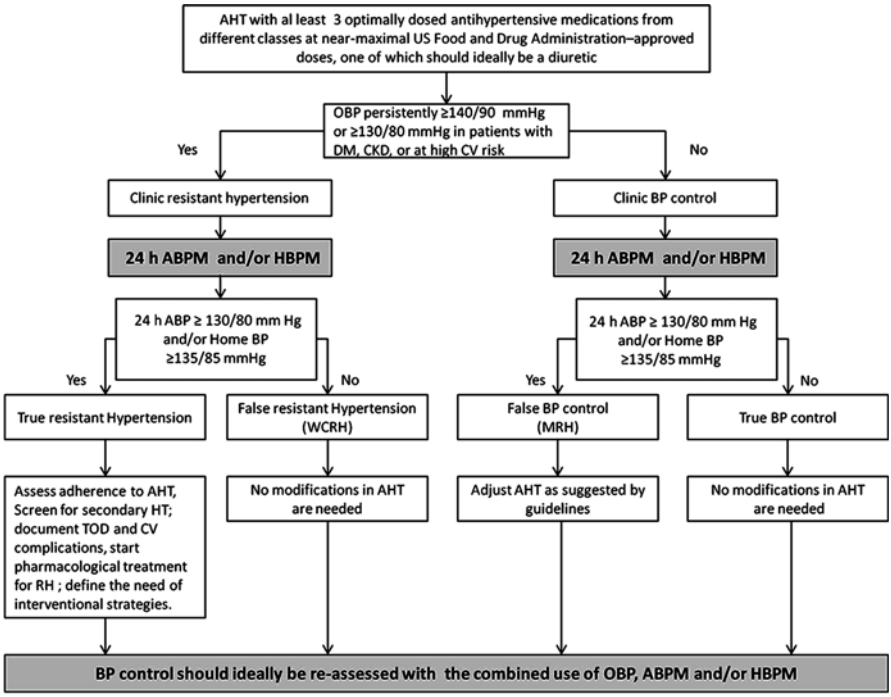

Fig. 2.15 Initial diagnostic approach to the patient with clinic resistant hypertension. *AHT* antihypertensive treatment, *HT* hypertension, *OBP*, office blood pressure, *DM* diabetes mellitus, *CKD* chronic kidney disease, *CV* cardiovascular, *BP* blood pressure, *ABPM* ambulatory blood pressure monitoring, *HBPM* home blood pressure monitoring, W*CRH* "white coat" resistant hypertension, *MRH* "masked" resistant hypertension, *RH* resistant hypertension (Taken from Parati et al. [70] with permission)

Although ABPM is considered the reference standard to characterize different subtypes of hypertension and resistant hypertension, HBPM has proved to be similarly effective to discriminate between false and true hypertension/resistant hypertension and between true and false normotension/BP control, thus reducing misclassification of hypertensive subjects [69]. Since there are individuals in whom an elevated clinic BP is associated with a normal home BP, but an elevated ambulatory BP, or vice versa, for a precise identification of WCH, either office, ambulatory, and home BP monitoring should ideally be implemented [71].

While confirmation of WCH would avoid starting antihypertensive treatment in subjects who have otherwise normal out-of-office BP levels, identifying WCRH in treated subjects may prevent performing unnecessary and costly additional diagnostic tests, also preventing from increasing doses or number of antihypertensive medications and the associated adverse effects of multidrug therapy. Despite all the above evidence, in clinical practice the efficacy of BP-lowering strategies is still often assessed just based on office BP without considering ambulatory and home BP measurements. The large number of patients with

WCH within the overall hypertensive population and the evidence summarized elsewhere in this book on the prognostic implications of WCH leave little doubt that, because of their higher risk of progression to sustained hypertension and likewise of a higher CV risk, patients with WCH deserve a more thorough evaluation and follow-up than normotensive patients.

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Neurogenic and Non-neurogenic Mechanisms of White-Coat Hypertension

3

Guido Grassi, Gino Seravalle, and Raffella Dell'Oro

3.1 Introduction

The past 30 years have seen a "renaissance" of the interest of investigators and clinicians for the possible contribution of sympathetic neural factors at the development and progression of essential hypertension [1]. This growing interest is based on a long series of findings and evidence. For brevity, they can be summarized as follows. First, it has been repeatedly shown that sympathetic neural factors are already activated in the early phases of hypertension and sometimes even in the prehypertensive states when blood pressure values are still in the high-normal range [1]. Second, it has been convincingly reported that adrenergic overdrive may parallel the blood pressure elevation and participate at the pathogenesis of end-organ damage [1]. Finally, results of some recent studies and clinical trials have suggested that in some forms of essential hypertension, such as resistant hypertension, therapeutic interventions capable to obtain a sympathetic denervation at the level of the kidney may trigger blood pressure lowering effects, thus reducing the very high cardiovascular risk of patients with elevated blood pressure levels resistant to three or more antihypertensive drugs (including a diuretic) administered at full daily dosage [2].

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Overwhelming evidence has been also provided that sympathetic neural factors contribute at the pathogenesis of white-coat hypertension. The present chapter will focus on this issue, reviewing the available evidence on three main topics: first, the concept that sympathetic overdrive is a common hallmark of several clinical models of hypertension; second, the evidence that the so-called white-coat phenomenon has in its pathophysiological background an important sympathetic neural component; and, third, the data showing the behavior of the sympathetic nervous system in white-coat hypertension, with a brief discussion focused on the possible consequences adrenergic overactivity has for the metabolic profile and the end-organ damage condition in this specific hypertensive state.

3.2 Sympathetic Activation in Hypertension: An Overview

Sympathetic neural factors participate to a consistent extent at the development and progression of the hypertensive state. This has been shown throughout a variety of methodological approaches used to assess human adrenergic drive, such as the assay of venous plasma norepinephrine, norepinephrine-radiolabelled technique, and direct microneurographic recording of efferent postganglionic muscle sympathetic nerve traffic [1]. The majority and more consistent data, however, have been obtained by assessing in humans efferent postganglionic sympathetic neural discharge throughout tungsten microelectrodes positioned at the level of the peroneal or brachial nerve [1]. Evidence indeed has been provided that an early activation of the sympathetic nervous system does already occur in the prehypertensive states when blood pressure values are in the high-normal range [3, 4]. Evidence is also available that a more consistent adrenergic overdrive takes place in mild to moderate essential hypertension, a further increase being detectable in the more severe hypertensive state (Fig. 3.1) [5].

Additional information on the sympathetic activation characterizing essential hypertension obtained in the past few years can be summarized as follows. First, the adrenergic overdrive of the essential hypertensive state is widespread to the whole cardiovascular system, an increase in norepinephrine spillover (a parameter reflecting the secretion of the neurotransmitter from adrenergic nerve terminals) being detectable at the level of the cerebral, coronary, and renal circulation as well [6]. Second, in the majority of the studies published so far, the hyperadrenergic state appears to be peculiar of essential hypertension, no sympathetic activation being detectable in secondary hypertensive states [1, 5]. Third, multiple and still largely undefined are the factors responsible for the onset of the sympathetic stimulation, although alterations in reflex cardiovascular control and metabolic influences (such as hyperinsulinemia and the related insulin resistance, renin-angiotensin-aldosterone activation, hyperleptinemia, etc.) are likely to play a role [1]. Finally, cross-sectional and longitudinal evidence indicate that sympathetic neural influences participate at the development and progression of the cardiovascular structural and functional changes associated with the high blood pressure state. This has been specifically shown for left ventricular hypertrophy and left ventricular diastolic dysfunction [7, 8].

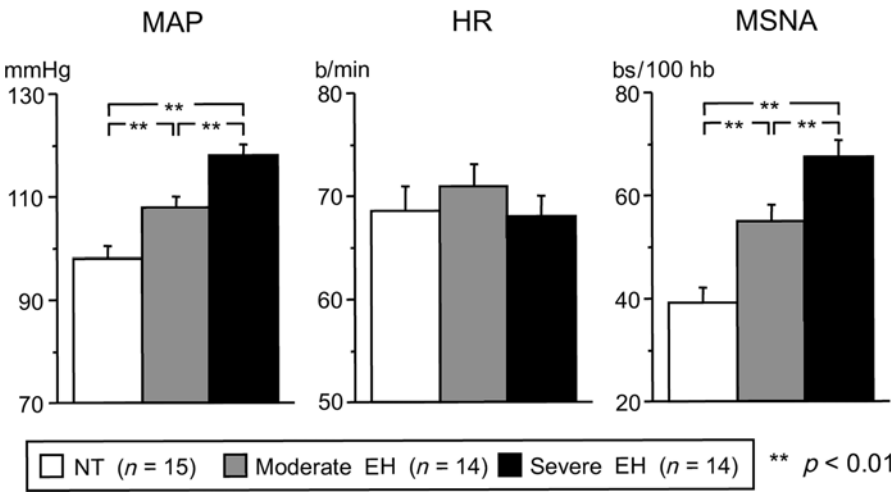

Fig. 3.1 Plots showing mean arterial pressure (*MAP*), heart rate (*HR*) and muscle sympathetic nerve activity (MSNA) in normotensive (*NT*), moderate hypertensive (*MH*), and severe essential hypertensive (*EH*) subjects. Data are shown as means ± SEM. *Asterisks* (** $P<0.01$) refer to the statistical significance between groups (Unpublished figure drawn using data from Ref. [5])

This has been also shown for arterial stiffness and arterial and arteriolar vascular hypertrophy [9]. This has been finally shown for microalbuminuria and impaired renal function [10].

3.3 Neurogenic Mechanisms and the "White-Coat" Effect

As already mentioned in other chapters of the book, the term "white-coat" effect refers to the marked pressor and tachycardic responses that can be triggered in a consistent number of subjects by the doctor when assessing sphygmomanometric blood pressure values [11]. For several years, it was thought that these hemodynamic changes were dependent on an alerting reaction triggered by the doctor in the process of measuring clinic blood pressure values, resembling a stressful condition eliciting a sympathetic stimulation. Only in recent years, however, it became clear that the abovementioned hemodynamic alterations may be accompanied to, and presumably triggered by, profound changes in regional sympathetic neural drive. This demonstration came from a study carried out by our group in which we quantified in patients with newly discovered hypertension the "white-coat" effect not only on blood pressure and heart rate but also on sympathetic neural outflow to the muscle and the skin circulation as assessed by the microneurographic technique [12]. What we did was to examine whether and to what extent muscle and skin sympathetic nerve traffic, which are regulated as shown in Fig. 3.2 by different mechanisms, are affected by the sphygmomanometric assessment of clinic blood pressure by a doctor. Figures 3.3 and 3.4 show the main study results. As expected

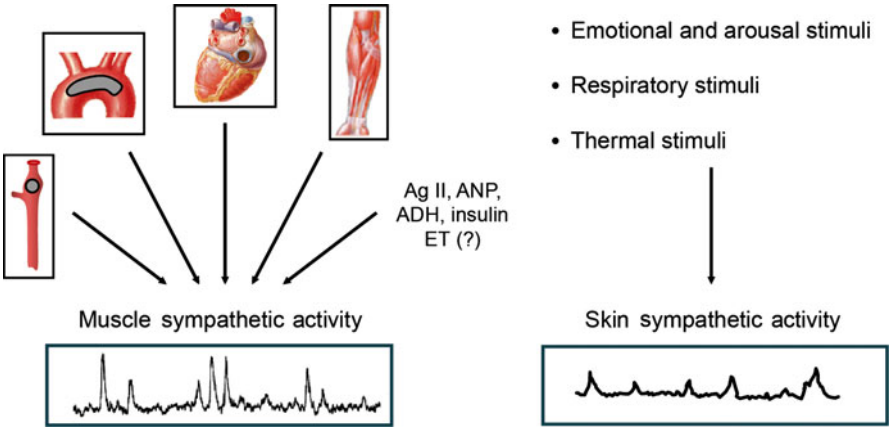

Fig. 3.2 Schematic drawing illustrating the factors modulating muscle and skin sympathetic activity. Reflex influences stemming from the carotid and aortic bodies, receptors located within the cardiac chambers, and muscle metaboreceptors as well as metabolic and humoral factors contribute to the regulation of muscle sympathetic nerve traffic (*left panel*), while emotional factors and thermal and respiratory stimuli modulate skin sympathetic nerve traffic (*right panel*). *Ag II* angiotensin II, *ANP* atrial natriuretic peptide, *ADH* vasopressin, *ET* endothelins

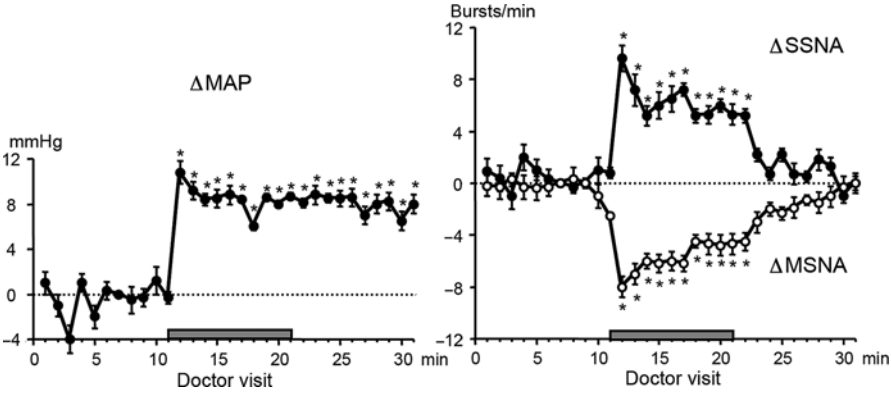

Fig. 3.3 Effects of sphygmomanometric blood pressure measurement by a doctor (doctor visit) on mean arterial pressure (*MAP*), muscle sympathetic nerve traffic (*MSNA*), and skin sympathetic nerve traffic (*SSNA*). Data are shown as mean ± SEM changes as compared to the pre-visit values. Note the marked pressor response associated with a sustained increase in SSNA and a pronounced reduction in MSNA. *Asterisks* (* $P<0.05$) refer to the statistical significance between single values obtained during doctor visit and pre-visit values (Unpublished figure drawn using data from Ref. [12])

sphygmomanometric blood pressure measurement by a doctor elicited a sudden marked increase in blood pressure (recorded on a beat-to-beat basis via a Finapres device) which was associated with a tachycardic response. These hemodynamic changes were accompanied by a decrease in muscle sympathetic nerve traffic, amounting on average to 27 %, and by a marked increase (+73 %) in skin

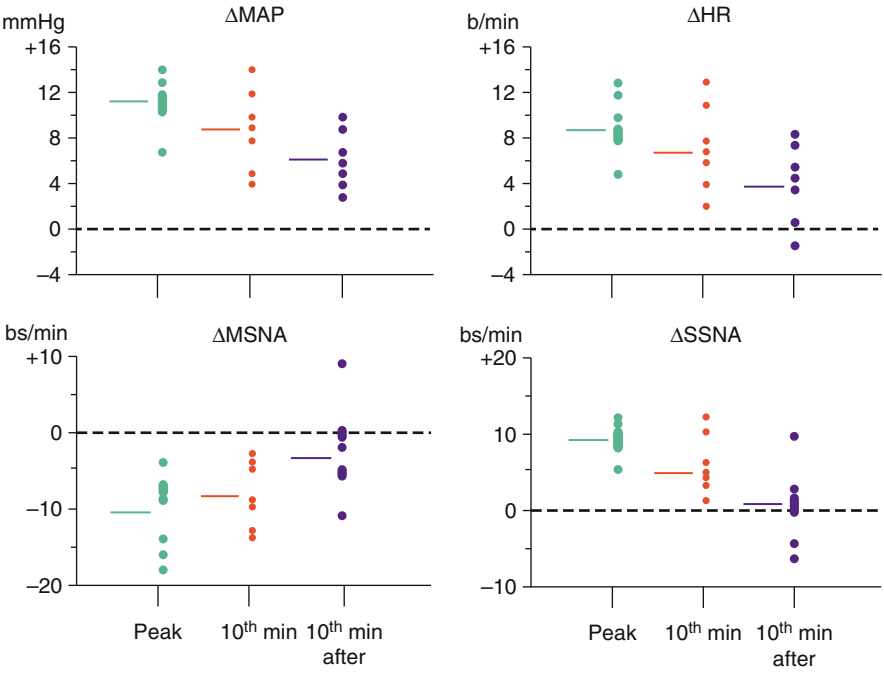

Fig. 3.4 Changes in mean arterial pressure (*MAP*), heart rate (*HR*), muscle sympathetic nerve activity (MSNA), and skin sympathetic nerve activity (SSNA) observed in the first 2 min (peak), at the 10th minute of the doctor visit (10th minute) and after 10th minute from the visit end (10th minute after). Data are shown as individual data (*circles*) and as average values (*horizontal lines* in each panel). *B/min* beats per minute, *bs/min* bursts per minute (Unpublished figure drawn using data from Ref. [12])

sympathetic nerve traffic. Interestingly, all the abovementioned hemodynamic and neural changes persisted throughout the 10 min doctor visit and showed, with the exception of the skin neural component, a slow rate of disappearance (Fig. 3.4). It thus appears that the emotional reaction known as "white-coat" effect is characterized by a behavior of the sympathetic nervous system that combines a skin sympathetic activation (and a resulting vasoconstriction) with a muscle sympathetic deactivation leading to muscle vasodilation. This heterogeneous neural behavior appears to be a peculiar feature of the human responses to emotional stimuli, which are characterized by a generalized vasoconstriction in different vascular districts (including the cutaneous one) except the skeletal muscle, in which a profound vasodilation has been reported [13].

A further set of data our group has collected throughout the years on the involvement of sympathetic neural factors in the "white-coat" effect concerns the behavior of the hemodynamic and sympathetic nerve traffic responses to blood pressure measurements performed by a nurse. The hypothesis tested in these studies was that the alerting reaction should be markedly attenuated by a nurse as compared to a physician, given the greater emotional impact on the patients physicians have as

compared to nurses. In the first study we compared the blood pressure and heart rate responses to the doctor's and nurse's sphygmomanometric blood pressure measurement in a group of 16 normotensive or hypertensive subjects who underwent intra-arterial recording of blood pressure via the Oxford technique [14]. By evaluating the intra-arterial blood pressure responses, we found that the nurse elicited a markedly less pronounced pressor response as compared to the one triggered by the doctor, with a parallel attenuation of the tachycardia observed during the doctor visit. In a recent study in which we made use of an experimental design similar to the one just mentioned, we were able to show that the attenuation of hemodynamic responses characterizing the alerting reaction by the nurse had as "neurogenic" counterpart a consistent reduction in the magnitude of the muscle sympathoinhibitory and skin sympathoexcitatory responses to the doctor's blood pressure measurement (Fig. 3.5) [15]. This finding provides further support to the hypothesis that neurogenic mechanisms are responsible in large part for the hemodynamic responses characterizing the "white-coat" effect.

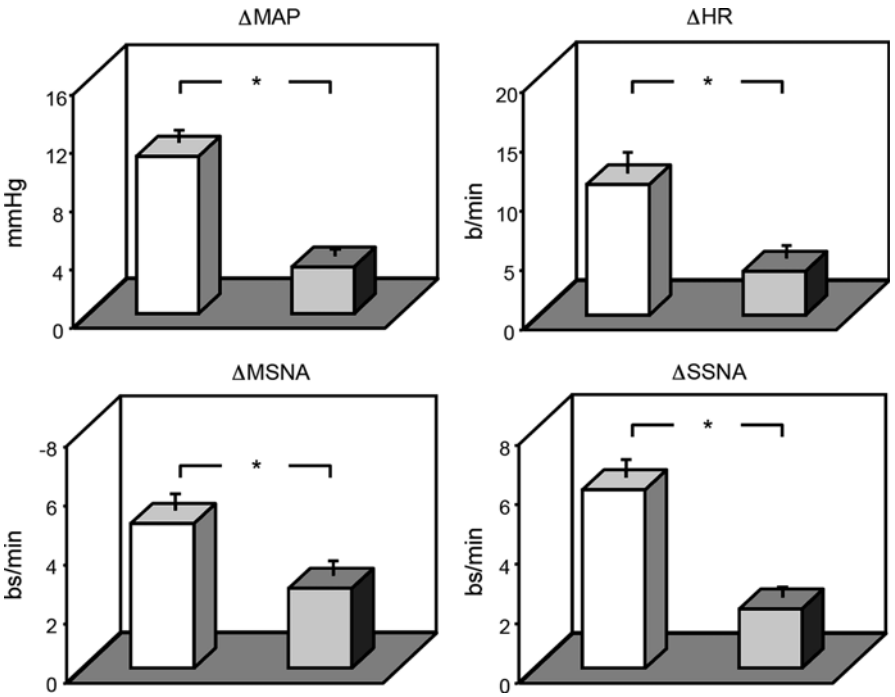

Fig. 3.5 Changes in mean arterial pressure (*MAP*), heart rate (*HR*), muscle sympathetic nerve activity (*MSNA*), and skin sympathetic nerve activity (*SSNA*) observed during doctor (*white bars*) or nurse (*black bars*) blood pressure measurement. Data are shown as mean ± SEM changes as compared to the pre-visit values. *Asterisks* (* $P<0.05$) refer to the statistical significance between doctor and nurse responses. Note the marked attenuation of the responses during nurse blood pressure assessment. *B/min* beats per minute, *bs/min* bursts per minute (Unpublished figure drawn using data from Ref. [12])

3.4 Sympathetic Abnormalities in White-Coat Hypertension

Indirect and direct methods to assess human sympathetic cardiovascular drive have provided conclusive evidence that a hyperadrenergic state can frequently be detected in white-coat hypertension. The indirect evidence has been provided by three studies in which via power spectral analysis of heart rate signal it has been possible to show that the low-frequency to high-frequency ratio was significantly higher in white-coat hypertensive patients as compared to pure normotensive individuals and that the increase was dependent on a higher low-frequency and a lower high-frequency component, indicating an augmented sympathetic and a reduced parasympathetic modulation of the heart rate signal [16–18]. Although intriguing these results, however, did not allow to clarify exactly whether sympathetic activation (1) does occur in white-coat hypertension and (2) is restricted to the heart or generalized to the whole cardiovascular system. This is because previous studies have shown that in other conditions characterized by a marked sympathetic activation, such as the aging process, power spectral analysis of the heart rate signal is unable to pick up any adrenergic overdrive, despite the marked increase in cardiac norepinephrine spillover and sympathetic nerve firing rate concomitantly documented by the norepinephrine-radiolabelled technique and the microneurographic nerve traffic recording [19].

The two direct evidence published so far [20, 21], on the other hand, provide demonstration that masked hypertension is a condition characterized by a marked adrenergic overdrive that appears to be widespread to the whole circulation. Indeed, in our own study [21] we found that muscle sympathetic nerve traffic is about 30 % greater in white coat as compared to age-matched normotensives and that the magnitude of the adrenergic overdrive is almost superimposable to the one characterizing masked hypertension (i.e., the clinical condition showing normal clinic but elevated ambulatory blood pressure values) and essential hypertension as well (Fig. 3.6). The adrenergic overactivity is associated with an impaired baroreflex control of heart rate, but not of sympathetic neural drive (Fig. 3.7).

3.5 Clinical Implications and Conclusions

The evidence that white-coat hypertension has as main pathophysiological hallmark a state of sympathetic overactivity has clinical relevance for a variety of reasons. First, it has been shown that white-coat hypertension is frequently associated with metabolic disarrays, the most important being the hyperinsulinemic state and the related insulin resistance condition [22]. Given the crucial role exerted by the hyperadrenergic state on insulin metabolism [1], the above-mentioned finding can be viewed as a metabolic consequence of the hyperadrenergic state. The same consideration applies to left ventricular hypertrophy, which is quite frequently detectable in white-coat hypertensives [23] and has in its pathophysiological background, as mentioned above, a clear-cut adrenergic component [1].

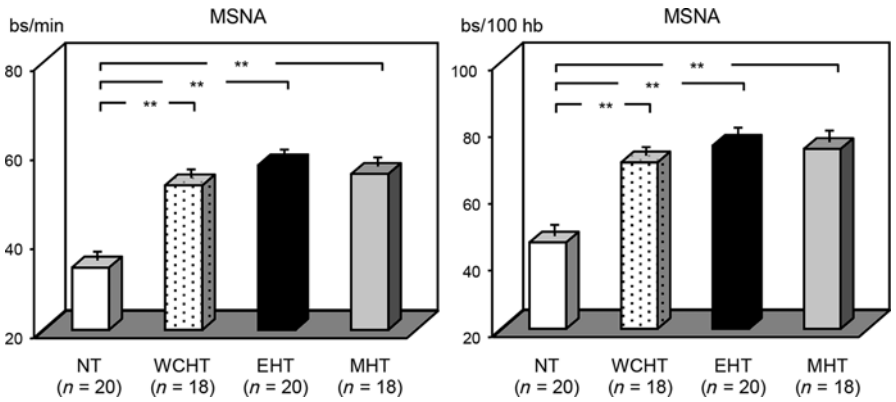

Fig. 3.6 Plots showing muscle sympathetic nerve activity (*MSNA*), expressed as bursts incidence over time (bs/min, *left panel*) and as bursts incidence corrected for heart rate (bs/100 hb), in normotensive subjects (*NT*), white-coat hypertensives (*WCHT*), severe essential hypertensive (*EHT*), and masked hypertensives (*MHT*). Data are shown as means ± SEM. *Asterisks* (** $P<0.01$) refer to the statistical significance between groups (Unpublished figure drawn using data from Ref. [21])

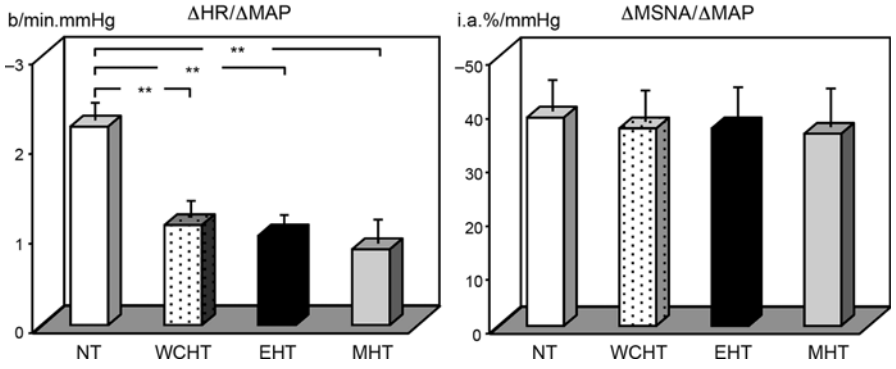

Fig. 3.7 Plots showing heart rate (ΔHR/ΔMAP) baroreflex sensitivity (*left panel*) and muscle sympathetic nerve activity (ΔMSNA/ΔMAP) baroreflex sensitivity (*right panel*) in the four groups of patients of Fig. 3.6. For symbols and explanations see Fig. 3.6 (Unpublished figure drawn using data from Ref. [21])

Finally, epidemiological evidence collected in large-scale observational studies with a prolonged follow-up period has shown that white-coat hypertension is not an innocent clinical condition and that its detection is associated with an increased risk of fatal and nonfatal cardiovascular events [24, 25]. It is likely, although still unproven, that among the various pathophysiological abnormalities characterizing white-coat hypertension (such as the endothelial dysfunction, the insulin resistance state, etc.), the sympathetic activation described in this chapter may play a major role. Future studies will be needed to test this hypothesis.

