Ambulatory blood pressure monitoring: 24-hour blood pressure control as a therapeutic goal for improving cardiovascular prognosis

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In this review, I discuss the important information that ambulatory blood pressure monitoring can provide in clinical practice and make the case once again for making this technique available to all doctors engaged in managing patients with hypertension. I review the evidence on how nocturnal variation in blood pressure (BP) can influence outcome, consider interesting preliminary evidence that some drug classes may be superior to others in modifying nocturnal BP, and suggest that the time of administration of medication may also have an influence on the correction of abnormal nocturnal patterns. There is a need to direct research to determine if correcting abnormal nocturnal patterns either with drugs specifically targeted at nocturnal BP or by manipulating the time of drug administration will improve outcome.

The technique for measuring blood pressure (BP) was introduced into clinical medicine in 1896 and has survived largely unchanged for over a century, despite being inherently inaccurate. Why, we might ask, have we connived for so long in perpetuating an inaccurate measurement in both clinical practice and hypertension research? The identification of white-coat and masked hypertension and the realization that many patients are being treated needlessly with BP-lowering drugs, whereas others are being denied drugs that could prevent cardiovascular (CV) sequelae, are the latest factors in the growing case against the traditional technique of BP measurement.

ABPM is indispensable to good clinical practice

These concerns have resulted in considerable research into techniques for assessing BP away from the medical environment, foremost among which has been ambulatory blood pressure monitoring (ABPM). Indeed, this technique is now accepted as being indispensable to good clinical practice. There are guidelines and recommendations laying down the criteria for validation of devices for ABPM and the website www.dableducational.org provides up-to-date information on recommended devices. The advantages of ABPM are many. First and foremost, the technique simply gives more measurements than conventional BP measurement, and 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 measured with an inaccurate technique under artifi-
cial circumstances. Rather than relying on one or a few conventional measurements confined to a short period of the diurnal cycle, the efficacy of antihypertensive medication over a 24-h period becomes apparent.

ABPM can identify patients with abnormal patterns of nocturnal BP; the technique can demonstrate a number of patterns of BP behavior that may be relevant to clinical practice. Finally and importantly, evidence is now available from longitudinal studies that ABPM is a much stronger predictor of CV morbidity and mortality than conventional measurement. Moreover, evidence is growing that nocturnal BP measured by ABPM may be the most sensitive predictor of CV outcome, from which it follows that the measurement of nighttime BP should be an important part of clinical practice.3

Windows of the 24-hour circadian profile

In contemporary clinical practice, mean daytime and nighttime BPs are generally taken as being the most valuable parameters of ABPM,6–9 but ongoing research indicates that there is much more information to be gleaned from the 24-h BP cycle. First, the 24-h period can be divided into a number of windows (Figures 1 and 2).

• **White-coat window**

The white-coat window is the period that extends from the beginning of ABPM recording and lasts for 1 hour.5,9 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 mm Hg systolic or 90 mm Hg diastolic, but when ABPM is performed the average BP is <135 mm Hg systolic and 85 mm Hg diastolic during the daytime period.10 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 subgroup 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 engaged in usual activities.11 For almost all subjects with hypertension, BPs during this window are lower than conventionally recorded pressures in the office, clinic, or surgery setting.12,13 However, BPs during this period are subject to stress, activity, arm movement, and the effect of exercise and other activities, such as driving, all of which may have an influence on the mean level of BP recorded.14 These effects are largely absent from BP measured during the nocturnal period.6,15

• **Vesperal window**

In the normal individual, there is a decline in BP in the vesperval window from daytime levels of BP that reaches 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 a time during which bed rest is inconsistent and, therefore, cannot be categorized reliably.16 In hypertensive patients or some normotensive patients with CV
The decline in BP during the vesperal window may be absent (nondipping) so that BPs do not reach basal levels. BP may even rise in the vesperal window to reach levels that are higher than daytime levels (reverse dipping). Alternatively, there may be a marked fall in BP during the vesperal window to give the phenomenon of extreme dipping. Therefore, what happens to BP in the vesperal window predicated the BP level 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. 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. There is compelling evidence that basal BP is superior to casual pressure in predicting outcome. Nighttime BP is superior to all other BP measurements in predicting CV outcome and mortality, which suggests that nighttime BP obtained by ABPM is similar to basal BP. Moreover, it has also been shown that the use of a mild sedative during ABPM may help in identifying patients with a very high CV risk, namely those patients who continue to manifest a blunted nocturnal dip despite sedation.

Valuable though the information derived from the basal window may be, there are a number of methodological limitations to recording BP at night. 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.

