Utility of ambulatory blood pressure monitoring for the management of hypertension

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Purpose of review
Hypertension is a leading cause of cardiovascular morbidity and mortality, affecting nearly 80 million individuals in the United States alone. Accurate measurement of blood pressure (BP) is the crucial first step to reduce the associated cardiovascular risk of hypertension. For decades, clinicians have relied on office BP measurements for the diagnosis and subsequent management of hypertension. However, it has been clearly demonstrated that ambulatory BP measurements are a better predictor of cardiovascular risk and can provide clinicians with important additional information to improve BP control and reduce cardiovascular risk. This article reviews the available data and provides clinical insights into the use of ambulatory BP monitoring for the management of hypertension.

Recent findings
Ambulatory BP monitoring is uniquely capable of identifying patients with white-coat hypertension (WCH), masked hypertension and abnormal nocturnal BP profiles. Recently, ambulatory BP data have demonstrated the negative impact of WCH on right ventricular function, a greater prevalence of masked hypertension than previously recognized and the detrimental impact of nocturnal hypertension even in controlled hypertension.

Summary
Ambulatory BP monitoring provides clinicians with the most comprehensive evaluation of hypertension and the ability to define individual BP phenotypes. Hence, these out-of-office measurements can be utilized to improve hypertension control, translating into a reduction of cardiovascular events.

Keywords
ambulatory blood pressure monitoring, chronotherapy, masked hypertension, white-coat hypertension

INTRODUCTION
Effective management and control of hypertension is dependent on accurate measurement of the blood pressure (BP). For decades, the office sphygmomanometer was the gold-standard for the diagnosis and management of hypertension. The development of ambulatory blood pressure monitors (ABPMs) provided clinicians and researchers with a method of assessing a more global BP profile. It was rapidly recognized [1–3] that ABPM was superior to office BPs for both the identification of various BP phenotypes and prediction of hypertensive target organ involvement. For example, ABPM allows for the identification of white-coat hypertension (WCH), masked hypertension and describes the circadian rhythms of the vascular system. A number of more recent prospective cohort studies, described below, show that 24-h BP is a better predictor of cardiovascular outcomes than BP measured in a medical care environment. Importantly, several national and international organizations [4,5] including the European Society of Hypertension [6] and the US Preventive Services Task force [7] have recognized the importance of ABPM for evaluating and treating patients with hypertension.

ACCURATE DIAGNOSIS OF HYPERTENSION
A clinician cannot properly assess the need for nor determine the efficacy of antihypertensive drug
therapy without accurate BP values. As ambulatory BP monitoring obtains many BP values in the patient’s own environment, the data obtained from ABPM help to confirm sustained hypertension or determine if WCH or masked hypertension is present, all which are essential to properly categorize BP management (Fig. 1) [8].

**WHITE-COAT HYPERTENSION**

WCH is the presence of isolated elevations of BP in the office, while having normal 24-h BP recordings in the absence of drug therapy. It is defined as a clinic BP at least 140/90 mmHg with 24-h ambulatory BP, awake and asleep BPs of less than 130/80, <135/85 and <120/70 mmHg, respectively (Table 1) [8]. The incidence of WCH is approximately 10–20% in stage I hypertension patients [9]. Interestingly, in the recently published SPRINT Trial [10], 42% of patients had well-controlled daytime systolic BP (<130 mmHg). Overall, the incidence of WCH was 20% in the SPRINT trial cohort. In the intensive strategy arm, there was significantly greater incidence of hypotension, syncope and acute renal failure [11], it is unclear at this time if these adverse events occurred more commonly in patients with WCH. The management of hypertension based solely on office reading poses many patients to unnecessary medications, medication side-effects and the risk of excessive BP reduction. Routine use of ABPM could identify patients with white coat effect (WCE) and reduce excessive doses of antihypertensive medications.

**KEY POINTS**

- Ambulatory BP monitoring provides a comprehensive assessment of BP profile.
- Evaluation of the circadian BP profile and nocturnal BP is only possible with ambulatory BP monitoring.
- Ambulatory BP is a stronger predictor of cardiovascular and cerebrovascular events than BP measured in the doctor’s office.
- Chronotherapy can normalize or improve abnormal circadian rhythms, reducing cardiovascular risk.
- Ambulatory BP monitoring is useful for the management of hypertension through more precise adjustment of antihypertensive therapies.

| Table 1. Definition of hypertension based on ambulatory blood pressure readings |
|---------------------------------|-----|------|------|
|                                | Optimal | Normal | Abnormal |
| Daytime                        | <130/80 | <135/85 | >140/90 |
| Nighttime                      | <115/65 | <120/70 | >125/75 |
| 24 h                           | <125/75 | <130/80 | >135/85 |

Adapted from [8]

