Chapter 4
Ambulatory Monitoring of Blood Pressure: An Overview of Devices, Analyses, and Clinical Utility

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Introduction

Ambulatory blood pressure monitoring (ABPM) has been available for more than 40 years, and despite substantial evidence that this diagnostic tool provides a more precise picture of BP status in individual persons, in most countries, clinic BP measurements remain the primary method used for hypertension screening, diagnosis, and management. Ambulatory blood pressure (ABP) monitors have become increasingly popular in clinical practice. The numerous benefits include the avoidance of potential blood pressure measurement errors such as observer bias and terminal digit preference and provision of more comprehensive information on blood pressure behavior than is possible with office or home blood pressure measurement [1].

Blood pressure varies reproducibly over a 24-h cycle with a number of well-recognized patterns. Most patients are "dippers;" these individuals are characterized by at least a 10 % decline in nocturnal blood pressure compared to their awake blood pressure [2]. Some patients may have an exaggerated drop in nocturnal pressures of >20 % and have been referred to as "extreme" dippers. Kario et al. demonstrated that extreme dippers in an older Japanese population were more likely to have ischemic lesions on magnetic resonance imaging compared to dippers; however, these data have not been reproduced in other populations [3]. Approximately 10–30 % of patients are "non-dippers," in whom the blood pressure decline is blunted or absent during sleep [4, 5]. This may be the result of various types of autonomic dysfunction

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W.B. White (ed.), *Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*, Clinical Hypertension and Vascular Diseases,
DOI 10.1007/978-3-319-22771-9_4

or certain causes of secondary hypertension and the loss of nocturnal BP decline is also a risk factor for target organ damage [6]. Multiple studies, in hypertensives as well as normotensives (NTs), have consistently shown that target organ damage is more likely in non-dippers than dippers [7]. Additionally, nocturnal BP is an independent, powerful indicator of cardiovascular disease [2]. A small proportion of patients exhibit an "inverse" dipping pattern [8]. Here, the nocturnal blood pressures do not fall during sleep and, in some cases, may actually be higher than the daytime readings. Other 24-h blood pressure patterns that have been observed resulting from the advent of ABP include "white coat" hypertension (WCH) or the "white coat effect" [9]. In these patients, medical care environment blood pressures are substantially higher than ambulatory awake blood pressure averages. There are also some individuals who may present with "masked hypertension," where ABP is elevated but office blood pressure is normal. This phenomenon may, in part, be the result of factors not present in the physician's office (e.g., smoking cigarettes, mental stress, or physical activity). Liu et al. reported that people with masked hypertension are as likely to have left ventricular hypertrophy (LVH) and carotid artery intimal-medial thickening as those patients with definite hypertension [10]. More recently, a 10-year follow-up of the Ohasama study showed that the cardiovascular mortality and stroke rates were significantly higher in masked hypertensives as compared with normotensives (relative hazard ratio = 2.1) [11]. Another pattern identified by ABP that has been linked to increased incidence of stroke in hypertensive patients is the "morning surge," which is a marked rise in BP during the early morning awakening hours [12].

Most research has shown that isolated clinic blood pressure values do not accurately estimate a patient's overall hypertension burden since they represent only one or two points in time on a patient's 24-h blood pressure profile. ABP monitors overcome this problem by obtaining multiple readings over the 24-h period and capturing the blood pressure variability. Numerous studies have also shown that clinic blood pressures are inferior in predicting hypertensive target end-organ damage, as well as long-term cardiovascular outcomes, compared with ambulatory BP averages. This chapter will focus on the various types of ABPM devices and their validation and discuss their clinical application in managing patients with hypertension.

ABPM Devices: Auscultatory and Oscillometric

Ambulatory BP monitors are automated and programmable devices that detect blood pressure either by the auscultatory method or the oscillometric route. Some devices have the option of using both techniques. Each method has its own advantages and limitations. The auscultatory devices employ the use of a microphone to detect Korotkoff sounds. Unfortunately, these devices are also sensitive to external artifact noise, which may limit their accuracy. They may also be less precise in the obese upper extremity. In some devices, these limitations have been overcome by synchronizing the Korotkoff sounds with the R-wave of the electrocardiogram (electrocardiographic gating) [13]. The oscillometric technique, which is utilized

in the majority of present-day monitors, detects the initial and maximal arterial vibrations or the mean arterial blood pressure and is less affected by external artifacts. The systolic and diastolic blood pressure values used in this technique are actually computed via set algorithms. Hence, the more sensitive the algorithm, the more accurate the device. Extreme blood pressure values increase the likelihood of error with the oscillometric devices [14]. Modern ABP recorders are compact, lightweight monitors that can be programmed to take blood pressure readings at various intervals (e.g., every 15 min during the day and every 30 min at night). In most devices, the bleed rates of deflation of the cuff and maximal inflation pressures can be programmed; some devices also have a patient-initiated event button (to monitor symptoms). Most devices have algorithms to screen out most erroneous readings and will perform a repeat of the blood pressure measurement within 1–2 min. Prior to initiation and again at the termination of a 24-h monitoring study, the ABP device may be calibrated against either an aneroid or a mercury-column sphygmomanometer to verify that the systolic blood pressure and diastolic blood pressure agree within about 5 mmHg. It is most practical that the cuff be fitted to the nondominant arm. If there is a large discordance between arms in BP measurement, it is recommended to apply the cuff to the higher value arm if the difference in systolic BP is greater than 10 mmHg [12, 15]. Patients should be educated regarding the use of the ABPM at device hookup. Most experts recommend that a written set of instructions be given for at-home reference along with verbal counseling [12]. For example, the patient needs to be aware that when the actual readings are being measured, the arm should be held motionless to avoid artifact and repetitive readings [16]. Excessive heavy physical activity during measurements should be discouraged, as it usually interferes with the accuracy of the measurements. A diary that records wake-up and sleep times, time of medication administration, meals, and any occurrence of symptoms should be maintained.

