

# Manual of Hypertension of the European Society of Hypertension

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Edited by

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# Preface

In the past few decades, hypertension has been the subject of a large number of books and manuals aimed at providing up-to-date reviews of the large amount of experimental and clinical studies performed in the pathogenesis, diagnosis, and treatment of the disease.

More than one year ago, the European Society of Hypertension thought that would it be helpful for both investigators and clinicians to have a manual that approaches the issue in a different fashion, reflecting the authoritative opinion of the Society. The aim of the book, indeed, is not to offer a full and detailed report on the

several pathogenetic and pathophysiological data collected in these years, but rather to focus on emerging new concepts that could affect the diagnostic and therapeutic approach of the disease.

This *Manual* has been made possible with the endeavouring help of many colleagues and friends who are eminent members of the European Society of Hypertension and are recognized world-wide as leading experts in their different areas of hypertension. We hope that the *Manual* will be regarded as an useful enterprise, continuing the high tradition of the European Society of Hypertension.

*Giuseppe Mancia*

*Guido Grassi*

*Sverre E. Kjeldsen*

# ASSESSMENT OF THE CIRCADIAN CARDIOVASCULAR RISK WITH AMBULATORY BLOOD PRESSURE MEASUREMENT

## 7

*Eoin O'Brien*

### INTRODUCTION

In this chapter, I review the evidence that ambulatory blood pressure measurement (ABPM) can provide a means of assessing circadian cardiovascular risk. I will not attempt to review the circadian risk from the biochemical, hormonal, and thrombotic viewpoints other than to acknowledge that there is considerable harmony in the physiological, hemodynamic adjustments that occur during each 24-h cycle, and to indicate at the outset that what may be measurable with ABPM may well be the effect of changes in other hemorheological mechanisms that are orchestrated to cope with the vast variation in activity and circumstance that characterizes human behavior during a 24-h period.

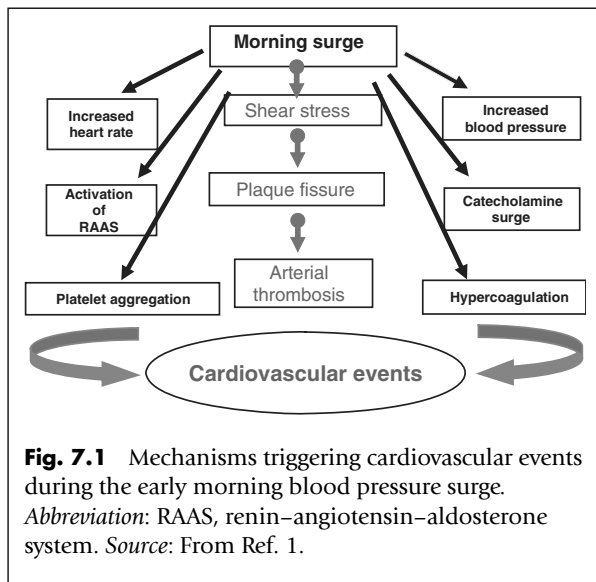
### THE CIRCADIAN RHYTHM OF THE CARDIOVASCULAR SYSTEM

While this review is confined to assessing the role of ABPM in circadian risk, it is important to acknowledge the complex associated perturbations that characterize the 24-h period. The subject has been well reviewed by Giles (1,2). The occurrence of several life-threatening acute cardiovascular events tend to peak at certain times of the day. For example, acute myocardial infarction, ischemic events, sudden cardiac death, and stroke are more likely to occur in the morning hours, soon after waking, than at other times of the day (3). An excess of cardiovascular events associated with circadian changes in blood pressure (BP), for example the morning surge, non-dipping, or excessive dipping, may be explained, or are at least associated with, circadian variations of various biochemical and physiological parameters. In other words, circadian variations in BP serve as sensitive indicators of a cascade of physiological events that include increased sympathetic and plasma rennin activity (4,5), leading to increased levels of angiotensin II (6), catecholamines, and cortisol (7), all of which may forecast

acute cardiovascular catastrophes. Increased myocardial oxygen demand in response to physical activity, and simultaneous increases in platelet aggregability and blood viscosity leading to an early morning hypercoagulable state further facilitate thromboembolism (8). As Giles has pointed out, it is not difficult to envisage these changes together with a morning surge in BP and enhanced platelet aggregation, thrombosis, and occlusion, culminating in shear stress and the fissure of unstable atherosclerotic plaques, leading to acute myocardial infarction, ischemic stroke, and sudden cardiac death (1) (Figure 7.1). Another example of BP being the reflecting mirror of complex biochemical circadian variation is the association of a nocturnal non-dipping pattern in hypertensive subjects prone to retaining sodium (9). The nocturnal consequences of altered BP patterns have been largely ignored in clinical practice because the methodology for assessing nocturnal profiles of BP—24-h ABPM—has been accepted only slowly in clinical practice, or used only sparingly for recording BP at night.

### MEASUREMENT OF BP AND RISK

The most commonly used method of BP measurement in clinical practice is the auscultation method with a mercury sphygmomanometer and stethoscope. This conventional technique undoubtedly provides information on cardiovascular risk. A meta-analysis of clinic BP measurement in 1 million adults participating in 61 prospective studies showed that a 10 mmHg higher usual systolic BP or 5 mmHg higher usual diastolic BP would be associated with approximately 40% higher risk of stroke death and around 30% higher risk of death from ischemic heart disease and other vascular causes (10). The technique, however, has many limitations, which include the presence of a white coat reaction, interobserver and intraobserver variability, and terminal digit preferences, all of which may bias the accuracy of measurement (11,12). Moreover, conventional sphygmomanometry as employed in clinical



practice fails to give any information on circadian risk. Interestingly though, efforts to improve the prognostic value of the technique and to gain insight into circadian effects were made in the first half of the 20th century. In 1922, Addis, recognizing the extreme variability of BP, endeavored to minimize this by obtaining BP measurements in the morning after awakening but before rising, and he termed this basal BP (13). Sir Horace Smirk developed this concept further in a series of experiments in which he measured BP under very standardized conditions in sedated hypertensive patients and normotensive controls. The lowest BP obtained by this technique was called the "basal BP" in contrast to conventionally measured BP in the hospital, which he termed "casual BP," with the difference between the two being called "supplemental BP." In health, the basal BP was found to be practically a physiological constant, but in hypertensive patients the basal BP, while more variable than in normotensive subjects, was much less variable than the casual BP. He showed that basal BP was a much better guide to

prognosis than casual pressures, and he likened basal BP to sleeping BP (14,15). Smirk's remarkable contribution, which has largely been overlooked in recent years, has been restored to historical probity by Pickering (16) and contributes to further reasoning in this review.

