

# The circadian nuances of hypertension: a reappraisal of 24-h ambulatory blood pressure measurement in clinical practice

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Received: 2 February 2007 / Accepted: 14 February 2007 / Published online: 24 April 2007  
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**Abstract** Ambulatory blood pressure measurement has been in use in clinical practice for nearly half a century. However, despite the benefits the technique brings to managing patients with hypertension it is much under-used in practice. The purpose of this review is to examine critically the information that can be derived from the technique and to highlight the application of this evidence in clinical practice.

**Keywords** Blood pressure measurement · Ambulatory blood pressure measurement · Hypertension · Patterns of blood pressure · Circadian blood pressure

## Introduction

The technique for measuring blood pressure was introduced into clinical medicine in 1896 and has survived largely unchanged for over a century despite being inherently inaccurate [1]. Why, we might ask, have we connived for so long in perpetuating an inaccurate measurement in both clinical practice and hypertension research? The technique has had problems from the outset. Within a few years of its introduction, Heinrich von Recklinghausen showed that the cuff used by Riva-Rocci, being only 5 cm in diameter, was causing serious errors and the cuff controversy has raged ever since. In 1904, Theodore Janeway, in an authoritative monograph, warned against relying on casual blood pressure readings. His message went largely

unheeded until it was taken up again by Sir George Pickering in the 1960s who showed the remarkable variability of blood pressure and cautioned against making our patients miserable by prescribing unneeded drugs [1]. The identification of white-coat and masked hypertension and the realization that many patients are being treated needlessly with blood pressure-lowering drugs, whereas others are being denied drugs that could prevent cardiovascular sequelae are the latest factors in the growing case against the traditional technique of blood pressure measurement.

## Ambulatory blood pressure measurement is indispensable to good clinical practice

These concerns have resulted in considerable research into techniques for assessing blood pressure away from the medical environment, foremost among which has been ambulatory blood pressure measurement (ABPM). Indeed, this technique is now accepted as being indispensable to good clinical practice [1, 2]. The advantages for ABPM are many. First and foremost, the technique simply gives more measurements than conventional measurement, and the real blood pressure is reflected more accurately by repeated measurements; ABPM provides a profile of blood pressure 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 blood pressure behaviour over a 24-h period rather than giving a snapshot of blood pressure 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;

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ABPM can identify patients with abnormal patterns of nocturnal blood pressure—dippers and non-dippers, extreme and reverse dippers, morning surge—all of whom are at high risk and ABPM can be used to target these potentially dangerous patterns with appropriate drugs; the technique can demonstrate a number of patterns of blood pressure behaviour 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 blood pressure is normal) who are at risk from future cardiovascular events. Moreover, the evidence is growing that nocturnal blood pressure measured by ABPM may be the most sensitive predictor of cardiovascular outcome, from which it follows that the measurement of night-time blood pressure should be an important part of clinical practice [3]. In this review, I will look to the future applications of ABPM in clinical practice.

### Technological considerations

An accurate device for ABPM is mandatory and whichever device is selected should have been validated independently according to the International Protocol of the European Society of Hypertension [4]. The subject has been well reviewed [3, 5] and an up-dated listing of all devices recommended for blood pressure measurement is available at [www.dableducational.org](http://www.dableducational.org).

Accurate hardware for ABPM must be accompanied by software that will allow the information derived from ABPM to be put to optimal use. The software should be capable of not only providing easy-to-view plots of blood pressure over the 24-h period, but also be able to provide detailed or simple statistics according to requirements and an interpretative report to facilitate use in busy clinical practice. The 24-h period can be divided into a number of windows, each of which yields information about blood pressure change, and each of which provides patterns of blood pressure behaviour that may be associated with varying risk [6]. The software programme should be capable, therefore, of demarcating these windows and providing separate or combined statistical analyses on the blood pressure patterns within these windows [7]. The *dabl*<sup>®</sup> ABPM program, which has been designed to differentiate the windows of the 24-h profile, demarcate the normal bands for 24-h blood pressure and provide statistical analyses and an interpretative report based on these analyses and the recommendations from the latest