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Predictive Factors for White-Coat Hypertension

4

Gianfranco Parati, Juan Eugenio Ochoa, Carolina Lombardi, and Grzegorz Bilo

4.1 Introduction

The alerting reaction associated with the doctor's visit or more in general with the situation of being in a medical environment causes important interference with blood pressure (BP) measurement in the clinical setting, possibly leading to misclassification of BP levels [1]. Indeed, more than 30 % of subjects who present an acute elevation of BP levels in the doctor's office (white-coat effect, WCE) may be diagnosed as having white-coat hypertension (WCH, or isolated office hypertension, i.e., the condition characterized by persistently elevated office BP levels and normal ambulatory and/or home BP levels). In recognition of this, current hypertension guidelines have included the suspicion of WCH among the clinical indications for performing out-of-office BP monitoring [2, 3]. However, since performing ambulatory BP monitoring in all subjects who present with elevation in BP levels in the medical office is not always feasible, several studies have been conducted in the attempt to identify clinical and demographic factors that could help the practicing physician to suspect WCH and thus to reasonably proceed with performance of ambulatory BP monitoring. However, no clear evidence has been so far provided regarding the clinical features that should be considered in order to raise this

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suspicion. The first pioneering studies implementing continuous intra-arterial BP recordings indicated that the magnitude of the WCE during a physician visit is largely variable among different subjects, which makes it hardly predictable in the individual patient [1]. Moreover, this interindividual variability in the magnitude of the WCE was not entirely explained by differences in clinical or demographic patients' characteristics (i.e., age, sex, 24-h BP levels) nor by the degree of spontaneous 24-h BP variability [1]. Inconclusive have also been the results of studies exploring the role of other potential predictors for WCE and WCH, such as the pressor response to physical and mental laboratory stress, psychobehavioral factors, or physical activity.

Notwithstanding these negative findings, however, when focusing on patients with uncomplicated hypertension, not yet receiving antihypertensive treatment, the probability of identifying WCH was shown to be higher in the presence of certain clinical characteristics, such as office systolic (S)BP in the range of 140–159 mmHg or diastolic (D)BP in the range of 90–99 mmHg, female sex, increasing age, nonsmoking status, hypertension of recent diagnosis, limited number of BP measurements in the doctor's office, and normal left ventricular mass at echocardiography [4–6]. These studies, despite their general interest and the fact that they have contributed to a better understanding of the mechanisms involved in the pathophysiology of WCH, have failed to identify a characteristic or a cluster of factors specific enough to predict the presence of this condition.

The present chapter will discuss the information currently available on the possibility for the practicing physician to raise the suspicion of WCH based on certain clinical characteristics of patients, in order to define the need to perform ambulatory BP monitoring.

4.2 Does the WCE Depend on the Alarm Reaction to the Medical Visit or on the BP Measuring Procedure?

Pioneering studies implementing 24 h intra-arterial ambulatory BP recordings not only made a precise direct quantification of the WCE ("real" WCE) possible, but they also allowed identification of factors influencing the magnitude of this phenomenon [1, 7]. Remarkable findings of these studies were the observation that WCE occurs even before performance of the arm cuff measurement [1] and that it is not triggered by automatic BP measurements [7] thus indicating that it is the alerting reaction to the medical visit and not the cuff inflation at the moment of BP measurement that causes the BP rise during the doctor's visit.

One of such studies also showed pronounced interindividual differences in the degree of BP increase during the medical visit, which were not explained either by clinical or demographic characteristics of patients such as age, sex, and average 24-h BP levels or by the degree of spontaneous 24-h BP variability [1]. Besides, the time of the maximal increase in BP levels during the medical visit was shown to be highly variable among individuals (Fig. 4.1).

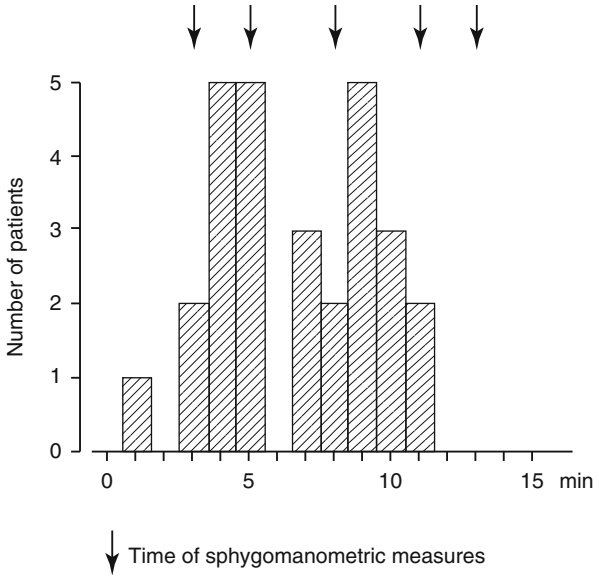

Fig. 4.1 Timing of the maximal increase in both systolic and diastolic finger blood pressure during the physician's visit. Vertical bars indicate number of subjects showing a maximal blood pressure increase during the 15-minute visit; *arrows*, timing of cuff blood pressure measurements by the physician (Taken from Parati et al. [10] with permission)

4.3 Influence on the Magnitude of the WCE by the Method Employed for Its Calculation, i.e.; by Use of Continuous or Intermittent BP Monitoring

A precise quantification of the pressor reaction triggered in the patient by physician's presence, commonly known as "WCE," needs implementation of continuous beat-to-beat BP recordings before, during, and after the medical visit. After the introduction in clinical practice of noninvasive techniques for intermittent out-of-office BP monitoring, the difference between office and average daytime ambulatory or home BP values was proposed as an alternative, indirect measure of the WCE, although this proposal faces important limitations (see Chap. 2) [4].

It was also assumed that the condition characterized by a persistently high BP in the clinic environment and a persistently normal BP in ambulatory daily life conditions, commonly referred to as "white-coat hypertension," could reflect the persistence over time of an alerting reaction to the physician's visit [4]. However, the evidence to support the concept that the difference between office and ambulatory daytime BP values specifically reflects the BP rise induced in the patient by the medical environment is limited and inconsistent. Indeed, the findings obtained by several studies comparing direct and indirect measures of the white-coat effect have shown limited [8] or no correlation [9–11] between these methods. One of such

studies exploring how much direct measures of the WCE, obtained by means of continuous, noninvasive BP recordings, were related with the clinic-ambulatory daytime BP difference showed no correlation between the direct and indirect measures of the WCE performed using these two approaches, respectively [10]. The clinic-ambulatory daytime BP difference did correspond only to less than 30 % of the peak BP increases continuously measured at the finger level during the physician's visit.

Overall, this study indicated that the difference between office and ambulatory daytime BP values is unrelated to the magnitude of the WCEs and does not necessarily reflect the alarm reaction to the medical visit [10]. The substantial discrepancies observed in this study suggested that although the alarm reaction may somehow contribute to the magnitude of the clinic-ambulatory BP difference, it might be largely influenced by mechanisms and predisposing factors other than those causing the alarm reaction (e.g., the degree of physical activity during daily life).

The type of BP measurements from which different indices of the WCE are derived may indeed importantly influence the estimation of this phenomenon. In the case of direct assessment, BP reactivity to the physician is precisely quantified both in its size and duration, taking the BP levels recorded under the standardized resting condition preceding the physician's visit as a reference. Conversely, in case of the surrogate approach based on the clinic-daytime BP difference, the magnitude of the "surrogate" WCE depends on the difference between BP levels assessed during the visit and in daily life conditions. In fact, observations from several studies have raised the possibility that variables known to affect daytime BP levels, such as psychosocial, behavioral factors, varying degrees of physical activity, variable wake and sleep time periods, and stressful conditions occurring in daily life, may be more important determinants of the clinic-ambulatory daytime BP difference than the alerting reaction triggered by the medical visit [10, 12, 13].

Interestingly, it has been suggested that subjects with a pronounced WCE also display a more pronounced BP response to physical activity during daily life conditions and may thus experience greater BP variability during daytime activities than in the doctor's office as a consequence of an enhanced BP reactivity to daily stress [12] (Fig. 4.2).

Other reports have also indicated that a "WCE" could be indirectly assessed by the presence of a pronounced rise in BP in the so-called white-coat window of an ABPM recording, with BP values being characteristically higher during the first and/or the last hour of a 24-h ABPM (i.e., during those hours when patients are in the hospital environment for fitting or removal of the BP recorder) compared to the remaining hours of the day and night [14, 15] (Fig. 4.3).

It is also likely, as mentioned above, that the size of the "real" WCE might reflect the features of a more generic BP and heart rate responsiveness to daily life stress, outside of the laboratory environment. In other words, subjects who are hyperreactive to the physician's visit might also be hyperreactive to daily life stress, leading to higher daytime BP levels and thus, at variance from the assumptions underlying the adoption of the surrogate method for assessing WCE based on clinic-daytime BP difference, being associated with a smaller, rather than a wider, clinic-daytime BP difference. Evidence on this regard has been provided by some studies (although

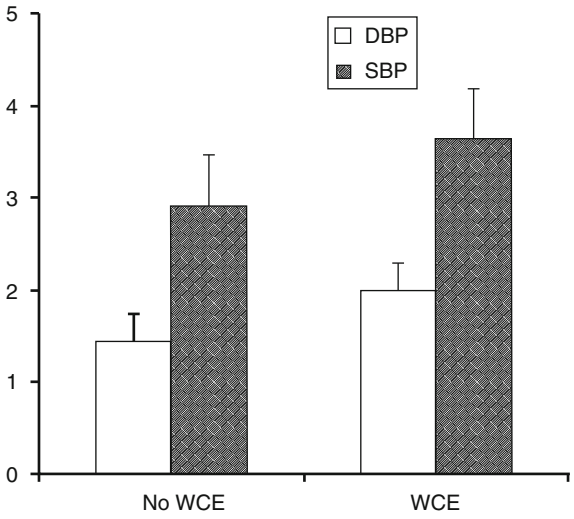

Fig. 4.2 Blood pressure (BP) response to an increase in mean physical activity in the 10 min preceding BP measurement of 1 log unit for subjects with and without a white-coat effect. For systolic BP (SBP), $P < 0.03$; For diastolic BP (DBP), $P < 0.02$; WCE, white coat effect (Taken from Leary et al. [12] with permission)

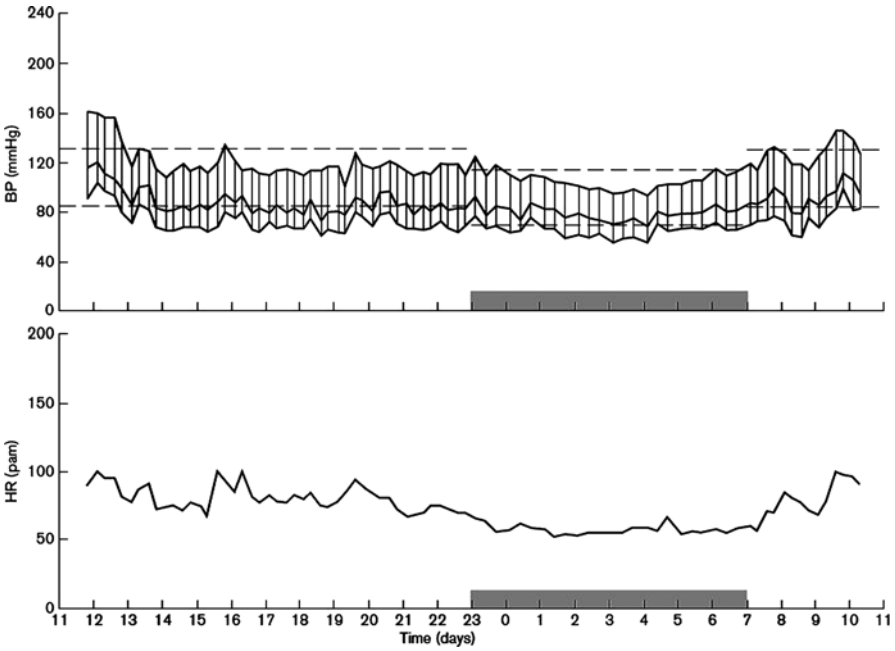

Fig. 4.3 Noninvasive discontinuous ambulatory blood pressure recording showing pronounced blood pressure reactivity in the first and last hours (hospital environment) and normal blood pressure behavior throughout the remaining portion of the recording. *BP* blood pressure, *HR* heart rate (Taken from Parati et al. [47] with permission)

not by all) showing that subjects with more pronounced direct measures of WCE also displayed increased daytime ABP levels and a higher level of 24-h average urinary epinephrine [11]. A further reason against the use of the clinic-daytime BP difference as a surrogate measure of WCE comes from the observation that, in different subjects, daytime BP levels may be differently influenced by the variable occurrence of physical activity, challenging emotional conditions, and periods of quiet rest during waking hours [11].

Finally, it should be considered that also errors in the BP measurement technique during the medical visit such as use of very small cuffs in obese subjects, fast deflation rates, measuring BP without the patient having rested enough, cigarette smoking, or coffee intake before the office measurements may cause overestimation of BP levels during the medical visit, thus increasing the magnitude of the white-coat effect. Conversely, the magnitude of the "surrogate" white-coat effect has been shown to be diminished if office BP is recorded with strict adherence to guidelines for proper BP measurement [16].

4.4 Role of the Person Who Conducts the Medical Visit: Physician vs. Nurse BP Measurements

The marked differences in the magnitude of the BP response to the medical visit and the absence of significant differences in clinical and demographic characteristics such as age, sex, and average 24 h BP levels explaining this interindividual variation [1] led to investigate the role of other potential contributing factors for this phenomenon. With the aim of assessing the relative contribution of the person who conducts the medical visit, one of these studies explored whether the alarm reaction would be attenuated if a nurse instead of a physician would be in charge of the visit and the related BP measurement. To this aim, researchers implemented 48 h beat-to-beat BP recordings in concomitance with two separate visits, one conducted by a doctor, the other by a nurse. Authors clearly showed a significantly much lower and more transient BP reaction when the visit and BP measures were performed by a nurse rather than by a doctor [17] (Fig. 4.4).

Also the BP response to automated BP measures triggered by the patient itself has been explored in other studies. While in studies implementing intra-arterial, continuous BP recordings in parallel to self-BP measurements performed by patients no alerting reaction was observed when it was the patient who triggered cuff inflation [7], other studies using intermittent 24 h ABPM have shown that even if the patient is alone and records BP by activating an automated sphygmomanometer, there may still be some alerting reaction although lower than that triggered by the presence of a physician or a nurse [18].

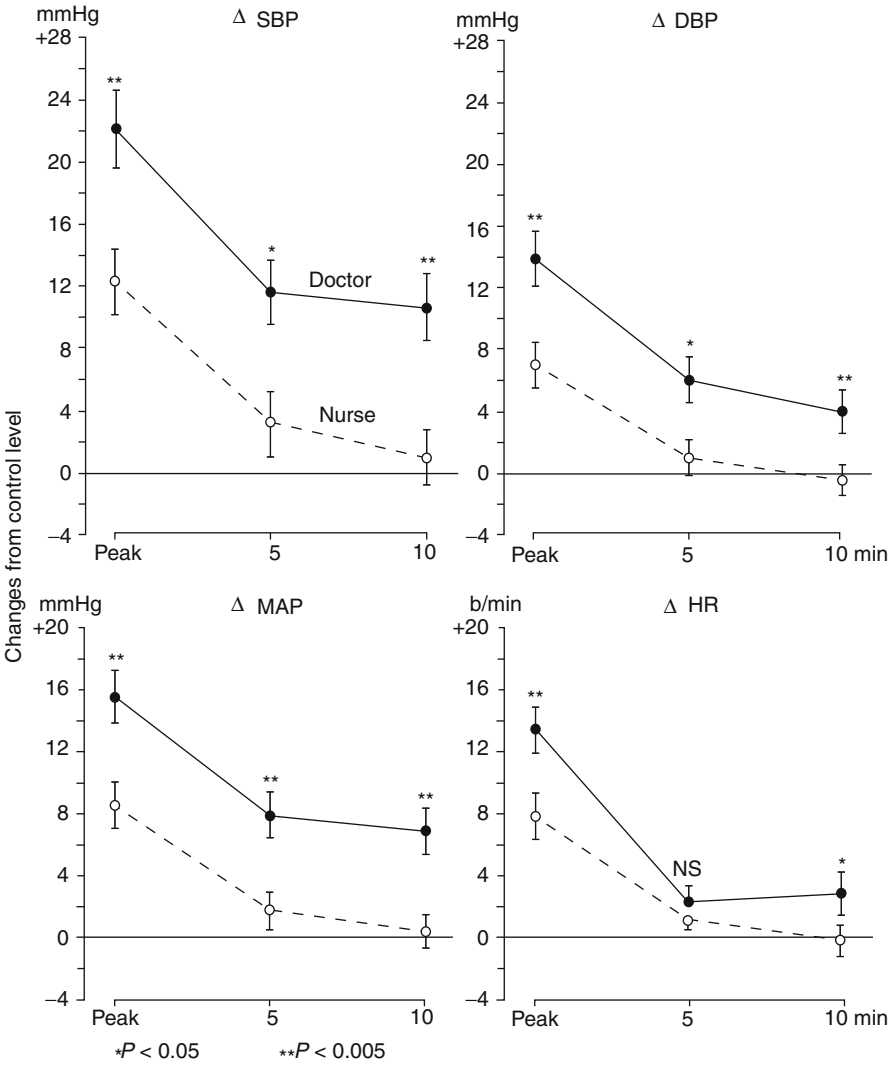

Fig. 4.4 Comparison of maximum (or peak) rises in systolic blood pressure (*SBP*), diastolic blood pressure (*DBP*), mean arterial pressure (*MAP*), and heart rate (*HR*) occurring in 30 hospitalized subjects during a physician's and a nurse's visits. The rises occurring at the 5th and 10th minutes of the visits are shown. Data are expressed as mean (±SEM) changes from a control value taken 4 min before each visit (Taken from Mancia et al. [17] with permission)

4.5 Does the Number of Medical Visits Influence the Magnitude of the WCE?

It has been postulated that when the patient becomes more familiar with the clinic environment or with the presence of the physician, the magnitude of the pressor response during repeated medical visits would tend to decrease. To address this question, different studies have been conducted implementing different BP measurement methodologies. One of these studies specifically explored whether the magnitude of the "true" WCE attenuates when the physician's visit is repeated several times (i.e., four consecutive visits repeated over a 48-h intra-arterial recording period) showing that the peak mean BP and heart rate increases that occurred in the early part of the physician's first visit (22.6 ± 1.8 mmHg and 17.7 ± 1.7 beats/min) remained of comparable magnitude during the three subsequent visits performed by the same physician throughout the 2 days of intra-arterial BP monitoring. Also the less pronounced pressor and tachycardic responses observed in the last part of the physician's visit were virtually identical among the four visits. This study thus indicated that the BP response to the medical visit does not easily fade away and that overestimation of BP inherent in cuff BP measurement by a physician cannot be avoided by repeated visits by the physician over a short time span [17] (Fig. 4.5).

At variance from studies implementing intra-arterial BP recordings to detect day-by-day changes in BP levels, other studies have explored the BP response to successive medical visits performed over wider time windows. One of such studies explored the BP response in subjects with mildly elevated BP levels over 12 consecutive medical visits in which BP readings were performed in duplicate. While during visits 1–3 BP showed a systematic decrease which varied from patient to patient (on average by 15/7 mmHg) [19], during visits 4–12 no further systematic changes in BP levels were observed. After visit 4, the chance of a clinic-daytime BP difference of ≥5 mmHg was 0.50 and 0.32 for systolic and diastolic BP, respectively, which was further reduced by increasing the number of visits to six or more. Although this reduction in office BP with subsequent visits might be ascribed to a reduction in the alerting reaction, it is likely that other factors such as a regression to the mean phenomenon, a placebo or a nocebo effect, may also have played a role [20].

4.6 Is It the Doctor's Office or the Clinical Environment That Causes the WCE?

On the background of the evidence showing that BP readings in the doctor's office are frequently higher than home or ambulatory BP values, several studies have been conducted with the aim of better clarifying the relative contribution of the physician in the etiology of the "WCE." In one of such studies, standard readings taken by the family physician were compared with readings obtained by an automated BP recording device, with the patient alone in the examining room, during the same office visit [21]. While, self-measurement of BP by the patient in the physician's

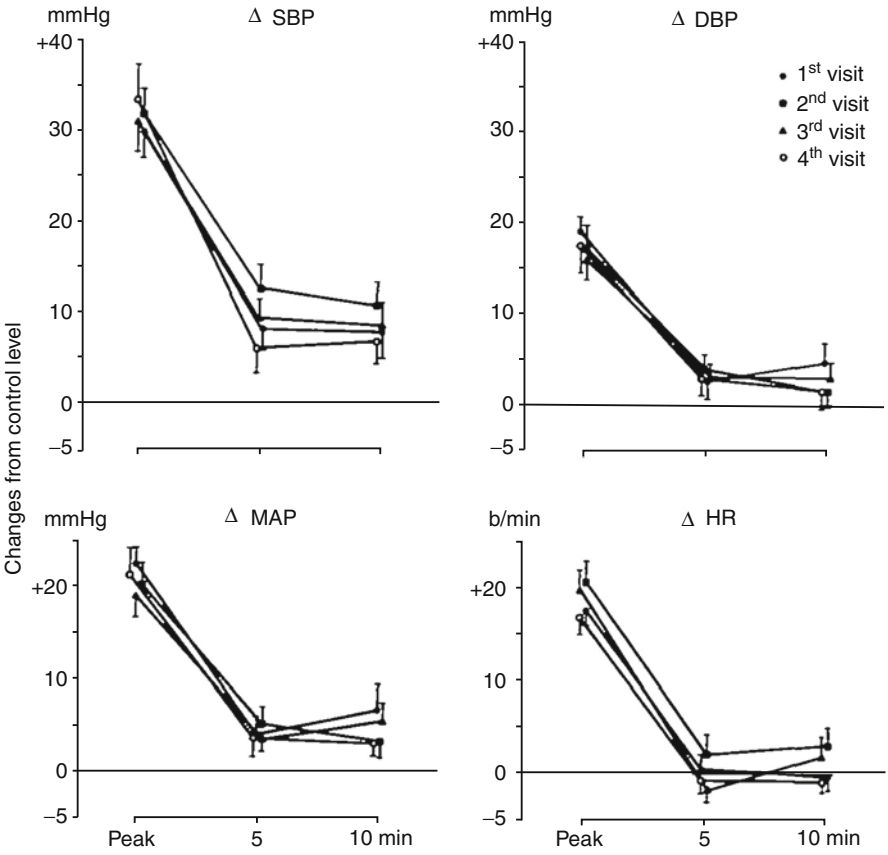

Fig. 4.5 Maximum (peak) rises in systolic blood pressure (*SBP*), diastolic blood pressure (*DBP*), mean arterial pressure (*MAP*), and heart rate (*HR*) occurring in 16 subjects during four visits by a physician. The peak rises occurred between the 2nd and 4th minute from the beginning of the physician's visit. The rises occurring at the 5th and 10th minute of the visits are also shown. Data are represented as mean changes (±SEM) from a control value taken 4 min before each visit of the physician (Taken from Mancia et al. [17] with permission)

office did not reduce the magnitude of the white-coat effect [21], a further report by the same authors showed that the white-coat effect was virtually eliminated if office BP readings were obtained through use of automated BP measurement in the office waiting room [15]. It was thus clear that even in the absence of the physician, the medical office itself may trigger an important pressor response in the patient, which is clearly higher than that occurring while the patient is seated in the office waiting room.

In another study, resting BP measures taken in a nonmedical setting (i.e., a laboratory room) by a research assistant were compared with the BP values obtained at rest and by the same researcher on a different day in the physician's office. Both sets of resting BP values were also compared with ABP values obtained during daytime

activities. Compared to BP measures obtained in the clinical environment (even before the patient had seen the physician), resting BP readings obtained in a non-medical setting were shown to be significantly lower. These findings were consistent both in normotensive and in hypertensive subjects. Consequently, the difference between clinic BP values taken by the physician and those taken in a nonclinical environment was significantly higher than the differences between BP values measured by the research assistant in the clinic when the patient was waiting to see the doctor and those obtained out of the medical environment [22].

In the same line, a study exploring the difference between self-BP measurements obtained at home and in a clinic environment showed that self-BP measures obtained in the clinical setting were higher than self-measured BP levels obtained by subjects at home, suggesting that the setting where BP is taken may be a more important contributor to the BP response during a doctor's visit than the subject who is in charge of the measurement [23]. Taken together these findings indicate that the WCE may characterize not only the time period when the patient actually sees the physician but also the entire period spent in a clinic setting.

4.7 Responses to Physical and Mental Stress as Predictors of the White-Coat Effect

An increased cardiovascular reactivity to stress in a given subject might predict elevation of BP levels during the medical visit. Based on this assumption several studies have been conducted in order to test if a higher BP response to active physical activity (i.e., dynamic or static exercise), passive physical stress (i.e., cold pressure test), or mental stress (i.e., as evoked via a problem of mathematical, technical, or decisional nature) in the laboratory setting is associated with a tendency of BP to increase during the medical visit. In one of such studies, mental (i.e., mental arithmetics and the mirror drawing test) and physical stress tests (i.e., cold pressor test and handgrip test) were performed along with 24 h ambulatory beat-to-beat intra-arterial BP recordings in a group of essential hypertensive patients and normotensive controls [24]. Whereas all stressors induced a significant increase in BP levels, the elevation in BP levels elicited by most of these laboratory stressors was not correlated with the BP or heart rate response to the doctor's visit, excepting a marginal relationship between the BP response to the mirror drawing test and the WCE [24]. Neither the pressor responses to laboratory stressors nor to the medical visit were correlated with the 24-h absolute or percent blood pressure variabilities (Fig. 4.6).

Overall, these studies indicated that the cardiovascular reactivity to laboratory tests is not a significant predictor of the BP response to the medical visit [24].

Along the same line other studies have indicated that the BP response to the laboratory tests is not a good predictor of the changes in BP occurring during real-life stressing situations since everyday physical activities, as well as outdoor and sport activities, differ in many respects from laboratory stress testing, so that a direct comparison cannot be made [25].

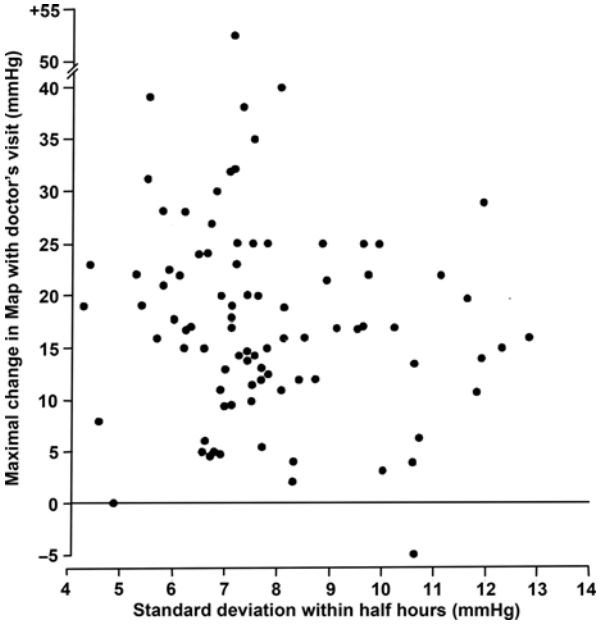

Fig. 4.6 Lack of relationship between pressor response to doctor's visit and 24 h mean arterial pressure variability. Short-term BP variability was assessed from intra-arterial beat-to-beat BP recordings performed over 24 h as the average of the standard deviations obtained for each half hour of the recordings (within half-hour absolute and percent variability) (Taken from Parati et al. [24] with permission)

In another study investigating a possible relationship between the BP response to stressors and the magnitude of the WCE (as assessed by means of continuous BP recordings in concomitance with the medical visit), contrasting results were reported between normotensive and hypertensive subjects [26]. While in normotensive subjects, the WCE effect was very small and not correlated with the responses to stress and standing, hypertensive subjects showed an enhanced BP response to orthostatic and mental stress (i.e., the color-word Stroop test) which was significantly correlated with the magnitude of the WCE [8, 26].

Other reports in essential hypertensive subjects have shown that mental stimuli known to increase BP levels such as talking and counting loud are correlated to the magnitude of the white-coat effect, likely as a consequence of the emotional content of communication between patient and physician during the medical visit [27]. In the same line other studies have shown that subjects presenting the WCE are characterized by an exaggerated response to psychosocial stimuli such as speaking in public [11].

Although the WCE might reflect an impaired cardiovascular autonomic modulation and a higher degree of BP fluctuations in response to challenging situations, the contrasting results reported by different studies prevent from deriving consistent conclusions in this regard.