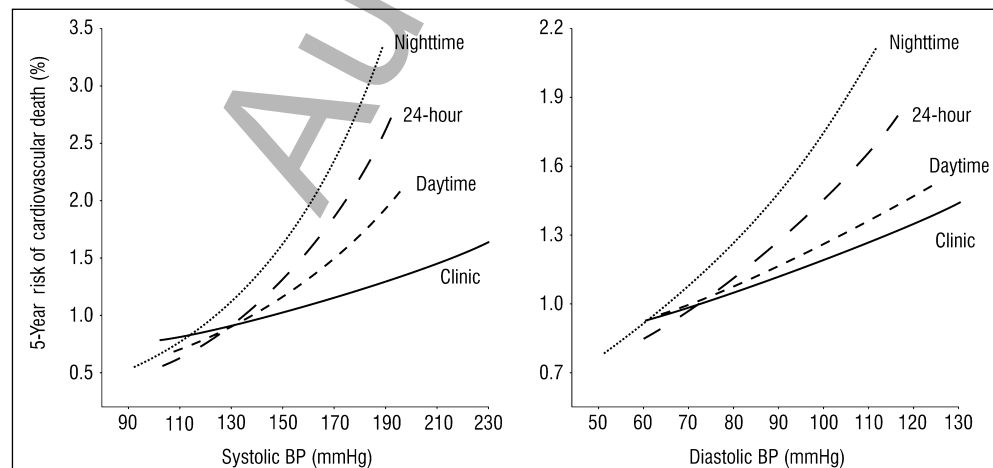
Self BP measurement also provides information on risk, but again is limited in the information it can provide on circadian risk, mainly because nocturnal BP measurements are not available (17). Recently, however, Imai and colleagues have modified a device for self-measurement of BP to provide nocturnal BP measurements (18). As technology develops and the cost of automated devices reduces, the day cannot be too far distant when BP measuring devices will provide the user with the facility to measure casual BPs, pressures at home or at work, and to perform intermittent measurements over a 24-h or longer period of time—effectively, a "device for all seasons."

At present, however, ABPM is the only technique that permits close examination of the circadian profile and identification of patterns that may be associated with risk. There is now general agreement that ABPM is indispensable to good clinical practice (12) and there is indisputable evidence showing that ambulatory BP is superior to office values in predicting cardiovascular risk (19–25). Moreover, recent evidence suggests that nighttime BP may be the most sensitive predictor of all measurements (26–29) (Figure 7.2).

## INDICES OF RISK IN THE CIRCADIAN PROFILE

### SYSTOLIC VERSUS DIASTOLIC BP

In Western countries, systolic BP is a stronger predictor of cardiovascular risk than diastolic BP in the majority of the adult population. This greater risk is attributable, at least in part, to systolic BP levels being more directly related to cardiovascular complications, a greater prevalence of systolic hypertension in older patients, and systolic hypertension being more resistant to treatment (30). However, the relative



**Fig. 7.2** Adjusted 5-year risk of cardiovascular death in the study cohort of 5,292 patients for clinic and ambulatory blood pressure (BP) monitoring. Using multiple Cox regression, the relative risk was calculated with adjustment for baseline characteristics, including gender, age, presence of diabetes mellitus, history of cardiovascular events, and smoking status. The 5-year risks are expressed as number of deaths per 100 subjects. Source: From Ref. 26.

## 50 Assessment of the circadian cardiovascular risk with ABPM

risk of systolic versus diastolic BP is age related. In the Framingham Heart Study, diastolic BP was a better predictor of coronary heart disease for participants aged less than 50 years of age: between the ages of 50 and 59 years, diastolic and systolic BP assume comparable risk; and after the age of 60 years, the risk of coronary heart disease remains positively correlated with systolic BP, but is inversely related to diastolic BP (31). Similar findings have been reported in a Japanese population (32). In the Dublin Outcome Study, systolic 24-h ABPMs predicted outcome more sensitively than diastolic BP in a population whose average age was 60 years, with nighttime systolic BP being the strongest predictor of outcome—for each 10 mmHg increase in mean nighttime systolic BP, the mortality risk increased by 21% (26).

### PULSE PRESSURE AND MEAN PRESSURE

Pulse pressure is an established cardiovascular risk factor (33,34). It has been shown that in a large sample of subjects with predominantly systolic and diastolic hypertension whose age spanned eight decades, the risk of cardiac complications of elevated BP showed a strong, positive, and independent association with its pulsatile component (pulse pressure) but not with its steady component (mean BP), whereas the risk of cerebrovascular complications showed a similarly strong, positive, and independent association with its steady component but not with its pulsatile component. Moreover, these associations persisted after adjustment for the significant influence of numerous risk factors (33). These findings suggest that elevated peripheral vascular resistance appears to be more damaging to the brain, and that increased large artery stiffness appears to be more damaging to the heart in middle-aged individuals with hypertension. In the Ohasama Study, the predictive power of four indices of ABPM—systolic, diastolic, mean, and pulse pressure—were assessed; ambulatory pulse pressure was the weakest predictor of stroke, but exclusion of age from covariates increased its predictive power, suggesting that the stroke risk of pulse pressure was a reflection of aging per se (35).

### AMBULATORY ARTERIAL STIFFNESS INDEX

Recently, a new index has been derived from ABPM. The ambulatory arterial stiffness index (AASI), defined as 1 minus the regression slope, a measure of the dynamic relationship between diastolic and systolic BP throughout the whole day, has been shown to predict cardiovascular mortality in a large cohort of hypertensive individuals (34). To date, one cross-sectional analysis (36) and three prospective cohort studies (34,37,38) have demonstrated an association of AASI either with signs of target organ damage in never-treated hypertensive patients or with the incidence of cardiovascular mortality and morbidity (36).

The AASI is particularly predictive of stroke (34,37,38), even at levels of BP within the normotensive range (34,38). Moreover, when adjusted for pulse pressure, AASI retains its predictive value (34,37,38). Currently ongoing analyses of a Copenhagen cohort have shown that AASI predicts stroke over and beyond aortic pulse wave velocity (39). AASI may therefore prove to be a readily applicable index that can be derived from a routine ABPM to predict outcome. The practical importance of such an index is that it may permit

early categorization of hypertensive patients into those at risk from cardiovascular events and, thus, indicate those in need of aggressive BP lowering.

### BP VARIABILITY

Many indices of BP variability can be derived from 24-h ABPM (40–42). BP variability is undoubtedly an important determinant of target-organ damage and of higher cardiovascular risk in hypertension, and smooth 24-h control of BP with antihypertensive drugs should be given consideration as a means of improving prognosis (40,41). However, in patients with uncomplicated mild hypertension, BP variability assessed by noninvasive ABPM was not an independent predictor of cardiovascular outcome (42).