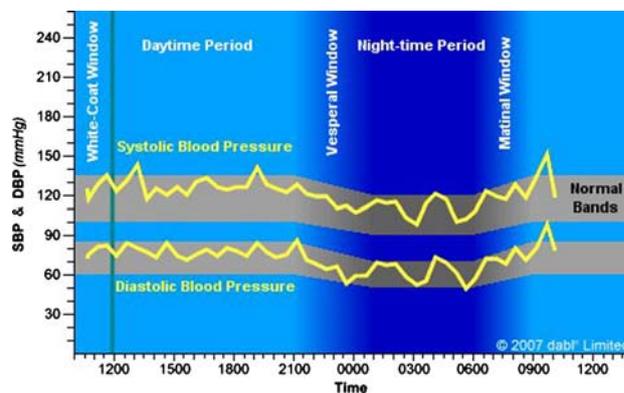
literature, will be used to illustrate the ABPM patterns in this review (Figs. 1, 2).

### Windows of the 24-h circadian profile

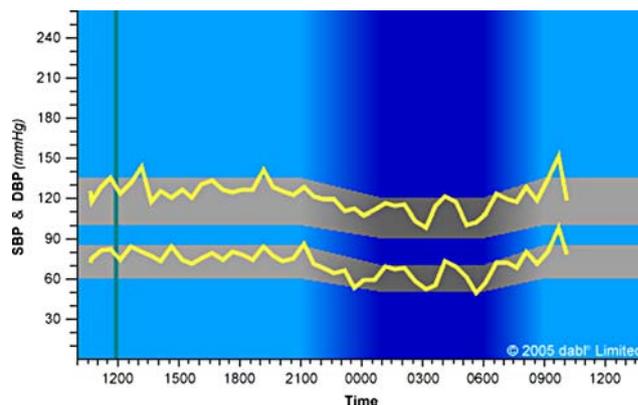
In contemporary clinical practice, the mean daytime and night-time blood pressures are generally taken as being the most valuable parameters of ABPM, but ongoing research indicates that there is much more information to be gleaned from the 24-h blood pressure cycle [8]. First, the 24-h period can be divided into a number of windows.

#### White coat window

The white coat window is the period that extends from the beginning of ABPM recording and lasts for 1 h. Ideally



**Fig. 1** Schema of ambulatory blood pressure. Plot generated by *dabl* ABPM—© *dabl* 2006 ([www.dabl.ie](http://www.dabl.ie))



**Fig. 2** Normal ambulatory blood pressure monitoring pattern: on the basis of the data recorded and the available literature, the ambulatory blood pressure monitoring pattern suggests normal 24-h systolic and diastolic blood pressure (128/78 mm Hg daytime, 110/62 mm Hg night-time). Plot and report generated by *dabl* ABPM—© *dabl* 2006 ([www.dabl.ie](http://www.dabl.ie))

ABPM recording should begin no later than 9 AM but when this is not possible, the dabl ABPM programme adjusts for a later time for ABPM recording to commence [7, 9]. During the white coat window, blood pressure may be influenced by the medical environment. The most popular definition of white coat hypertension is that blood pressure measured by conventional techniques in the office, clinic, or surgery exceeds 140 mm Hg systolic or 90 mm Hg diastolic, but when ABPM is performed the average blood pressure is <135 mm Hg systolic and 85 mm Hg diastolic during the daytime period. Currently, an average daytime ABPM of <135 mm Hg systolic and 85 mm Hg diastolic is generally considered normal and levels <130/80 mm Hg are considered optimal [10]. However, it has been shown that the white coat window on ABPM recordings cannot only diagnose the white coat phenomenon but also allows identification of a white coat hypertensive sub-group with significantly higher pressures, who may be at greater risk and in need of antihypertensive medication [11]. ABPM remains the method of choice for diagnosing white coat hypertension [2, 11, 12].

#### 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 [11]. For almost all subjects with hypertension, blood pressures during this window are lower than conventionally recorded pressures in the office, clinic or surgery setting [12, 13]. However, blood pressures 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 blood pressure recorded [14]. These effects are largely absent from blood pressure measured during the nocturnal period [6, 15].