These discrepant results regarding the relationship between the BP response to stressors and the WCE may in part be due to the poor reproducibility of the pressor response to different stressors but also to the different type of tests employed in different studies. Indeed, the responses to the "mental" and "physical" stressors have been shown to be unrelated, suggesting that these tests may selectively evaluate

Table 4.1 Regression coefficients (b) between mean arterial pressure (MAP) or heart rate (HR) responses to different laboratory stressors

		Mental arithmetic test	Mirror drawing test	Handgrip
MAP responses				
Mental arithmetic test	b	–		
	r^2			
Mirror drawing test	b	0.64*	–	
	r^2	0.62		
Handgrip	b	0.32	0.70	–
	r^2	0.08	0.24	
Cold pressor test	b	0.07	0.30	0.54*
	r^2	0.005	0.07	0.52
HR responses				
Mental arithmetic test	b	–		
	r^2			
Mirror drawing test	b	0.86*	–	
	r^2	0.55		
Handgrip	b	0.65	1.30	–
	r^2	0.04	0.23	
Cold pressor test	b	0.71	0.20	0.27
	r^2	0.11	0.01	0.16

*$p < 0.01$ for statistical significance of the regressions

specific cardiovascular responses [28], i.e., while public speaking might more likely reflect the BP response associated with emotional or psychological stress, other tests such as hand grip and cold exposure might reflect a more "physical" cardiovascular response to stressors (Table 4.1).

4.8 Psychobehavioral Factors

The possible influence of psychobehavioral factors such as emotions and type of personality (i.e., anger, anxiety, tension, type A behavior pattern, and nervousness) on the BP reaction to the medical visit was explored in a group of essential hypertensive subjects not yet receiving antihypertensive treatment. BP levels were continuously monitored at the finger level at rest and under mental stress (i.e., counting backward) and the WCE assessed as the difference between clinic and daytime ambulatory BPs [29]. Overall, this study showed that the psychobehavioral factors related to the clinic-daytime BP difference were different from those related to the alarm reaction associated with the physician's visit: while the score for type A behavior pattern tended to be inversely correlated to the clinic-ambulatory BP difference, the nervousness score was positively correlated to stress-induced increase in BP levels [29].

4.9 Clinical and Demographic Predictors of White-Coat Hypertension

Since performing ABPM in all subjects who show an elevation of BP levels in the medical office is not always feasible, several studies have been conducted in an attempt to identify clinical and demographic factors that could help the practicing physician to raise the suspicion of WCH and thus reasonably proceed with ABPM.

Regarding demographic characteristics of subjects, while some studies have found younger age to be an independent predictor or WCH [4, 30], contrasting results were reported in an analysis of a large international database composed of 2,492 subjects with office hypertension (i.e., BP more than 140 mmHg systolic or 90 mmHg diastolic) [31]. This analysis showed that the probability of having WCH (defined as elevated OBP levels in the office and an average 24-h ambulatory BP below the 95th centile of a normotensive control group) was directly associated with increasing age, was more frequent in women, and was inversely associated with office BP levels and the number of BP measurements performed in the office [31].

Although the role of age as a predictor of WCH remains still controversial, it has to be emphasized that no age group seems to be exempt from presenting WCH, which may affect the young, elderly, normotensive individuals, and pregnant women.

When it comes to basal BP levels of subjects, an analysis of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, classifying subjects according to Joint National Committee V criteria, reported a prevalence for white-coat hypertension of 33.3 % in stage I (systolic 140–159 mmHg and/or diastolic BP 90–99 mmHg), 11.8 % in stage II (systolic 160–179 mmHg or diastolic BP 100–109 mmHg), and 3 % in stage III hypertension (systolic $\geq$180 mmHg or diastolic BP $\geq$110 mmHg), indicating the higher probability of white-coat hypertension among subjects with stage I hypertension [32]. This study also showed that the white coat effect, calculated as the difference between clinic BP and average daytime ambulatory BP, was 13.9/5.7 mm Hg (systolic/diastolic BP) in the overall hypertensive group, and greater in the group with white coat hypertension than in that with ambulatory hypertension (both $P < 0.01$) [32] (Table 4.2).

A further analysis of the Hypertension and Ambulatory Recording Venetia Study (HARVEST) and PIUMA collaboration study, in 1,564 subjects with stage I hypertension, not yet receiving antihypertensive treatment, showed that WCH is most frequent among women, nonsmokers, and subjects with low clinic BP and smaller LV mass. In multivariate logistic regression analyses, lower values of office diastolic BP, female gender, and nonsmoking status were the sole independent predictors of WCH. In the subjects with adequate echocardiographic tracings, a smaller value of left ventricular mass was a further independent predictor of WCH [5].

Evidence has also been provided that metabolic alterations may predict development of white-coat and sustained hypertension in the long term. In the frame of a population-based longitudinal study in elderly men (enrolled at age 50), individuals who after a 20-year follow-up period were diagnosed as having white-coat or sustained hypertension showed significantly higher BP levels, heart rate, and impaired glucose tolerance compared to normotensive controls. Remarkably, compared to

Table 4.2 Difference between office blood pressure and average daytime ambulatory blood pressure ("white coat effect") in the hypertensive group (n = 1,280) and in the two subsets of subjects with white coat hypertension and ambulatory hypertension. Data are expressed as mean (SD)

	Normotensive group	Hypertensive group		
	(n = 178)	All subjects (n = 1,280)	White-coat HT (N = 238)	Ambulatory HT (N = 1,042)
Systolic BP (mmHg)	+1.8 (9.7)	+13.9 (15)	+19.7 (13)	+12.6 (15)*
Diastolic BP (mmHg)	+0.1 (7.3)	+5.7 (9)	+12.5 (8)	+4.2 (9)*
Mean BP (mmHg)	+0.7 (7.0)	+8.4 (9)	+14.9 (7)	+6.9 (9)*

*$P < 0.01$ vs white coat hypertension
Modified from Verdecchia et al. [32] by permission

sustained hypertensive subjects, those with white-coat hypertension showed a lower body mass index and more favorable lipid profile. By the end of the prospective follow-up (when participants had reached the age of 70), compared to normotensive subjects, both white-coat and sustained hypertensive subjects showed a significant impairment in insulin sensitivity, higher glucose and insulin levels, and an increased heart rate, without significant differences in left ventricular mass and prevalence of microalbuminuria. This study could thus consistently identify the presence of metabolic abnormalities and elevated heart rate as predictors of incident white-coat hypertension [33].

Also the potential role of indices of endothelial dysfunction has been studied. While some reports have shown a reduced endothelial function (assessed as variation in the diameter of the brachial artery produced by flow-mediated dilation) in subjects with white-coat hypertension (which has been shown to be similar to that of subjects with sustained hypertension) compared to healthy controls [34], other studies, however, have found no significant differences in indices of endothelial function among sustained hypertensives, white-coat hypertensives, and normotensive controls [35].

Overall, the data provided by different studies have indicated that in untreated subjects with essential hypertension, the probability of having WCH increases in subjects with mild hypertension (i.e., office systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg), subjects with female gender, subjects with nonsmoking status, subjects with hypertension of recent onset, subjects with a limited number of BP measurements in the office, and subjects without evidence of target organ damage (i.e., a small left ventricular mass on echocardiography) [5, 6].

However, given the heterogeneity of the populations studied and the different study designs implemented, it is hard to outline a consistent cluster of clinical predictors specific enough for identifying WCH. Further studies are thus required to better understand the determinants and mechanisms underlying WCE and WCH.

4.10 Predictive Factors for White-Coat Effect and White-Coat Resistant Hypertension in Treated Subjects

Although the WCE phenomenon was initially described in subjects not yet receiving antihypertensive treatment, the presence of a pressor response to the medical environment may still be present in treated subjects. Also a substantial and sometimes higher than expected frequency of white-coat resistant hypertension (i.e., the equivalent to white-coat hypertension identified in non-treated subjects) has been reported among treated subjects [36–38].The few studies exploring the effects of antihypertensive treatment on the magnitude of the WCE have indicated that the clinic-ambulatory daytime BP difference decreases following starting of treatment [39, 40]. Although this attenuation might be the result of patient's habituation to repeated BP measurement in the medical office, it might as well correspond to an effect of antihypertensive treatment per se [41].

In an attempt to provide clues to facilitate discrimination between patients with true resistant hypertension (i.e., persistent elevation of in-office and out-of-office BP levels) and false or "white-coat" resistant/uncontrolled hypertension (persistently elevated in-office but normal out-of-office blood pressure levels), some studies have comparatively studied the clinical characteristics of these two conditions. In a recent report of the National Health and Nutrition Examination Surveys (NHANESs), clinical characteristics associated with apparently treatment-resistant hypertension included ≥4 visits per year, obesity, chronic kidney disease, and Framingham 10-year coronary risk >20 % [42]. In the same line, an analysis of the Spanish registry showed significant differences in the prevalence of CV risk factors between false and true resistant hypertensive patients, the subgroup of subjects with true resistant hypertension being characterized by a significantly higher prevalence of cigarette smoking, diabetes, and target organ damage (i.e., left ventricular hypertrophy, microalbuminuria, or impaired renal function) and a history of previous cardiovascular events [36].

A recent analysis of the Blood Pressure (BP) control rate and CArdiovascular Risk profilE (BP-CARE) study exploring the main clinical features of resistant hypertension in 1,312 treated hypertensive patients Living in Central and East European countries showed that compared to true treatment-resistant hypertension patients, those with white-coat resistant hypertension were younger and showed a significantly lower frequency of obesity, renal failure, organ damage, and history of cardiovascular events [43].

Despite the effort of these studies to identify consistent characteristics and trends in order to distinguish true from false resistant hypertension, the strength of the associations was very week. It is thus unlikely that the differences in risk factor profiles or in selected clinical characteristics might be sufficient to discriminate between these conditions.

Conclusions

Since ambulatory BP monitoring is not feasible for all subjects who present with elevation in BP levels in the medical office, current hypertension guidelines [2, 44] and guidelines for ABPM [3] recommend out-of-office BP monitoring when there is clinical suspicion of WCH. However, how to support this decision is less clear. Despite the evidence provided by several studies suggesting that the likelihood of identifying WCH in untreated patients with uncomplicated hypertension increases in the presence mild hypertension, female sex, nonsmoking status, hypertension of recent diagnosis, limited number of BP measurements in the doctor's office, and absence or target organ damage [4–6], neither pathognomonic diagnostic features nor a cluster of clinical predictors highly specific for diagnosing this condition have been identified. In the absence of clinical characteristics specific enough to support the suspicion of white-coat hypertension, the best clue to suspect this condition is the finding of persistently high office BP levels in subjects with otherwise normal BP readings outside of the medical office (i.e., at home or in the community). Finally, it must be emphasized that ABPM, ideally accompanied by the use of HBPM for assessment of BP control in the long term, remains the standard method for a correct differentiation between true resistant and white-coat or false resistant hypertension in treated hypertensive patients who present with persistent elevation of BP levels in the medical office [3, 45].

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White Coat Hypertension and Target Organ Damage

5

Cesare Cuspidi, Marijana Tadic, Carla Sala, and Guido Grassi

5.1 Introduction

Over the past decades clinic blood pressure (BP) has been increasingly recognized as a poor estimate of BP levels outside the doctor's office. The alerting reaction induced by the doctor or nurse during office BP measurement usually impairs the accuracy of this conventional approach in estimating the BP levels of subjects [1]. White coat hypertension and isolated clinic hypertension (ICH) are the most common terms categorizing individuals whose BP is elevated in the doctor's office while self-measured or ambulatory BP values are normal. Available evidence indicates that ICH is frequently observed in the general as in the hypertensive population, its prevalence depending on the criteria used to define this condition [2, 3]. The clinical relevance of ICH has not been fully established; in particular, the cardiovascular risk associated with this BP phenotype remains undefined. Cross-sectional studies on the association between ICH and markers of organ damage with proven

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prognostic value have yielded conflicting results. According to some studies, cardiac and vascular structures were not different in subjects with ICH as compared to normotensive individuals; in contrast, other studies provided evidence of similar prevalence of organ damage in ICH as in sustained hypertension. Accordingly, the incidence of cardiovascular events in subjects with ICH has been alternatively reported to be as lower as in normotensive subjects, as higher as in hypertensive patients, or intermediate between the two populations [4, 5].

Subclinical organ damage is currently regarded as an intermediate stage in the continuum of vascular disease and as a strong determinant of total cardiovascular risk in both normotensive and hypertensive individuals. A growing body of evidence underlines the relevance of cardiac, vascular, and renal damage as a determinant of cardiovascular morbidity and mortality. Quantitative markers of organ damage (i.e., increased left ventricular mass, carotid intima-media thickening, reduced glomerular filtration rate, and increased urinary albumin excretion) have been associated with a higher incidence of cardiovascular events [6–8]. Due to the role of high BP per se or associated with other risk factors in determining subtle structural and functional alterations in target organs, signs of organ involvement should be carefully sought in the initial evaluation of hypertensive patients in order to quantify total cardiovascular risk [9]. This point is of major clinical relevance as BP thresholds for treatment, BP goals during treatment, and intervention on concomitant risk factors in the hypertensive patient all depend on the global cardiovascular risk, which may largely vary among patients. Evaluation of organ damage not only provides an estimate of total cardiovascular risk in the initial work-up but also may document treatment-induced improvement in damaged organs; in particular, reduction in proteinuria or regression of left ventricular hypertrophy (LVH) has been shown to be associated with a lower incidence of fatal and nonfatal cardiovascular events [10, 11]. The purpose of this chapter is to provide an updated and comprehensive review on the association of ICH with subclinical structural and functional alterations in the heart, vessels, and kidney.

5.2 ICH and Cardiac Damage

A variety of cardiac structural and functional changes, such as increased LV mass, left atrial and aortic root enlargement, LV dysfunction, impaired coronary reserve, myocardial fibrosis, and prolonged ventricular repolarization, all have been described in patients with long-standing arterial hypertension (Fig. 5.1). Subtle alterations in LV structure and geometry have been shown to occur also in the early phases of the natural history of essential hypertension [12]. Among the manifestations of organ damage, most attention has been devoted to LVH, because of the high prevalence of this phenotype and the associated increased risk of cardiovascular morbidity and mortality [13–15]. LVH reflects the long-term exposure of the heart to pressure overload and may identify individuals more exposed to the adverse effects of high BP [16]. Several studies underlined the relationship between LVH at baseline examination, either assessed by electrocardiography or by the more accurate echocardiographic method and morbidity/mortality in population-based

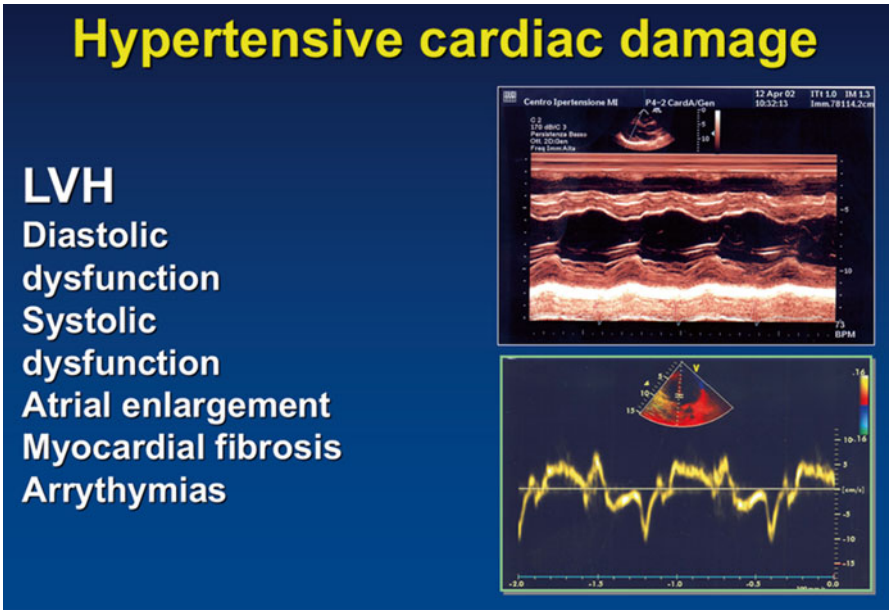

Fig. 5.1 Manifestations of subclinical cardiac organ damage related to hypertension: the association between left ventricular hypertrophy (*LVH*, *upper panel*) and diastolic dysfunction (*lower panel*)

samples and in hypertensive cohorts. Furthermore, both electrocardiographic and echocardiographic studies performed in population-based samples, in high-risk individuals, and in hypertensive cohorts clearly documented that LVH regression significantly decreased the risk cardiovascular events, while LVH persistence or progression implied a worse prognosis, independently of BP control and treatment modality [17, 18].

Several methods characterized by different diagnostic sensitivity and specificity, namely, electrocardiography, chest X-ray, echocardiography, and magnetic resonance imaging, are available for LVH detection. Standard ECG at rest is largely available in clinical practice due to its simplicity and low cost; its sensitivity, however, is relatively low [19]. Among noninvasive methods evaluating cardiac anatomy and function in hypertensive patients, echocardiography is the most widely used. The advantages of this procedure include high sensitivity/specificity, large availability, absence of biological harmful effects, excellent tolerability, and lower cost compared with techniques of similar accuracy. Echocardiographic prevalence of LVH in hypertension depends mostly on demographic and clinical variables and partly on cutoff values applied. Although the pathogenesis of hypertensive LVH is not fully understood, a consistent body of evidence indicates that the severity of pressure overload, as better reflected by out-of-office than in-office BP levels, in combination with non-hemodynamic variables, including genetic, ethnical, and humoral factors, plays a pivotal role in its development [20]. A number of echocardiographic studies performed in different clinical settings (i.e., hypertension clinics,

primary care, pediatric setting, and population-based cohorts) explored the association between ICH and subclinical cardiac damage in terms of LVH and/or LV concentric remodeling. Most studies focused their attention on untreated subjects with ICH, but other reports investigated the impact of this condition in patients on antihypertensive drugs.

In a pioneering investigation by Haegholm et al. including a total of 143 patients with newly diagnosed mild-to-moderate hypertension (53 with ICH as defined by daytime ambulatory DBP <90 mmHg), LV mass index was higher in the group with established hypertension compared to ICH group (102 ± 27 g/m^2 versus 94 ± 23 g/m^2, $p = 0.04$) [21]. This was also the case for LV relative wall thickness, an index of LV concentric geometry (0.36 ± 0.07 versus 0.33 ± 0.06, $p = 0.004$). Of note, LV geometry and structure was normal in up to 83 % ICH patients as compared to 61 % established hypertensives. Left atrial dimensions were not different between the groups. In a multiple regression model, ambulatory BP values but not office BP values were significantly associated with the extent of cardiac hypertrophy. In a subsequent study conducted at the New York Hospital-Cornell Medical Center by Devereux's group, the authors compared echocardiographic data of LV structure and function in 24 untreated individuals with ICH (i.e., ambulatory awake BP <134/90 mmHg) with those of sustained hypertensive and normotensive subjects matched for age and gender [22]. Absolute LV mass, LV mass indexed either to body surface area or height$^{2.7}$, and wall thicknesses were higher in sustained hypertensives than in ICH and normotensive subjects. Prevalence of LVH (i.e., LV mass index >125/110 g/m^2) was higher in sustained hypertensives than in normotensives (25 % versus 0 %, $p < 0.01$); the difference with ICH group (4 %) did not reach the statistical significance. LV systolic function and hemodynamic parameters including cardiac output were similar in the three groups. Ourselves, examining a group of 82 untreated patients with mild essential hypertension, 51 of them with established hypertension and 31 with ICH (average 24-h BP <132/85 mmHg), we found that the prevalence of LVH (LV mass index ≥125/110 g/m^2) and/or LV concentric remodeling was higher in the former (51 %) compared to the latter (19 %) group [23]. In the Hypertension and Ambulatory Recording Venetia Study (HARVEST) carried out in 942 young participants with untreated borderline or mild hypertension who underwent 24-h ambulatory BP monitoring, early cardiac involvement was detected in 722 subjects with reliable echocardiographic data [24]. Ninety-five normotensive subjects with similar age and sex distribution were studied as controls; ICH was defined on the basis of two thresholds of daytime BP (i.e., <130/80 mmHg and <135/85 mmHg): LV mass index and LV wall thickness in ICH subjects (irrespective of the ambulatory BP criteria used to define this condition) turned out to be smaller than in sustained hypertensives but greater than in normotensive subjects. Relative wall thickness in normotensive subjects was lower than in both hypertensive groups, and this parameter was not different between sustained hypertensives and ICH subjects. Of note, LV systolic function and diastolic filling parameters were similar among the three groups either for unadjusted or adjusted data. Among 345 adult patients with untreated mild hypertension (39 % with ICH) attending a primary care setting, LV mass index was higher in women with sustained

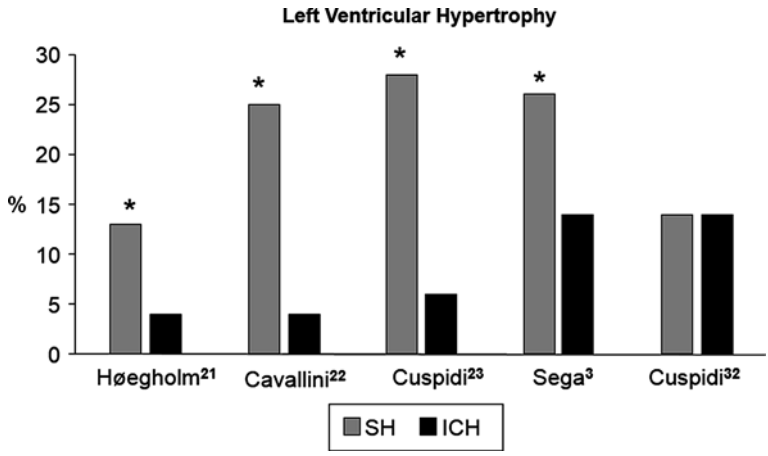

Fig. 5.2 Prevalence rates of echocardiographic left ventricular hypertrophy (*LVH*) in subjects with isolated clinic hypertension (*ICH*) and in subjects with sustained hypertension (*SH*) as reported in five studies (* means *P* at least <0.05)

hypertension as compared to the ICH counterparts (108 ± 19 g/m^2 versus 99 ± 19 g/m^2, $p < 0.05$); the same was not true for male gender (125 ± 27 g/m^2 versus 122 ± 28 g/m^2 p = ns, respectively) [25]. As for LV relative wall thickness, no difference was found between genders. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, ICH prevalence in a population subsample of untreated adult and elderly individuals ranged from 9 to 12 %, depending on whether out-of-office BP was defined by ambulatory (24-h <125/80 mmHg) or home (<135/85 mmHg) BP values [3]. In subjects with ICH, LV mass index and wall thickness were on average lower than in hypertensives with both office and ambulatory or home monitoring but higher than in normotensives with normal office, ambulatory, or home BP values. Similar findings were obtained when data were separately analyzed in men and women and adjusted for age. Furthermore, in these individuals LVH was less frequent (15–18 %) than in subjects with both office and daytime hypertension (23–26 %) but more frequent than in sustained normotensives (4 %) (Fig. 5.2).

Less information is available regarding the relevance of ICH (the white coat effect) in terms of extent of organ damage in treated hypertensives compared to hypertensives with sustained controlled office and ambulatory BP. In a previous study, we assessed LV structure in 33 treated hypertensives with good BP control at home or during ambulatory BP monitoring but elevated office BP values and in 35 age- and sex-matched hypertensives with good BP control in- and out-office [26]. As compared to patients with fully controlled hypertension, those with BP control only at home (<132/82 mmHg) or during ambulatory monitoring (average 24-h BP <125/80 mmHg) exhibited a higher prevalence of LVH, as defined by LV mass index >134/110 m^2 (15.1 % versus 2.8 %). Salles et al. investigated the role of uncontrolled ICH as an independent risk factor for LVH in a cohort of treated hypertensives with type 2 diabetes by comparing echocardiographic findings in

172 patients with ICH (average 24-h BP <130/80 mmHg) and in 152 patients with controlled office and ambulatory hypertension [27]. The authors found that LV mass index was higher (62 ± 22 g/m$^{2.7}$ versus 53 ± 17 g/m$^{2.7}$, $p < 0.001$) and LVH (LV mass index >48/44 g/m$^{2.7}$) was more prevalent (77 % versus 60 %, $p = 0.02$) in ICH than controlled group. A study including both untreated and treated (72 %) subjects compared echocardiographic indices of LV structure in three groups characterized by masked ICH (mean daytime BP <135/85 mmHg) and sustained hypertension and showed that LV mass index was significantly lower in ICH than in the other two groups [28]. In particular, prevalence rates of LVH (i.e., LV mass index >125/110 g/m^2) were 33 % in ICH, 48 % in masked, and 67 % in sustained hypertension.

Little is known about the clinical significance and natural history of ICH in children. In a study aimed to evaluate target organ damage in children with ICH, Lande et al. assessed LV mass index in 27 subjects with ICH, in 27 matched normotensive and 27 hypertensive controls [29]. Each ICH subject was matched by body mass index (±10 %), age (±1 year), and sex to a normotensive and hypertensive control. Mean LV mass index was 29 g/m$^{2.7}$, 32 g/m$^{2.7}$, and 35 g/m$^{2.7}$ in normotensive, ICH, and sustained hypertensive children, respectively (normotensives versus ICH, $p = 0.03$; ICH versus sustained hypertensives, $p = 0.07$). LVH (defined as LV mass index ≥ the 95th percentile, namely, 39.4 g/m$^{2.7}$ for boys and 36.9 g/m$^{2.7}$ for girls) was absent in all subjects of the normotensive and ICH group, but was present in 26 % of sustained hypertensives ($p < 0.001$). No difference in LV structure was observed by Pall et al. when echocardiographic data were compared in 59 normotensive and 50 ICH adolescents (LV mass index 35 g/m and 38 g/m respectively, $p = 0.87$).

It is worth noting that in the abovementioned studies ICH was defined according to a single ambulatory BP monitoring session. Unfortunately, this approach has relevant limitations: first, ambulatory BP although more reproducible than clinic BP may vary from one recording session to another due to variations in environmental stimuli, physical activity, and duration and quality of sleep. Secondly, ICH patients may have different degrees of organ damage, thereby accounting for the conflicting data published in the literature. These limitations have been recognized by the 2013 European Society Hypertension/European Society Cardiology (ESH/ESC) guidelines which recommend that subjects with ICH should have the diagnosis confirmed by periodical out-of-office measurements [9]. Unfortunately, the reproducibility of the ICH classification has been evaluated in a limited number of studies.

In the HARVEST study, this issue and its relationship with cardiac organ damage has been investigated by Palatini et al. in 565 subjects aged 18–45 years with grade 1 hypertension and in 95 normotensive individuals by repeating an ambulatory BP monitoring within a 3-month interval [31]. From the first ambulatory BP monitoring, 90 hypertensive subjects were classified as having ICH (mean daytime <130/80 mmHg): in these subjects, 24-h BP was similar as in normotensives, but LV mass index was greater than in the normotensive group. After the second ambulatory BP monitoring, only 38 out of 90 subjects (42.2 %) had a reproducible ICH pattern, the remaining 52 subjects having only a minor increase in 24-h BP above

the normal limits. LVMI in the 38 subjects with ICH on both recordings was greater than in normotensive subjects and similar as in 52 subjects with not reproducible ICH. These results show that ICH is not a stable condition and that more than 50 % of ICH subjects identified by the first BP monitoring have sustained hypertension after a second ambulatory BP monitoring. It should be pointed out that these findings pertain to a selected sample of young subjects (mean age 32 years) with recently diagnosed hypertension and should not be generalized to the hypertensive population.

In order to overcome these limitations, our group examined the reproducibility of ICH by performing two 24-h ambulatory BP monitoring at 1–4 week interval and evaluated its impact on cardiac organ damage in a population with a broader range of age (17–79 years, mean age 46 years) and hypertension values (40 % with grade 2 hypertension) than previous studies [32]. As many as 46 % of patients labeled as having ICH after the first ambulatory BP monitoring had mean daytime BP >135 mmHg systolic or 85 mmHg diastolic at the second ambulatory BP monitoring, thereby showing a not reproducible ICH pattern. When ICH was identified by lower ambulatory cutoff values, i.e., mean 24-h BP <125 mmHg systolic or 80 mmHg diastolic or daytime BP <130 mmHg systolic or 80 mmHg diastolic, even higher portions of patients shifted to sustained hypertension after the second ABPM (54 and 66 %, respectively). LV mass index was higher in patients with not reproducible than in those with reproducible ICH. These findings show that (1) classification of ICH on the basis of a single ambulatory BP monitoring has a limited short-term reproducibility and (2) a reproducible and not reproducible ICH pattern may have different cardiovascular risk profiles.