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**FIGURE 1.** Proposed schema for using ambulatory BP monitoring for the diagnosis and management of hypertension. Adapted from [8].
However, WCH cannot be ignored as it does carry significant risk in some people. Many patients progress to sustained hypertension and should be monitored every 2–3 years with ABPM to ensure timely intervention when appropriate. A subpopulation of about 50% of patients with WCH carries higher risk for cardiovascular disease and target organ damage. In 2014 for example, Cupididi et al. [12] demonstrated that patients with WCH experienced deleterious changes in left ventricular mass, left atrial size and measures of diastolic parameters. More recently, Tadic et al. [13] demonstrated for the first time, similar effects of WCH on the right ventricle. In a recent meta-analysis of 14 studies comprising more than 29,000 patients [14], WCH was associated with a significantly higher incidence of cardiovascular events compared with a normotensive population. The WCH group experienced a 73% higher risk of cardiovascular events compared with normotensive group and the risk of cardiovascular mortality was also higher.

The detrimental effect of WCH is not limited to the heart. Data from the Dallas Heart Study [15] showed that WCH was associated with higher pre-clinical renal damage as evidenced by increased cystatin-c and albuminuria levels compared with a normotensive population. Interestingly, the patients with treated WCH had cystatin-c levels comparable with the normotensive cohort.

There are limited data on the effect of drug therapy for patients with WCH. The data that are available is inconsistent. In the Syst-Eur (Systolic Hypertension is Europe) [16] and IDACO (International Database on Home Blood Pressure in Relation to Cardiovascular Outcomes) [17] studies, treated WCH was not associated with increased cardiovascular events, whereas a meta-analysis of the International Database on Home Blood Pressure in Relation to Cardiovascular Outcome (IDHOCO) [18] demonstrated that untreated WCH was associated with increased cardiovascular events. Individually, these studies may not provide significant guidance for the treatment of WCH, however, when viewed in combination, a pattern emerges suggesting a benefit in the treatment of WCH depending on which parameters are used to make the diagnosis. In older studies, a 24-h mean BP of 135/85 mmHg was used as the ‘cut-off’ for normotension, whereas in more modern analyses, the cut-off values have been 130/80 mmHg. Clearly, patients with ambulatory BP values of 135/85 mmHg are not normotensive and that value should not be used to define WCH any longer.

There are no randomized control trials, but there is evidence to support treating WCH to potentially reduce cardiovascular events. In the ELSA trial [19], treatment of WCH resulted in substantial reductions in office BPs (−19 ± 11 mmHg) without any resultant reduction in the 24-h ambulatory BPs. The study may alleviate some concerns that treating WCH will result in deleterious daytime BP reductions. In a subanalysis [16] of the Syst-Eur Trial, treatment of both sustained and WCH resulted in reduction of cardiovascular events and stroke rates compared with the placebo group, however, it was not statistically significant in the WCH group, possibly because of a lack of statistical power.

At the very least, patients with documented WCH should be candidates for more aggressive risk factor modification, closer monitoring of home and office BPs and more routine ABPM to assess for the conversion to sustained hypertension. Those patients at higher cardiovascular risk should also be considered for drug therapy.

**WHITE COAT EFFECT**

The WCE is the isolated elevation of BP in the office setting in patients currently on antihypertensive drug treatment for hypertension. The utility of ABPM in this setting is similar to that for the untreated population of WCH. It can identify those patients who have well-controlled BP and are at risk for unnecessary additional drug therapy, which can increase the risk of medication-related adverse events. As ABPM is a stronger predictor of cardiovascular risk, physicians should resist the urge to intensify drug therapy in the setting of confirmed WCE.

**MASKED HYPERTENSION**

The concept of masked hypertension was introduced relatively recently, being first raised as a clinical concern by Pickering et al. [20] in 2002. Masked hypertension is the presence of normal BP during office measurements and elevated readings on ABPM. Masked hypertension exists in the presence or absence of drug treatment. It is generally defined as an office BP less than 140/90 mmHg but with 24 h, daytime or nighttime ambulatory readings of at least 130/80, at least 135/85 or at least 120/70 mmHg, respectively (Table 1). Masked hypertension is more prevalent in patients with stressful occupations, chronic kidney disease, family history, sleep apnea, diabetic patients, smokers, obesity and left ventricular hypertrophy (LVH) [21,22]. These populations could be screened with ABPM to evaluate for masked hypertension. The prevalence of masked hypertension (MH) in the normotensive population is approximately 10–15% [23,24], and is associated with increased cardiovascular risk and target organ damage [25,26]. In the Jackson Heart Study [26], the prevalence of masked hypertension
Hypertension

was significantly higher, approaching 30% in the African American population. In multivariate analysis, the presence of daytime masked hypertension carried twice the risk of cardiovascular events. In the Masked Hypertension Study of healthy middle-aged normotensive individuals, ambulatory systolic BP measurements identified 15% of participants as masked hypertensive patients [27**].