**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 a time during which bed rest is inconsistent and, therefore, cannot be categorized reliably. However, the magnitude of the rise in BP in the matinal window may yield the 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. However, this preawakening rise in BP in hypertensive patients may exceed the daytime average—the preawakening or morning surge—and this phenomenon is associated with a poor CV outcome.

**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 subforms and patterns. ABPM may also be used to gauge the severity of BP—the higher the initial 24-h ABPM, the more frequent the occurrence of cardiovascular events.

**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 (Figure 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 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 (Figure 4, page 244).5

**Masked hypertension**

This phenomenon denotes subjects classified as normotensive by conventional office or clinic measurement that 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 and increased CV morbidity. The logical extension of this line of reasoning is that future studies will also show CV 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.
**Ambulatory hypotension**

Hypotension is particularly common in the elderly, who may have autonomic or baroreceptor failure and who may also experience postprandial and postural hypotension. 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 BP that may have untoward effects in patients with compromised arterial circulation, such as individuals with coronary and cerebrovascular disease (Figure 5).33

**Daytime systo-diastolic hypertension**

Many patterns of BP behavior can be discerned from ABPM. By far the most common pattern is systo-diastolic hypertension.28 Generally, mean daytime levels of BP are superior to clinic BPs in predicting outcome, but inferior to nocturnal BP.15,34

**Isolated systolic hypertension**

Isolated systolic hypertension can be apparent on clinic BP measurement, but it can be overestimated. ABPM allows for confirmation of the diagnosis as well as predicting outcome more accurately. The results of the ABPM substudy of the Systolic Hypertension in Europe Trial showed that systolic blood pressure (SBP) measured conventionally in the elderly may average 20 mm Hg more than daytime ABPM, thereby leading to the inevitable overestimation of isolated systolic hypertension in the elderly and probable excessive treatment of the condition.35 In women with CV disease, SBP is most strongly related to the risk of secondary CV events (Figure 6).36

**Isolated diastolic hypertension**

Isolated diastolic hypertension, which can be present on clinic measurement, can be more readily studied with ABPM. The prevalence of the condition in one study was 3.6%.29 It is generally accepted that if SBP is normal, high diastolic blood pressure (DBP) is not associated with an adverse prognosis.37

**Dipping and nondipping**

The “dipper/nondipper” classification was first introduced in 1988 when a retrospective analysis suggested that nondipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern.18 It is generally accepted that a diminished nocturnal BP fall is associated with a poor prognosis.2,16 For example, blunted nighttime dipping of BP is independently associated with angiographic coronary artery stenosis in men.28 In elderly people with long-standing hypertension, a blunted nocturnal dip in BP is independently

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**Figure 4.** ABPM suggests mild daytime systolic hypertension (150 mm Hg), borderline daytime diastolic hypertension (87 mm Hg), borderline nighttime systolic hypertension (123 mm Hg), and normal nighttime diastolic blood pressure (68 mm Hg) with a white-coat effect (187 mm Hg/104 mm Hg). Normal dipping pattern.

**Figure 5.** ABPM suggests low daytime systolic and diastolic blood pressure (100 mm Hg/59 mm Hg) and moderate nighttime systolic and diastolic hypertension (146 mm Hg/89 mm Hg) with a white-coat effect (181 mm Hg/102 mm Hg). Reverse dipping pattern.

**Figure 6.** ABPM suggests severe daytime isolated systolic hypertension (176 mm Hg/68 mm Hg), severe nighttime systolic hypertension (169 mm Hg), and borderline nighttime masked diastolic hypertension (70 mm Hg). Nondipping pattern.
associated with lower cognitive performance. Among elderly patients with recently diagnosed isolated systolic hypertension, those with a nondipping nocturnal pattern have been shown to have significantly higher left ventricular masses on echocardiography than dippers. A nondipping nocturnal pattern is also associated with renal and cardiac target organ involvement. Moreover, nocturnal BP is now known to be an independent risk factor for CV outcome over and above all other measures of BP. For example, in the Dublin Outcome Study for each 10-mm Hg increase in mean nighttime SBP, the mortality risk increased by 21% (Figures 6 and 7).

Reverse dipping
In some patients, BP rises above daytime pressures rather than falling during the night. These patients (also referred to as risers, or extreme nondippers) have the worst CV prognosis, both for stroke and cardiac events (Figure 5).

Extreme dipping
Patients with a marked nocturnal fall in BP, known as extreme dippers, are at risk for nonfatal ischemic stroke and silent myocardial ischemia. This is particularly likely in extreme dippers who already have atherosclerotic disease and in whom excessive BP reduction is induced by injudicious antihypertensive medication. This possibility was originally enunciated by Floras as long ago as 1988. 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 (Figure 8).