#### Vesperal window

In the normal individual, there is a decline in blood pressure in the vesperal window from daytime levels of blood pressure to reach a plateau during the night-time 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 [16]. In hypertensive patients (or some normotensive patients with cardiovascular disease), the decline in the vesperal window may be absent (non-dipping) so that blood pressures do not reach basal levels [15, 17–19]. Blood pressure may even rise in the vesperal window to reach levels that are higher

than daytime levels (reverse dipping) [20]. Alternatively, there may be a marked fall in blood pressure during the vesperal window to give the phenomenon of extreme dipping [21]. Therefore, what happens to blood pressure in the vesperal window predicates the level of blood pressure in the basal window.

#### Basal window

The night-time window follows the vesperal window and is the period between 1.00 AM and 6.00 AM [11]. Blood pressures 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 applied the term ‘basal’ to this window in acknowledgement of the seminal paper written by Horace Smirk [22]. The compelling conclusion from Smirk’s analysis was that basal blood pressure was superior to casual pressure in predicting outcome [6, 22]. This evidence is very similar to recent evidence from my department [15] and others [19] showing that night-time blood pressure is superior to all other blood pressure measurements in predicting cardiovascular outcome and mortality, which suggests that night-time blood pressure obtained by ABPM is similar to the basal blood pressure 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 [23].

Valuable though the information derived from the basal window may be, there are a number of methodological limitations to recording blood pressure 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 ambulatory blood pressure recordings 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 [17, 24], and the influence of sleep disturbance, and sleep apnoea [6, 24]. Ironically, despite doubts about reproducibility of the night-to-day ratio, it may be that night-time blood pressure is more standardized and consequently more reproducible than daytime blood pressure (sleep being a more stable state than activity) and that it is this feature that gives nocturnal blood pressure its predictive value. In clinical practice when the sleep and awakening periods are clearly defined, nocturnal changes in blood pressure are surprisingly reproducible [25, 26].

## 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 [16]. However, the magnitude of the rise in of blood pressure in the matinal window may yield most valuable prognostic information. In normal subjects, a modest rise in blood pressure occurs in the matinal window preceding awakening from sleep to merely restore the previous daytime level of blood pressure [27]. However, this pre-awakening rise in blood pressure in hypertensive patients may exceed the daytime average—the pre-awakening or morning surge—and this phenomenon is associated with a poor cardiovascular outcome [21].

## Patterns of ABPM

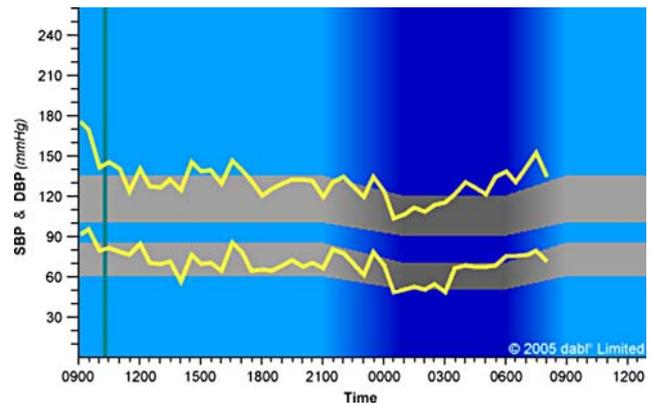
Within the windows of the 24-h blood pressure profile, several variations of blood pressure behaviour may be discerned allowing differentiation of patients into sub-forms and patterns [2, 3, 5, 28]. ABPM may also be used to stage the severity of blood pressure—the higher the initial 24-h ABPM, the more frequent the occurrence of cardiovascular events [29]. The most commonly used aggregate to denote levels of ABPM is the mean 24-h blood pressure [2]. However, though this may be an acceptable estimate of the blood pressure 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.