### HEART RATE

As heart rate is readily obtainable from ABPM, it has the potential to add another dimension to the assessment of risk. Several epidemiological studies have shown an association between heart rate and both cardiovascular and non-cardiovascular mortality. Heart rate is inversely proportional to life expectancy, and an elevated heart rate is a risk factor for hypertension, atherosclerosis, and cardiovascular morbidity and mortality (43). The relationship between resting heart rate and mortality has been observed in the general population and in patients with hypertension, coronary artery disease, and after acute myocardial infarction (43). In most of these studies, clinic measurements of heart rate have been used to investigate the association with cardiovascular risk. A consensus meeting of the European Society of Hypertension to provide recommendations on the influence and management of heart rate in clinical practice concluded that there was no available evidence demonstrating an advantage of heart rate measured out-of-office over clinical heart rate, but was of the opinion that, for hypertensive subjects who monitor their BP at home with automatic devices, the reporting of heart rate data together with BP may provide useful information (44). An ongoing analysis of the data in the Dublin Outcome Study confirms that ambulatory heart rate predicts mortality risk. In particular, nighttime heart rate, as is the case with nocturnal BP, is the strongest predictor of outcome. In keeping with previous studies, an increased heart rate also predicted non-cardiovascular deaths, suggesting that an increased heart rate is a nonspecific marker for all-cause mortality (43).

Several complex statistical and chronobiological methods have been proposed for the analysis of circadian BP recordings (45). Cusum-derived statistics are simply calculated from ambulatory data but have never gained popularity in clinical or research practice (45).

### WINDOWS OF THE 24-H CIRCADIAN PROFILE

The predictive value of ABPM, and its superiority to office BP measurements, has been demonstrated in prospective studies, which have been well summarized by Giles (1,2). This being so, it is of interest to look more closely at the information that may be derived from 24-h ABPM recordings. The 24-h period

can be divided into a number of windows, each of which yields information about BP change, and each of which provide patterns of BP behavior that may be associated with varying risk. The dabl® ABPM program (dabl Ltd., Blackrock, County Dublin, Ireland) has been designed to allow demarcation of these windows and separate or combined statistical analyses to be performed on the BPs within these windows (46–48) (Figure 7.3).

### WHITE COAT WINDOW

The white coat window is the window that extends from the beginning of ABPM recording and lasts for 1 h. Ideally, ABPM recording should begin no later than 9 AM, but, when this is not possible, the dabl® ABPM program adjusts for a later time for ABPM recording to commence (48). During the white coat window, BP may be influenced by the medical environment. The most popular definition of white coat hypertension is that BP measured by conventional techniques in the office, clinic, or surgery exceeds 140 mmHg systolic or 90 mmHg diastolic, but, when ABPM is performed, the average BP is less than 135 mmHg systolic and 85 mmHg diastolic during the daytime period. Currently, an average daytime ABPM of less than 135 mmHg systolic and 85 mmHg diastolic is generally considered normal and levels less than 130/80 mmHg are considered optimal (49). However, it has been shown that the white coat window on ABPM recordings can not only diagnose the white coat phenomenon, but also allows identification of a white coat hypertensive subgroup, with significantly higher pressures, who may be at greater risk and in need of antihypertensive medication (47). ABPM remains the method of choice for diagnosing white coat hypertension (25,47,50).

### DAYTIME WINDOW

The daytime window follows the white coat window and is the period when the subject is away from the medical

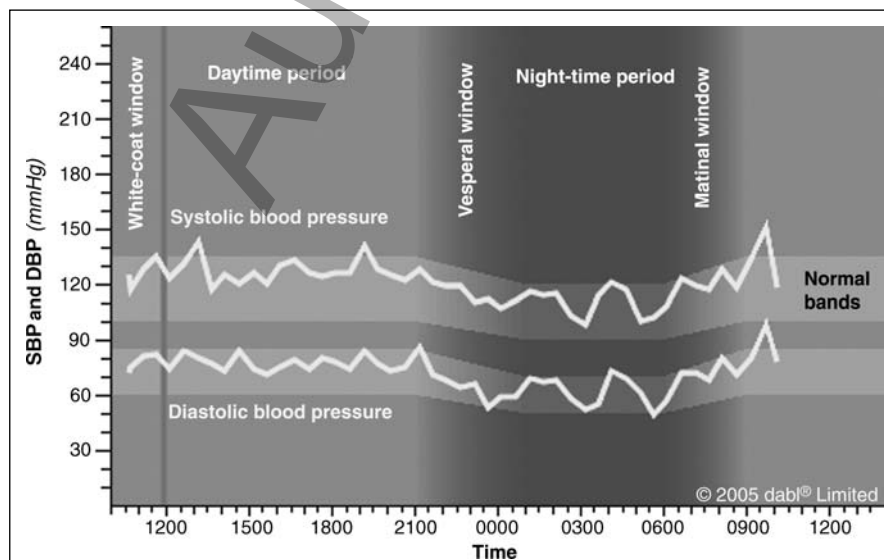
environment and engaging in usual activities (47). For almost all subjects with hypertension, BPs during this window are lower than conventionally recorded pressures in the office, clinic, or surgery setting (50,51). However, BPs during this period are subject to stress, activity, arm movement, the effect of exercise, and other activities, such as driving, all of which may have an influence on the mean level of BP recorded (52). These effects are largely absent from BP measured during the nocturnal period (26,53).

### VESPERAL WINDOW

In the normal individual there is a decline in BP in the vesperal window from daytime levels of BP to reach a plateau during the nighttime period. This period (9:01 PM to 0:59 AM on the basis of ABPM commencing at 9 AM) is not included in the estimation of day and night mean pressures because this period represents time during which bed rest is inconsistent and, therefore, cannot be categorized reliably (54). In hypertensive patients (or some normotensive patients with cardiovascular disease) the decline in the vesperal window may be absent (non-dipping) so that BPs do not reach basal levels (26,27,55,56). BP may even rise in the vesperal window to reach levels that are higher than daytime levels (reverse dipping) (57). Alternatively there may be a marked fall in BP during the vesperal window to give the phenomenon of extreme dipping (58). Therefore, what happens to BP in the vesperal window predicates the level of BP in the basal window.

### BASAL WINDOW

The nighttime window follows the vesperal window and is the period between 1:00 AM and 6:00 AM (47). BPs in this window are most likely to coincide with sleep or, if not with actual sleep, with the greatest cessation of activity and are likely, therefore, to represent a steady state (46). I have



**Fig. 7.3** Schema of ambulatory blood pressure. *Abbreviations:* DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source:* Plot generated by dabl ABPM, 2006 (<http://www.dabl.ie>).