Figure 5.3 reports the results of the meta-analysis from six studies [3, 21–24, 32] providing data on average LV mass indexed to body surface area and SD in sustained hypertensive and ICH subjects. The standardized difference in means (SMD) was positive in favor of sustained hypertensives (0.38, 95 % CI 0.27–0.50, $p<0.01$).

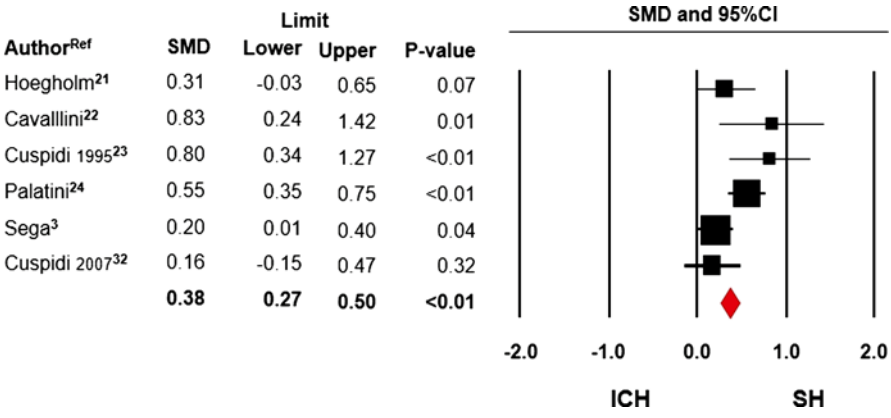

Fig. 5.3 Forest plot for standardized mean difference (*SMD*) and 95 % confidence intervals (*CI*) of left ventricular mass index (gr/m^2) between patients with sustained hypertension (*SH*) and isolated clinic hypertension (*ICH*). Meta-analysis from six studies, fixed model

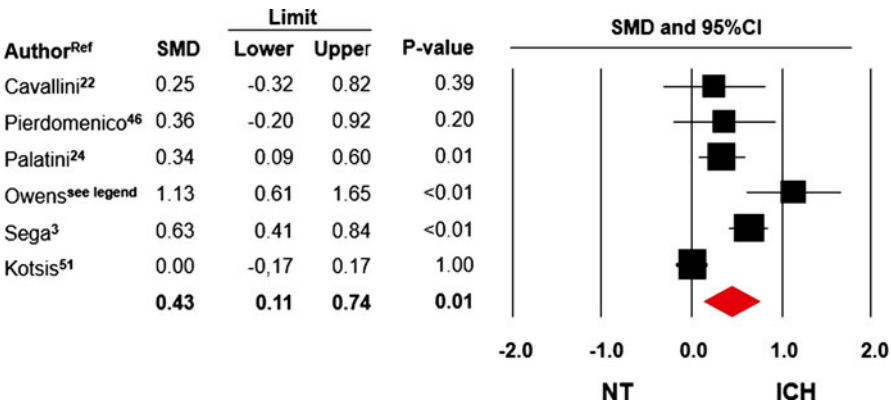

Fig. 5.4 Forest plot for standardized mean difference (*SMD*) and 95 % confidence intervals (*CI*) of left ventricular mass index (gr/m^2) between normotensive subjects (*NT*) and patients with isolated clinic hypertension (*ICH*). Meta-analysis of six studies, random model ($I^2 = 84.1$)

The findings of the meta-analysis from six studies in ICH and normotensive controls are shown in Fig. 5.4. In this comparison the SMD was positive in favor of ICH subjects (0.43, 95 % CI 0.11–0.74, $p < 0.01$).

5.3 ICH and Carotid Damage

The noninvasive evaluation of carotid artery structure is increasingly implemented in epidemiologic studies and interventional trials. The measurement of intima-media thickness (IMT) and the assessment of the presence of plaques and stenosis provide a reliable, quantitative index of atherosclerotic damage. As a consequence, ultrasonic assessment of the carotid artery structure has attracted considerable interest and is currently applied either in the clinical as in the research field. Since the mid-1980s when the pioneering studies by Pignoli et al. [33] investigated the correlation of ultrasonic interfaces with anatomical components of the carotid wall, hundreds of cross-sectional and longitudinal studies have assessed the prevalence of carotid atherosclerosis, its association with risk factors and incident cardiovascular disease [34, 35]. Numerous studies have consistently shown an association between carotid IMT and traditional risk factors, subclinical organ damage such as LVH, cerebral white matter lesions, peripheral arterial atherosclerosis, microalbuminuria, coronary calcifications, and, more importantly, overt CV diseases [36–38]. In particular, hypertension has been demonstrated to be the major risk factor for carotid IM thickening and plaque progression, due to the synergistic effect of mechanical stress on the arterial wall and the growth/inflammatory factors operating in hypertension [39]. Since the mid-1990s, a number of prospective trials performed in population-based samples and selected cohorts of individuals at high risk, such as the Atherosclerotic Risk in Communities (ARIC) [40], the Rotterdam Study [41],

the Cardiovascular Health Study (CHS) [7], the European Lacidipine Study on Atherosclerosis (ELSA) [42], and the Carotid Atherosclerosis Progression Study (CAPS) [43], reported that carotid IMT and/or plaques are strong predictors of coronary events and stroke. These findings have been recently reinforced by larger prospective studies. Among 6,257 people aged 25–84 years who participated in a population-based study, the Tromsø study, the risk of myocardial infarction during a mean 15-year follow-up period was found to increase significantly across the quartiles of mean IMT (P for trend <0.001) and total plaque area (P for trend <0.001) [44]. The results of the IMPROVE study, a multicenter observational European trial carried out in 4,482 subjects with 3 or more vascular risk factors, showed that progression of carotid IMT over a median follow-up period of 21.5 months was an independent predictor of subsequent vascular events [45]. Thus, available information supports the view that carotid IMT is a valuable surrogate end point for assessing subclinical organ damage in different clinical conditions. A significant increase in IMT has been reported by several studies in patients with various degrees of hypertension compared with age-matched normotensive controls, after adjustment for confounding variables. Relatively few reports, however, addressed this issue in ICH. The first study providing some evidence on the carotid artery structure in ICH was published in the early 1990s by Cavallini et al. who compared echocardiographic and carotid ultrasonographic findings in true normotensive ($n=24$, mean age 58 ± 8 years), in ICH ($n=24$, mean age 61 ± 9 years), and in sustained hypertensive patients (mean age 61 ± 10 years) [22]. Common IMT was greater in sustained hypertensives (0.98 mm) than in ICH (0.84 mm, $p<0.05$) and normotensive group (0.76 mm, $p<0.001$). The prevalence of atherosclerotic plaques (defined as presence of discrete plaques at least greater than the surrounding wall in any segment of the arteries) was similar in ICH (25 %) as in normotensive (21 %) group and higher in sustained hypertensives (58 %, $p<0.05$) (Fig. 5.5). According to these results, the authors concluded that sustained rather than episodic BP

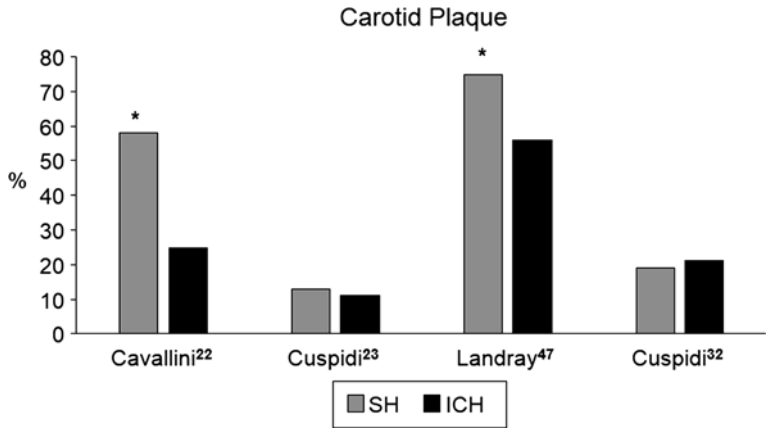

Fig. 5.5 Prevalence rates of carotid plaque in subjects with isolated clinic hypertension (*ICH*) and in subjects with sustained hypertension (*SH*) as reported in four studies (* means p at least <0.05)

elevation is important in producing preclinical disease of the arterial tree; thus, ICH may be regarded as a benign condition. A significant difference in terms of carotid IMT and plaques area between sustained hypertensives and ICH patients was also reported in an early study by our group carried out in a sample of 82 untreated individuals (mean age 44 ± 11 years) [23]. Common carotid artery IMT (average of both the right and left side) was higher in sustained hypertensives (0.68 mm) than in ICH subjects (0.58 mm, $p < 0.001$). At difference from data provided by Cavallini et al., carotid plaques were similarly prevalent among ICH (11 %) and sustained hypertensive (13 %). Pierdomenico et al. assessed carotid structural parameters in 50 sustained hypertensives, 25 ICH and 25 normotensive controls [46]. Compared with sustained hypertensives, ICH group had lower values of IMT (0.85 ± 0.18 versus 0.71 ± 0.15 mm, $p < 0.05$) and IM thickening (28 % versus 4 %, $p < 0.01$); no significant difference in these parameters was observed between ICH patients and normotensive controls.

Landray et al. analyzed the relationship between office and out-of office BP (assessed by ambulatory BP monitoring) and atherosclerotic vascular disease in a sample of 79 individuals categorized as true normotensive, ICH, and sustained hypertensives [47]. The authors found that the prevalence of carotid plaque was lower in normotensive (53 %) and ICH subjects (56 %) as compared to sustained hypertensives (75 %). In contrast, significantly greater IMT values were documented by Zakopoulos et al. in 22 ICH (0.68 ± 0.14 mm) and 41 sustained hypertensive subjects (0.67 ± 0.18 mm) compared to 17 normotensive controls (0.50 ± 0.09 mm, $p < 0.001$) [48]. Nakashima et al. compared IMT values in 30 ICH, 30 untreated sustained hypertensives, and 30 normotensive subjects without evidence of carotid plaque matched for age/gender. IMT and carotid cross-sectional areas were similar in patients with ICH and sustained hypertension and significantly higher than in normotensive subjects [49]. Among 74 never-treated grade I hypertensive subjects and 20 normotensive control subjects, Puato et al. measured carotid wall as mean IMT and maximum IMT at baseline and after a 5-year follow-up in order to define the rate of IMT increment and the potential role of various risk factors, including office and ambulatory BP [50]. During the follow-up, mean IMT and mean of maximum IMT increased to a greater degree in ICH subjects ($n = 35$) and sustained hypertensives ($n = 39$) than in normotensive controls. No differences were found between ICH and sustained hypertensive subjects for both mean IMT and maximum IMT. These findings indicate that IMT in ICH subjects grows faster than in normotensives and to a similar extent as in sustained hypertensive patients. Among 274 subjects with ICH attending an outpatient hypertension clinic in Greece, average carotid IMT value tended to be higher than in sustained normotensive controls, although the difference was not significant (0.67 ± 0.15 versus 0.63 ± 0.15 mm) [51]. A cross-sectional survey of 2,915 community-dwelling Japanese aged ≥40 years investigated the relationship between carotid atherosclerosis and BP patterns defined on the basis of combined measurements of office blood pressure and home blood BP [52]. Geometric average of mean IMT was higher among subjects with ICH (0.73 mm), masked hypertension (0.77 mm), and sustained hypertension (0.77 mm) compared to normotensives (0.67 mm; $p < 0.001$ for all). All types of hypertension

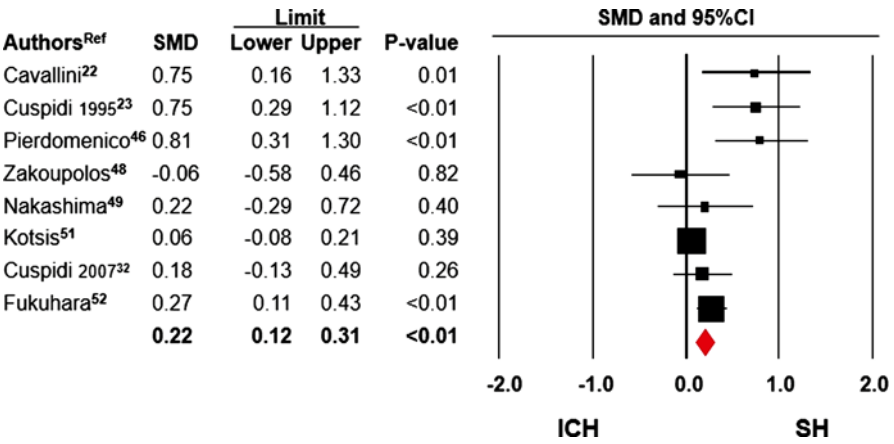

Fig. 5.6 Forest plot for standardized mean difference (*SMD*) and 95 % confidence intervals (*CI*) of intima-media thickness (mm) between patients with sustained hypertension (*SH*) and isolated clinic hypertension (*ICH*). Meta-analysis from eight studies, fixed model [65]

were also associated with an increased likelihood of carotid stenosis as compared with normotensives (age- and sex-adjusted odds ratio, 2.36, 95%CI: 1.27–4.37 for ICH; 1.95, 95%CI: 1.25–3.03 for masked hypertension; and 3.02, 95%CI: 2.01–4.54 for sustained hypertension). These associations remained significant even after adjustment for other cardiovascular risk factors.

Conflicting results have been also reported in the pediatric setting. Pall et al. showed that IMT was higher both in ICH and sustained hypertensives compared with healthy normotensive individuals (controls: 0.48 ± 0.1 mm, ICH: 0.56 ± 0.1 mm, sustained hypertension: 0.54 ± 0.1 mm, both $p < 0.001$ compared with controls) [30]. No significant difference was found between the hypertensive groups. On the contrary, similar average IMT values were reported by Stabouli et al. in true normotensive, ICH, masked, and sustained hypertensive children [53].

Our meta-analysis from eight studies [22, 23, 32, 46, 48, 49, 51, 52] providing data on average carotid IMT and SD in sustained hypertensive and ICH subjects documented a significant SMD in favor of the former group (0.22, 95 % CI : 0.12–031, $p < 0.01$) (Fig. 5.6). Finally, the pooled data from six studies comparing IMT between ICH and normotensive subjects [22, 46, 48, 49, 51, 52] showed that SMD was significantly higher in ICH individuals (0.36, 95 % CI :0.26–0.46) (Fig. 5.7).

5.4 ICH and Microalbuminuria

Microalbuminuria (MA) is a biomarker of impaired renal function and, more generally, of endothelial dysfunction; MA is an established risk factor for CV morbidity and mortality and for end-stage renal disease in individuals with a high cardiovascular risk profile (i.e., diabetes mellitus). Increasing evidence deriving from prospective observational trials indicates that urinary albumin excretion

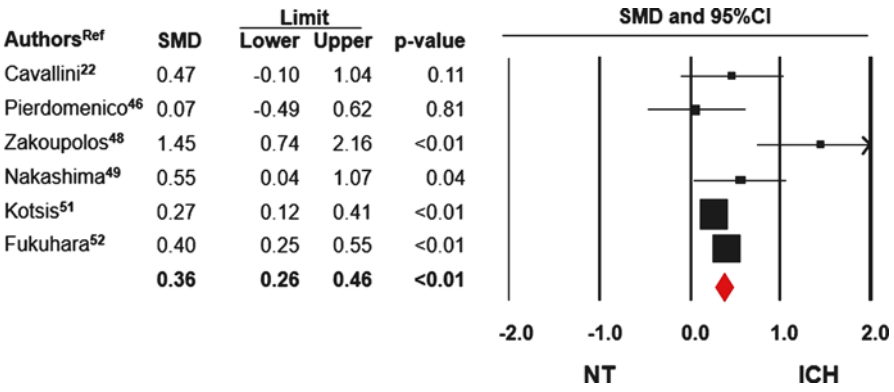

Fig. 5.7 Forest plot for standardized mean difference (*SMD*) and 95 % confidence intervals (*CI*) of intima-media thickness (*mm*) between normotensive subjects (*NT*) and patients with isolated clinic hypertension (*ICH*). Meta-analysis of eight studies (fixed model, $I^2 = 0.64$)

levels well below current MA thresholds are associated with an increased risk of CV disease and all-cause mortality [54]. Even in healthy normotensive, nondiabetic individuals, such an association has been documented. MA is present in about 4–8 % of apparently healthy subjects in the absence of CV risk factors. Several studies suggest that MA prevalence is highest in populations with both hypertension and diabetes. MA in essential hypertensive patients is the result of an increased trans-glomerular passage of albumin rather than a decreased proximal tubule reabsorption. In the i-SEARCH study, an international survey which enrolled 21,050 hypertensive patients from 26 countries, the prevalence of MA, as assessed by onetime dipstick, was quite high (58 %) with large variation across countries (from 53 to 71 %) [55]. Independent correlates of MA were male gender, metabolic syndrome, diabetes mellitus, congestive heart failure, and coronary artery disease. Rates of MA reported in i-SEARCH exceeded prevalence rates previously published in the hypertensive setting (ranging from 4 to 46 %) as well as in a primary health-care large-scale study performed in Germany (<20 %) [56]. A key point in considering MA as a marker or renal organ damage arises from the demonstration that reduction in urinary albumin excretion induced by antihypertensive therapy appears to be predictive of long-term cardiovascular and renal protection. Thus, MA assessment in hypertensive patients is now regarded as a cost-effective method to investigate renal subclinical damage and monitor the beneficial effects of BP-lowering treatment.

In the HARVEST study, negligible differences in MA were found at baseline evaluation between the ICH (7.9 ± 11.3 mg/24 h) and normotensive subjects (7.9 ± 8.0 mg/24 h) [24]. In sustained hypertensive subjects MA prevalence was 7 %, significantly higher than that observed in either ICH (1.3 %) or normotensive subjects (2.8 %). In line with the results of the HARVEST study, MA was approximately 60 % higher among sustained hypertensives than in their ICH counterparts studied by Martinez et al. [25]. In a study of our group, urinary albumin excretion tended to be greater in sustained hypertensives than in ICH subjects (12.6 mg/24 h

versus 8.7 mg/24 h), but prevalence rates of MA were superimposable between the groups (7.8 % versus 7.7 %) [32]. Of note, 20 out of 43 patients with ICH at the first ambulatory BP monitoring had a mean daytime BP ≥135/85 mmHg at the second ambulatory BP monitoring session thereby showing a not reproducible ICH. In these patients urinary albumin excretion and MA prevalence were significantly higher than in those with reproducible ICH. An investigation performed in an elderly setting, including 29 ICH subjects and 33 age-matched normotensive controls, showed that urinary albumin excretion levels were similar in both groups and correlated only with ambulatory daytime systolic BP [57]. In a study comprising 52 children with hypertension referred at three pediatric nephrology centers (26 children with sustained hypertension and 26 with ICH), MA (>3.2 mg/mmol creatinine) was present in 20 % of children with persistent hypertension but in none of ICH children ($P<0.01$) [58]. Children with sustained hypertension had a higher median urinary albumin excretion than those with ICH (1.27 ± 1.92 versus 0.66 ± 0.46 mg/mmol creatinine, $p<0.05$).

5.5 ICH and Microvascular Retinal Changes

Subtle changes in retinal microcirculation, characterized by diffuse or focal arteriolar narrowing and arteriovenous crossings, represent an early frequently observed stage of hypertensive retinopathy [59]. The clinical and prognostic value of such retinal changes, assessed either by clinical ophthalmology or by qualitative evaluations of eye ground photography, remains controversial partly due to the limited reproducibility of the technique and, more importantly, to the low specificity, as they reflect alterations related to aging and other cardiovascular risk factors. More advanced stages of retinopathy, including the so-called exudative stage (i.e., disruption of the blood-retina barrier, exudation of blood and lipids, retinal ischemia) characterized by microaneurysms, hemorrhages, hard exudates, cotton-wool spots, and papilledema, are rarely found in contemporary hypertension [60, 61]. Due to these limitations, the 2013 ESH/ESC guidelines state that examination of the retina is not recommended in mild-to-moderate hypertensive patients without diabetes, except in young subjects, and should be considered in uncontrolled or resistant hypertensive patients in order to detect hemorrhages, exudates, and papilledema, namely, the alterations associated with an increased cardiovascular risk [9].

Overall, available data on retinal alterations in ICH are scanty. The prevalence of hypertensive retinopathy, as assessed by qualitative fundoscopy, did not differ in 17 untreated ICH and 34 sustained hypertensive patients (33 % versus 58 %) examined by Pose-Reino et al. [62]. In a larger series including 90 ICH and 101 sustained hypertensive patients, Karter et al. reported that retinopathy was significantly less severe and frequent in the former than in the latter group (13 % versus 27 %) [63]. More recently, Triantafyllou et al. conducted a study using non-mydriatic retinal photography to assess retinal arteriovenous ratio in a group of 103 individuals with never-treated sustained hypertension of recent (<1 year) diagnosis, 28 individuals

with masked hypertension, 20 with ICH, and 50 normotensive individuals [64]. Arteriovenous ratio was lower in patients with sustained hypertension (0.736 ± 0.102, $p < 0.001$), masked hypertension (0.716 ± 0.123 $p < 0.001$), and ICH (0.739 ± 0.127, $p = 0.03$) compared to normotensives (0.820 ± 0.095). These findings, obtained with a reliable diagnostic method, suggest that initial retinal microvascular signs may occur in hypertensive patients at early stages of hypertension and that they are already present in patients with both masked and ICH.

Conclusions

Several factors account for the different results obtained in studies aimed to investigate the impact of ICH on subclinical organ damage. The relatively small number of subjects examined in the majority of the studies, the wide range of age and clinical characteristics, the different ambulatory BP thresholds used to define ICH, the limited reproducibility of the ICH pattern over time, and the methods used to assess cardiac, vascular, and renal damage are all variables that may have influenced the conflicting results reported in the literature. Notably, data provided by population-based studies, at variance from those reported in numerous small studies, support the view that ICH is not an entirely benign condition. Indeed, these studies including a large number of subjects with different office and out-of-office BP profiles have consistently shown that subclinical organ damage (i.e., LV mass index and carotid IMT value) is greater in ICH than in true normotensives [3, 52]. This kind of evidence is further supported by the results of our meta-analyses showing that alterations in cardiac and carotid structure in ICH are intermediate between sustained hypertensives and normotensive subjects. In conclusion, when ICH is diagnosed, examinations aimed at assessing subclinical cardiac and vascular damage are recommended in order to provide a comprehensive evaluation of cardiovascular risk related to this condition, especially in subjects with associated metabolic alterations, overweight/obesity, and high-normal out-of-office BP levels.

Disclosure The authors report no conflicts of interest.

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White Coat Hypertension, Metabolic Risk Factors and Cardiovascular Risk Profile

6

Michele Bombelli, Rita Facchetti, Gianmaria Brambilla, Guido Grassi, and Giuseppe Mancia

6.1 Introduction

Several studies have investigated the cardiovascular risk profile of individuals with white coat hypertension, focusing not only on the prevalence of asymptomatic organ damage (Chap. 5) but also on the concomitance of metabolic and other classical cardiovascular risk factors [1–8]. This chapter will address the evidence that has been obtained on this issue, largely based on the data provided by the PAMELA population in which the association of white coat hypertension with cardiovascular risk factors has been examined more in depth than in other studies, via both a cross-sectional and a longitudinal approach. The conclusion will be that white coat hypertension is associated with an unfavourable cardiovascular risk profile, which supports its abnormal nature and adverse clinical significance.

6.2 White Coat Hypertension and Metabolic Risk Factors: Cross-Sectional Data

In line with earlier findings [2, 8] in the PAMELA population [2] individuals in whom office BP was elevated but ambulatory blood pressure was normal body mass index, total serum cholesterol and serum triglycerides were always significantly greater than in individuals in whom office and ambulatory blood pressures were both normal, their values being sometimes only slightly less than those of patients in whom office and ambulatory

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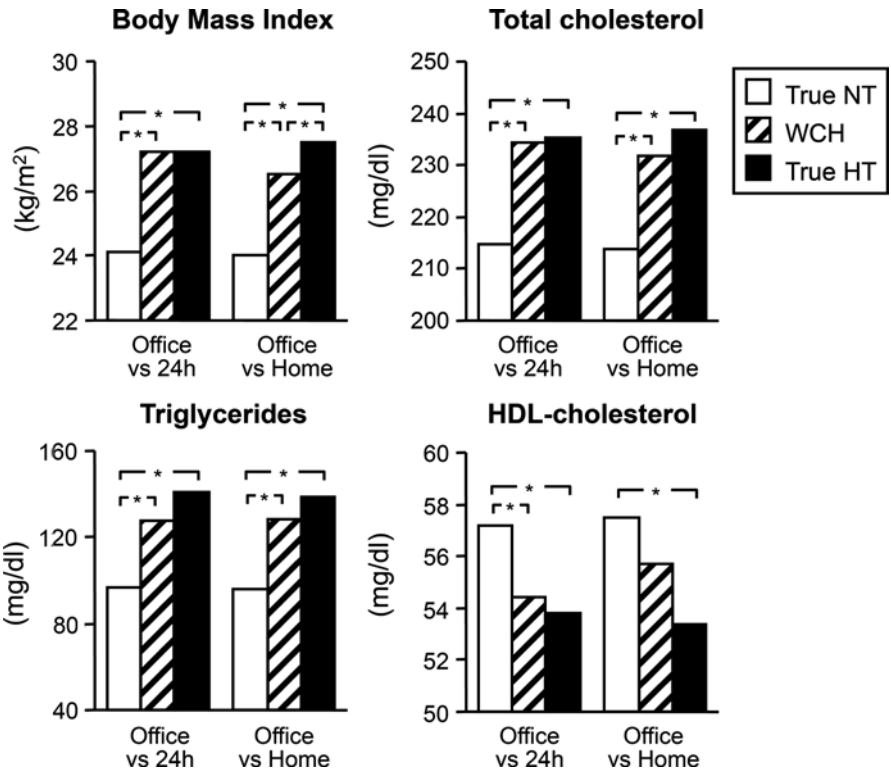

Fig. 6.1 Body mass index, serum total cholesterol, serum triglycerides and serum HDL cholesterol in true normotensive (N), white coat hypertensive (*WCH*) and true hypertensive (*H*) subjects of the PAMELA population. The three conditions were diagnosed by office versus ambulatory (24 h mean values) or office versus home blood pressures. *Asterisk* refers to $P<0.05$ (Modified from Mancia et al. [3], with permission)

blood pressures were both elevated (Fig. 6.1) [3]. Serum HDL cholesterol showed a trend in an opposite direction (Fig. 6.1) [3], while serum glucose values as well as prevalence of metabolic syndrome, diabetes mellitus or an impaired fasting glucose state also showed a progressive increase from true normotensive to white coat and true hypertensive individuals (Fig. 6.2) [3]. The results were similar regardless of whether the three conditions were identified by office versus ambulatory or office versus home BP values, suggesting the diagnostic validity and similar clinical value of either approach.