### White coat hypertension

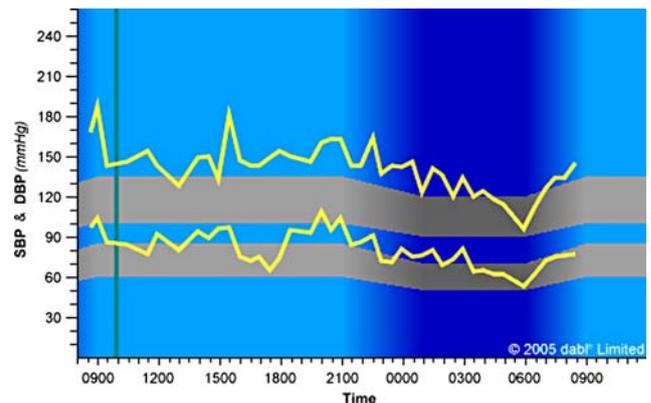
The risk associated with white coat hypertension remains controversial but there is general agreement that the condition should not be regarded as benign, with the risk of developing sustained hypertension at some time being almost inevitable [30, 31, 32] (Fig. 3).

### White-coat effect

White-coat hypertension must be distinguished from the ‘white-coat effect’, which is the term used to describe the increase in pressure 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 blood pressure is usually greater



**Fig. 3** 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 mm Hg) with otherwise normal 24-h systolic and diastolic blood pressure (133/71 mm Hg daytime, 119/59 mm Hg night-time). Plot and report generated by dabl ABPM—© dabl 2006 (www.dabl.ie)



**Fig. 4** White coat effect: on the basis of the data recorded and the available literature, the pattern suggests mild daytime systolic hypertension (149 mm Hg), borderline daytime diastolic hypertension (87 mm Hg), borderline night-time systolic hypertension (121 mm Hg) and normal night-time diastolic blood pressure (67 mm Hg) with white coat effect (187/104 mm Hg). Plot and report generated by dabl ABPM—© dabl 2006 (www.dabl.ie)

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 measurement may have only moderate or mild hypertension on ABPM because of a marked white-coat effect [5] (Fig. 4).

### Masked hypertension

This phenomenon denotes subjects classified as normotensive by conventional office or clinic measurement 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 is that cardiovascular morbidity will also be greater and such 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 ten million people in the USA [5, 32].

### Ambulatory hypotension

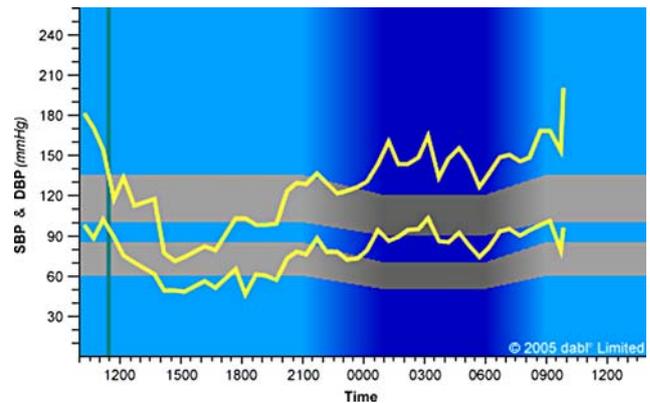
Hypotension is particularly common in the elderly, who may have autonomic or baroreceptor failure and who may also experience post-prandial and postural hypotension—conditions which may lead to risk from falls and accidents. ABPM may also be useful in identifying hypotensive episodes in young patients in whom hypotension is suspected of causing symptoms [2, 32]. In treated hypertensive patients, ABPM may also demonstrate drug-induced decreases in blood pressure that may have untoward effects in patients with a compromised arterial circulation, such as individuals with coronary and cerebrovascular disease [33] (Fig. 5).

### Daytime systo-diastolic hypertension

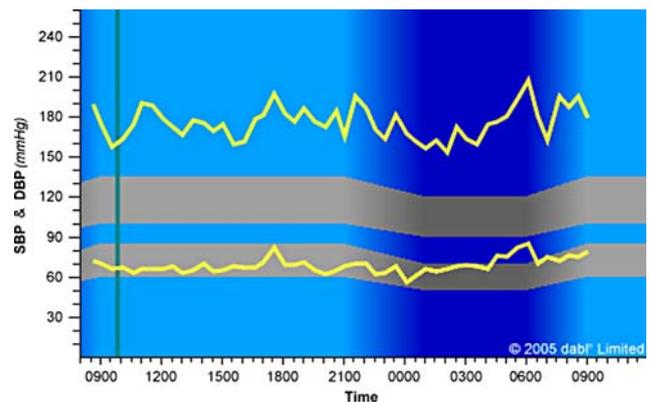
Many patterns of blood pressure behaviour can be discerned from ABPM. By far the most common pattern is systo-diastolic hypertension [28]. Usually, daytime blood pressure levels are lower than clinic readings—the white coat effect. Generally, mean daytime levels of blood pressure are superior to clinic blood pressures in predicting outcome but inferior to nocturnal blood pressure [15, 34].