Ambulatory BP monitoring should be performed on a routine working day rather than a nonworking day or on the weekend to obtain the most representative blood pressure values. A study conducted by Devereux et al. demonstrated that daytime (work) blood pressures were a more sensitive determinant of left ventricular mass index compared to daytime values taken at home [17]. The clinical advantages of ABPM studies are many and the disadvantages are few (Table 4.1). Ambulatory BP monitoring eliminates observer error as well as the white coat effect, and it allows for a more comprehensive assessment of antihypertensive therapy. In addition, ABP is a superior prognostic indicator for hypertensive target end-organ damage as compared to clinic blood pressures. The potential limitations of ABP devices include poor technical results in patients with rapid atrial fibrillation or in those patients with very obese or large, muscular upper arms that exceed a mid-bicep circumference of 44 cm. Imprecise data may also be recorded in patients with weak pulses or an auscultatory gap. The devices are usually well-tolerated by patients, although occasionally there may be bruising or petechiae at the upper or distal arm, particularly in the elderly or patients on anticoagulation therapies. Some subjects may experience a lack of sleep at night or poor sleep quality because of the repeated cuff inflations.

Table 4.1 Advantages and disadvantages of ambulatory blood pressure monitoring compared to clinic blood pressures

Advantages	Disadvantages
Elimination of observer bias/error	Cost
Elimination of the white coat effect	Time commitment on behalf of
More comprehensive assessment of antihypertensive therapy	Patient
	Disturbed sleep
Superior prognostic indicator	Cuff discomfort
Calculation of blood pressure loads	May be inaccurate in atrial fibrillation
Evaluation of dipping/non-dipping status	
Ability to better assess blood pressure variability	
More reproducible over time	

Validation of ABP Monitors

The Association for the Advancement of Medical Instrumentation (AAMI) has long recognized the importance of evaluation of the accuracy of ABP monitors. A protocol was first developed in 1987 for the assessment of device accuracy and reliability [18]. The AAMI protocol was followed by a more complex method of independent validation from the British Hypertension Society (BHS) in 1990 [19]. Although the protocols differed, their aim was to establish minimum accuracy standards for these devices in order for them to be considered reliable clinical tools. Since then, both protocols have been revised [20, 21]. In addition to clinical testing, the protocols include recommendations such as labeling information, details for environmental performance, as well as stability and safety requirements.

In an updated version in 1992, the AAMI [20] advised that blood pressure should be measured at the onset and conclusion of the validation study in three positions (supine, seated, and standing) and the difference between the ABPM vs. the reference standard should not be more than 5 mmHg with a standard deviation of 8 mmHg. Additionally, the disparity between the ABPM and the reference sphygmomanometer should be assessed in 20 subjects at the beginning and at the end of a 24-h blood pressure study. This difference should not exceed 5 mmHg in at least 75 % of the readings. For reliability testing, three different instruments should be assessed in a minimum of ten subjects for a total of thirty 24-h ABP studies. It is recommended that a minimum of 75 readings in each of the 24-h studies be obtained, with 15-min intervals during the awake period and 30-min intervals during sleep. The number of satisfactory readings (i.e., no error codes) should exceed 80 % of the total number of readings programmed for the day.

The BHS protocol is a more complex validation protocol that has the grading system outlined in Table 4.2. The BHS protocol calls for multiple phases of validation: (1) before use device validation, (2) in-use (field) assessment, (3) after-use device calibration, (4) static device calibration where the device is rechecked after 1 month of usage, and (5) report of evaluation. Each phase has its passing criteria [21].

Table 4.2 British Hypertension Society Grading Criteria

Absolute difference between standard and test device (mmHg)			
Grade	≤5 (%)	≤10 (%)	≤15 (%)
A	60	85	95
B	50	75	90
C	40	65	85
D		Worse than C	

Grades are derived from percentages of readings within 5, 10, and 15 mmHg. To achieve a grade, all three percentages must be equal to or greater than the tabulated values
From ref. [21]

In 2002, the Working Group on Blood Pressure Monitoring of the European Society of Hypertension approved a new protocol—the European Society of Hypertension International Protocol (ESH_IP) [22]. The main purpose of this protocol was to simplify the previous protocols without compromising their integrity. Briefly, this protocol consists of the following steps:

1. Observer training and assessment.
2. Familiarization session.
3. Validation measurements (done in two phases, with 15 patients required in the first phase and 33 in the second).
4. Analysis after each phase.
5. Reporting of results.

This protocol uses "pass" or "fail" for grading the devices as opposed to the A–D classification of the BHS protocol. One of the other differences from the BHS protocol is the exclusion of the pre-validation phases (phases 1–3 in the previous list), thereby considerably reducing time and labor. Also, the specifications regarding observer training reduce errors in the actual measurement of blood pressures and resolve major differences between individual observers. A reduced sample size, a refinement in the range of test blood pressure, and a two-phase system of evaluation will decrease the time and cost required for validation by using fewer total subjects and eliminating extremely inaccurate devices in an initial phase of testing. The international protocol has also been criticized for certain differences from prior protocols [23]. First, the protocol does not specify a range of arm circumference over which the device must be tested. Arm circumference is known to affect the accuracy of blood pressure measurement. Second, the protocol does not specify the maximum number of subjects that can be excluded. Some experts have brought up concerns that this might give the manufacturers excessive control over data reporting. In 2010, the ESH-IP was revised with more stringent validation specifications [24]. These specifications include forms with standardized options for responses in the place of open-ended responses, an age restriction of ≥25 years, and more stringent pass levels [25]. The 2002 ESH-PI1 and 2010 ESH-PI2 have been the most frequently used validation protocols primarily due to their ease of use compared to the AAMI and BHS guidelines [15, 26].

Hodgkinson et al. conducted a systematic review of validation studies using the AAMI, BHS, ESH-IP1, ISO, and ESH-IP2 protocols and found that the less complicated ESH-IP generated fewer major protocol deviations than the AAMI and BHS [27]. Ultimately, Hodgkinson et al. recommended the ESH-IP2 protocol citing its "simplicity of method and greater accuracy requirement" [27].

Analysis of ABPM Data

Upon completion of the 24-h ABP recording, the data are downloaded and analyzed statistically to calculate blood pressure averages (i.e., 24-h, awake or daytime, and sleep or nighttime) as well as variations on the blood pressure load. The American Society of Hypertension as well as other expert groups have proposed limits of normal blood pressure and blood pressure loads as depicted in Table 4.3 [28].