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applied the term “basal” to this window in acknowledgement of the seminal paper written by Horace Smirk in 1964 (15). As previously outlined, the compelling conclusion from Smirk’s analysis was that basal BP was superior to casual pressure in predicting outcome (14,15). This evidence is very similar to recent evidence from my department (26) and others (56), showing that nighttime BP is superior to all other BP measurements in predicting cardiovascular outcome and mortality, which suggests that nighttime BP obtained by ABPM is similar to the basal BP described by Smirk. Moreover, it has also been shown that the use of a mild sedative during ABPM may help in identifying patients with a very high cardiovascular risk; namely, those patients who continue to manifest a blunted nocturnal dip despite sedation (59).

Valuable though the information derived from the basal window may be, there are a number of methodological limitations to recording BP at night. These include different criteria for defining dipping/non-dipping status, arbitrary dichotomization of a continuous and variable measurement (night-to-day ratio), inappropriate selection of cases (non-dippers) and controls (dippers), insufficient sample size, poor reproducibility of the night-to-day ratio, a “regression-to-the-mean” phenomenon when ABPMs are repeated in subjects classified as extreme dippers or non-dippers on the first ambulatory recording, the influence of daytime physical activity on the dipping phenomenon (27,60), and the influence of sleep disturbance and sleep apnea (53,60). Ironically, despite doubts about reproducibility of the night-to-day ratio, it may be that nighttime BP is more standardized and consequently more reproducible than daytime BP (sleep being a more stable state than activity), and that it is this feature that gives nocturnal BP its predictive value. In clinical practice when the sleep and awakening periods are clearly defined, nocturnal changes in BP are surprisingly reproducible (61,62).

### MATINAL WINDOW

The matinal window extends from the end of the basal window to the commencement of daytime activities following rising. This period (6:01 AM to 8:59 AM) is not included in the estimation of day and night mean pressures because this period represents time during which bed rest is inconsistent and, therefore, cannot be categorized reliably (54). However, the magnitude of the rise in BP in the matinal window may yield most valuable prognostic information. In normal subjects, a modest rise in BP occurs in the matinal window, preceding awakening from sleep to merely restore the previous daytime level of BP (46). This pre-awakening rise in BP in hypertensive patients may exceed the daytime average—the pre-awakening or morning surge—and this phenomenon is associated with a poor cardiovascular outcome (58).

### PATTERNS OF ABPM

Within the windows of the 24-h BP profile, several variations of BP behavior may be discerned, allowing differentiation of patients into sub-forms and patterns (25,63–65). ABPM may also be used to stage the severity of BP—the higher the initial

24-h ABPM, the more frequent the occurrence of cardiovascular events (19). The most commonly used aggregate to denote levels of ABPM is the mean 24-h BP (25). However, though this may be an acceptable estimate of the BP load over the 24-h period, the information deriving from individual windows of the 24-h profile is such that critical consideration has to be given to the association of ABPM patterns with cardiovascular outcome (Figure 7.4).

### WHITE COAT HYPERTENSION

The risk associated with white coat hypertension remains controversial but there is general agreement that the condition should not be regarded as benign, with the risk of developing sustained hypertension at some time being almost inevitable (66,67) (Figure 7.5).

### WHITE COAT EFFECT

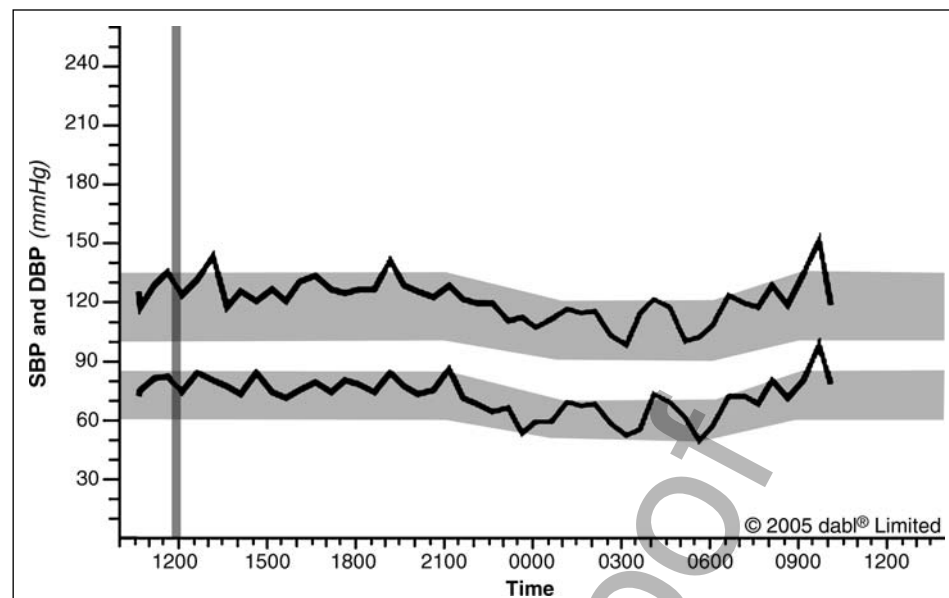
White coat hypertension must be distinguished from the white coat effect, which is the term used to describe the increase in BP that occurs in the medical environment, regardless of the daytime ABPM. In other words, the term indicates the phenomenon, found in most hypertensive patients, whereby clinic BP is usually greater than the average daytime ABPM, which is nonetheless increased above normal. The importance of the phenomenon is that patients diagnosed as having severe hypertension by conventional measurements may have only moderate or mild hypertension on ABPM because of a marked white coat effect (65) (Figure 7.6).

### MASKED HYPERTENSION

This phenomenon denotes subjects classified as normotensive by conventional office or clinic measurement, but who are hypertensive with ABPM or self-measurement. The prevalence of masked hypertension in adults seems to be at least 10%, and may indeed be higher, with a tendency to decrease with age. Adult subjects with masked hypertension have increased target organ involvement as denoted by left ventricular mass and carotid atherosclerosis. As might be expected when target organ involvement is increased, the likelihood that cardiovascular morbidity will also be greater is indeed the case. The logical extension of this line of reasoning is that future studies will also show cardiovascular mortality to be increased. The problem for clinical practice is how to identify and manage these patients who, it is estimated, may number as many as 10 million people in the United States (23,65).