6.3 White Coat Hypertension and Blood Pressure: Cross-Sectional Data

White coat hypertensives have been found to differ from true normotensives not only for a greater prevalence of metabolic risk factors but also for their higher out-of-office blood pressure values [8–10]. This is illustrated in Fig. 6.3 which shows that, compared to individuals defined as normotensive based on both office and ambulatory or home blood pressure, white coat hypertensives had, in line with the definition of this condition, an

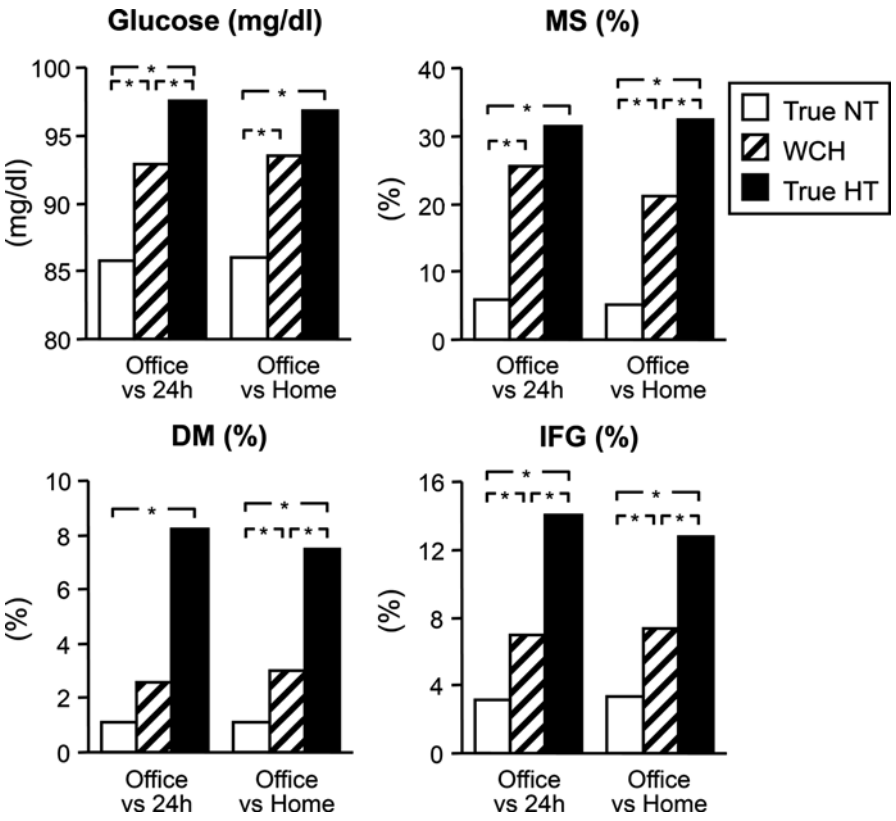

Fig. 6.2 Serum glucose and prevalence of metabolic syndrome (*MS*), diabetes mellitus (*DM*) and impaired fasting glucose (*IFG*) in N, WCH and H of Fig. 6.1. Symbols as in Fig. 6.1 (Modified from Mancia et al. [3], with permission)

office systolic and diastolic blood pressure ≥ 140 mmHg or >–90 mmHg, respectively. However, ambulatory and home blood pressures, although lower than their upper limit of normality [11–14], were nevertheless several mmHg higher (+5/+2 mmHg and +8/+5 mmHg for the definition based on office versus ambulatory and office versus home systolic and diastolic values, respectively) than those of truly normotensive individuals. Based on the follow-up of the PAMELA population, these increases amount to a measurable greater incidence of cardiovascular as well as all-cause mortality [15].

6.4 White Coat Hypertension and New-Onset Diabetes: Longitudinal Data

Re-examination of the PAMELA population 10 years after the first examination provided the chance to determine the long-term risk of developing diabetes (blood glucose ≥ 126 mg/dl) as well as an impaired fasting glucose state (blood glucose ≥ 100 mg/dl) in individuals with white coat hypertension vis à vis truly normotensive and hypertensive subjects [16]. As shown in Fig. 6.4, compared to true

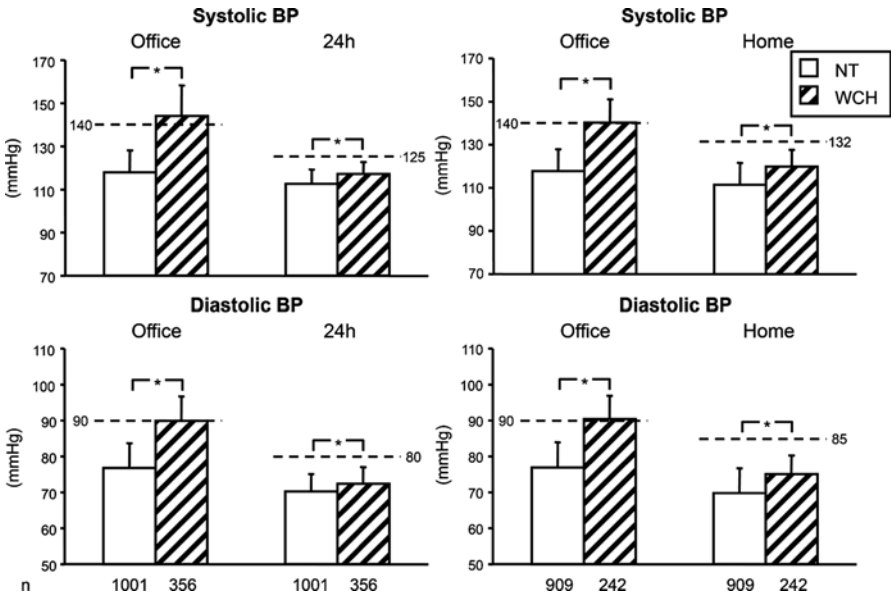

Fig. 6.3 Office and out-of-office systolic and diastolic blood pressure (*BP*) values in normotensive N and WCH subjects of the PAMELA population. Data are shown separately for WCH defined by office versus ambulatory (24 h) and office versus home blood pressure. The *dashed horizontal line* indicates the upper level of normality for each pressure as calculated from the PAMELA data. These values are similar or only slightly lower than those recommended by European Guidelines. Symbols as in preceding figures (Modified from Mancia et al. [3], with permission)

normotension, the incidence of new-onset diabetes was more than three times as large in white coat hypertensive subjects, with a three times increase in age- and gender-adjusted risk that was of the same order of magnitude of the increased risk of new-onset diabetes exhibited by truly hypertensive individuals. Similar observations were made when calculation included progression to an impaired fasting glucose state in individuals with a normal blood glucose at the first examination, the results being once again similar irrespective of whether identification of white coat hypertension was made by office versus ambulatory or office versus home blood pressure. The increase in the risk of developing diabetes was clearly visible also when data were adjusted for the antihypertensive drugs taken by the patients between the first and the second examination, to minimize the well antidiabetogenic or diabetogenic effects of some of the most commonly employed medicaments for the treatment of hypertension [17] (Fig. 6.5).

6.5 White Coat Hypertension and New-Onset Hypertension: Longitudinal Data

Replication of the observations made 10 years before also allowed to investigate whether individuals with white coat hypertension of the PAMELA population had a different risk of progressing to true hypertension, i.e. moving to both an in- and

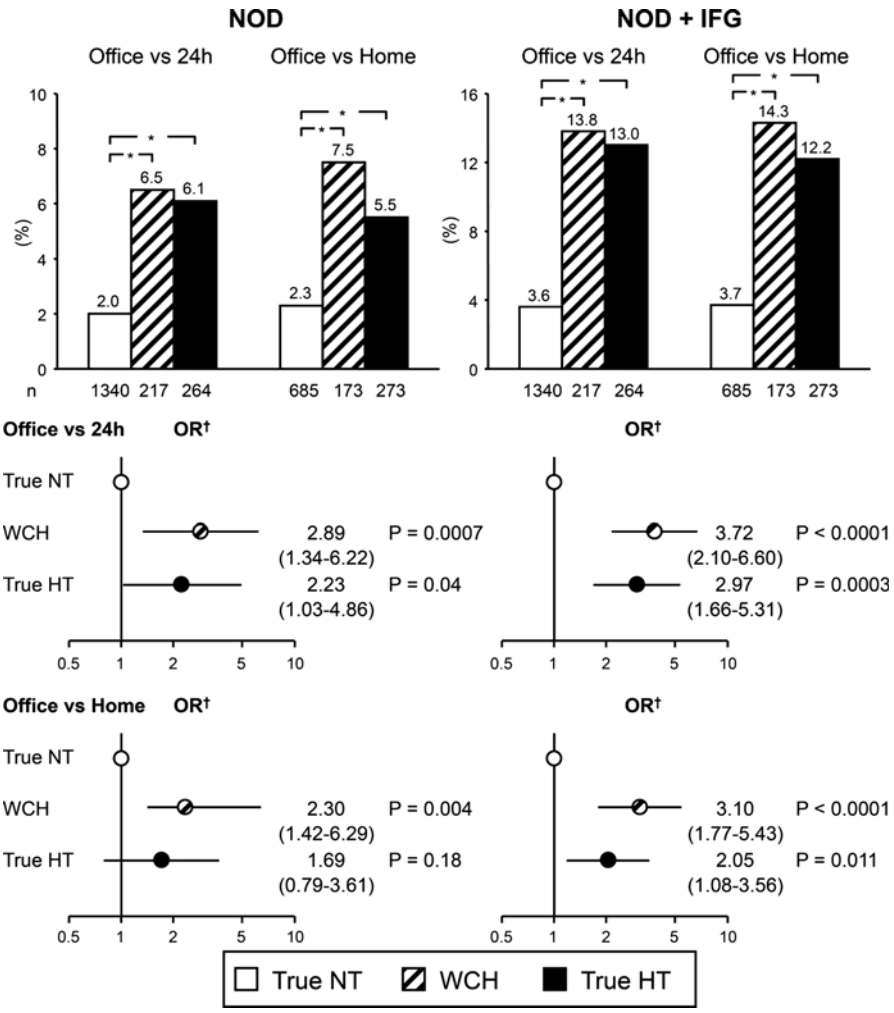

Fig. 6.4 Incidence and adjusted (for age and gender) risk of new-onset diabetes (*NOD*) or NOD plus an impaired fasting glucose (*IFG*) state in true normotensive (*NT*), white coat hypertensive (WCH) and true hypertensive (*HT*) individuals of the PAMELA population (Modified from Mancia et al. [16], by permission). $P < 0.05$. Numbers in parenthesis refer to 95 % confidence intervals

out-of-office BP elevation, than true normotensive subjects [18]. The results are shown in Figs. 6.6, 6.7, and 6.8. Figure 6.6 shows that in more than 50 or 60 % of truly normotensives, the blood pressure status remained stable, whereas in the remaining one it worsened and moved subjects into the white coat hypertension, masked hypertension (normal office and high out-of-office blood pressure) or true hypertension categories. This was the case also in white coat hypertensives, about 20 % of which improved and became truly normotensives. Compared to truly normotensives, however, white coat hypertensives showed a much greater incidence of progressing to in- and out-of-office hypertension, regardless whether its definition (1) was based on office versus ambulatory or office versus home blood pressure and

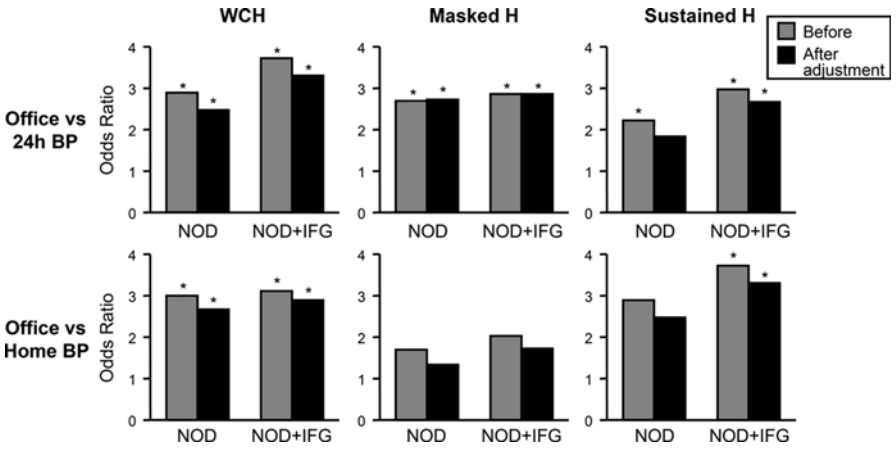

Fig. 6.5 Age- and gender-adjusted risk of new-onset diabetes in truly normotensive, WCH and truly hypertensive subjects before and after further adjustment for use of antihypertensive drugs. Symbols as in preceding figures (Modified from Mancia et al. [16], with permission)

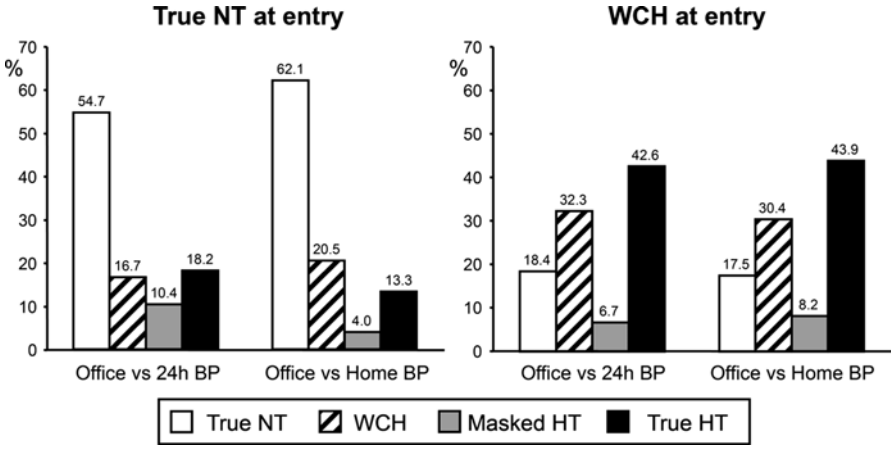

Fig. 6.6 Change of blood pressure (*BP*) status over the 10-year period from the first to the second examination in truly normotensive (*NT*) and WCH subjects. Definition of the two conditions is based on office versus ambulatory (24 h) or office versus home BP. *HT* hypertension. Other symbols as in preceding figures

(2) out-of-office hypertension separately considered an elevation of ambulatory and home blood pressure in line with other findings [19, 20]. The increase in the adjusted risk of true hypertension exhibited by white coat hypertensive subjects ranged from more than two to more than three times that of true normotensive subjects, which indicated a substantial elevation over the background risk of the true normotensive

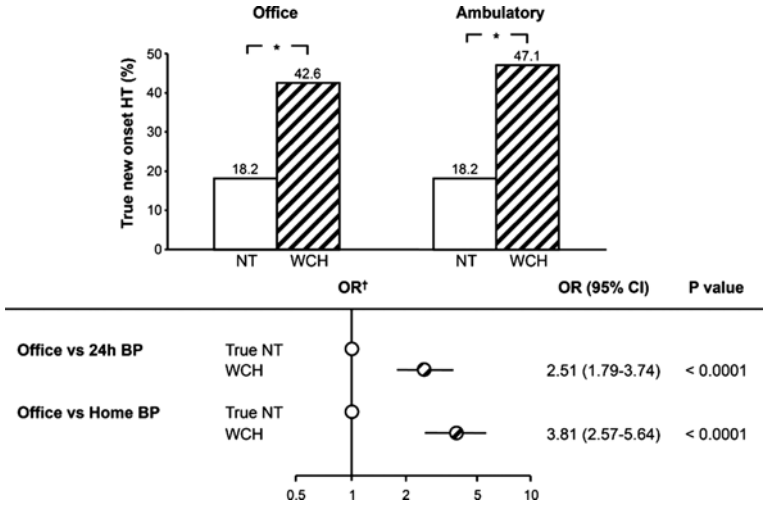

Fig. 6.7 Progression to in- and out-of-office HT in true NT and WCH subjects over a 10-year period. The *upper panel* shows the 10-year incidence of (1) office + ambulatory HT in subjects with entry NT or WCH based on office BP elevation and ambulatory BP normality and (2) office + home HT in subjects with entry NT or WCH based on office BP elevation and home BP normality. The *lower panel* shows the age- and gender-adjusted risk of developing one or the other condition taking NT as reference. Definition of home and ambulatory blood pressure elevation was based on previous analysis of the PAMELA data. Numbers in parenthesis refer to 95 % confidence intervals. Other symbols as in preceding figures

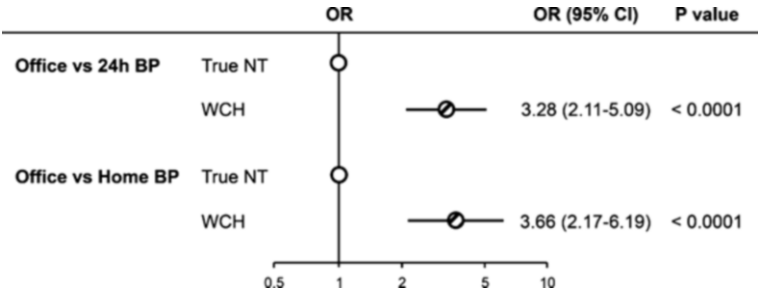

Fig. 6.8 Age- and gender-adjusted increase in risk of developing true hypertension in truly NT and WCH subjects, after exclusion of patients under antihypertensive drug treatment. Symbols as in preceding figures (Modified from Mancia et al. [18], with permission)

population (Fig. 6.7). The results were not modified by limiting the analysis to the population that did not take antihypertensive drugs over the follow-up period, excluding a confounding effect of between group differences in blood pressure lowering interventions on the results (Fig. 6.8).

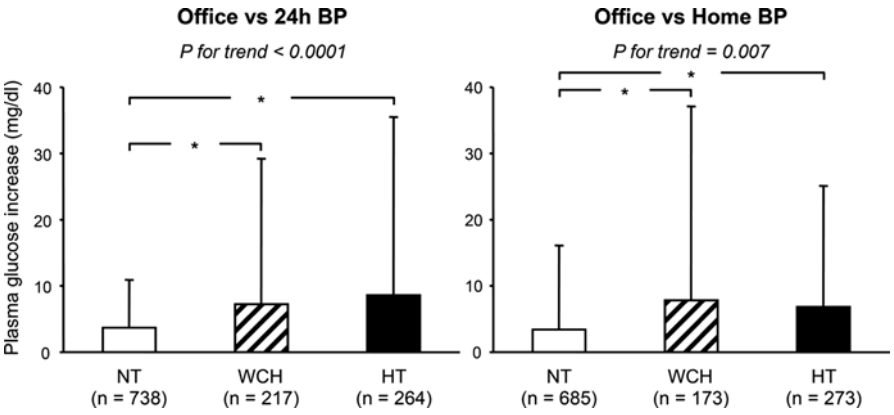

Fig. 6.9 Ten-year increase of plasma glucose in true NT and WCH subjects of the PAMELA population. Definition of WCH was based on office versus ambulatory or office versus home BP. Symbols as in preceding figures (Modified from Mancia et al. [16], with permission)

6.6 Factors Involved in the Increased Risk of New-Onset Diabetes and True Hypertension of White Coat Hypertensives

Because white coat hypertensive subjects have higher blood glucose and out-of-office blood pressures (Figs. 6.2 and 6.3) than truly normotensive subjects, their greater incidence and risk of developing diabetes or true hypertension might be explained by a shorter distance of these values to the thresholds defining these two conditions. However, compared to truly normotensives, the increase of blood glucose that occurred over the 10-year period between the first and the second examination was significantly greater in white coat hypertension both when diagnosed by office versus ambulatory and when diagnosed by office versus home blood pressure (Fig. 6.9) [16]. This was the case also for the ambulatory or home increases of systolic blood pressure which were associated with a much greater increase in out-of-office pulse pressure as well (Fig. 6.10) [18]. Thus, in addition to the contribution of initially greater blood glucose and out-of-office blood pressure values, the much greater risk of developing diabetes and true hypertension exhibited by white coat hypertensive individuals also depends on a greater tendency to adverse modifications of their metabolic and blood pressure profile. Their much more marked increase in pulse pressure further suggests that the adverse modifications include a greater progression of arterial stiffening, i.e. a large artery alteration with documented prognostic significance both for the development of isolated systolic hypertension [21] and for the incidence of fatal or nonfatal cardiovascular events [22]. It is likely that in white coat hypertensive subjects, a more pronounced increase of arterial stiffness reflects a tendency to a greater worsening of organ damage in general because, compared to true normotensive subjects, individuals with white coat hypertension also showed a greater increase of left ventricular mass index and incidence of echocardiographic left ventricular hypertrophy, the increased risk being only slightly less than the one of true hypertensives (Fig. 6.11) [23].

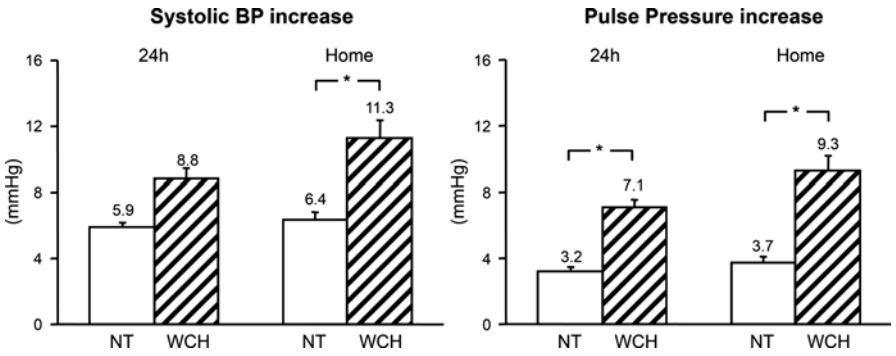

Fig. 6.10 Ten-year increase of out-of-office systolic (*S*) BP and pulse pressure in true NT and WCH subjects of the PAMELA population. Definition of WCH was based on office versus ambulatory BP data. Other symbols as in preceding figures (Modified from Mancia et al. [18], with permission)

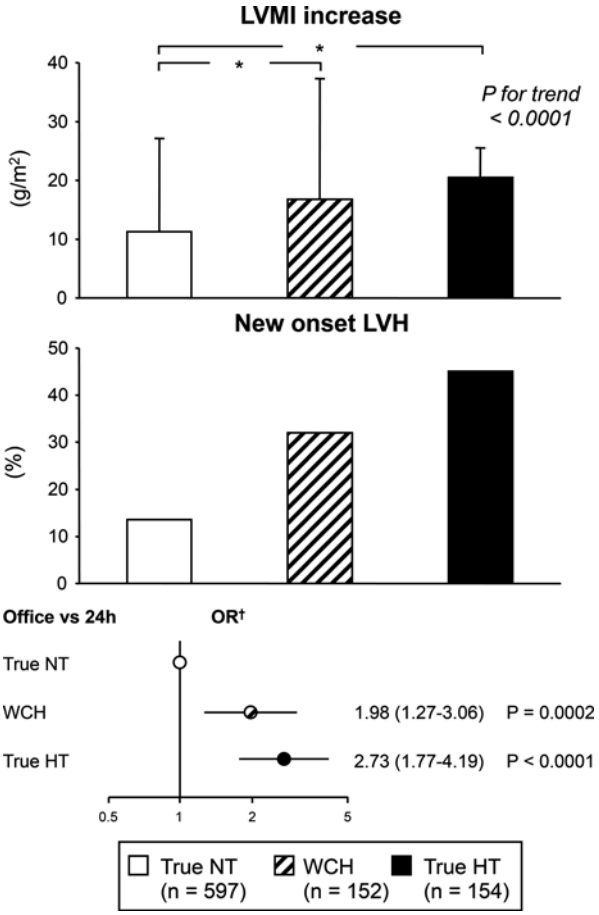

Fig. 6.11 Ten-year increases of left ventricular mass index (*LVMI*), incidence of new-onset left ventricular hypertrophy (*LVH*) and adjusted (for age and gender) risk of new-onset LVH in true NT, WCH and true hypertensive HT subjects of the PAMELA population over a 10-year time interval. Definition of the three conditions was based on office versus ambulatory (24 h) BP. *OR* odds ratio. Numbers in parenthesis refer to 95 % confidence intervals. Other symbols as in preceding figures data were collected via echocardiographic examinations (Modified from Zanchetti and Mancia [23], with permission)

Table 6.1 Independent predictors of new-onset diabetes, true hypertension and left ventricular hypertrophy in WCH

	χ^2 score	*P*
Diabetes		
Serum glucose	121.32	<0.0001
Body mass index	22.45	<0.0001
Antihypertensive drugs	10.35	0.001
24 h DBP	4.00	0.047
True hypertension		
SBP, office	110.90	<0.0001
DBP, 24 h	35.65	<0.0001
SBP, home	19.60	<0.0001
Serum glucose	7.61	0.0058
Left ventricular hypertrophy		
Left ventricular mass index	237.93	<0.0001
Age	64.92	<0.0001
Total serum cholesterol	10.82	0.001
Serum triglycerides	5.73	0.002
SBP, home	4.34	0.004

6.7 Blood Pressure Alterations of White Coat Hypertension as Predictors of New-Onset Diabetes, True Hypertension and Left Ventricular Hypertrophy

The independent contribution of the blood pressure values of white coat hypertensives to the risk of developing diabetes, true hypertension and cardiac damage was assessed by a multivariable analysis that included a large number of covariates obtained at the first examination [16, 18]. As shown in Table 6.1, top part, the most important independent predictor of new-onset diabetes was, as expected, the baseline blood glucose value, followed at great distance by body mass index. However, there was, in addition, an overall independent contribution of blood pressure-related factors such as antihypertensive drug treatment and out-of-office diastolic values.

Office and, to a lower degree, out-of-office blood pressure values were the most important independent contributors to the development of new-onset true hypertension, with a small additional contribution of blood glucose (Table 6.1, middle part), whereas the baseline left ventricular mass index value was by far the most important contributor of new-onset left ventricular hypertrophy followed by age and baseline lipid variables with again, however, an independent contribution of out-of-office blood pressure, although less pronounced than it might be expected (Table 6.1, bottom part). Thus, blood pressure values were independently involved in the more frequent development of all three conditions in white coat hypertensive individuals, with a primary predictive role in their much more frequent progression to new-onset true hypertension. Interestingly, this role appeared to be independently related to the level of office rather than out-of-office blood pressure values.

6.8 White Coat Hypertension and Blood Pressure Variability

Blood pressure variability has been repeatedly shown to have an independent prognostic significance, i.e. to predict the risk of a cardiovascular morbid or fatal event independently on other cardiovascular risk factors [24]. In the PAMELA population, white coat hypertensive subjects have been found to have day and night standard deviations of the respective mean values less than those exhibited by true hypertensive patients but greater than those exhibited by normotensive individuals, irrespective on whether white coat hypertension was defined based on normality of ambulatory or home blood pressure values. Similar observations have been made with regard to the so-called "residual" variability, i.e. the blood pressure variations that are not accounted by cyclic changes as detected by Fournier analysis of the blood pressure tracing and therefore have an erratic nature (Fig. 6.12). This may be listed as an additional potential risk factor because in the PAMELA population erratic blood pressure variability has been found to relate to both cardiovascular and all-cause mortality, the weight of the relationship accounting for more events than 24 h mean blood pressure [25].