Descriptive Blood Pressure Data from ABPM

Data are generally reported separately for the 24-h, daytime, and nighttime periods. These averages should be accompanied by the standard deviations as a simple indicator of blood pressure variability. A study by Kikuya et al. found an association between increased cardiovascular mortality risk and daytime SBP variability [29]. Some studies have indicated that there is a significant relationship between blood pressure variability and target end-organ damage [30], especially with beat-to-beat intra-arterial data. Frattola et al. conducted a study on 73 essential hypertensives that underwent intra-arterial blood pressure monitoring at the initiation of the study [31]. Subsequently, echocardiography was performed to assess left ventricular mass

Table 4.3 Suggested upper limits of normal average ambulatory blood pressure and load

Blood pressure measure	Probably normal	Borderline	Probably abnormal
Systolic average			
Awake	<135	135–140	>140
Asleep	<120	120–125	>125
24-h	<130	130–135	>135
Diastolic average			
Awake	<85	85–90	>90
Asleep	<75	75–80	>80
24-h	<80	80–85	>85
Awake	<15	15–30	>30
Asleep	<15	15–30	>30
Awake	<15	15–30	>30
Asleep	<15	15–30	>30

From ref. [28]

on subjects at the onset and at the conclusion of the study 7 years later. The standard deviations were obtained, and the average blood pressure variability for the group was calculated as 10.8 mmHg. The authors observed that end-organ damage was significantly higher in patients who had a greater than average blood pressure variability (for the group as a whole) given that the 24-h mean arterial pressure was similar in both groups. Unfortunately, 24-h blood pressure monitoring was not conducted at the end of the study to confirm if the same level of blood pressure variability persisted.

Blood Pressure Loads

The blood pressure load is calculated as the proportion of blood pressures >135/85 mmHg during the awake period and >120/75 mmHg during the sleep hours. White et al. was one of the first groups to introduce the concept of blood pressure loads [32]. They conducted a study in 30 previously untreated hypertensives and observed that the blood pressure load was a sensitive predictor of indices of hypertensive cardiac involvement. The results demonstrated that when the systolic or diastolic blood pressure loads were less than 30 %, the likelihood of LVH was negligible. However, with a systolic blood pressure load exceeding 50 %, the incidence of LVH approached 90 %, and with the diastolic blood pressure load more than 40 %, LVH occurred in 70 % of the subjects [33]. Similar results were obtained when Mule et al. studied 130 patients with mild to moderate hypertension [34]. Subjects with a higher systolic blood pressure load, adjusted for average 24-h SBP, were found to have increased relative myocardial wall thickness and total peripheral vascular resistance as well as increased prevalence of hypertensive retinopathy. These studies suggest that blood pressure load is an independent predictor of hypertensive target organ damage and adverse cardiovascular risk profile. However, this parameter has fallen out of favor in recent years since 'load' is not a continuous variable and has no means to differentiate moderate versus severely hypertensive individuals.

White Coat Hypertension (WCH) and the White Coat Effect (WCE)

White coat hypertension (also called isolated clinic hypertension) is diagnosed when the untreated patient's 24-h blood pressure is within normal limits, but blood pressure in the clinic is persistently elevated (Fig. 4.1), with clinic BP measurements ≥140/90 mmHg, 24-h ABPM <130/80 mmHg, awake ABPM <135/85 mmHg, and nocturnal ABPM <120/70 mmHg [35]. The prevalence of WCH is reported to be 10 to 20 % of patients with untreated Stage 1 hypertension [36]. Originally thought to be a benign condition, recent WCH studies have found evidence that CV risk in individuals with WCH is between that of normotensives and sustained hypertensives. A meta-analysis by Cuspidi et al. in 2014 showed that people with WCH had

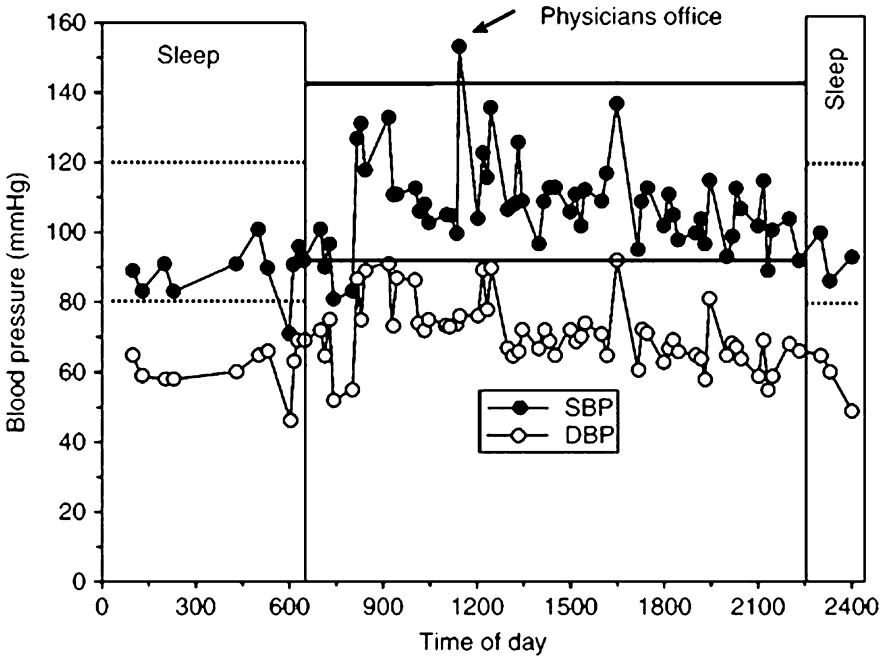

Fig. 4.1 *Plot* showing 24-h pressure curve depicting white coat hypertension (WCH) and dipping status. The patient's blood pressure in the physician's office is 153/76 mmHg. The daytime ambulatory average is normal at 108/71 ± 13/9 mmHg. The subject has WCH with a 45/5 mmHg rise in blood pressure in the physician's office. The patient also has a normal drop in nocturnal pressures, with a night time average of 90/60 ± 7/6 mmHg

increased left ventricular mass index, decreased mitral E/A ratio, and greater left atrial diameter compared to a matched group of normotensive individuals [37]. A key utility of ambulatory BP monitoring in clinical practice is its ability to identify WCH, thereby preventing excessive drug therapy [12, 15]. Nevertheless, patients with WCH do need close observation with ABP performed every 2–3 years to determine whether a more sustained hypertensive pattern has developed [38]. The white coat effect (WCE) is defined as an additional presser response in patients with established and treated hypertension, which causes an overestimation of true blood pressure when measured in the clinic setting (Fig. 4.2). White coat effect parameters are typically defined as: treated patients with hypertension where the office BP is ≥140/90 mmHg, 24-h ABPM <130/80 mmHg, daytime ABPM <135/85 mmHg, and nocturnal ABPM <120/70 mmHg [12].