### AMBULATORY HYPOTENSION

Hypotension is particularly common in the elderly, who may have autonomic or baroreceptor failure, and who may also experience post-prandial and postural hypotension—conditions which may lead to risk from falls and accidents. ABPM may also be useful in identifying hypotensive episodes

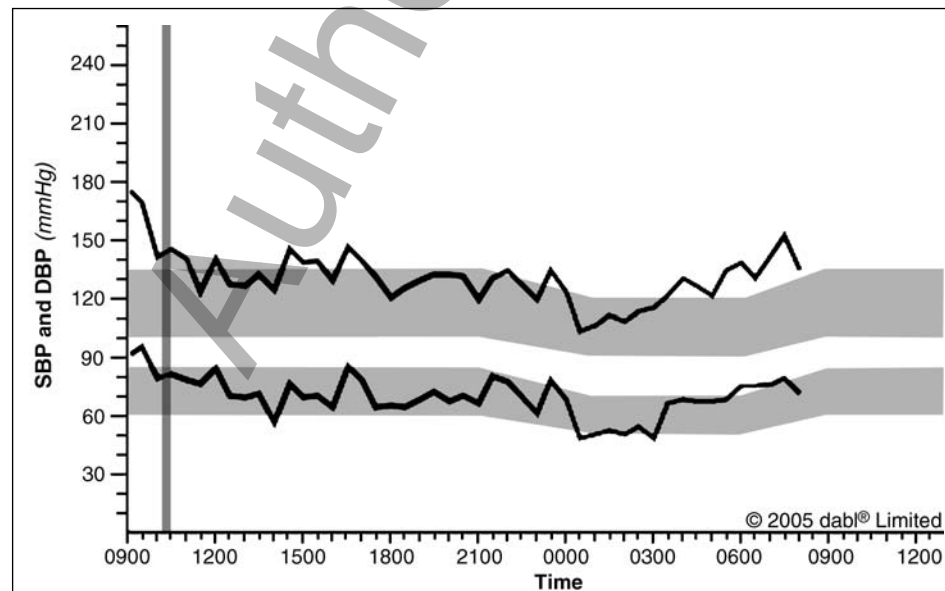


**Fig. 7.4** Normal ambulatory blood pressure monitoring (ABPM) pattern. On the basis of the data recorded and the available literature, the ABPM pattern suggests normal 24-h SBP and DBP (128/78 mmHg daytime, 110/62 mmHg nighttime). *Abbreviations:* DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source:* Plot and report generated by dabl ABPM, 2006 (<http://www.dabl.ie>).

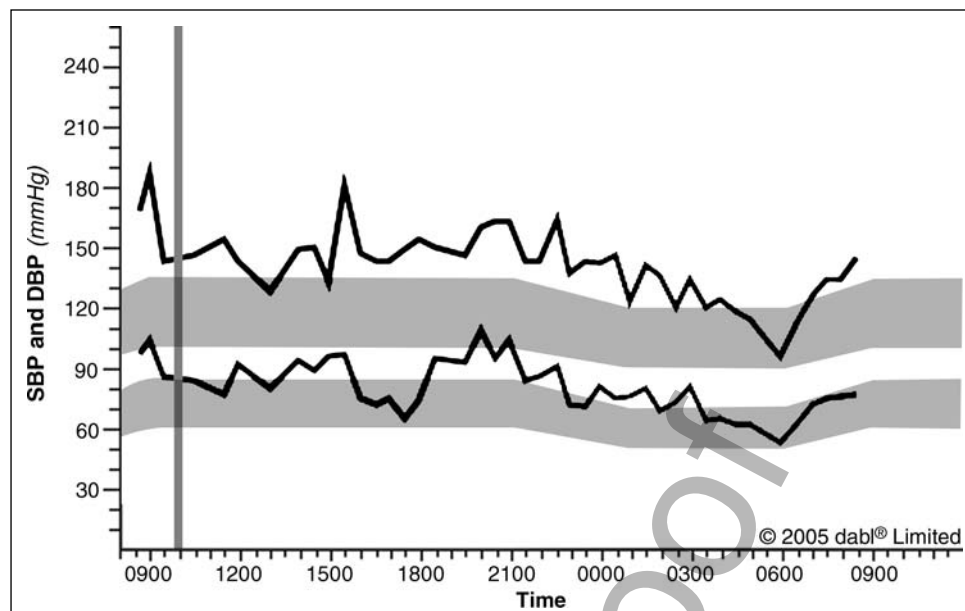
in young patients in whom hypotension is suspected of causing symptoms (23,25,65). In treated hypertensive patients, ABPM may also demonstrate drug-induced decreases in BP that may have untoward effects in those with a compromised arterial circulation, such as individuals with coronary and cerebrovascular disease (68) (Figure 7.7).

#### DAYTIME SYSTO-DIASTOLIC HYPERTENSION

Many patterns of BP behavior can be discerned from ABPM, but by far the most common pattern is systo-diastolic hypertension (63). Usually, daytime BP levels are lower than clinic



**Fig. 7.5** White coat hypertension. On the basis of the data recorded and the available literature, the ambulatory blood pressure monitoring pattern suggests white coat hypertension (175/95 mmHg) with otherwise normal 24-h SBP and DBP (133/71 mmHg daytime, 119/59 mmHg nighttime). *Abbreviations:* DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source:* Plot and report generated by dabl ABPM, 2006 (<http://www.dabl.ie>).



**Fig. 7.6** White coat effect. On the basis of the data recorded and the available literature, the pattern suggests mild daytime systolic hypertension (149 mmHg), borderline daytime diastolic hypertension (87 mmHg), borderline nighttime systolic hypertension (121 mmHg), and normal nighttime diastolic hypertension (67 mmHg) with white coat effect (187/104 mmHg). Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. Source: Plot and report generated by dabl ABPM, 2006 (<http://www.dabl.ie>).

readings—the white coat effect. Generally, mean daytime levels of BP are superior to clinic BPs but inferior to nocturnal BP in predicting outcome (26,68,69).

### ISOLATED SYSTOLIC HYPERTENSION

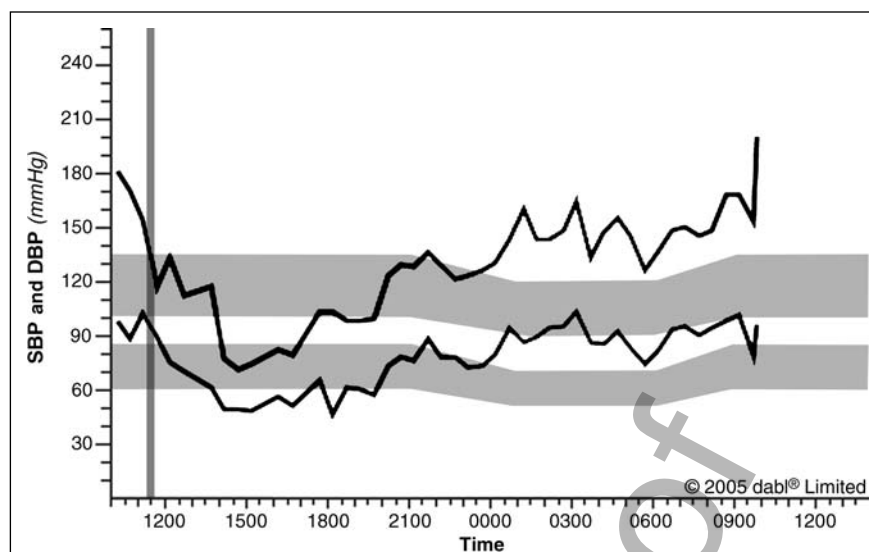
Isolated systolic hypertension can, of course, be apparent on clinic BP measurement, but it can be overestimated, and ABPM allows for confirmation of the diagnosis, as well as predicting outcome more accurately. The results of the ABPM sub-study of the Systolic Hypertension in Europe Trial showed that systolic BP measured conventionally in the elderly may average 20 mmHg more than daytime ABPM, thereby leading to inevitable overestimation of isolated systolic hypertension in the elderly and probable excessive treatment of the condition. Moreover, results from this study also show that systolic ABPM was a significant predictor of cardiovascular risk over and above conventional systolic BP (70). In women with cardiovascular disease, systolic BP was the BP measure most strongly related to the risk of secondary cardiovascular events (71) (Figure 7.8).