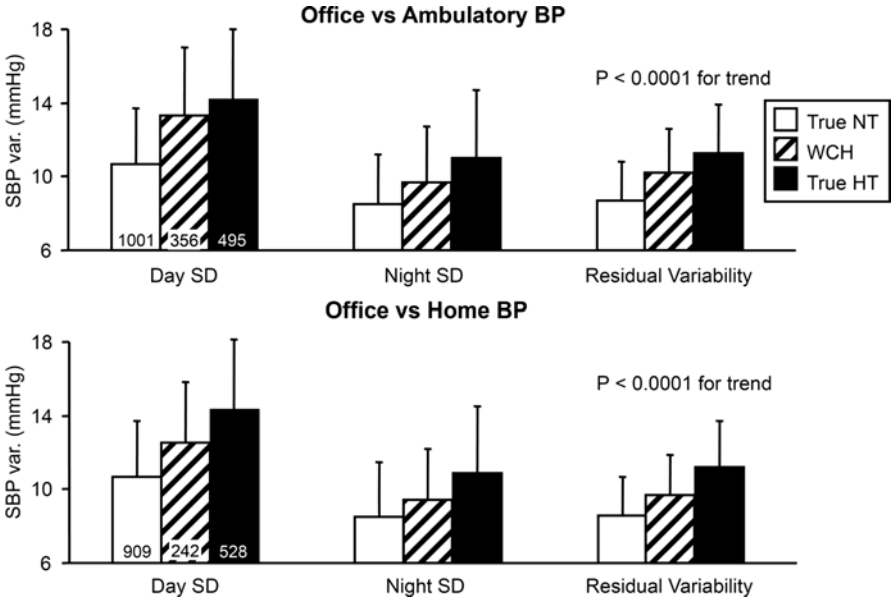

Fig. 6.12 Day, night and residual SBP variability in true normotensive (*N*), WCH and true hypertensive (*H*) subjects of the PAMELA population. The three conditions were identified based on office versus ambulatory or office versus home BP. Residual variability was the fraction of the 24 h BP variability unaccounted by the cyclic variability components identified by Fournier analysis of the 24 h blood pressure tracing. Symbols as in preceding figures (Modified from Mancia et al. [25], with permission)

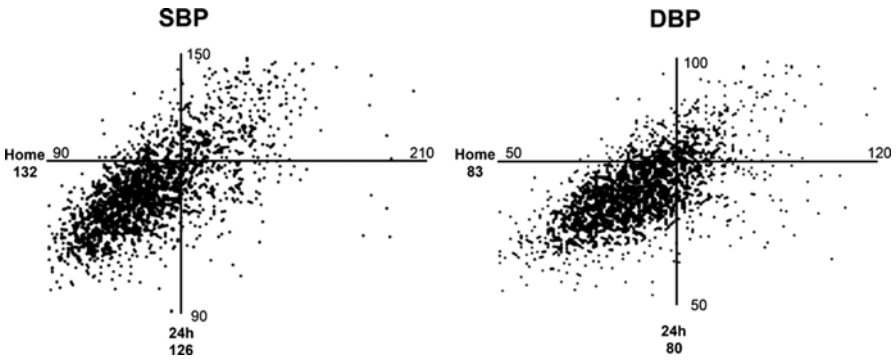

Fig. 6.13 Relationship between 24 h mean and home SBP and diastolic (*D*) BP in the PAMELA population. Symbols as in preceding figures

6.9 Partial Versus True White Coat Hypertension

Twenty-four-hour blood pressure normality does not invariably mean home blood pressure normality, and evidence is available that in a certain number of subjects, normal ambulatory blood pressure values may be associated with home hypertension and vice versa (Fig. 6.13) [3, 4]. This raises the possibility that the adverse cardiovascular risk profile and tendency to develop high cardiovascular risk conditions reported for white coat hypertension depend on a spurious diagnosis, i.e. on the fact that only one of the two available daily life blood pressures was normal. However, this has been excluded by an analysis of the PAMELA population in which white coat hypertension was diagnosed only if an increase in-office blood pressure was accompanied by normal ambulatory and home blood pressure values. As shown in Fig. 6.14, compared to normotensive subjects, these "true" white coat hypertensives were still characterized by metabolic and blood pressure-related risk factors with in addition also a higher risk of new-onset true hypertension (Figs. 6.14 and 6.15) [18].

Conclusion

The results of several studies and in particular the analysis of the data provided by the PAMELA population leave no doubt that white coat hypertension is associated with a number of metabolic and blood pressure-related risk factors (Table 6.2) that make the overall cardiovascular risk profile of this condition unfavourable when compared to the true normotensive fraction of the population. They also leave no doubt that, because of this unfavourable risk profile and other factors, individuals with white coat hypertension stand a much greater risk of developing diseases that further increase the cardiovascular risk, such as diabetes, office and daily life hypertension and left ventricular hypertrophy (Table 6.2) [26–29]. In these individuals, a further increase in their cardiovascular risk should thus be expected to occur over the years, which argues against considering their status superimposable to that of the truly normotensive fraction of the

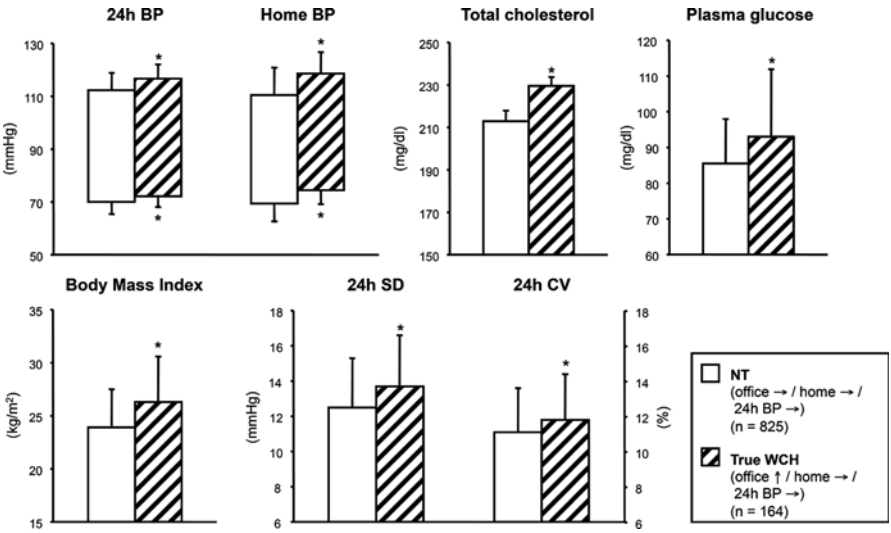

Fig. 6.14 BP and metabolic alterations in subjects in whom normotension was defined as normality of three BPs (office, home and ambulatory; $n = 825$) versus subjects in whom WCH was defined as increase in office but normality of both the two available out-of-office BPs, i.e. ambulatory and home ($n = 164$). $P < 0.05$ vs. normotensives. Symbols as in preceding figures

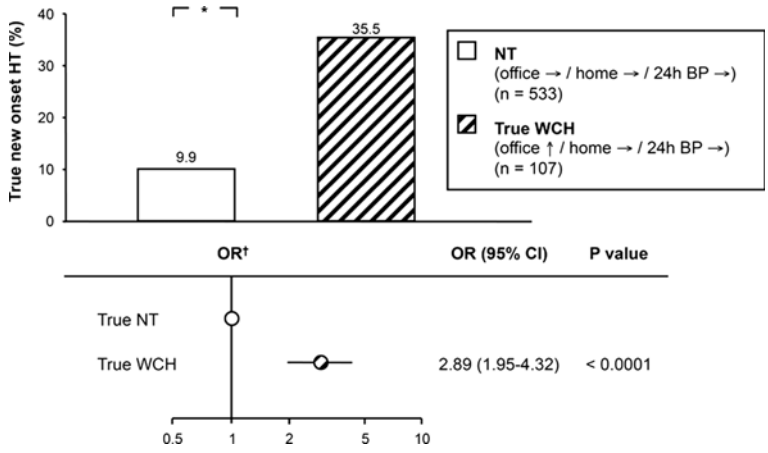

Fig. 6.15 Ten-year incidence of new-onset true hypertension in subjects in whom normotension was defined by office, home and ambulatory BP normality while true WCH was defined by elevation in office but normality of the other two pressures. Symbols as in preceding figures (Modified from Mancia et al. [18], with permission)

Table 6.2 Increased cardiovascular risk factors in white coat hypertension

Increased plasma glucose values
Greater prevalence of DM/IFG status
Greater serum total cholesterol/triglyceride levels
Lower serum HDL-cholesterol levels
Greater body mass index
Greater metabolic syndrome prevalence
Greater out-of-office (ambulatory/home) blood pressure values
Greater short-term (24 h) BP variability
Marked increase in long-term risk of developing
Diabetes mellitus
Impaired fasting glucose
True hypertension
Left ventricular hypertrophy

population, as concluded in some recent guidelines [30]. Irrespective of the decision to start or not start antihypertensive treatment (chapter), these patients should be followed closely after detection of the white coat hypertension condition, as recommended by the recent guidelines of the European Society of Hypertension and the European Society of Cardiology [13].

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White Coat Hypertension and Cardiovascular Morbidity and Mortality

7

Giuseppe Mancia, Michele Bombelli, Gianmaria Brambilla, Rita Facchetti, and Guido Grassi

7.1 Introduction

Few issues of modern cardiovascular medicine have been as controversial as the relationship between white coat hypertension and the incidence and risk of cardiovascular morbid and fatal events [1, 2]. This is because while some studies have shown this condition to be associated with an increased risk of cardiovascular events, other studies have denied that this is the case and even equaled the prognostic value of white coat hypertension to normotension [3–15]. This chapter will review some of this conflicting evidence and focus, also on this respect, on the contribution of the PAMELA study.

7.2 White Coat Hypertension and Cardiovascular Morbidity and Mortality: Negative Reports

A number of studies have found no increased risk of cardiovascular events in white coat hypertensive as compared to truly normotensive individuals [7–14]. To quote few examples in some detail, in 1994 Verdecchia et al. [10] observed that white coat hypertensive subjects had an incidence of cardiovascular events of 0.49 per 100 pt years, which was similar to that of truly normotensive individuals but much lower than that seen in truly hypertensive individuals with a more or less effective nighttime blood pressure reduction, i.e., the dippers and non-dippers (1.79 and 4.99,

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respectively) (Fig. 7.1). Kario et al. [11] found that the incidence of stroke was similar in normotensive and white coat hypertensive subjects, a marked increase being observed only in patients in whom office hypertension was accompanied by an out-of-office blood pressure elevation (Fig. 7.2, right panel). Similar findings were reported for silent single or multiple brain infarcts as quantified by nuclear magnetic resonance, although both types of outcome were slightly more common in white coat hypertensive than in truly normotensive subjects (Fig. 7.2, left panel). Ohkubo et al. [12], Bobrie et al. [13], and Pierdomenico et al. [14] found white coat hypertension to carry a greater risk of cardiovascular events (+28, +18 and +22 %) than true normotension again, however, without the difference achieving statistical significance. Finally, no significant difference in the risk of cardiovascular morbid or fatal events was detected in two meta-analyses that included some of the previously

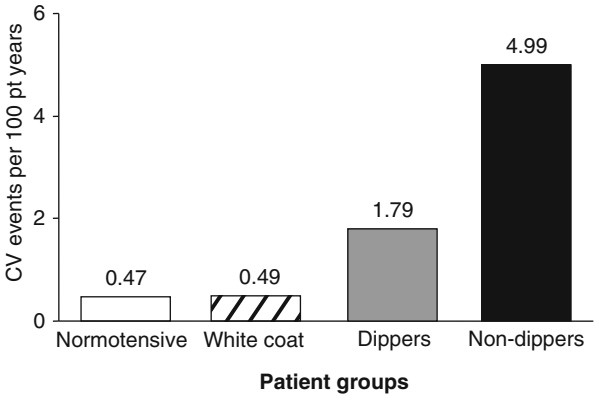

Fig. 7.1 Cardiovascular (*CV*) morbid and fatal events in normotension, white coat hypertension, and true hypertension with effective or noneffective (dippers and non-dippers) blood pressure reductions at night (From Verdecchia et al. [10], with permission)

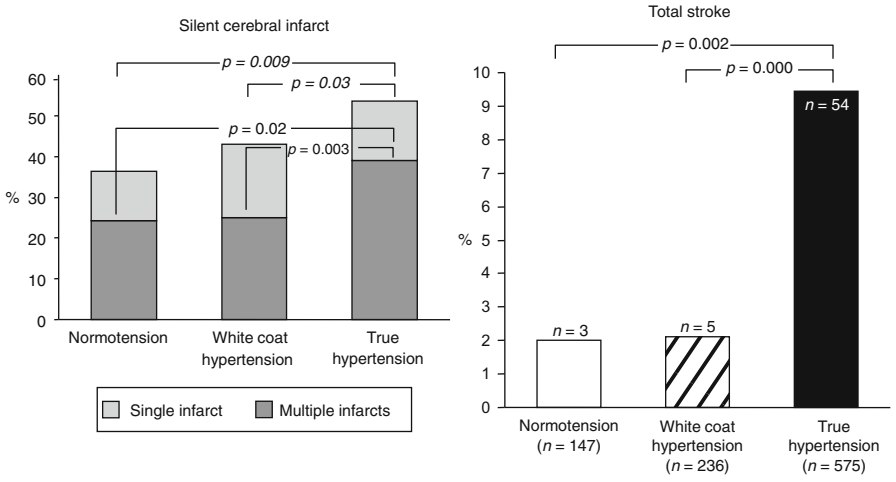

Fig. 7.2 Prevalence of silent cerebral infarcts and stroke in normotension, white coat hypertension, and true (sustained) hypertension (Modified from Kario et al. [11], with permission)

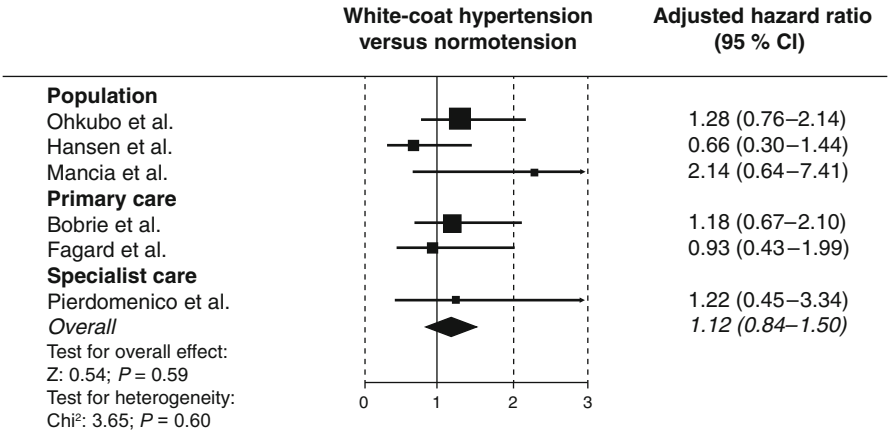

Fig. 7.3 Adjusted hazard ratios and 95 % confidence intervals (*CI*) of individual studies and overall analysis for the incidence of cardiovascular events in white coat hypertension compared to true normotension (From Fagard et al. [15], with permission)

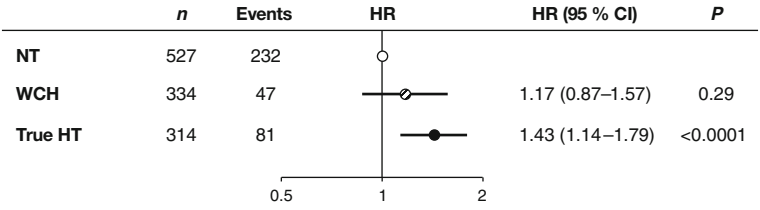

Fig. 7.4 Adjusted hazard ratios (*HR*) for cardiovascular events in untreated normotensives (*NT*), white coat hypertensives (*WCH*), and true (sustained) hypertensives (*HT*) in a large database (IDACO) from several sources. Hypertension consisted of an isolated systolic blood pressure elevation. Diagnosis was based on office and home blood pressure measurements (Modified from Franklin et al. [17], with permission)

mentioned studies plus other investigations [15, 16]. In one meta-analysis [15] white coat hypertensives showed a 12 % greater risk of events than true normotensives with, however, large 95 % confidence intervals (0.84–1.50) that encompassed the no difference line and therefore did not support the conclusion that this condition is prognostically adverse (Fig. 7.3). A similar conclusion was reached by a database that included a large number of subjects from several small or large individual studies, with an overall number of events greater than that available in the previously mentioned smaller investigations. Compared to untreated normotensive individuals, untreated subjects with an elevation of office and a normal home systolic blood pressure exhibited an 18 % increase in risk of cardiovascular events, which again failed to show a significant difference from the normotensive condition, at variance from the 43 % increase in event risk exhibited by individuals with combined office and out-of-office isolated systolic hypertension (Fig. 7.4) [17].

7.3 White Coat Hypertension and Cardiovascular Morbidity and Mortality: Positive Reports

Few years ago Verdecchia et al. [18] reported the results of a meta-analysis of several studies in which a comparison was made between the incidence of stroke in truly normotensive subjects, white coat hypertensives, and individuals with an elevation of ambulatory blood pressure. Compared to truly normotensives, the incidence of stroke was from the beginning much greater in subjects with ambulatory hypertension. In contrast, the incidence of stroke did not differ between truly normotensives and white coat hypertensives over the first 4–6 years, after which the latter group exhibited a steep rise that made the stroke cumulative incidence superimposable to that of ambulatory hypertension over the remaining observation time (Fig. 7.5) [18]. The implication was that white coat hypertension is associated with an increased risk of cardiovascular events which takes time to become manifest and therefore can mainly be seen in studies with an adequate duration of the follow-up.

A long follow-up of subjects with white coat hypertension has been made available by a few studies only [19, 20]. In the PAMELA study, cardiovascular morbid and fatal events were assessed from the initial examination in 1991–1992 to 2004 with an average observation period longer than 11 years [19]. As shown in Fig. 7.6,

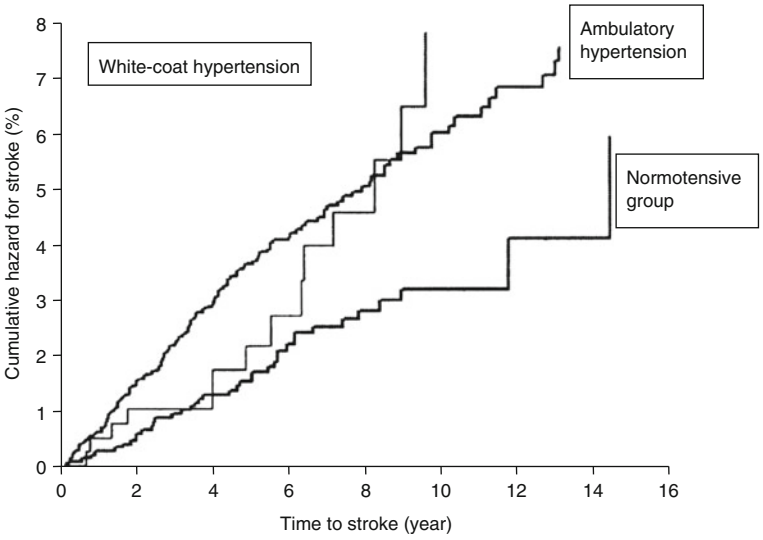

Fig. 7.5 Cumulative hazard for stroke in normotensive, white coat hypertensive, and ambulatory hypertensive subjects (From Verdecchia et al. [18], with permission)

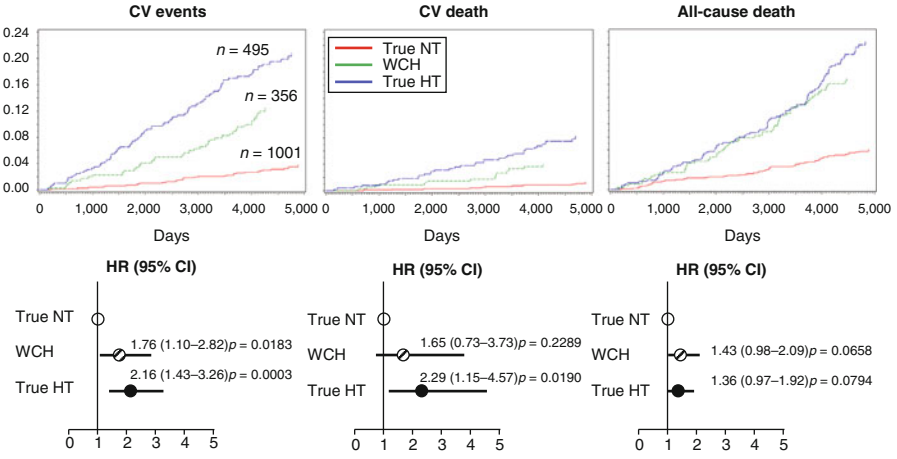

Fig. 7.6 The *upper* panel shows the Kaplan-Meyer curves for cardiovascular (*CV*) events, CV death, and all-cause death in true normotensives (*NT*), white coat hypertensives (*WCH*), and true hypertensives (*HT*). The *lower* panel shows the age- and gender-adjusted risk of these events, taking NT as reference. Data from the PAMELA study (Modified from Mancia et al. [19], with permission, and unpublished data)

the cumulative incidence of cardiovascular morbid and fatal events increased progressively from true normotension to white coat and true hypertension, identification of the three conditions being based on office versus ambulatory blood pressure. In the white coat hypertensive group, the age- and gender-adjusted risk of morbid plus fatal or only fatal cardiovascular events amounted to 76 and 65 %, respectively, an increase that was less than that seen in true hypertension (+116 and 129 %) but that nevertheless differed significantly and substantially from what was seen in the true normotensive group. White coat hypertensives additionally showed a 46 % increase in age- and gender-adjusted risk of all-cause mortality that was of borderline statistical significance.

More recently, the follow-up of the white coat hypertensive subjects from the PAMELA population has been extended to an average of 16 years [21]. As shown in Fig. 7.7, over this long follow-up white coat hypertensives (diagnosed as done in clinical practice, i.e., by an elevation of office with a normal ambulatory or home blood pressure) continued to show an incidence of cardiovascular mortality that was intermediate between true normotensive and true hypertensive individuals. Compared to the normotensive group, the age- and gender-adjusted cardiovascular mortality risk was substantially greater, and the significance extended to fully adjusted data, i.e., to baseline variables reflecting metabolic factors and other clinical conditions, to indicate an independent contribution to prognosis of the elevated blood pressure values.

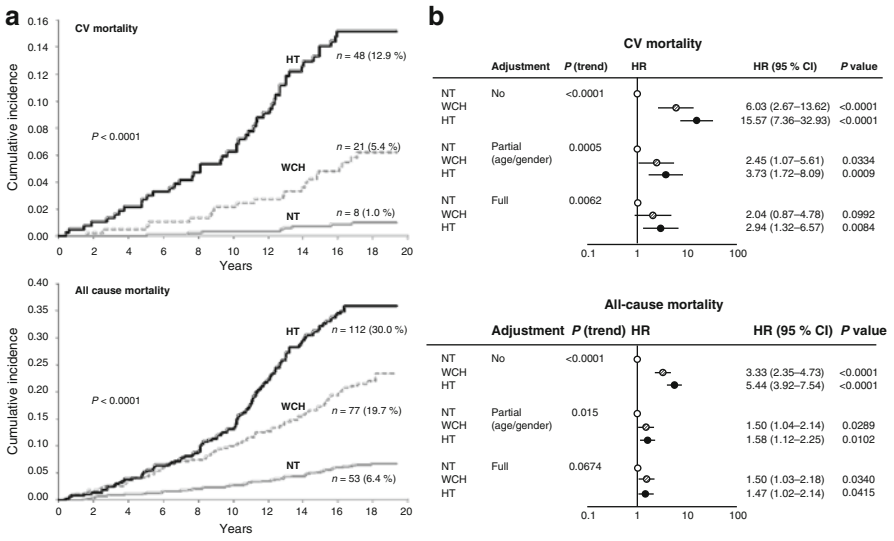

Fig. 7.7 (**a**) Cumulative incidence and (**b**) hazard ratio (*HR*) for cardiovascular (*CV*) and all-cause mortality in normotensives (*NT*), white coat hypertensives (*WCH*), and true hypertensives (*HT*) of PAMELA study over a long observation period (average 16 years). NT and true HT were defined by office, home, and ambulatory blood pressure normality and elevation, respectively. WCH was defined by elevation of office blood pressure and ambulatory or home blood pressure normality. Full adjustment refers to adjustment for age, sex, smoking, blood glucose, serum total cholesterol, body mass index, antihypertensive treatment, and history of cardiovascular events (From Mancia et al. [21], with permission)

7.4 Identification of Higher and Lower Cardiovascular Risk Subjects with White Coat Hypertension

The different results of studies on the prognostic value of white coat hypertension justify the hypothesis that this condition may have a high prognostic heterogeneity. Namely, that depending on its more or less frequent coexistence with metabolic risk factors, subclinical organ damage, and other features involved in cardiovascular risk, its relationship with an increased incidence of morbid or fatal cerebrovascular or cardiac events may turn out to vary within a range that has at one extreme a similarity with true normotension and at another extreme a similarity with true hypertension. Analysis of the PAMELA data has detected two possibilities to differentiate the cardiovascular risk level within the white coat hypertension category. One, because in all individuals of the PAMELA study measurements included both ambulatory and home blood pressure, white coat hypertensives were subdivided into those in whom both out-of-office blood pressure values were normal and those in whom one blood pressure was normal, while the other was elevated or vice versa

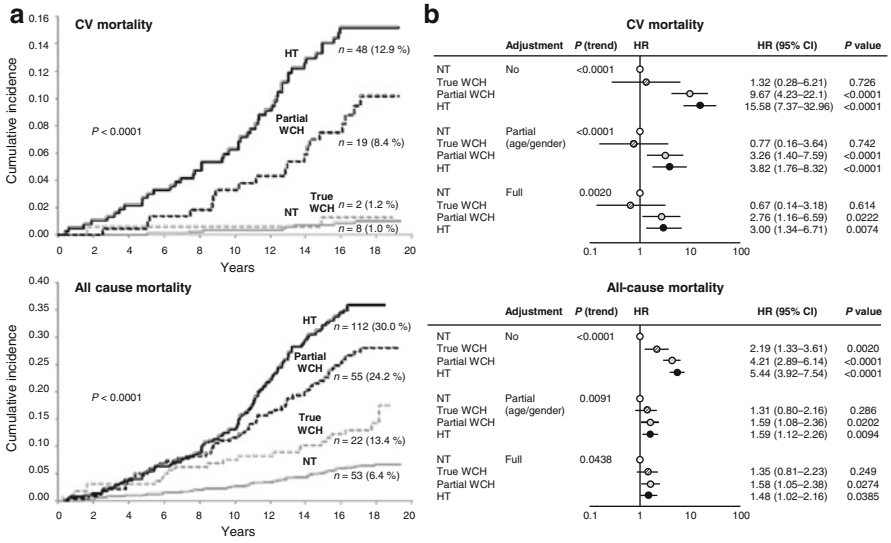

Fig. 7.8 (**a**) Cumulative incidence and (**b**) hazard ratio (*HR*) for CV and all-cause mortality in NTs, WCHs, and HTs of PAMELA study over a long follow-up. NTs and true HTs were defined as in Fig. 7.7. WCH was defined as true or partial according to whether, respectively, (1) both ambulatory and home blood pressures were normal and (2) or only one of these blood pressures was normal. For other explanations and symbols, see Fig. 7.7 (From Mancia et al. [21], with permission)

[21]. As shown in Fig. 7.8, the incidence of cardiovascular events was markedly greater in the latter as compared to the former group in which the risk was only slightly and nonsignificantly increased compared to that seen in true normotensive subjects. Thus, the information provided by ambulatory and home blood pressure is by no means redundant. Indeed, the combined use of these two diagnostic approaches may serve the important purpose to identify white coat hypertensives in whom a substantial increase of cardiovascular risk may justify not only a close follow-up but perhaps also initiation of antihypertensive drug treatment.

The second possibility is offered by repetition of office blood pressure measurements. Because in the PAMELA study office blood pressure was measured three times at a visit performed before and three times at a visit performed after completion of 24 h blood pressure monitoring, white coat hypertensive subjects could be subdivided into four groups according to whether this condition was found twice or in only one of the office visits. As shown in Fig. 7.9, patients with "stable" white coat hypertension had an incidence of cardiovascular fatal events that was greater than that of individuals in whom the office BP elevation was seen one time only. This was the case also for all-cause mortality which in subjects with stable white coat hypertension was only slightly less than that of patients with true hypertension.