Masked Hypertension

Masked hypertension ("white coat normotension" or "reverse white coat hypertension") is an entity that has been closely studied during the past decade.

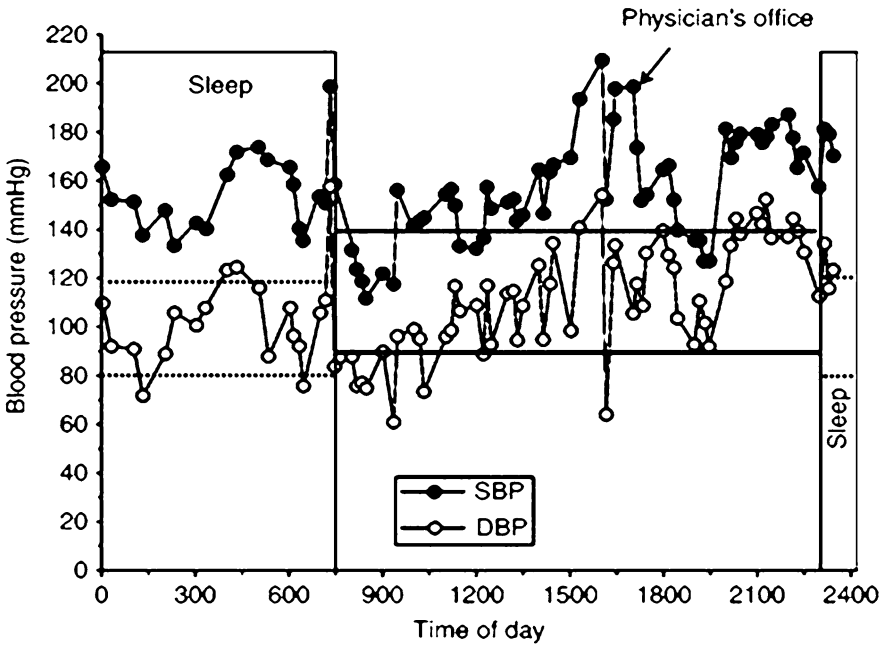

Fig. 4.2 *Plot* showing 24-h blood pressure curve depicting white coat effect and non-dipper status. The patient is hypertensive with a daytime average of 158/110 ± 21/23 mmHg. The nighttime blood pressure does not drop significantly (157/105 ± 15/16 mmHg). The patient, in addition to his hypertension, has a significant white coat effect in which the blood pressure is 216/98 mmHg in the physician's office

Masked hypertension is diagnosed when an individual has a normal office (or clinic) blood pressure and an elevated ABP in those patients either not currently being treated for hypertension or on therapy which is not controlling the BP during a 24-h period. The parameters for this condition are typically: untreated patients with office BP <140/90 mmHg, 24-h ABP ≥130/80 mmHg, daytime ABP ≥135/85 mmHg, and/or nighttime ABP ≥120/70 mmHg [35]. Patients with normal office BP in conjunction with stressful occupations, kidney disease, obstructive sleep apnea, LVH, target organ damage, familial history of hypertension, and increased blood pressure during exercise should be considered for ambulatory BP assessment to confirm or deny a diagnosis of masked hypertension [12]. Masked hypertension, which occurs in 10–15 % of normotensive people, is associated with an increased risk of target organ damage as well as cardiovascular mortality [10].

Dipping/Non-dipping/Extreme Dipping

Blood pressure normally has a circadian pattern in which blood pressure drops during sleep and is higher during the awake hours of the day. This pattern is referred to as "dipping" (Fig. 4.1). The dipping status can be determined by evaluating awake

and sleep blood pressures and calculating differences between the two averages. The percentage "dip" is then determined by dividing this difference by the awake average. The degree of decline in blood pressure varies from person to person, but a general consensus is that 10–20 % drop in blood pressure during sleep is "normal" [39]. The patient who has *less* than a 10 % drop in blood pressure at night is referred to as a "nondipper" (Fig. 4.2).

Reporting of Ambulatory BP Data for Medical Records

Using all of the above-referenced values, an informative report can be generated indicating the status of the patient's blood pressure. The reports should include demographics, all medications taken during the study, the number of accurate readings obtained, the awake/sleep times, and any symptoms that were experienced. The clinical report could also graphically depict blood pressures and heart rates over a 24 h period as shown in Figs. 4.1, 4.2, and 4.3.

Reproducibility of ABPM

The majority of clinical trials conducted to evaluate ABP reproducibility confirm both superior short-term (<1 year) [40, 41] and long-term (>1 year) [42–44] reproducibility of ABPM as compared to clinical blood pressure measurement. One

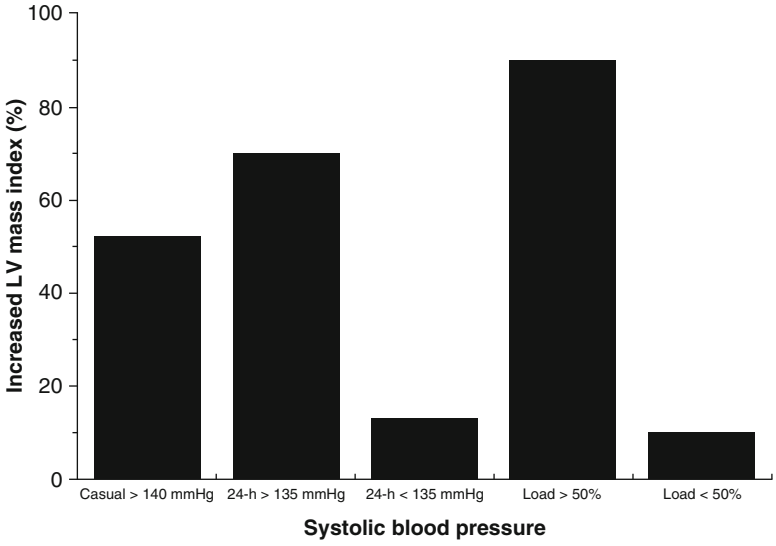

Fig. 4.3 Bars show percentage of increased left ventricular (LV) mass in subjects with elevated systolic blood pressures (both clinical and ambulatory) and systolic blood pressure loads (From ref. [45])