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 part of the daily routine. There is evidence that ignoring the dipping pattern associated with a siesta distorts the day/night ratio of ABPM, and the magnitude of the siesta dip may have prognostic implications (Figure 8).

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 CV outcome. Further confirmation of the importance of nocturnal hypertension comes from a recent study showing that a nondipping pattern and increased nighttime DBP predicted the occurrence of congestive heart failure independently of antihypertensive treatment and established risk factors for cardiac failure (Figures 4 to 8).

The morning surge
CV events, such as myocardial infarction, ischemia, and stroke, are more frequent in the morning hours soon after waking than at other times of day. Circadian variations in biochemical and physiological parameters help to explain the link between acute CV events and the early morning BP surge. The occurrence of stroke and heart attack is more common during this period than at any other time of the day. In older hypertensive subjects, a morning surge in BP—defined as a rise in BP >55 mm Hg from the lowest nighttime reading—carries a risk of stroke almost three times greater than that seen in patients without a morning surge. Greater carotid intima-media thickness and circulating inflammatory markers coexist in hypertensive patients with a morning BP surge and might contribute to the increased CV risk in these patients (Figure 8).

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. These include pulse and mean BP, heart rate, indices of BP variability, chronobiological calculations, Cusum derived statistics, and most recently the ambulatory arterial stiffness index (AASI), which has been shown to predict CV mortality in a large cohort of hypertensive individuals (particularly from stroke). This association was evident even in normotensive subjects. As a result, AASI may prove to be a readily applicable index that can be derived from routine ABPM to predict outcome. The practical importance of such an index is that it may permit early categorization of hypertensive patients at risk from CV events thus indicating those in need of aggressive BP lowering.

**Treatment of hypertension using ABPM**

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed significantly lower rates of all-cause mortality (11% lower), CV mortality (24% lower), and stroke (23% lower) with an amlodipine/perindopril combination compared with an atenolol-thiazide combination, even in hypertensive patients without coronary heart disease. The intertreatment difference in event rates was only partly explained by better lowering of clinic BP with amlodipine/perindopril. In fact, it now seems possible that the explanation for this discrepancy may be because the amlodipine/perindopril combination reduced both mean BP and BP variability.

An ambulatory substudy of ASCOT was performed in 1900 patients from four ASCOT centers who had repeated ABPMs over 5.5 years in order to examine the impact of the two BP-lowering treatment regimens on ambulatory BP. Clinical BP was examined every 6 months. ABPM was performed once a year from recruitment. ABPM was measured every half an hour throughout a 24-h period—mean daytime BP [9.00 AM to 9.00 PM], nighttime BP [1.00 AM to 6.00 AM], 24-h SBP, 24-h DBP, pulse pressures, and heart rates were calculated from each ABPM. Three post hoc–defined composite endpoint events were analyzed: total CV events + revascularization procedures; total coronary events (fatal coronary heart disease) + coronary revascularization procedures; and fatality from each ABPM. Three posthoc–defined composite endpoint events were analyzed: total CV events + revascularization procedures; total coronary events (fatal coronary heart disease) + coronary revascularization procedures; and fatal + nonfatal stroke.

Like all the total ASCOT blood pressure–lowering arm population, patients from the ABPM substudy were treated with amlodipine/perindopril. Clinical BP values were 1.4/1.1 mm Hg lower. No difference in SBP was found between treatment groups during the 24-h period, but nighttime systolic BP was significantly lower (2.2 mm Hg) with amlodipine/perindopril treatment. This difference might be explained by the synergistic effect of amlodipine and perindopril with trough-to-peak ratios of 85%-87% and 75%-100%, respectively on 24 hour BP control. The ABPM substudy showed that the amlodipine/perindopril and atenolol/thiazide regimens had different effects on daytime and nighttime BP, which may have contributed to the lower rate of events in patients treated with amlodipine/perindopril (Figure 9). Nocturnal ABPM values complemented clinical BP values for the prediction of CV risk in hypertensive patients receiving treatment. These data reinforce the concept that BP-lowering treatment should be directed towards the reduction of nocturnal BP.

**Can drugs be targeted to reduce BP in circadian periods of greatest risk?**

Traditionally, BP-lowering drugs with a once-daily regimen of administration are taken in the morning. The hypertension guidelines require that antihypertensive medication with once-daily administration should possess at least a 50% trough-to-peak (T/P) ratio to ensure a 24-hour duration of action. It is surprising how little attention has been paid to the possibility of achieving more beneficial effect on CV outcome by reducing nocturnal BP either by nighttime dosing or by designing drugs aimed specifically to reduce nocturnal BP. The importance of 24-hour BP coverage, even if achieved by manipulating the timing of drug administration, has been well illustrated in the Heart Outcomes Prevention Evaluation study.