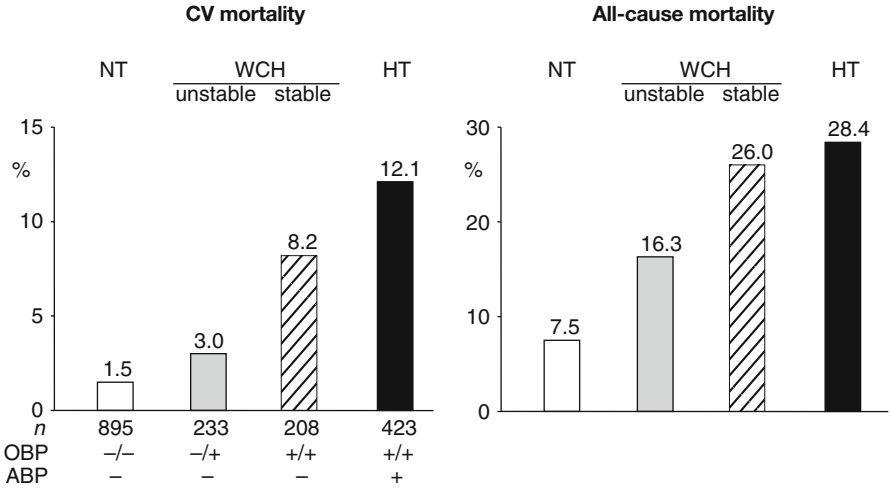

Fig. 7.9 Incidence of cardiovascular (*CV*) and all-cause mortality in true normotensives, unstable and stable white coat hypertensives, and true hypertensives. Stability or instability of WCH was determined by consistency or inconsistency of the office BP elevation (*OBP*) over two separate visits. *ABP* ambulatory blood pressure. Other symbols as in preceding figures

7.5 Final Considerations

All available evidence indicates that white coat hypertension is associated with a lower risk of cardiovascular morbidity and mortality than true hypertension. Despite the results of the majority of the studies and their meta-analyses, valid considerations can be advanced against the conclusion that white coat hypertension is clinically innocent and should be regarded as not substantially different from true normotension [22]. One, as illustrated in other chapters of this book, white coat hypertension is associated with a greater prevalence of metabolic risk factors and subclinical damage of the kidney, the brain, the heart, and the arteries of documented prognostic significance. Two, as previously mentioned, data from the PAMELA study suggest that over the years white coat hypertension favors appearance of diabetes, true hypertension, and left ventricular hypertrophy in subjects free from these conditions [23–25], thereby promoting progression from a lower to a higher cardiovascular risk profile. Three, the conclusion of several studies that out-of-office blood pressure is a more sensitive predictor of cardiovascular events than office blood pressure [26, 27] should not be interpreted as to mean that office blood pressure values are devoid of any prognostic significance because (1) this denies the evidence provided by a huge number of long-term epidemiological studies [28] and (2) if properly measured, office blood pressure has been found to independently predict cardiovascular outcomes or damage not less well than out-of-office blood pressure [29, 30] which exhibits a steeper relationship with cardiovascular events because of its narrower distribution range in the population [31, 32]. Indeed, in the

PAMELA population office blood pressure was found to be an independent predictor of the adverse consequences of white coat hypertension sometimes more important than out-of-office blood pressure. Office but not out-of-office blood pressure, for example, was among the independent predictors of the increased risk of developing true hypertension. It also independently participated in the prediction of the increased risk of diabetes of the white coat hypertensive group [33], and in the same group it was found to predict cardiovascular mortality independently of and more importantly than ambulatory or home blood pressure [21].

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White Coat Hypertension: To Treat or Not to Treat

8

Giuseppe Mancia, Rita Facchetti, Michele Bombelli, Guido Grassi, Gianmaria Brambilla, and Alberto Zanchetti

8.1 Introduction

Three views exist on whether white coat hypertensive patients should or should not be given antihypertensive treatment [1–12]. The first view maintains that because it does not differ from normotension, white coat hypertension needs no therapeutic intervention, the only requirement being remeasurements of in and out-of-office blood pressure, at various intervals after this condition has been detected [1, 2, 10]. The second view points out that in white coat hypertension, cardiovascular risk, although less than in true hypertension, is greater than that of truly normotensive individuals. This suggests an active therapeutic intervention to be limited, however, to lifestyle changes that can improve the adverse risk profile because no evidence exists that antihypertensive drugs are beneficial [5, 6, 9]. The third view acknowledges that the protective effect of antihypertensive drug treatment in white coat hypertension has never been documented. It emphasizes, however, that the high prevalence of this condition makes it likely that white coat hypertensive individuals shared the protective cardiovascular effect seen in trials on mild-to-moderate or elderly hypertensive patients. It thus suggests an extension to these individuals of the same treatment strategy adopted in individuals with either office and home or

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ambulatory blood pressure elevation, particularly if assessment of organ structure and function shows, as it may not rarely happen, organ damage [3, 12, 13].

This chapter will review four sets of data on the treatment of white coat hypertension, i.e., (1) the lowering effect of antihypertensive drugs on office blood pressure; (2) the concomitant treatment-dependent changes in ambulatory and home blood pressure; (3) the treatment-induced modifications of the so-called white coat effect [1], i.e., the office-ambulatory or home blood pressure difference; and (4) the ability of blood pressure changes to modify in white coat hypertension the asymptomatic organ damage and the incidence and risk of cardiovascular events.

8.2 Antihypertensive Drugs and Office Blood Pressure

Several studies have shown that antihypertensive drug treatment can effectively reduce office blood pressure in white coat hypertension. Years ago, this was documented with the use of the alpha-1-blocker doxazosin which lowered office blood pressure in white coat hypertensive subjects to a degree similar to that seen in sustained hypertensives, i.e., in individuals with in and out-of-office blood pressure elevations [14]. It was then reported with the use of a variety of calcium channel blockers [15–18] as well as with different ACE inhibitors [19, 20] and other drugs [21]. An example is given in Fig. 8.1 which is taken from the European Lacidipine Study on Atherosclerosis (ELSA) on patients with moderate essential hypertension in whom blood pressure was measured in the office and over the 24 h at baseline and at regular intervals during a 4-year treatment period [22]. In patients with office and ambulatory (sustained) hypertension, administration of lacidipine or atenolol caused a marked and persistent systolic and diastolic blood pressure reduction. This was the case, to only a slightly lesser extent, in individuals in whom the normality of ambulatory blood pressure values allowed to detect their belonging to the category of white coat hypertension. The blood pressure-lowering effect was similar when data were separately calculated for the two treatment types (Fig. 8.2), the only difference being an atenolol-related bradycardic effect, which caused some persistent reduction of office heart rate in the overall group of patients as well.

The conclusion that in white coat hypertension office blood pressure can be effectively lowered by antihypertensive drugs independently of its type and mechanism of action is in contrast with a phenomenon that has come to the attention of clinicians and investigators years ago. That is, that in a notable fraction of patients with resistant hypertension, i.e., those in whom three or more antihypertensive drugs administered at adequate doses do not show a satisfactory therapeutic effect, ambulatory or home blood pressure is found to be within their normal limits (Fig. 8.3), with a cardiovascular risk that is definitively less pronounced than that of resistant hypertensive individuals in whom both in and out-of-office blood pressure is elevated [23–26]. These patients are therefore white coat hypertensives in whom drug treatment does not lower office blood pressure values, no matter how intensive and protracted. As far as the response of office blood pressure to drug treatment is concerned, it thus seems that we have to consider a population of white coat hypertensive individuals who respond to antihypertensive treatment but also a number of

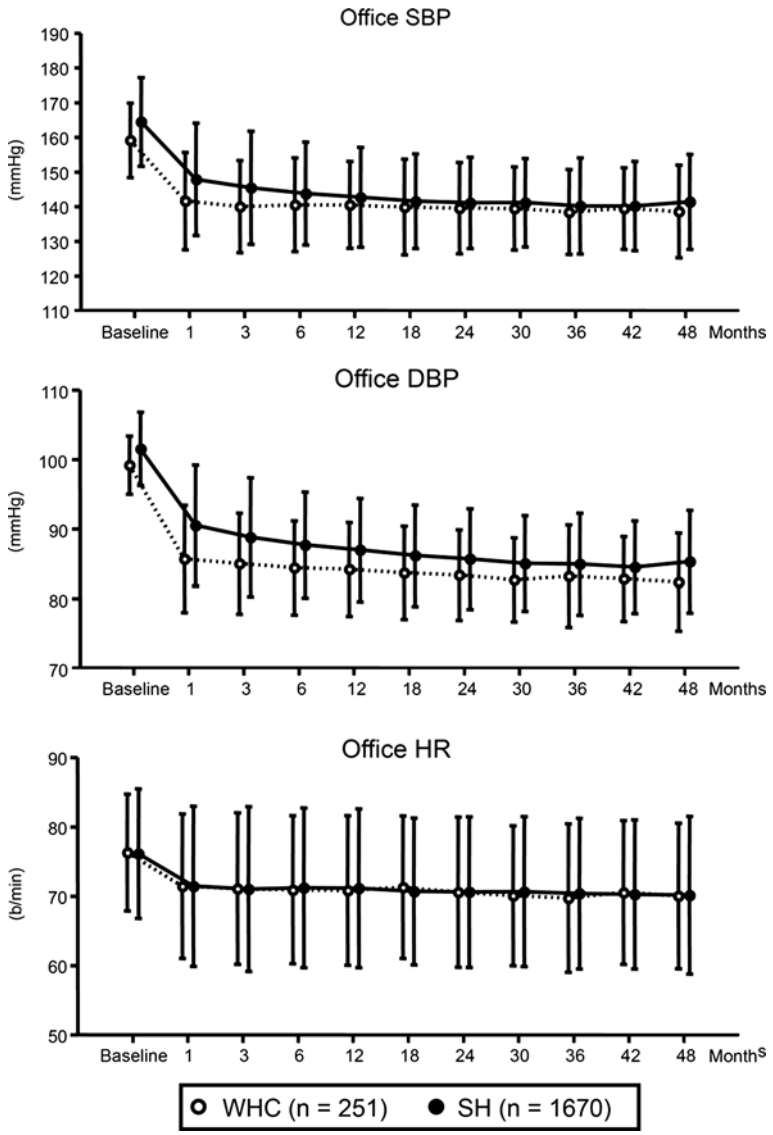

Fig. 8.1 Office systolic blood pressure (*SBP*), diastolic (*D*) BP, and heart rate (*HR*) values at baseline and during antihypertensive drug treatment (1–48 months) in subjects with white coat hypertension (*WCH*) ($n=251$) and sustained hypertension (*SH*) ($n=1,670$). Data are shown as means ± standard deviation. Treatment consisted of the initial administration of lacidipine or atenolol followed if needed by the addition of other drugs

patients in whom the elevated office blood pressure values remain persistently high, despite use of multiple medicaments and repeated changes of treatment strategies [13]. The clinical characteristics of the two groups have never been compared, and it is unknown whether the factors responsible for the lower ambulatory or home versus the office blood pressure values differ in the two groups.

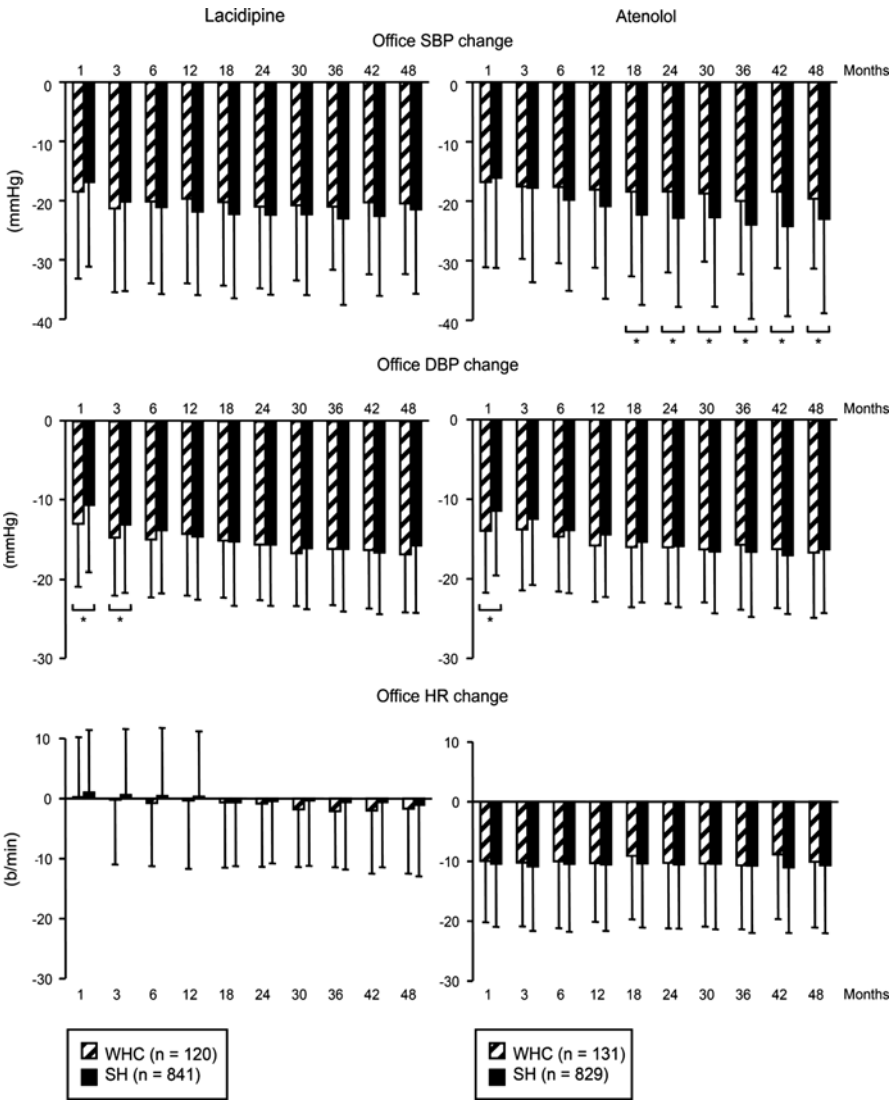

Fig. 8.2 Office SBP, DBP, and HR changes induced by treatment in subjects with WCH and SH. Data (means ± standard deviation) are shown separately for patients treated with lacidipine and atenolol. Symbols as in Fig. 8.1

8.3 Antihypertensive Drugs and Out-of-Office Blood Pressure

Several years ago the concept has been expressed that in white coat hypertension, drug treatment has no effect on ambulatory blood pressure [1]. This was based on a report of Pickering et al. [14] that, although effectively reducing office blood

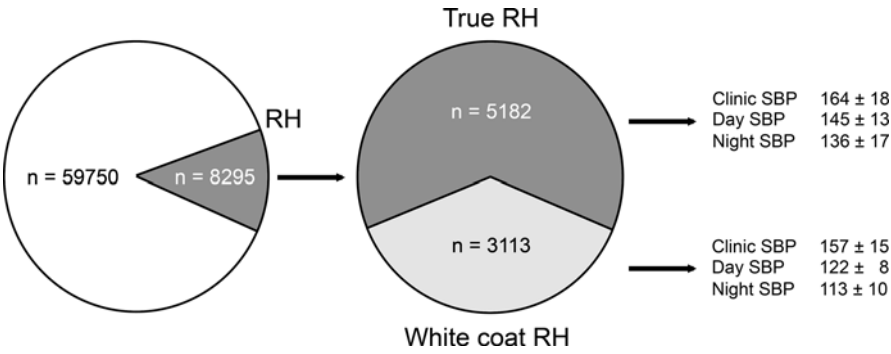

Fig. 8.3 Prevalence of true and white coat resistant hypertension (*RH*) based on office and ambulatory blood pressure values. True resistant hypertension was defined by office and ambulatory blood pressure elevations, whereas pseudohypertension was defined as elevation in only office blood pressure. Data from about 60,000 patients followed in the clinical practice setting. RH was found in 13.9 % of the hypertensive population. In 37.5 % of them, ambulatory blood pressure was normal (From de la Sierra et al. [26], with permission)

pressure, doxazosin did not have any lowering effect on ambulatory blood pressure values in white coat hypertension. It was also based on studies in which white coat hypertensives were given calcium channel blockers, ACE inhibitors, or other drugs which all caused reductions in office blood pressure without, however, any substantial reduction of day or 24-h blood pressure values [15–19]. However, other observations have turned out not to be entirely in line with the conclusion that in white coat hypertension ambulatory blood pressure is unaffected by treatment. Two studies have reported that the ambulatory blood pressure values of white coat hypertensive individuals were reduced by treatments based on ACE inhibitors, although not by the ones based on calcium channel blockers [19, 20]. Another study has reported a marked and sustained (1 year) reduction of both office and ambulatory blood pressure in black hypertensives treated with long-acting nifedipine [27]. Finally, a recent analysis of the data obtained by the Hypertension in the Very Elderly Trial (HYVET) on hypertensive patients aged $\geq$ 80 years has shown that an antihypertensive treatment based on indapamide with the frequent addition of the ACE inhibitor perindopril lowered to a notable degree not only office but also ambulatory blood pressure both in subjects with sustained hypertension and in those defined as white coat hypertensives based on ambulatory blood pressure normality [28].

Detailed evidence on the effect of antihypertensive drug treatment on ambulatory blood pressure in sustained and white coat hypertensive subjects has been provided by a post hoc analysis of the data obtained in the ELSA trial [29] because in this trial all recruited patients underwent an ambulatory blood pressure monitoring at baseline and at yearly intervals over a 4-year treatment period with either lacidipine or atenolol [22]. As shown in Fig. 8.4, treatment significantly lowered 24-h mean systolic and diastolic blood pressure in sustained hypertension with no loss of the blood pressure-lowering effect throughout the study duration. In striking contrast, ambulatory blood pressure did not exhibit any reduction in white coat hypertensive patients. On the contrary, from the first to the fourth year of treatment, there was a

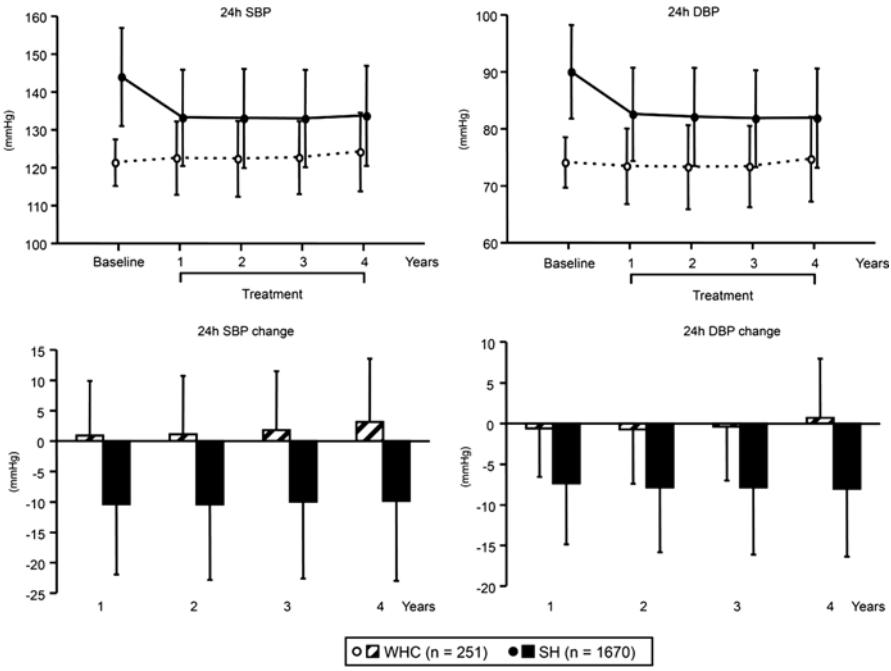

Fig. 8.4 Twenty-four-hour mean SBP and DBP in white coat and sustained hypertension before and during treatment with lacidipine or atenolol. Data are shown as absolute values (*top panels*) and changes from baseline (*bottom panels*). Changes were calculated by averaging the data provided by the yearly ambulatory BP monitorings ($n=4$). Symbols as in preceding figures

slight but significant progressive increase in the 24-hour (h) mean systolic and diastolic blood pressure values, which at the end of the treatment period were 2.8 and 0.59 mmHg greater than before treatment. This provides strong support to the conclusion that antihypertensive treatment is by and large not capable of lowering ambulatory blood pressure in white coat hypertension. It also provides evidence that the opposite is indeed the case, i.e., that despite drug treatment, there is a tendency for daily life blood pressure values to increase over years.

Why in white coat hypertension ambulatory blood pressure is unaffected by antihypertensive treatment is not clear. The most obvious possibility is that the "law of the initial value" makes the blood pressure reduction achievable by antihypertensive drugs proportionally less pronounced as the baseline blood pressure becomes progressively less, with little no effect when it is normal or low. Indeed, this has been found to occur for ambulatory blood pressure [30], the absence of any treatment-induced fall being predicted at values around 125 mmHg systolic and 80 mmHg diastolic [31]. However, in studies on sustained hypertensives, treatment has been found to be able to lower ambulatory blood pressure to values less than 125/80 mmHg (Fig. 8.5) [32, 33]. Furthermore, when in the ELSA study white coat hypertensive patients were divided into three groups according to their baseline ambulatory blood pressure values, no treatment-induced blood pressure reduction was seen

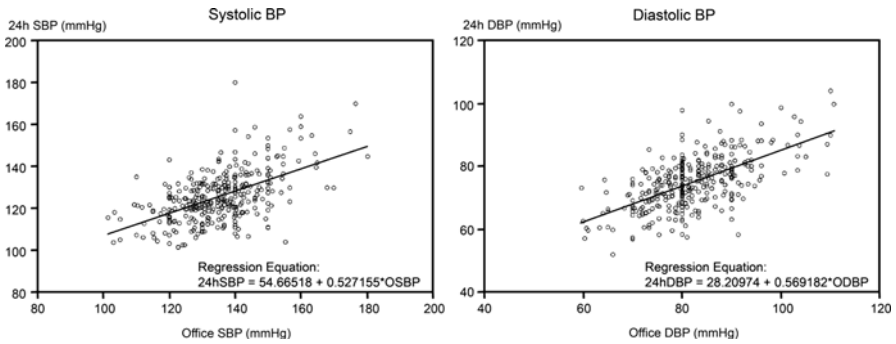

Fig. 8.5 Relationship between office and 24-hour (h) mean SBP and DBP in the treated hypertensive patients of a mulTicenter study evALuating the Efficacy of Nifedipine GITS–Telmisartan combination in blood pressure control and beyond (TALENT) study. Data refer to a treatment duration of 24 weeks. Treatment consisted of nifedipine GITS and telmisartan. Symbols as in preceding figures (From Mancia et al. [32], with permission)

also in patients with the highest values and thus with more room for a treatment-induced fall [34]. Finally, as mentioned above, in white coat hypertensive individuals, antihypertensive treatment appears to be accompanied not just by no blood pressure-lowering effect but by a blood pressure increase. This may be due to the regression to the mean phenomenon, i.e., to the fact that whenever a biological value is low there is a high chance that the following measurement will be higher and vice versa. The possibility also exists, however, that white coat hypertension represents a prehypertensive condition, i.e., that it has a high chance of progressing to sustained hypertension. Verdecchia et al. found year ago that 37 % of 83 white coat hypertensives moved to sustained hypertensives over 2.5 years [35]. This has been confirmed by other studies [36, 37], and a much greater risk of white coat hypertensive individuals to develop sustained hypertension has more recently been provided by a 10-year observation period of the PAMELA population [38].

8.4 Antihypertensive Treatment and White Coat Effect

Studies on antihypertensive drug treatment agree that the lowering effect is greater for office than for ambulatory blood pressure [39], which means that the office-ambulatory blood pressure difference, i.e., the phenomenon known as the "white coat effect" [1], is usually reduced by treatment. With few exceptions [40], this appears to be the case not only in sustained but also in white coat hypertension [1], a condition in which absence of an ambulatory blood pressure-lowering effect of treatment can make the white coat effect attenuation particularly pronounced. This is exemplified in Fig. 8.6, which is again taken from the data obtained in the ELSA trial. Patients with white coat hypertension exhibited a marked office-ambulatory blood pressure difference at baseline, but the difference was markedly less pronounced during treatment, consistently over the 4-year duration of the trial.

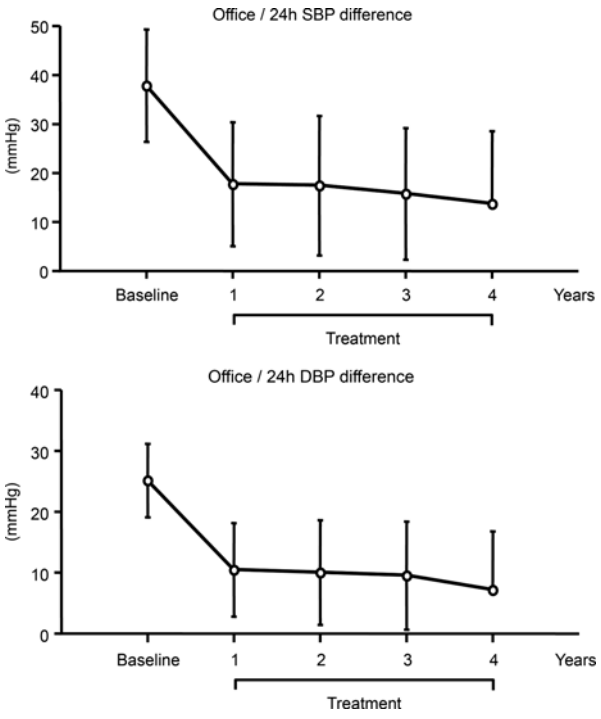

Fig. 8.6 Office-ambulatory SBP and DBP differences before and during treatment in the white coat hypertensive patients of the ELSA study. Symbols as in preceding figures

Does the marked reduction of the office-ambulatory blood pressure difference with treatment just reflect a reduction with time of the alerting response and the office blood pressure rise associated with the doctor's visit? [41]. This is not an easy question to answer because no conclusive evidence exists on the extent to which repetition of the visit attenuates the pressor effect of blood pressure measurements by a doctor [42].It is also uncertain whether the difference between office and ambulatory blood pressure reflects the alerting response to the abovementioned procedure and thus deserves to be termed the "white coat effect," as commonly done [11]. This has indeed been challenged by a study in which the office-ambulatory blood pressure difference did not exhibit any significant relationship with the white coat effect quantified directly by beat-to-beat blood pressure monitoring before, during, and after the physician's visit [43]. It is made unlikely also by indirect arguments such as that (1) when directly assessed by beat-to-beat blood pressure monitoring before, during, and after the doctor's visit the white coat effect exhibits an increase in both blood pressure and heart rate whereas the office-daytime difference is limited to the blood pressure values [11, 41–43]. Furthermore, the office-ambulatory blood pressure difference shows a progressive increase with age, but elderly people are not characterized by a hyperreactivity to environmental stimuli, their alerting response to the physician's visit being also similar to that of younger people [41]. Finally, the difference between office and ambulatory blood pressure is not only directly related to office blood pressure but also inversely related to ambulatory blood pressure [44], which is not influenced by the alerting response to blood pressure measurements [45].

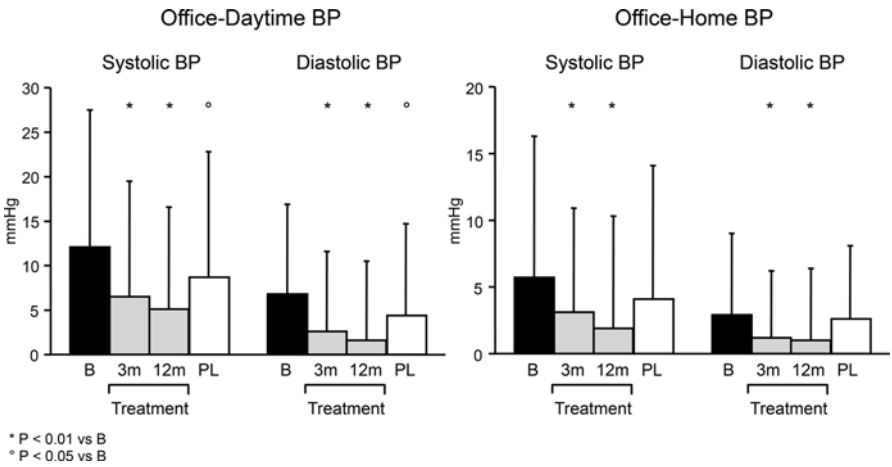

Fig. 8.7 Office-ambulatory SBP and DBP differences in hypertensive patients in whom the difference was measured before treatment after 3 and 12 months of treatment (an ACE inhibitor with the possible addition of a diuretic) and after a final 1-month period of placebo (From Parati et al. [47], with permission)

Is the attenuation of the office-ambulatory blood pressure difference with treatment then a treatment-related effect, i.e., the consequence of the ability of antihypertensive drugs to lower office more than ambulatory blood pressure? Although data on white coat hypertension are not available, other observations indicate that this is the case. As shown in Fig. 8.7, compared to the baseline values, the office-ambulatory blood pressure difference was reduced during the visits performed after 3 and 12 months of antihypertensive treatment. There was, however, a recovery during a final month of placebo which proved that the previous attenuation was at least in part due to the differential effect of the drugs employed on in and out-of-office blood pressure [46, 47].