substudy from the Systolic Hypertension in Europe (SYST-EUR) trial evaluated 112 patients who were randomized to receive placebo [42]. Clinical and ABPM readings done at baseline were repeated after 1 month in 51 subjects and a full year in 112 subjects. The results indicated that differences in 24-h ambulatory systolic blood pressure (2.4 ± 10.7 mmHg [$p < 0.05$]) were far less than for clinical systolic blood pressure (6.6 ± 15.9 mmHg [$p < 0.001$]) taken at 1 year (Fig. 4.4). Another large-scale trial that also observed better reproducibility for ABP monitoring than clinical blood pressure was the Hypertension and Ambulatory Recording Study (HARVEST), in which 508 subjects were evaluated [43]. Ambulatory BP monitoring was conducted at baseline and 3 months later in the untreated state. A very modest difference in the two sequential ABPMs for the group as a whole was observed (0.4/0.7 mmHg).

Studies evaluating the reproducibility of the circadian rhythm have not had such promising results. For example, in a study by Mochizuki et al., it was found that there was limited reproducibility of the circadian rhythm [45]. In that study, 253 untreated essential hypertensives were monitored for 48 h. In these 2 days, 16 % of dippers "converted" into non-dippers and 13 % of non-dippers "converted" into dippers (Fig. 4.5). The authors suggested that 48-h ABP monitors be performed to assess the circadian blood pressure profile of an individual [46]. Although this will not solve the problem entirely, it should decrease the likelihood of error.

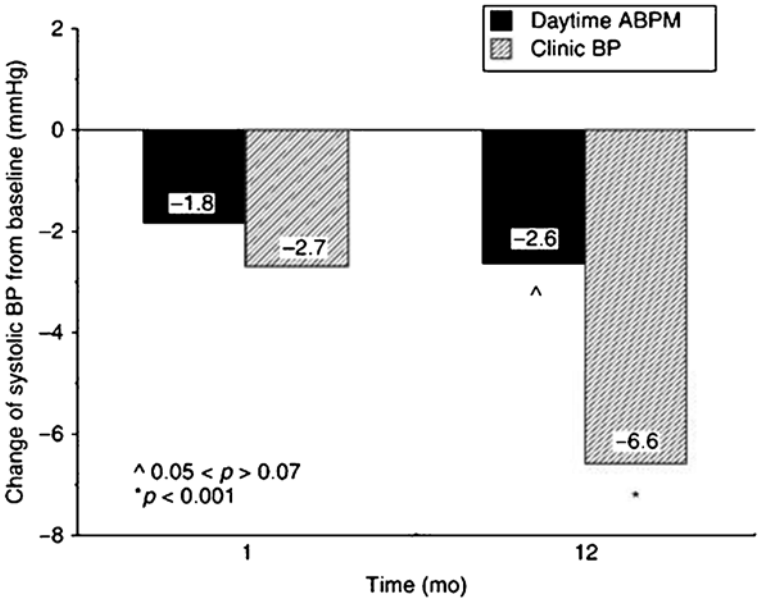

Fig. 4.4 *Bars* show the superior reproducibility of ambulatory blood pressure (ABP) vs. clinic/office blood pressure from the SYST-EUR trial ($n = 112$). Blood pressures were measured 1 and 12 months after baseline measurements (From ref. [42])

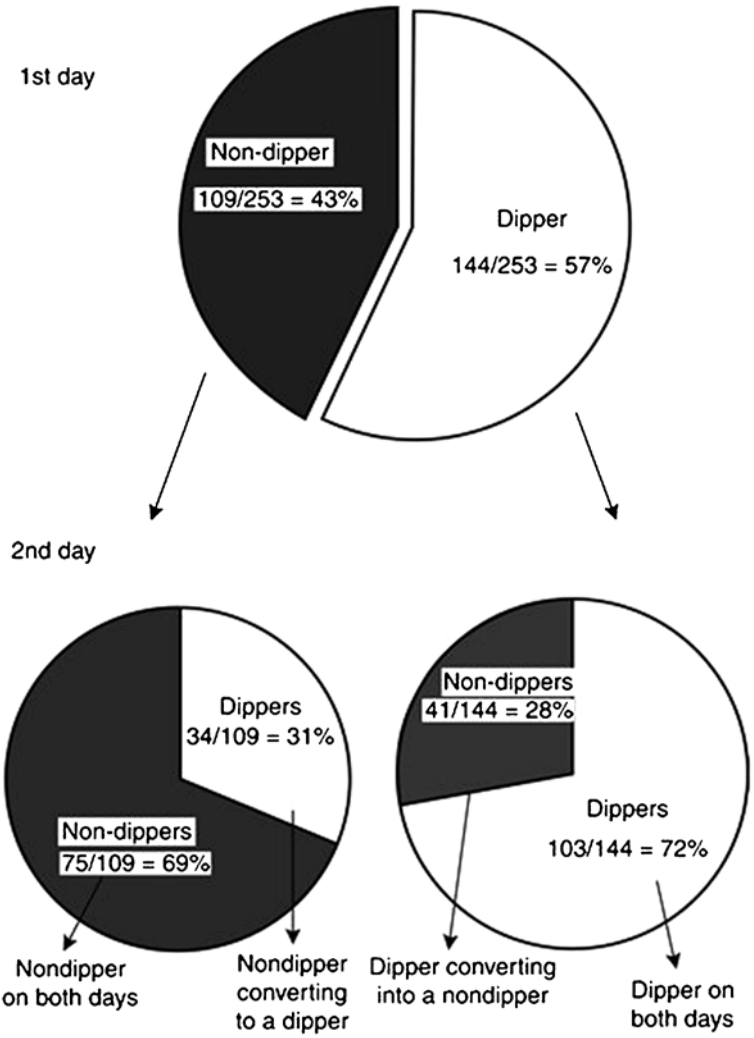

Fig. 4.5 Illustration of the limited reproducibility of the circadian rhythm (i.e., the dipping/non-dipping status) with ambulatory blood pressure monitoring studies conducted over 48 h in 253 subjects (From ref. [45])

Indications for ABPM

ABPM has been recognized as an important clinical tool by a number of expert medical groups and societies. In the US, the Joint National Committee (JNC VII) recommended ABP monitoring for a number of clinical situations (Table 4.4) [39].