In the main study, the group receiving ramipril had approximately 35% fewer CV events, despite an insignificant reduction in BP of 3/2 mm Hg; 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 a later analysis of the ABPM substudy that ramipril (T/P ratio 50%-63%) was actually taken in the evening with outpatient BP measured some 10 to 14 hours later the following day. The reported insig-
Efficacies of the various classes of antihypertensive drugs for calcium channel blockers appear to be superior to diuretics, ACE inhibitors, angiotensin II receptor blockers, and slow-release propranolol lowered nighttime BP, whereas metoprolol and pindolol did not. A few years later, we presented data showing a discrepancy between antihypertensive drug efficacy when measured by clinic and noninvasive ambulatory daytime measurement methods. We concluded that "noninvasive ambulatory blood pressure measurement should be considered an essential part of the evaluation of antihypertensive drugs." 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. However, diuretics, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers appear to be superior to α- and β-blockers. Individualized antihypertensive medication targeting abnormal diurnal patterns may offer particularly good protection in high-risk groups, such as patients with a rise in nocturnal BP and in extreme dippers.

As much of the morning surge may be mediated by involvement of the renin-angiotensin system, it would seem logical to assess agents targeting angiotensin II. Another mechanism worthy of manipulation to enhance nocturnal pharmacological therapy is dietary potassium supplementation and sodium restriction to restore normal dipping. The consistent lowering of nocturnal BP by the renin inhibitor aliskiren in combination with a thiazide diuretic, an ACE inhibitor, or an angiotensin receptor blocker is a potential therapeutic strategy for reducing nocturnal hypertension.

The evidence to date clearly suggests that pharmacological research should be directed towards designing drugs with the primary purpose of modifying nocturnal manifestations of hypertension. However, it should also be possible to modify nocturnal BP using the drugs or drug combinations presently available with 24-hour BP coverage. Hermida and colleagues examined the hypothesis that nondipping in hypertensive patients might be due, at least in part, to the absence of 24-hour therapeutic coverage in patients treated with single morning doses. 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-hour mean of SBP and DBP, and this reduction was much more prominent at nighttime. Bedtime dosing with an ACE inhibitor in patients with a nondipping pattern of hypertension improves efficacy during the nocturnal period.

Antihypertensive medication directed at nighttime BP may not necessarily alter nocturnal hypertension patterns for the better. For example, a nondipping or dipping pattern could be transformed into an extreme dipping pattern with injurious therapy. The objective should be to reduce BP at the same time as preserving the physiological circadian dipper pattern. This is particularly important in stroke survivors, in whom ABPM is mandatory because it determines the appropriate dose of antihypertensive drug and the optimum time of administration to avoid inducing nondipper, riser, and extreme dipper circadian profiles with treatment.

Given the extensive evidence for the increased prevalence of CV events in the early morning hours, antihypertensive drugs that provide BP control during 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. Pharmacological research into ways of altering the morning surge is limited. However, reduction of the morning surge in BP may be beneficial in preventing target-organ involvement in hypertension.

From the evidence available there is a need in clinical practice to use antihypertensive therapies with proven 24-hour duration of action and with superior nighttime BP coverage, as demonstrated in the ASCOT trial with an amlodipine/perindopril regimen. There is a need for pharmaceutical research to develop drugs that correct nocturnal BP abnormalities and for clinical research to determine if correcting nocturnal BP abnormalities will result in improved outcome.

References
ABPM control as a therapeutic goal for improving CV prognosis – O’Brien


MESURE AMBULATOIRE DE LA PRESSION ARTÉRIELLE : LE CONTRÔLE DE LA PRESSION ARTÉRIELLE SUR 24 h, UN OBJECTIF THÉRAPEUTIQUE POUR AMÉLIORER LE PRONOSTIC CARDIO-VASCULAIRE

Cet article analyse les informations importantes délivrées en pratique clinique par la mesure ambulatoire de la pression artérielle, et défend une fois de plus l'intérêt de mettre cette technique à disposition de tous les médecins impliqués dans la prise en charge des hypertendus. L'article fait également le point sur la façon dont les variations nocturnes de la pression artérielle (PA) influent sur l'évolution de la maladie ; il examine d'intéressants arguments préliminaires suggérant la supériorité de certaines classes thérapeutiques sur d'autres quant à l'action sur la PA nocturne ; et enfin conclut en avançant l'hypothèse que l'horaire de la prise médicamenteuse pourrait avoir une influence sur la correction des schémas tensionnels nocturnes anormaux. Ce dernier point nécessite plus ample étude afin de déterminer si cette correction serait plus efficace en termes d'amélioration du pronostic en utilisant des médicaments spécifiquement orientés vers la PA nocturne ou en modifiant l'horaire de la prise.

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