### ISOLATED DIASTOLIC HYPERTENSION

Isolated diastolic hypertension, which can be present on clinic measurement, can be more readily studied on ABPM. The prevalence of the condition in one study was 3.6% (63). There are few studies to date on the prognostic relevance of the condition, but the consensus from a review of the literature is that, if the systolic BP is normal, high diastolic BP is not associated with an adverse prognosis (72).

### DIPPING AND NON-DIPPING

The “dipper/non-dipper” classification was first introduced in 1988, when a retrospective analysis suggested that non-dipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern (55). Whether this classification is associated with adverse outcome has been the subject of much debate (60). On balance, most large-scale prospective studies currently support the concept that a diminished nocturnal BP fall is associated with a worse prognosis (25,27). For example, blunted nighttime dipping of BP is independently associated with angiographic coronary artery stenosis in men (73). In elderly people with long-standing hypertension, a blunted nocturnal dip in BP is independently associated with lower cognitive performances (74). Among elderly patients with recently diagnosed isolated systolic hypertension, those with a non-dipping nocturnal pattern have been shown to have significantly higher left ventricular masses on echocardiography than dippers (75). A non-dipping nocturnal pattern is also associated with renal and cardiac target organ involvement (76). It has been well documented that, in hypertensive subjects, non-dippers are more likely than dippers to suffer silent, as well as overt, hypertensive target organ damage. However, it has also been demonstrated that a non-dipper status is associated with target organ damage in normotensive subjects (76). Moreover, nocturnal BP is now known to be an independent risk for cardiovascular outcome over and above all other measures of BP (26,28). For example, in the Dublin Outcome Study, for each 10 mmHg increase in mean nighttime systolic BP, the mortality risk increased by 21% (26). In a Japanese population, a diminished nocturnal decline in BP was an independent risk factor for cardiovascular mortality, with each 5% decrease in the decline in nocturnal



**Fig. 7.7** Ambulatory hypotension. On the basis of recorded data and available literature, ambulatory blood pressure monitoring pattern suggests low daytime SBP (100 mmHg), normal daytime DBP (61 mmHg), and moderate night-time systolic and diastolic hypertension (146/89 mmHg) with white coat effect (200/102 mmHg). *Abbreviations:* DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source:* Plot and report generated by dabl ABPM, 2006 (<http://www.dabl.ie>).

systolic/diastolic BP being associated with an approximately 20% greater risk of cardiovascular mortality (28).

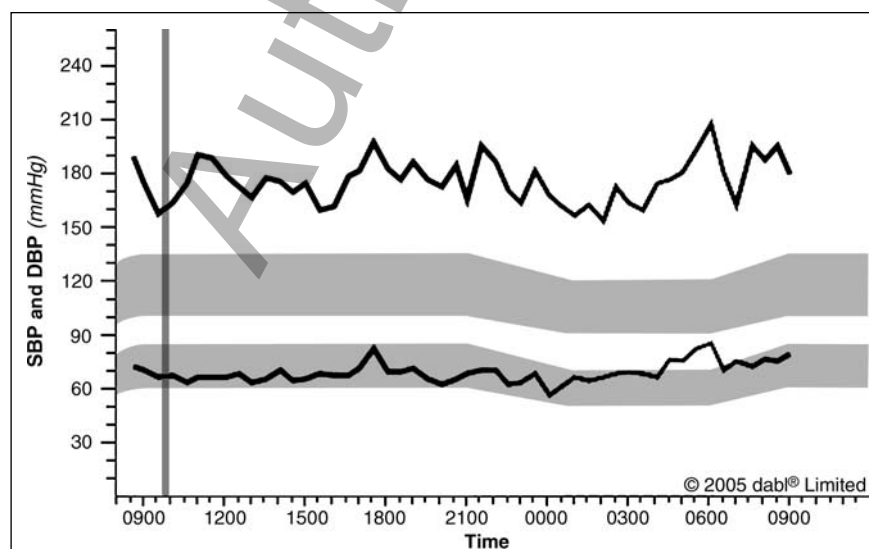
cardiovascular prognosis, both for stroke and cardiac events (77) (Figures 7.9 and 7.10).

## REVERSE DIPPING

In some patients, BP rises above the daytime pressures rather than falling during the night. These patients (also referred to as risers or extreme non-dippers) have the worst

## EXTREME DIPPING

Patients with a marked nocturnal fall in BP, known as extreme dippers, are at risk for non-fatal ischemic stroke and silent myocardial ischemia. This is particularly likely in extreme



**Fig. 7.8** Isolated systolic hypertension. On the basis of recorded data and available literature, the pattern suggests severe 24-h isolated systolic hypertension (176/68 mmHg daytime, 169/70 mmHg nighttime). *Abbreviations:* DBP, diastolic blood pressure; SBP, systolic blood pressure. *Source:* Plot and report generated by dabl ABPM, 2006 (<http://www.dabl.ie>).

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dippers who already have atherosclerotic arterial stenosis, and in whom excessive BP reduction is induced by injudicious antihypertensive medication (77). This possibility was originally enunciated by Floras, as long ago as 1988, when he postulated that patients with critical coronary stenoses or hypertrophied ventricles could have impaired coronary vasodilator reserve and would, therefore, be at greatest risk of myocardial ischemia or infarction if subendocardial perfusion pressure fell below the lower threshold of blood flow autoregulation. This was most likely to occur during sleep, when excessive antihypertensive treatment might cause unrecognized nocturnal hypotension leading to coronary artery hypoperfusion, thereby offering an explanation why treatment had not diminished the risk of myocardial infarction in patients with hypertension (78). Extreme dipping is closely associated with an excessive morning surge in BP, which is associated with cerebral infarction and a high risk of future stroke (77).