The 2014 ESH practice guidelines for ambulatory blood pressure monitoring report that ABPM should be extended to not only to WCH, but also to suspected

Table 4.4 Primary indications for ambulatory blood pressure monitoring

Suspected white coat hypertension
Apparent drug resistance
Hypotensive symptoms with antihypertensive medications
Episodic hypertension
Autonomic dysfunction
Suspected white coat effect
Suspected masked hypertension, particularly in treated patients

cases of nocturnal hypertension, dipping, to assess 24 h BP, masked controlled and uncontrolled hypertension , and daytime hypertension [47]. These guidelines also highlighted that ABP analysis could be used in any patient who is hypertensive with presence of target organ damage, diabetics, and those who have a family history of CVD [47]. Recently, the National Institute for Health and Clinical Excellence (NICE) updated their guidelines for the management of hypertension to include ABPM as a confirmatory test in patients with an office blood pressure ≥140/90 mmHg, citing ABPM's cost-effectiveness and greater accuracy over HBPM [48]. A 2014 systematic review found that hypertension is inaccurately diagnosed at an exceedingly higher rate when office BP measurements are solely used; they found that studies that required confirmatory testing had better accuracy in diagnosis and concluded that ABPM should be employed as a confirmatory test in instances for which office BP is elevated [49].

White Coat Hypertension

WCH, a well-recognized clinical entity since 1983 [9], is a result of the presser response that patients experience when entering a medical environment. These patients have normal blood pressure outside of the doctor's office during activities of regular daily life. The prevalence has been estimated to be approximately 20 % in untreated borderline and stage I hypertensives [50]. The prognostic significance of this diagnosis has been the subject of considerable debate over the past three decades. Multiple prospective as well as cross-sectional studies have been performed looking at this issue, a large majority of which have shown no significant difference in long-term cardiovascular outcomes in people with WCH versus those with normotension. In one of the initial long-term studies, Verdecchia et al. prospectively followed 1187 subjects from the PIUMA registry for up to 7.5 years [51]. In their study, WCH was defined as an ambulatory daytime blood pressure of <131/86 mmHg for women and <136/87 mmHg for men, and the clinic blood pressure was >140/90 mmHg. No difference was initially observed between the WCH and normotensive groups, although follow-up of this database was later conducted with the use of a larger number ($n = 1500$) of patients [52]. The WCH patients were stratified into two subgroups. The first subgroup had a more restrictive and conservative definition of WCH (daytime ABP <130/80 mmHg), whereas the second

group had more liberal limits for ABP (daytime ABP <131/86 mmHg for women and <136/87 mmHg for men). Cardiovascular morbid events in the first group were similar to the normal BP controls, but event rates in the more liberally defined group were significantly higher than the normotensive population. In the HARVEST trial, 722 hypertensive patients were evaluated using a more restrictive threshold to define WCH [53]. There was a significantly higher left ventricular mass index in the population with WCH (threshold <130/80 mmHg) when compared with the normotensive population (Fig. 4.6). The PAMELA study also showed that patients with WCH have cardiac morphological and functional indices that seem to be intermediate between normals and sustained hypertensives [54]. Given the results of these rather large trials, WCH might be considered a prehypertensive state in some patients. Thus, close monitoring and follow-up is required, and at some point the institution of therapy may be needed. Careful follow-up is necessary even in the 6–8 % of true WCH patients with daytime ABP <130/80 mmHg.

Therapeutic Interventions

Accurate blood pressure measurement is the key step in formulating an effective treatment plan for hypertensive patients. ABPM can be used to assess the need for and effectiveness of both initial and additional antihypertensive therapy. To illustrate this benefit, Staessen et al. conducted a randomized controlled trial evaluating 419 untreated hypertensive patients over a course of approx. 6 months [55]. The

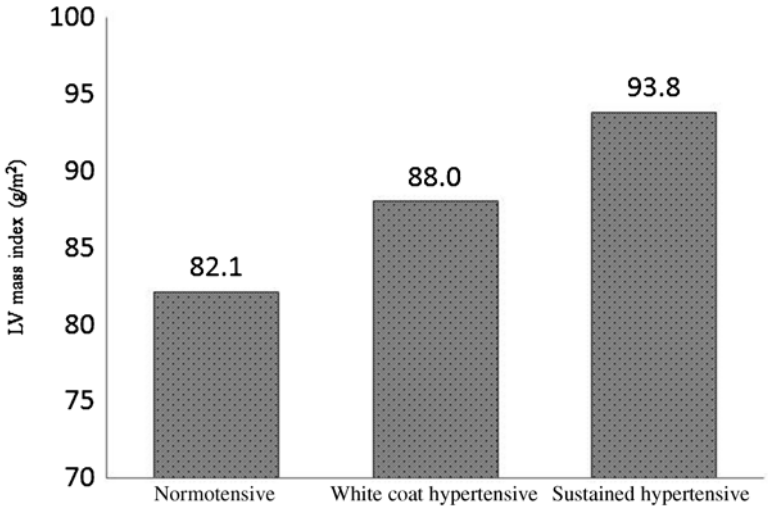

Fig. 4.6 *Bars* show the left ventricular mass in three categories of patients ($n = 722$): normotensives, those with white coat hypertension (threshold <130/80 mmHg), and sustained hypertensives (HARVEST trial) (From ref. [53])

Ambulatory Blood Pressure Monitoring and Treatment of Hypertension (APTH) trial randomized patients to an ABP arm vs. a clinical blood pressure arm.

Drug treatment was adjusted in a stepwise fashion based on daytime ABP readings vs. the average of three clinical measurements. At the end of the study, it was shown that more subjects in the ABP group discontinued antihypertensive drug therapy. Furthermore, fewer subjects in the ABP group had progressed to receive multiple antihypertensive drugs (Fig. 4.7). There were no significant differences in the final blood pressure, left ventricular mass, or reported symptoms between groups. Therefore, ABP monitors can complement conventional approaches in determining optimal medication dosage and frequency of dosing.