### Isolated systolic hypertension

Isolated systolic hypertension can, of course, be apparent on clinic blood pressure 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 blood pressure measured conventionally in the elderly may average 20 mm Hg 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 blood pressure [35]. In women with



**Fig. 5** Ambulatory hypotension: on basis of recorded data and available literature, ambulatory blood pressure monitoring pattern suggests low-daytime systolic blood pressure (100 mm Hg) and normal daytime diastolic blood pressure (61 mm Hg) and moderate night-time systolic and diastolic hypertension (146/89 mm Hg) with white coat effect (200/102 mm Hg). Plot and report generated by dabl ABPM—© dabl 2006 (www.dabl.ie)



**Fig. 6** Isolated systolic hypertension: on basis of recorded data and available literature, the pattern suggests severe 24-h isolated systolic hypertension (176/68 mm Hg daytime, 169/70 mm Hg night-time). Plot and report generated by dabl ABPM—© dabl 2006 (www.dabl.ie)

cardiovascular disease, systolic blood pressure was the blood pressure measure most strongly related to the risk of secondary cardiovascular events [36] (Fig. 6).

### 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% [28]. 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 blood pressure is normal, high-diastolic blood pressure is not associated with an adverse prognosis [37].

## Dipping and non-dipping

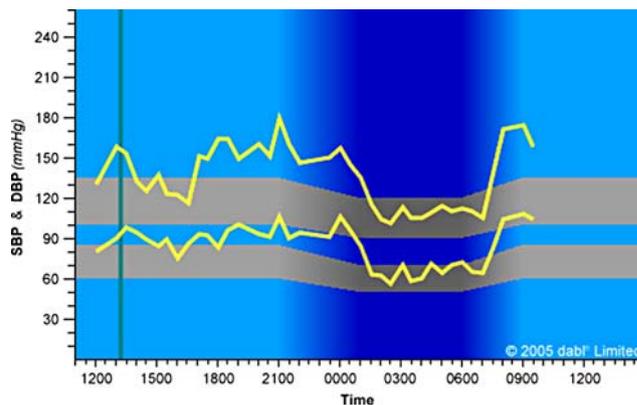
The ‘dipper/non-dipper’ classification was first introduced in 1988 when a retrospective analysis suggested that non-dipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern [18]. Whether this classification is associated with adverse outcome has been the subject of much debate [24]. On balance, most large-scale prospective studies currently support the concept that a diminished nocturnal blood pressure fall is associated with a worse prognosis [2, 16]. For example, blunted night-time dipping of blood pressure is independently associated with angiographic coronary artery stenosis in men [38]. In elderly people with long-standing hypertension, a blunted nocturnal dip in blood pressure is independently associated with lower cognitive performances [39]. 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 [40]. A non-dipping nocturnal pattern is also associated with renal and cardiac target organ involvement [41]. It has been well documented, therefore, 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 [41]. Moreover, nocturnal blood pressure is now known to be an independent risk for cardiovascular outcome over and above all other measures of blood pressure [15, 42]. For example, in the Dublin Outcome Study for each 10-mm Hg increase in mean night-time systolic blood pressure, the mortality risk increased by 21% [15]. In a Japanese population, a diminished nocturnal decline in blood pressure was an independent risk factor for cardiovascular mortality, with each 5% decrease in the decline in nocturnal systolic/diastolic blood pressure being associated with an ~20% greater risk of cardiovascular mortality [42] (Figs. 7, 8).