### SIESTA DIPPING

A siesta dip in BP on ABPM is common in societies in which an afternoon siesta is an established practice. But, in many elderly patients, regardless of cultural practice, a siesta is often a part of the daily routine. There is evidence that ignoring the dipping pattern associated with a siesta distorts the day/night ratio of ABPM (79,80), and it should therefore be taken into account in assessing overall 24-h circadian patterns. The magnitude of the siesta dip may have prognostic implications, though the evidence to date is scarce (81).

### NOCTURNAL HYPERTENSION

Although daytime ambulatory hypertension is a good predictor of outcome, a number of studies have shown that ambulatory nocturnal hypertension is associated with a worse cardiovascular outcome (26,28,82). Further confirmation of the importance of nocturnal hypertension comes from a recent study showing that a non-dipping pattern and increased nighttime diastolic BP predicted the occurrence of congestive heart failure independently of antihypertensive treatment and established risk factors for cardiac failure. Furthermore, this association was present even after adjusting for office BP measurement, thereby showing that ABPM once again conveys important information that cannot be obtained with conventional measurement (83).

### THE MORNING SURGE

Cardiovascular events, such as myocardial infarction, ischemia, and stroke, are more frequent in the morning hours soon after waking than at other times of day (1). Circadian variations in biochemical and physiological parameters help explain the link between acute cardiovascular events and the early morning BP surge (1,2). The clinical consequences of these hemodynamic and neurohumoral changes are numerous. Transient myocardial ischemia and peak ischemic activity has been documented. The occurrence of stroke and heart attack is commoner in this period than at any other time of the day (2). Kario et al. have shown that, in older

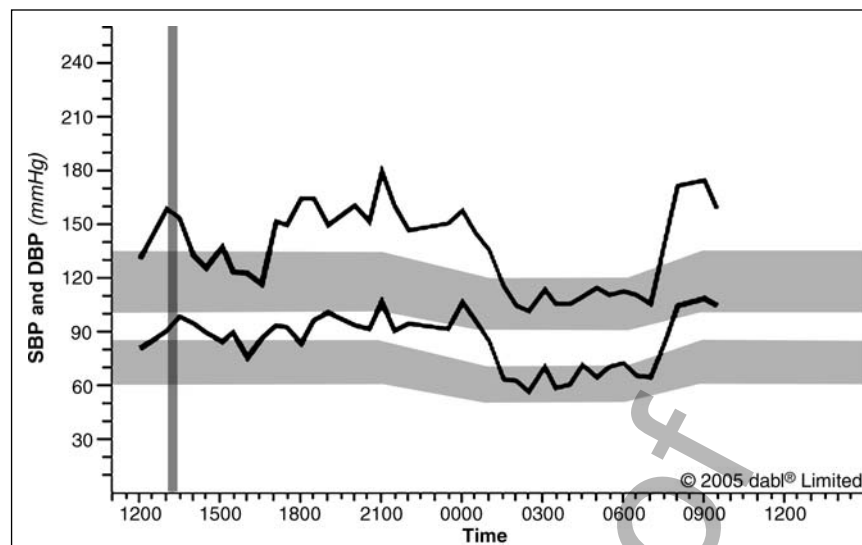
hypertensive subjects, a morning surge in BP—defined as a rise in BP greater than 55 mmHg from the lowest nighttime reading—carries a risk of stroke almost three times that seen in patients without a morning surge. A pattern of morning surge in BP was also associated with the presence of more clinically silent cerebral infarction (84). Higher carotid internal-medial thickness and circulating inflammatory markers coexist in hypertensive patients with morning BP surge, and might contribute to the increased cardiovascular risk in these patients (85).

### CAN DRUGS BE TARGETED TO REDUCE BP IN CIRCADIAN PERIODS OF GREATEST RISK?

Traditionally BP lowering drugs are taken in the morning, but the scientific rationale for the timing of medication may not always be based on sound evidence. It is surprising how little attention has been given to the possibility of achieving a more beneficial effect on cardiovascular outcome by reducing nocturnal BP, either by nighttime dosing, or by designing drugs specifically to reduce nocturnal BP (24). The practice of morning dosing of medication may have had more to do with the practice of conducting antihypertensive drug trials at morning clinics and being able to make an assessment of efficacy based on BP effect some hours after dosing than with scientific evidence based on the pharmacodynamic realities of the drug under study. This lapse in scientific reasoning was well illustrated in the Heart Outcomes Prevention Evaluation (HOPE) study (86). In the main study, the group receiving ramipril had an approximately 35% reduction in cardiovascular events, despite an insignificant reduction in BP of 3/2 mmHg; the outcome benefit was attributed to angiotensin-converting enzyme (ACE) inhibition, which was recommended in all high-risk patients regardless of baseline BP. However, it became evident from later analysis of an ABPM sub-study that ramipril was actually taken in the evening, with outpatient BP measured the following day, some 10–14 h later (87). The reported insignificant change in BP in the main study gave no indication of a “whopping” 17/8 mmHg reduction in BP during the nighttime period, which translated into a 10/4 mmHg average reduction in BP over the entire 24-h period (88).

Interestingly, from an historical perspective, the first paper to describe the effects of antihypertensive medication on 24-h BP was in 1982, when Floras and his colleagues demonstrated, using direct intra-arterial BP measurement, that atenolol and slow-release propranolol lowered nighttime BP, whereas metoprolol and pindolol did not (89). A few years later, we presented data showing a discrepancy between antihypertensive drug efficacy as judged by clinic and non-invasive ambulatory daytime measurement, and concluded that “noninvasive ABPM should be considered an essential part of the evaluation of antihypertensive drugs” (90). Why, we might ask, have we had to wait nearly a quarter of a century to explore the therapeutic potential of nocturnal BP lowering and the differing effects of drugs on ambulatory BP?

Efficacies of the various classes of antihypertensive drugs for restoring normal dipping are not well studied, but diuretics, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin-1 receptor blockers and calcium channel blockers appear to be superior to alpha and beta-blockers



**Fig. 7.9** Hypertensive dipper: On the basis of the recorded data and available literature, ambulatory blood pressure suggests mild daytime systolic and diastolic hypertension (147/93 mmHg) and normal nighttime SBP and DBP (111/66 mmHg) with white coat effect (158/90 mmHg). Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. Source: Plot and report generated by dabl ABPM, 2006 (<http://www.dabl.ie>).