Resistant Hypertension

Resistant hypertension has been defined as the failure to achieve goal blood pressure despite strict adherence to near-maximal doses of an appropriate 3- or 4-drug therapy regimen that includes a diuretic [39]. Ambulatory BP monitors have proven useful in the evaluation of those patients who do not appear to be responding to therapy or for those on complicated medication regimens. With data derived from an ABPM, one can ascertain if and at what time additional therapy is needed or if it is needed at all. Mezzetti et al. evaluated 27 subjects with resistant hypertension by ABPM [56]. They observed that more than 50 % of the subjects showed a large white coat effect and were actually normotensive (<135/85 mmHg) on their current

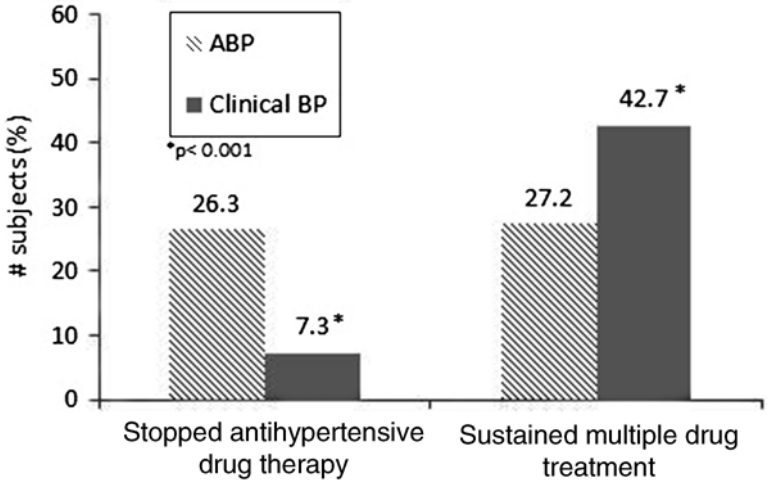

Fig. 4.7 *Bars* depict the percentage of subjects ($n=419$) who stopped antihypertensive therapy and those who sustained multiple-drug therapy with the medication regimen being controlled either by ambulatory blood pressure monitoring results or by clinical measurements (APTH trial) (From ref. [55])

medication regimens. Later, Muxfeldt et al. conducted a cross-sectional study in 286 resistant hypertensives and divided them based on their ABP into a true resistant group (56.3 %) and a white coat resistant group (43.7 %) [57]. The former group was found to have a significantly increased prevalence of both LVH and nephropathy. In a 5-year follow-up study, Pierdomenico et al. found that the cardiovascular event rate was much lower in false resistant patients than true resistant hypertensives (1.2 vs. 4.1 events per 100 patient–year) [58]. Finally, Redon et al. conducted a study in 86 refractory hypertensives over 49 months [59]. These patients were divided into tertiles of average diastolic blood pressure from the ABPM. The office blood pressures were not different among the three groups. It was found that subjects in the highest tertile group (diastolic blood pressure > 97 mmHg) had greater progression of hypertensive end-organ damage compared to the lower two tertile groups. Thus, ABPM was capable of identifying high-, medium-, and low-risk patients with refractory hypertension that was not apparent by office blood pressure measurements alone.

Type of Therapy/Chronotherapeutics

It has been well-documented that a majority of cardiovascular events occur in the morning hours because of a number of inciting hemodynamic, hormonal, and hematological factors. Gosse et al. established in 181 patients that the arising blood pressure correlated with left ventricular mass better than did the office blood pressures [60]. Hence, the higher the early morning blood pressure, the greater the left ventricular mass. The rise in post-awakening morning blood pressure can be obtained best by a 24-h ABP monitoring study. More recently, a prospective study performed in older hypertensives showed a higher incidence of stroke (relative risk = 2.7; $p = 0.04$) in subjects with a morning blood pressure surge after matching for age and 24-h blood pressures [61]. These studies stress the importance of identifying vulnerable subjects and targeting antihypertensive therapy to avoid morning surges of blood pressure.

Orthostatic Hypotension/Autonomic Dysfunction

Individuals with autonomic dysfunction (e.g., diabetics) or orthostatic hypotension tend to lose the normal circadian variation in blood pressure and may even demonstrate an inverse dipping phenomenon (Fig. 4.8).

The Ohasama, Japan, study clearly demonstrated in 1542 subjects that patients with inverse dipping had a significantly worse cardiovascular outcome as compared to the other patient groups (Fig. 4.9) [8]. Generally, there is also considerable variability of blood pressure noted in the inverse-dipping patient population. Patients with inverse dipping may benefit from short-acting medications that can be taken at bedtime to reduce the nighttime blood pressure average. In addition, some complicated patients with idiopathic orthostatic hypotension may be severely hypertensive

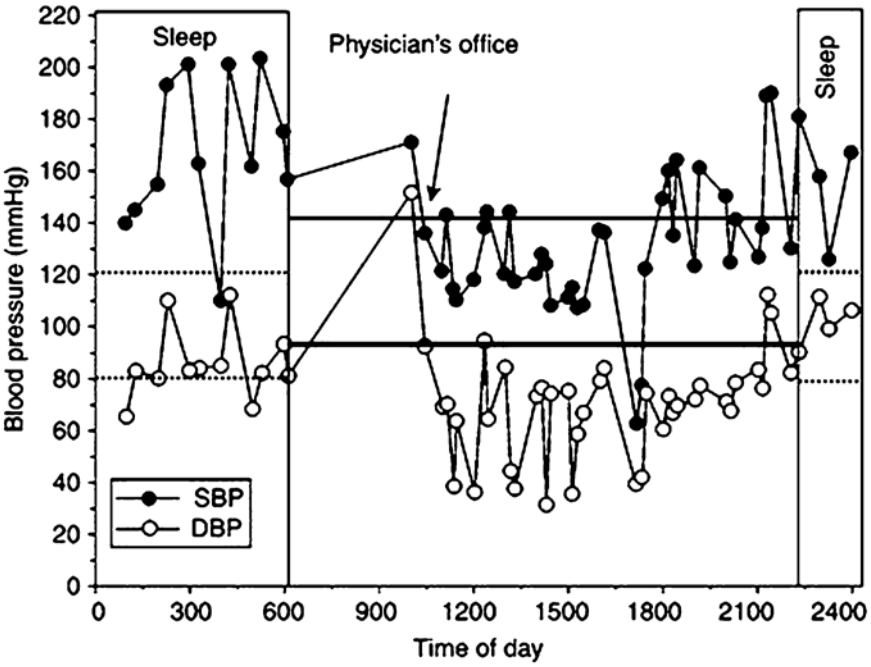

Fig. 4.8 *Plot* showing a 24-h blood pressure curve depicting autonomic dysfunction and inverse dipping. There is significant variability of blood pressure, as seen by the standard deviation. The awake blood pressure average is 132/71 ± 26/23 mmHg, and the sleep average is 164/89 ± 28/15 mmHg. The sleep averages are higher than awake averages, indicating an inverse dipping pattern