### Reverse dipping

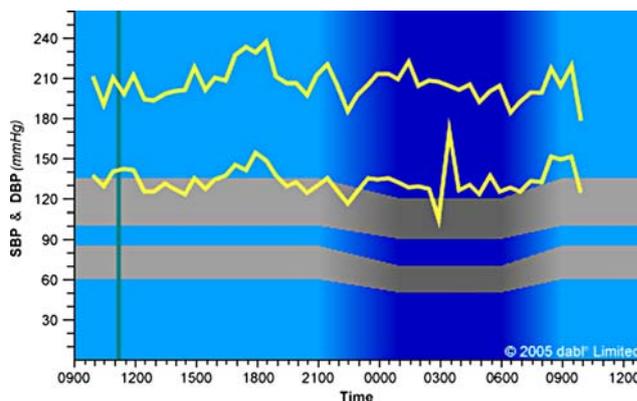
In some patients, blood pressure rises above the daytime pressures rather than falling during the night. These patients (also referred to as risers, or extreme non-dippers) have the worst cardiovascular prognosis, both for stroke and cardiac events [20].

### Extreme dipping

Patients with a marked nocturnal fall in blood pressure, known as extreme-dippers, are at risk for non-fatal ischaemic stroke and silent myocardial ischemia. This is



**Fig. 7** Hypertensive dipper: on basis of recorded data and available literature, ambulatory blood pressure suggests mild daytime systolic and diastolic hypertension (147/93 mm Hg) and normal night-time systolic and diastolic blood pressure (111/66 mm Hg) with white coat effect (158/90 mm Hg). Plot and report generated by dabl ABPM—© dabl 2006 (www.dabl.ie)



**Fig. 8** Hypertensive non-dipper: on basis of recorded data and available literature, the pattern suggests severe systolic and diastolic hypertension over 24 h (209/135 mm Hg daytime and 205/130 mm Hg at night). Plot and report generated by dabl ABPM—© dabl 2006 (www.dabl.ie)

particularly likely in extreme-dippers who already have atherosclerotic arterial stenosis and in whom excessive blood pressure reduction is induced by injudicious anti-hypertensive medication [20]. 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 ischaemia or infarction if sub-endocardial 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 [43]. Extreme dipping is closely associated with an excessive morning surge in blood pressure, which is associated with cerebral infarction and a high-risk of future stroke [20].

### Siesta dipping

A siesta dip in blood pressure 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 ration of ABPM [44, 45], 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 [46].

### 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 [15, 42, 47]. Further confirmation of the importance of nocturnal hypertension comes from a recent study showing that a non-dipping pattern and increased night-time diastolic blood pressure 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 blood pressure measurement, thereby showing that ABPM once again conveys important information that cannot be obtained with conventional measurement [48].

### The morning surge

Cardiovascular events, such as myocardial infarction, ischaemia and stroke are more frequent in the morning hours, soon after waking, than at other times of day [49]. Circadian variations in biochemical and physiological parameters help to explain the link between acute cardiovascular events and the early morning blood pressure surge [49, 50]. The clinical consequences of these haemodynamic and neurohumoral changes are numerous. The occurrence of stroke and heart attack is commoner in this period than at any other time of the day [50]. Kario et al. have shown that in older hypertensive subjects, a morning surge in blood pressure—defined as a rise in blood pressure >55 mm Hg from the lowest night-time reading—carries a risk of stroke almost three times greater than that seen in patients without a morning surge. A pattern of morning surge in blood pressure was

also associated with the presence of clinically silent cerebral infarction [51]. Higher carotid internal-medial thickness and circulating inflammatory markers coexist in hypertensive patients with a morning blood pressure surge and might contribute to the increased cardiovascular risk in these patients [52].

### Indices of risk in the circadian profile

ABPM can also provide interesting and informative indices that are associated with outcome. The subject has been reviewed recently [9]. These include pulse and mean blood pressure, heart rate, indices of blood pressure variability, chronobiological calculations, Cusum derived statistics and most recently the Ambulatory Arterial Stiffness Index (AASI), which has been shown to predict cardiovascular mortality in a large cohort of hypertensive individuals (particularly from stroke) and this association was evident, even in normotensive subjects. 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 blood pressure lowering [53].

### Conclusion

In this review, I have shown that there is a wealth of statistical information to be obtained from ABPM not only in identifying different forms and patterns of hypertension, but also in applying statistical analyses, such as measures of cardiovascular load and variability. It is surely timely, therefore, to reappraise the value of the technique not only in clinical practice but also in clinical research.

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