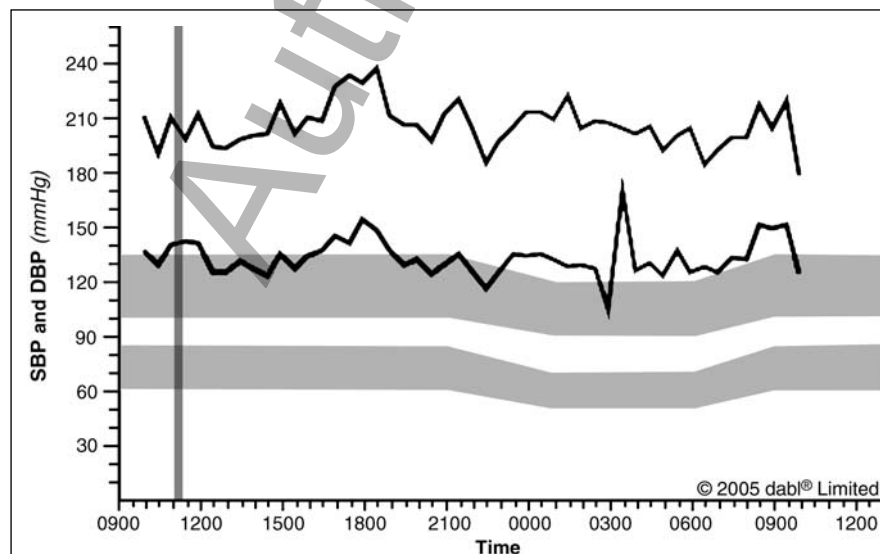
(1,9,91). Individualized antihypertensive medication targeting disrupted diurnal BP variation may be particularly protective in the high-risk groups, such as patients with a rise in nocturnal BP and in extreme dippers (57,92).

As much of the morning surge may be mediated by involvement of the renin-angiotensin-aldosterone system (RAAS), it would seem logical to assess agents targeting angiotensin II (1,93,94). Another mechanism worthy of manipulation to enhance nocturnal pharmacological

therapy is dietary potassium supplementation and sodium restriction to restore normal dipping (9).

The consistent lowering of nocturnal BP by the renin inhibitor aliskiren, in combination with a thiazide diuretic, an ACEI or an angiotensin receptor blocker, opens up potential for these therapeutic strategies to be used to reduce nocturnal hypertension (95).

The evidence to date clearly suggests that pharmacological research should be directed toward designing drugs with the



**Fig. 7.10** Hypertensive non-dipper: On the basis of the recorded data and available literature, the pattern suggests severe systolic and diastolic hypertension over 24 h (209/135 mmHg daytime and 205/130 mmHg at night). Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. Source: Plot and report generated by dabl ABPM, 2006 (<http://www.dabl.ie>).

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primary purpose of modifying the nocturnal manifestations of hypertension.

However, it should also be possible to modify nocturnal BP by using the drugs presently available, but dosing at bedtime rather than in the morning. As has been shown in the HOPE study, the simple expedient of dosing at night rather than in the morning may have a profound effect on nocturnal BP (86–88). Hermida and his colleagues examined the hypothesis that non-dipping in hypertensive patients might be due, at least in part, to the absence of 24-h therapeutic coverage in patients treated with single morning doses, and they showed that, in patients taking bedtime medication, ABPM control was double that of patients taking morning medication. Moreover, in patients with true resistant hypertension, bedtime medication resulted in a significant reduction in the 24-h mean of systolic and diastolic BP, and this reduction was much more prominent during nighttime (96). Bedtime dosing with an ACEI in patients with a non-dipping pattern improves efficacy during the nocturnal period (97).

Antihypertensive medication directed at nighttime BP may not necessarily alter nocturnal patterns for the better. For example, a non-dipping or dipper pattern could be transformed into an extreme dipping pattern with injudicious therapy. The objective should be to reduce BP at the same time as preserving the physiological dipper circadian pattern. This is particularly important in stroke survivors in whom ABPM is mandatory to determine the appropriate dose and the optimum time of administration of antihypertensive drugs so as to avoid the non-dipper, riser, and extreme-dipper circadian profiles induced by treatment (98). Given the extensive evidence for the increased prevalence of cardiovascular events in the early morning hours, antihypertensive drugs that provide BP control at the time of the early morning surge should provide greater protection against target-organ damage and enhance patient prognosis. This period has been dubbed the “blind spot” in current clinical practice (99). Pharmacological research into ways of altering the morning surge is limited, but candesartan has been shown to be superior to lisinopril in decreasing morning BP and the morning BP surge (2,100). Moreover, reduction in the morning rise in BP may be beneficial in preventing target organ involvement in hypertension (101).

### CONCLUSION—ABPM IS INDISPENSABLE TO GOOD CLINICAL PRACTICE

Not for the first time, a review of this nature serves to reinforce the clinical message that is so sadly being neglected: ABPM is indispensable to good clinical practice (12). The advantages for the technique are many. First and foremost, the technique simply gives more measurements than conventional measurement, and the real BP is reflected more accurately by repeated measurements; ABPM provides a profile of BP away from the medical environment, thereby allowing identification of individuals with a white coat response, or masked hypertension, who are in need of careful management; ABPM shows BP behavior over a 24-h period, rather than giving a snapshot of BP performed with an inaccurate technique under artificial circumstances, so that the efficacy of antihypertensive medication over a 24-h period becomes apparent, rather than relying on one or a few conventional measurements confined to a short period of the diurnal cycle; ABPM can identify patients with abnormal patterns of nocturnal BP—dippers

and non-dippers, extreme and reverse dippers, and those with a morning surge—all of whom are at high risk, and ABPM can be used to target these potentially dangerous patterns with appropriate drugs; ABPM can demonstrate a number of patterns of BP behavior that may be relevant to clinical management—isolated systolic and isolated diastolic hypertension, post-prandial hypotension, autonomic failure, etc. Finally, and importantly, evidence is now available from longitudinal studies that ABPM is a much stronger predictor of cardiovascular morbidity and mortality than conventional measurement—in other words, ABPM identifies patients with hypertension (and subjects whose BP is normal) who are at risk of future cardiovascular events. Moreover, the evidence is growing that nocturnal BP measured by ABPM may be the most sensitive predictor of cardiovascular outcome, from which it follows that the measurement of nighttime BP should be an important part of clinical practice. However, there are those who would disagree. Pickering argues that, until more evidence is available, “it would seem reasonable not to recommend routine measurement of the nighttime BP” (102). This recommendation, in my view, flies contrary to the evidence. But, arguable though this might be, surely we can only learn about the importance of nocturnal BP by measuring it! Had I decided in my clinical practice not to record nighttime BPs when I began recording ABPM in the 1980s I would not now have the data from some 20,000 patients in the Dublin Outcome Study that has permitted analyses to show that nocturnal BP is superior to all other measurements in predicting cardiovascular outcome (26). The inevitable conclusion of this review would seem, therefore, that there should now be international acceptance that 24-h ABPM is an indispensable investigation in patients with established and suspected hypertension, and that it should therefore be available to all hypertensive patients.

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