8.5 Antihypertensive Treatment and Cardiovascular Protection

Ultimately, whether treatment is protective on patients with white coat hypertension needs documentation from prospective studies having a proper control group and outcomes of undisputable prognostic significance as endpoints. At present, no such studies have been performed, and the only available evidence is the one obtained from limited number of patients with isolated systolic hypertension recruited from the Systolic Hypertension in Europe trial (SystEur) in whom also ambulatory blood pressure data were collected [48]. Compared to the placebo group, patients with sustained hypertension showed a reduction of office blood pressure, ambulatory blood pressure, and cardiovascular morbid and fatal events. In contrast, white coat hypertensive patients only exhibited an office blood pressure reduction, the

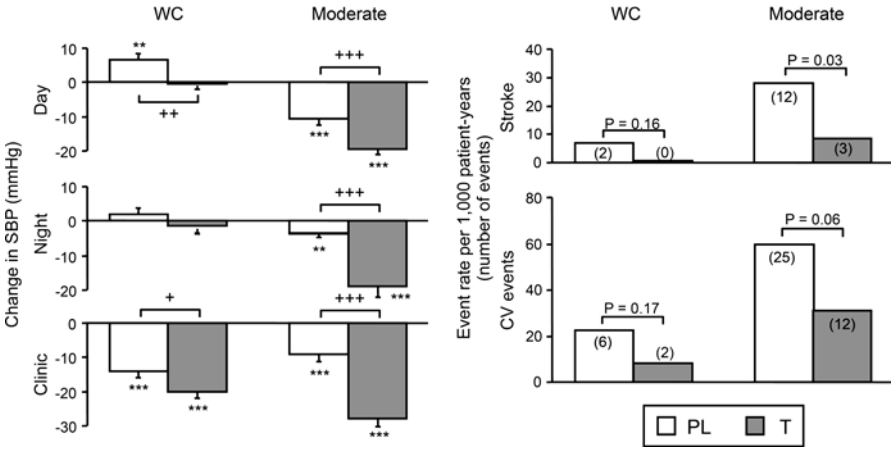

Fig. 8.8 The *left panels* show the reduction of office (clinic), day and night SBP in a group with a sustained moderate hypertension and a group with WCH. The *right panels* show the rate of stroke and cardiovascular (*CV*) events in either group. Patients were recruited from the SYSTEUR trial on isolated systolic hypertension and belonged to subgroups in which both office and ambulatory blood pressure were measured. Data refer to a placebo (*PL*) group and a group under active drug treatment. $^{*}P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$ of the SBP change vs baseline; $^{+}P \leq 0.05$; $^{++}P \leq 0.01$; $^{+++}P \leq 0.001$ between PL and T groups (From Fagard et al. [48], with permission)

nonsignificant fall in ambulatory blood pressure being accompanied by a more modest and nonsignificant reduction of cardiovascular morbidity and mortality as well (Fig. 8.8). However, the study could count on only few events in each group which limited the statistical power to detect between-group differences and made the conclusion that antihypertensive treatment may carry little benefit in individuals in whom blood pressure elevations are limited to office values only tentative. This limitation is shared by the other available evidence, i.e., the one provided by the post hoc analysis of the ELSA trial in which the cumulative 4-year incidence of cardiovascular morbidity and mortality showed a similar slope in white coat and sustained hypertensive patients.

Deciding that white coat hypertensive patients can be spared antihypertensive drugs would be of great practical importance because this condition is common and may account for up to 40 % of the mild and elderly hypertensive population [21, 43]. Demonstration that treatment is unnecessary would thus substantially reduce healthcare costs. However, at present the decision to avoid administration of antihypertensive drugs in white coat hypertension does not only lack appropriate experimental support, but it is also against a number of considerations. One of them is that reduction of office blood pressure by treatment has been indisputably shown to predict patient protection, whereas this has not yet been the case for ambulatory blood pressure changes. Furthermore, the high prevalence of white coat hypertension means that this condition might have shared the protective effects of antihypertensive treatment repeatedly demonstrated in randomized trials, those on mild hypertension and hypertension in the elderly in particular. This has been recently suggested by the

results of the HYVET trial on octogenarian hypertensives which have shown that (1) white coat hypertension accounted for more than 50 % of the recruited population [28] and (2) only an involvement of white coat hypertensive individuals could explain the beneficial effects of treatment in the overall patients of the trial [49]. As mentioned by the recent guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology, sufficiently powered randomized controlled trials are needed to provide undisputable evidence on this issue [13].

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White Coat Hypertension: The History of the Irresistible, Resistible Ascent of a Misnomer

9

Alberto Zanchetti

9.1 Early Suspicions on the Doctor's Influence on BP Measurement

The notion that blood pressure (BP) is highly variable and can be easily influenced by environmental stimuli goes back to the two seminal papers in which Riva-Rocci described the mercury sphygmomanometer and its use in the clinical measurement of BP [1, 2]: "The mental state of the patient has a transient but considerable effect on blood pressure. It is enough to speak to the patient, invite him to read, or look at him suddenly, or perhaps it will take a sudden noise, a carriage going fast in the street, a shout, or a loud but distant voice to make the blood pressure rise, and not necessarily to the same extent in all cases" [3]. The influence of the doctor measuring BP is also remarked by Riva-Rocci: "The simple application of the instrument can cause a temporary rise in blood pressure" [3], but it must be acknowledged that during the early years of BP measurement this was considered to be the task of expert physicians and, rather than a usual medical procedure, it was a kind of liturgy, as witnessed by the picture of Professor Vaquez surrounded by as many as 13 associates taking a BP measurement during one of his ward rounds at the Hôpital de la Charité in 1910 (Fig. 9.1) [4].

The first report of a hypertensive patient repeatedly measuring his BP dates back to 1930, when Brown described the daily and monthly rhythm in BP in a man with hypertension who self-measured his BP at home for 3 years [5]. No correlation was made between clinic and home readings, however. The first systematic study of the differences between clinic and home readings was published by Ayman and Goldshine in 1940 [6] in 34 hypertensive patients followed up for an average period

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Fig. 9.1 Professor Vaquez measures blood pressure at Hôpital de la Charité in 1910 (From Postel-Vinay [4], by courtesy of John Wiley & Sons)

of 22 months, during which 2,800 clinic readings and 40,000 home readings were made. Statistics was not popular in medicine at that time, and a statistical analysis of this large amount of BP data was not made. However, the authors reported that the home readings by the patient or a member of the household were systematically lower than the clinic readings and also noticed that both in the clinic and at home initial BP values were the highest and then progressively declined, though remaining higher in the clinic. The phenomenon is explicitly attributed by the authors "to the excitement and tension associated with the visit to the clinic or doctor's office" [6], i.e. what will be later named "the white coat effect". The authors did not attempt an explanation for the progressive decline of BP values with repeated measurements also occurring at home where the doctor was absent, but the concept of the emotional context in which BP measurement is taken was further elaborated a few years later, in 1943, by Alam and Smirk [7] when these authors remarked the contrast between "casual" BP to denote the BP measured under uncontrolled conditions in the physician's office or clinic and the "basal" BP measured in a rigorously defined basal environmental state.

The matter was resumed with the advent of the first effective antihypertensive drugs, the ganglionic blocking agents, "when it became necessary to follow blood

pressure more closely than could be accomplished with occasional visits to the office or clinic" [8]. For this reason, use of self-measurement of BP at home became more frequent, and there are three reports in 1954 showing home BP to be lower than clinic BP [8–10]. Smirk [10] remarked that in patients treated with ganglionic blockers "casual blood pressures are taken, but they are of very little use in the control of dosage. Quite high blood pressures may be encountered in outpatients whose blood pressure is satisfactory under home conditions" and referred these findings to some previous study of his group [11] showing that certain emotional stimuli may counteract the hypotensive effects of the ganglionic blocking agents. In a more systematic study of 32 hypertensive patients receiving the ganglionic blocker, pentapyrrolidinium, Freis reported that, while 31 of the 32 cases had a drug-induced systolic BP decrease of at least 30 mmHg when BP was measured at home, 68 % of the patients had a BP reduction lower than 30 mmHg when clinic measurements were used and interpreted the phenomenon as "occasioned by the apprehension associated with the visit to the doctor's office or clinic" [8]. Additional data on differences between clinic and home BP values were published by Julius and his associates in 1964 [12], and the suggestion was given that home BP measurements could be particularly useful in the decision in favour or against treatment in borderline hypertension [13].

9.2 The Advent of Ambulatory BP Monitoring: New Evidence New Questions

Differences between BP values measured in the office and out of office became more evident and could be investigated in greater detail when methods for automatic continuous or repeated measurements in the ambulatory patient became available. After the introduction of the first non-invasive portable BP recorder developed by Hinman et al. [14], Sokolow et al. [15] in a seminal paper showed that BP values semiautomatically measured during daytime were lower than those measured casually and were more closely associated with severity of hypertensive complications. The authors correctly refrained from interpreting the reasons for the differences between the two types of BP measurements and interpreted the closer correlation of semiautomatically measured BP values with organ damage as a consequence of the larger number of measurements provided by the portable machine.

Introduction of a device for continuous direct (invasive) recording of arterial pressure in unrestricted patients by Littler et al. [16] in 1972 provided further and more detailed information. Littler et al. [17] found that in a small group of treated hypertensive patients, lower BP were measured over 24 h than in the clinic, suggesting that "the difference may have been due to the well-known effect of exercise in augmenting the hypotensive action of drugs" or, alternatively, that the "clinic readings were biased by an unusually sensitive defense reflex" [17], the fault being placed more on the patient's than the doctor's shoulders. These observations were expanded a few years later by Floras et al. [18] in a number of untreated "borderline" hypertensive patients. In one group ambulatory mean arterial pressure was

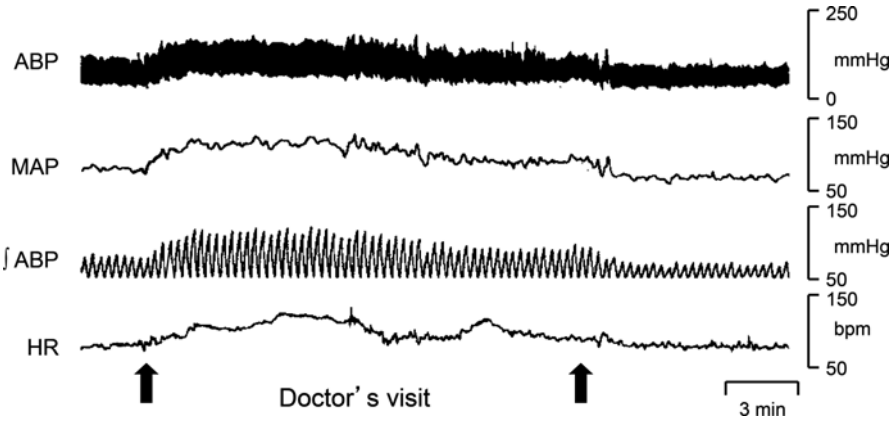

Fig. 9.2 Original tracing from one subject of blood pressure and heart rate in 15 min when a doctor was at bedside and measured blood pressure by the cuff method four times. *Arrows* indicate beginning and end of visit, *ABP* pulsatile arterial blood pressure, *MAP* mean arterial blood pressure, *∫ABP* arterial blood pressure integrated over regular time period, *HR* heart rate (From Mancia et al. [19], by courtesy of Lancet)

25 mmHg lower than clinic BP, whereas ambulatory and clinic BP values were similar in another group of patients. As patients in whom there was a large difference between clinic and ambulatory BP had no evidence of greater sympathetic activity and of greater blood pressure responses to mental arithmetic and bicycle exercise, the authors concluded that "the reason for the discrepancy between cuff and ambulatory readings is not clear" [18].

If the possibility that the doctor's involvement in BP measurement may increase BP values dates back to Riva-Rocci himself [2, 3], the demonstration that this really occurs had to wait a specific study by our group in 1983 when Mancia et al. [19] in a number of hypertensive patients with continuous intra-arterial BP recording could demonstrate the transient increase in SBP and DBP initiating when the doctor entered the patient's room, persisting through the several minutes of the "clinic" measuring procedures and disappearing at the end of the visit (Fig. 9.2). In this paper, and in a following one in which we compared the effect of the doctor's measurement with the smaller effect of the nurse's measurement [20], we refrained from using the term "white coat effect" and cautiously used that of "alarm" or "alerting" reaction. Even more cautiously we avoided to suggest that the doctor's effect on BP was the explanation of the frequent difference between clinic and ambulatory blood pressure.

9.3 Birth of "White Coat Hypertension"

When were the terms "white coat effect" and "white coat hypertension" coined and successfully entered into the medical literature? The first mention I could find of "white coat hypertension" is in a paper by Pickering's group in 1984 [21]: "The

anxiety provoking experience of an office visit may cause a transient rise in BP, which we have designated *white-coat hypertension*". Although in that sentence the authors cite two previous papers of theirs [22, 23] in which they would have used the term, I have been unable to find the term in these two articles, but both papers explicitly attribute the difference between the clinic and ambulatory or home BP values to "the defense reaction in hypertensive subjects which causes a rise of BP during a visit to a physician's office" [22].

Spreading of the term was apparently an unwanted consequence of our demonstration of the BP raising effect of the doctor's presence to measure BP. Indeed, in a 1985 paper, Pickering et al. [24] wrote: "this pressor effect of a physician, often referred to as white coat hypertension was most dramatically illustrated in a recent study by Mancia and colleagues…". Although this is only the second occasion, to my knowledge, that the term white coat hypertension was used in the medical literature, the way it was reported in the paper by Pickering et al. [24] ("often referred to as…") means it was already used in current medical language. Three years later, in 1988, the term "white coat hypertension" was already in the title of a paper by Pickering's group [25], with the meaning that became commonly accepted thereafter of a patient with elevated blood pressures in the clinic who has normal daytime ambulatory pressures or normal blood pressure at home measurements. In 1993, the term "white coat hypertension" triumphantly entered into the Fifth Report of the Joint National Committee (JNC V) [26].

While the finding that there are patients whose BP is in the hypertensive range when measured in the office but not in out-of-office measurements is undoubtedly useful in clinical practice, the correctness of the term "white coat hypertension" has been debated. In a 1996 editorial, Mancia and I [27] summarized the arguments against interpreting the clinic-daytime ambulatory blood pressure difference as an accurate reflection of the blood pressure rise induced by a doctor's intervention in the measurement, that is what can properly be described as the real "white coat effect": (a) the real white coat effect is characterized both by a blood pressure increase and by a tachycardia, whereas the clinic-daytime ambulatory blood pressure difference is not accompanied by any similar difference in heart rate; (b) the real white coat effect has been shown to be independent of the patient's age and clinic blood pressure, whereas the clinic-daytime ambulatory blood pressure difference increases progressively with ageing and clinic blood pressure values; and (c) in hypertensive patients there appears to be no significant correlation between the white coat effect assessed directly by continuous blood pressure measurements before, during and after a doctor's visit and the clinic-daytime ambulatory blood pressure difference. We concluded that "the term white coat hypertension, based as it is on an interpretation of the cause of the difference between clinic and daytime ambulatory blood pressure, is a *misnomer* because this difference does not measure the white coat effect and may be caused by several other mechanisms; it also underlies a *misconception*, because the interpretation that white coat hypertension is purely emotional in nature is, at best, unproven [27].

The 1996 World Health Organization report on Hypertension Control suggested a more descriptive term "isolated clinic (or office) hypertension" [28], that was

certainly more appropriate to our state of ignorance. This term was recommended in the 1999 World Health Organization/International Society of Hypertension guidelines on the management of hypertension [29] and also reported in all European Society of Hypertension/European Society of Cardiology Hypertension guidelines [30–32]. This was definitely a lost war. The term "white coat hypertension" combined the winning aspects of reassuring the experts and the doctors with the (false) belief they knew what they were talking about and the patients with the (equally false) belief theirs was a false hypertension. The term "white coat" could be easily translated in all major languages (e.g. blouse blanche, bata blanca, camice bianco, etc.) and even resisted the current trend to a change in colour of the doctor's or nurse's coat. A consultation of Scopus in April 2014 gives 491 references the title of which used the term "white coat hypertension" and only 20 and 19 references, respectively, using the term "isolated clinic hypertension" or "isolated office hypertension". A final witness of this lost war is the surrender to the use of "white coat hypertension" in the title of this volume.

9.4 The Physician's Fault or the Statistician's?

Does a lost war mean a war for a wrong cause? The perplexities expressed in 1996 about the real nature of the clinic-ambulatory BP difference [27, 28] have been strengthened by further research. In the PAMELA population study, in which all individuals with a wide range of clinic BP values had clinic, ambulatory and home BP measurements, we found the clinic-ambulatory (as well the clinic-home) BP differences were directly proportional to clinic BP values, in such a way that the difference (i.e. the so-called white coat effect) was progressively smaller the lower was office BP [33] (Fig. 9.3). This finding has recently been replicated in an analysis of data from the European Lacidipine Study on Atherosclerosis (ELSA), in which all hypertensive patients were followed up both by clinic and ambulatory BP measurements [34]. This type of relationship can also be found in some of the papers investigating the "white coat effect" (see, e.g. Fig. 1 in the paper by Kleinent et al. [21] and Fig. 2 in the paper by Hoegholm et al. [35]), but was not remarked by the authors, and no conclusion was drawn from this finding. A regression line of ambulatory over office BP values was also derived by Perloff et al. [36] in the paper in which they described the better prognostic value of ambulatory BP, but they used the equation only to identify those patients whose ambulatory BP was higher than expected and were found to have higher incidence of cardiovascular events. The statistical meaning of the regression was not remarked or discussed.

The relationship of the clinic-ambulatory BP difference with clinic BP has been further illustrated and extended by some recent observations of our group in normotensive and hypertensive children and adolescent [37]: the previously described phenomenon of ambulatory BP being most often higher than clinic BP in younger children was found to be due not so much to age, but to be related to clinic BP

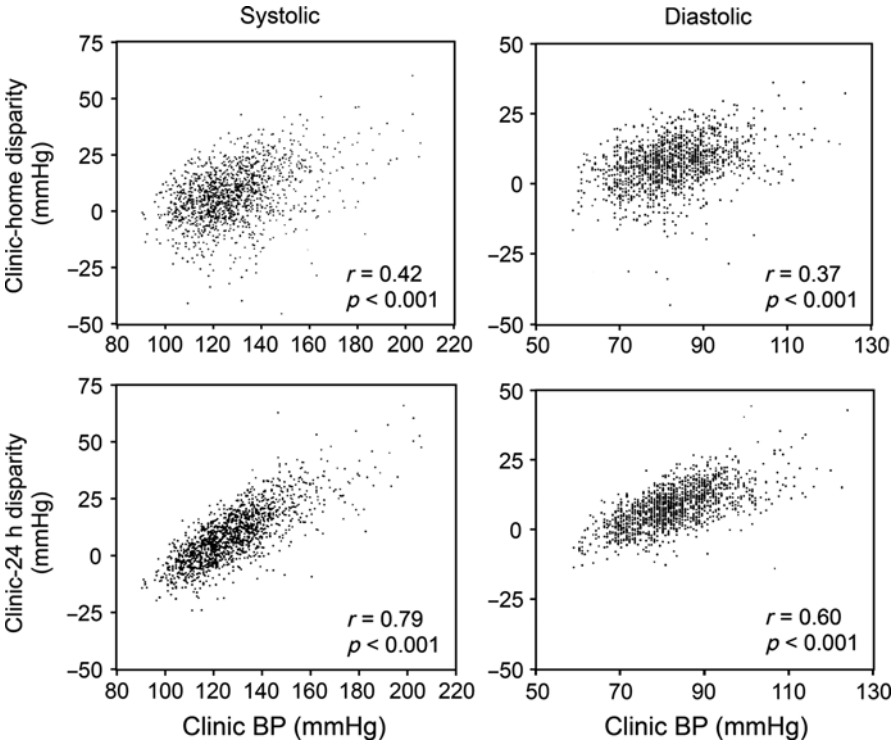

Fig. 9.3 Relationship of clinic-home blood pressure difference and clinic-24-h average blood pressure difference to clinic blood pressure values in individuals of the PAMELA population study. Coefficients of correlation (*r*) and their p values are given. *BP* blood pressure (From Mancia et al. [33], by courtesy of Lippincott, Williams and Wilkins)

values in such a way that for clinic SBP and DBP values higher than about 117 and 73 mmHg, respectively, 24-h ambulatory BP was progressively lower than clinic BP as in adults, but for lower clinic BP values, ambulatory BP was progressively higher than clinic BP (Fig. 9.4). When data from this study on children and adolescents [37] were combined with those from the adult population of PAMELA [33], a continuous relationship between the clinic-ambulatory BP difference (the "white coat effect") and the wide range of clinic BP values was found, with the sign of the difference changing from positive (clinic BP higher than ambulatory BP) to negative (clinic BP lower than ambulatory) around values indicating optimal clinic BP [37] (Fig. 9.5). These observations support the interpretation that regression to the mean is at least an important component of the clinic-ambulatory BP difference and strengthen the opinion that, attractive as they may be, the terms "white coat effect", to denote this BP difference, and "white coat hypertension", to denote patients with clinic BP in the hypertensive range and ambulatory BP in the normotensive range, are certainly misnomers and possibly misconceptions.

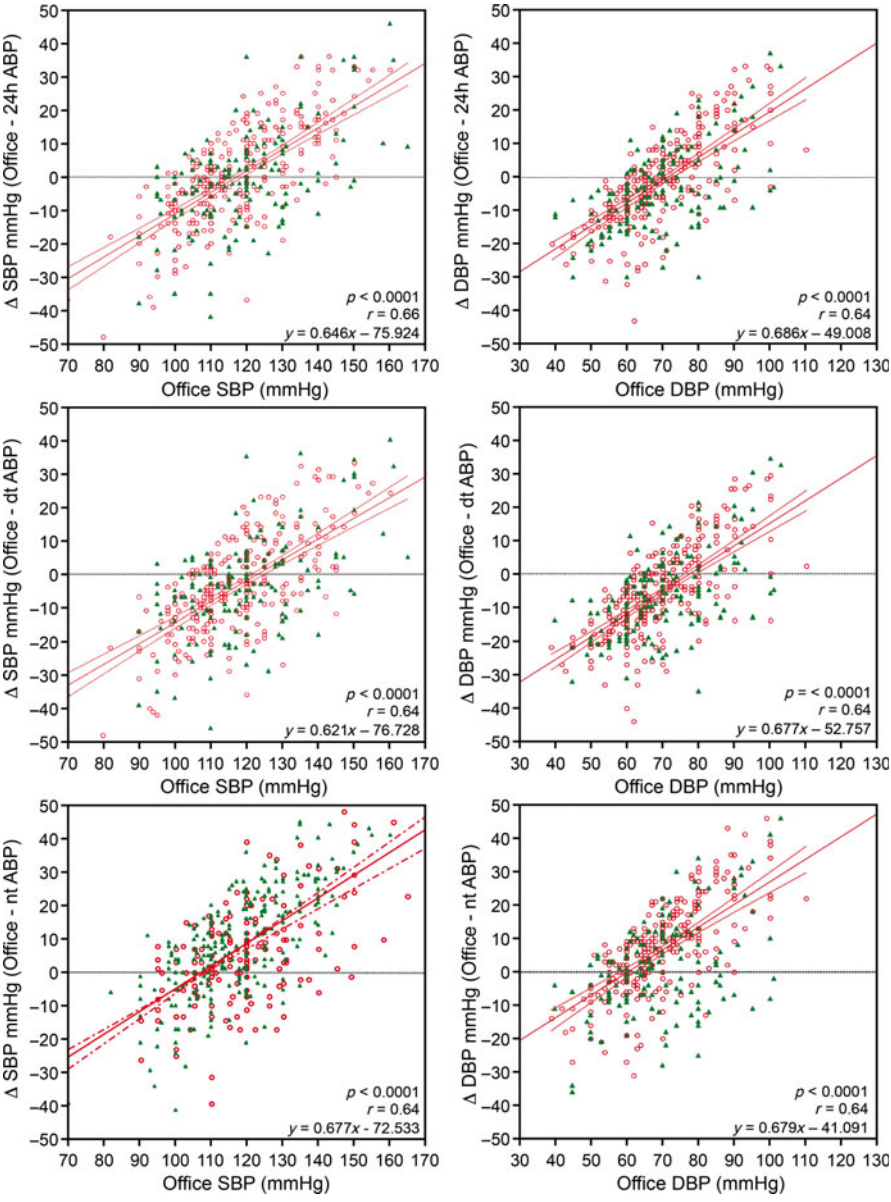

Fig. 9.4 Relationships of office blood pressure-ambulatory BP differences with office blood pressure values in a group of children and adolescents attending a hospital blood pressure clinic. Systolic values (*SBP*) in the vignettes at left; diastolic values (*DBP*) in the vignettes at right. **Δ** mmHg, differences in mmHg. In each vignette regression equation correlation coefficient (*r*) and statistical significance (*p*) are indicated. Regression lines and their 95 % confidence limits are drawn in *red. Red circles*, subjects without antihypertensive treatment; *green triangles*, subjects on antihypertensive treatment (From Salice et al. [37], by courtesy of Lippincott, Williams and Wilkins)

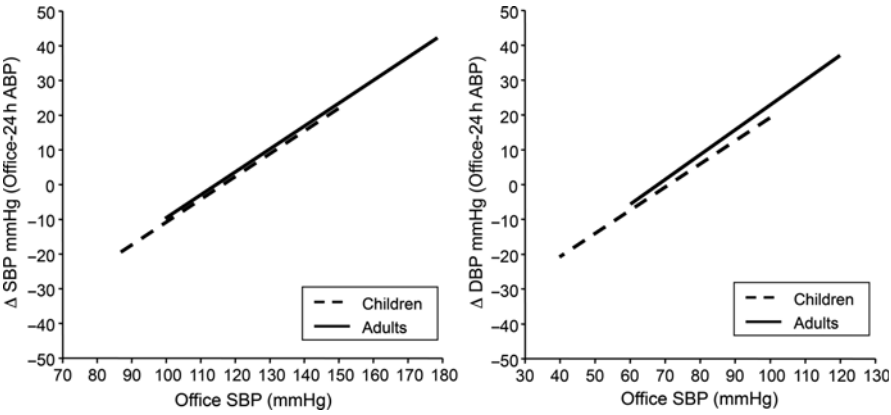

Fig. 9.5 Similar relationships of office blood pressure with office-24-h ambulatory blood pressure differences in the adults of the PAMELA study [33] and the children and adolescents of the Salice et al. study [37]. *ABP* ambulatory blood pressure, *DBP* diastolic blood pressure, *SBP* systolic blood pressure; *ΔDBP* and *ΔSBP*, differences in diastolic and systolic blood pressure

Indeed, the very design of the study [22] that initiated the concept of "white coat hypertension" was paradigmatic for finding regression to the mean: a comparison of a group of individuals selected because of high BP in the office and a group of individuals selected because of low or normal BP in the office could be easily predicted, on simple statistical terms, to reveal lower home BP in the former group and higher in the latter. This consideration, by the way, can also be applied to another term, more recently accessed to medical fame, "masked hypertension" [38]. When seen from a statistical viewpoint, the surprise shown by the authors of the paper cited above [22] in noticing that, in contrast with BP, there was no difference between office and home heart rate in high blood pressure individuals is surprising: group selection had been done on the basis of BP values with no selection bias for heart rate and, consequently, no regression to heart rate mean.

The continuous relation of the office minus out-of-office BP differences with office BP shown in a population study such as PAMELA, hence with no selection bias (see Fig. 9.3 above), is an unreproachable demonstration of what appears to be the major explanation of the "white coat effect", i.e. regression to the mean. Admittedly, Fig. 9.3 shows that even in the PAMELA population for the same value of office BP, a range of different out-of-office (home or ambulatory) BP values were measured in different individuals, which suggests other mechanisms, such as differences in 24-h BP variability, may also add to explain the phenomenon entirely.

If "white coat" has become too attractive a name to be eradicated from use, it should be accompanied by the experts' awareness they do not really know the mechanisms of the phenomenon and by making patients informed that we do not really know whether white coat hypertension is a fully innocent condition [39]. At a time like the present one when twitting is making abbreviations so popular, placing an acronym popular with twitters, aka, "also known as", in front of "white coat effect" and "white coat hypertension" may be an acknowledgment of our limited

understanding and a warning for physicians' decisions and patients' reassurance. Perhaps, the "aka white coat effect", the difference between the office and ambulatory BP, is not so much the fault of the physician causing the alarm reaction as the fault of the statistician who did not carefully review the evidence upon which the terms "white coat effect" and "white coat hypertension" were coined.

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