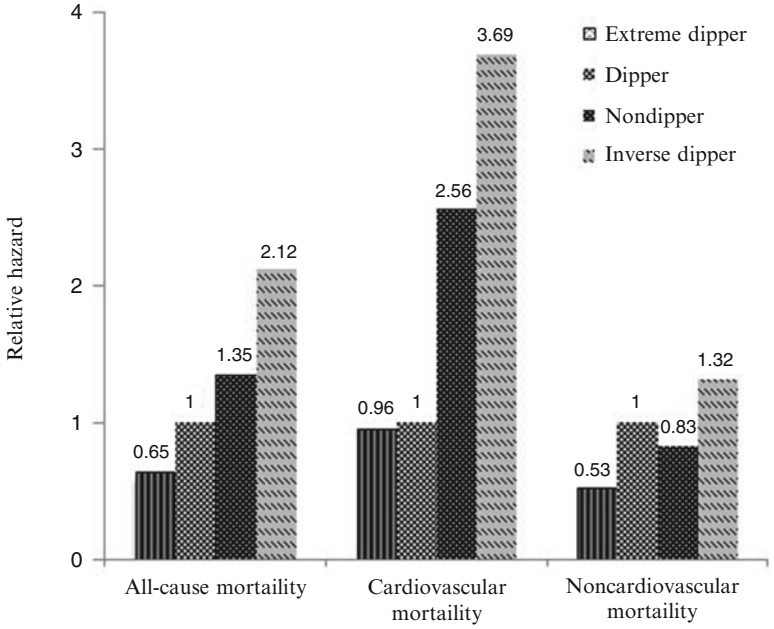

Fig. 4.9 *Bars* show the relative hazard of all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality in four subsets of patients ($n = 1542$): the extreme dipper, the dipper, the non-dipper, and the inverse dipper (From ref. [8])

in the supine position and markedly hypotensive in the upright position. Medication regimens can be tailored individually for these patients by using the detailed blood pressure information obtained via a 24-h ABPM.

Other indications for an ABPM study include evaluation of symptoms and episodic hypertension. With the help of a patient-initiated event button, the physician can determine if the symptoms correlate with either a severely hypertensive (in the case of pheochromocytoma) or hypotensive period (in the case of excessive medication or autonomic dysfunction).

Cost-Effectiveness of ABPM

ABPM studies generally cost $150–400 in the United States. In 2002, a national insurance policy was created by the Centers for Medicare and Medicaid Services to cover 24-h ABPM for "suspected white coat hypertension." The International Classification of Diseases (ICD)-9 code for this diagnosis is somewhat elusive, since it is under a different category than the hypertension codes (transient increases in blood pressure, hypertension nonconfirmed, 796.2). Many private insurance carriers have followed the lead of Medicare and also cover some of the cost of an ambulatory blood pressure monitoring study. Kent et al. looked at ABPM claims submitted between 2007 and 2010 and found that claims that used code 796.2 (International Classification of Diseases, Ninth Revision, diagnosis code) were reimbursed 93.8 % of the time [62].

However, there has been some controversy regarding the cost-effectiveness of ABPM. Moser argued that if 24-h ABPM were to be performed on just 3–5 million of persons with hypertension in the United States, it would add an additional $600 million to $1.75 billion per year to the cost of management [63]. However, the APTH trial [55] performed a cost–benefit analysis of ABPM vs. clinical blood pressure monitoring. They observed that the cost of medication was less for the ABP arm compared to patients who were solely evaluated by office blood pressures ($3390 vs. $4188 per 100 patients per month of therapy). Additionally, the ABP arm required fewer office visits for close blood pressure monitoring, thereby reducing physician fees. The authors concluded that the potential savings in the ABP group were offset by the cost of the study, rendering it equally cost-effective but therapeutically more beneficial. Ambulatory BP guidelines published by the ESH in 2014 suggested that pharmacies equipped with ABP monitors could place these on patients with doctor's referrals reducing the individual financial burden of such monitors on physicians and expanding the availability of such services [47]. In 1994, Yarows et al. from Michigan also conducted a cost-effective study in clinical practice [64]. They followed two sets of patients: the treatment group that had documented hypertension on an ABPM and was given appropriate antihypertensive therapy ($n = 192$) and a diagnostic group that was documented to be hypertensive in the physician's office and was off all antihypertensive therapy ($n = 131$). The diagnostic group had a 24-h ABPM conducted, and the prevalence of WCH in this group was determined to be 34 % (using a 24-h mean diastolic pressure of 85 mmHg) [65].

The authors ascertained the average yearly cost of antihypertensive medications for the 192 hypertensive subjects to be $578.40 (range $94.90–$4361.75). They concluded that in the diagnostic group, the fee for the ABPM ($188) would be offset by the savings for 1 year of antihypertensive therapy (if no medications were used for the WCH patients). In a cost-effectiveness analysis, Krakoff used the most up-to-date information on the prevalence of WCH, probability of WCH transitioning to a sustained hypertension, and the costs of medical care and testing [66]. His analysis predicted savings of 3–14 % in healthcare costs for hypertension when ABP monitoring was routinely used as a diagnostic tool. The annual cost savings calculated for secondary screening using ABPM was also less than 10 % of treatment costs, based on the current reimbursement rates. Hopefully, these types of important analyses [66, 67] will convince the payers as well as clinicians that ambulatory blood pressure monitoring has matured into a useful tool for both the diagnosis and management of many patients with hypertension.

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