Interestingly, many studies have demonstrated significantly higher incidence of masked uncontrolled hypertension (MUCH), treated patients with adequately controlled blood readings in the clinic but elevated ABPM readings, compared with MH in untreated patients. Naser et al. [22**] found that nearly one-third of treated patients in their cohort had MUCH. Data from the IDHOCC registry [18] demonstrated that MUCH carried higher cardiovascular risk than MH in an untreated population. Some studies have demonstrated that MH and MUCH are often a result of isolated elevations of nocturnal BP [22**,28] occurring in as many as 25% of treated patients to account for the diagnosis of MH.

There are no cardiovascular outcome data demonstrating benefit of treating masked hypertension. A study of that nature would be a massive undertaking and require many thousands of patients followed for long periods. However, it is clinically intuitive that MH and MUCH represent populations at high risk of cardiovascular events. Although the beneficial effect of the normalization of ABPM BP measurements is unclear, reducing risk in a high cardiovascular risk population is certainly desired. In a recent analysis by Ruilope et al. [29], treatment of MUCH in patients with chronic kidney disease with the mineralocorticoid receptor antagonist finerenone reduced the incidence of MUCH by 65% [29]. Currently, only the European Society of Hypertension and the European Society of Cardiology recommend the treatment of masked hypertension [30], but concerns are mounting on an international basis to do so. In most instances, it would be advisable for clinicians to treat MH with both lifestyle modifications and drug therapies, particularly in those patients with high cardiovascular risk profiles. Repeated ABPM and home BP readings would be required to ascertain the benefits of the therapy.

CIRCADIAN VARIATION OF BLOOD PRESSURE

There exists a normal rhythm to BP characterized by a highly reproducible pattern. BP is lowest at night during sleep with an early morning rise during the awakening period and followed with higher, more variable daytime BP. Perturbations of this natural circadian cycle of BP are associated with adverse clinical events [31,32].

DIPPING PROFILE

A normal decline in nocturnal BP of 10–30% compared with daytime BP is referred to as a ‘dipper’ profile. Those who experience a less than 10% decline in night:day BP are considered ‘nondippers’ and those whose BP increases at night are defined as ‘risers’. The presence of a nondipper profile, which may be as high as one-third of hypertensive patients, is associated with an increased risk of cardiovascular events [33], LVH [34], stroke [35], new onset atrial fibrillation [36].

FIGURE 2. The risk of cardiovascular events and all-cause mortality based on dipping profile as described by ambulatory blood pressure monitoring. Modified from [37].

Adjusted for cohort, sex, age, body mass index, smoking and drinking, cholesterol, history of CV disease, diabetes mellitus, AH treatment, and 24-hour SBP.
fibrillation [36] and renal disease [33] Figure 2 [37]. A nondipping profile has been shown to increase cardiovascular risk even in normotensive patients [38]. Defining the dipper profile using a percentage decline in BP has limited reproducibility, therefore, many define the dipper status based on a more reproducible absolute value, defining a nondipper as a nocturnal BP of more than 125/75 mmHg. Regardless of how it is defined, the risk of a non-dipper profile remains. A blunted decline in nocturnal BP is associated with high-risk cardiovascular phenotypes including: African Americans [39], diabetic patients, chronic kidney disease, obesity and advancing age [40,41].

There are limited data demonstrating benefit to the restoration of a normal circadian BP profile on cardiovascular outcomes. However, there are studies suggesting a potential role for chronotherapy in the treatment of abnormal circadian BP profiles.

Recently, several studies have demonstrated some benefits from drug therapies targeted at restoring a normal dipping pattern. In the largest of these studies, the MAPEC (Monitorizacion Ambulatoria para Prediccion de Eventos Cardiovasculares), more than 2000 patients were randomized to either standard morning dosing of their BP medications versus administration of at least one medication at bedtime. Patients treated with at least one bedtime medication experienced a lower incidence of a non-dipper profile, lower nocturnal BP, better control of their 24-h ambulatory BP and a reduction in the number of cardiovascular events. Although the number of events was low, there was a 65% reduction in major cardiovascular events including stroke and myocardial infarction [42]. In another smaller randomized controlled trial, administration of the combination valsartan/hydrochlorothiazide at bedtime compared with morning dosing resulted in a greater reduction in nocturnal BP, a 35% reduction in the prevalence of a nondipper profile and greater 24-h BP control [43]. In a recent Cochrane review [44] evaluating the effects of chronotherapy, there were no significant differences in outcomes or adverse events. There is a planned randomized clinical trial aimed at assessing the safety and efficacy of chronotherapy [45], however, it will be several years before the results of this study are available.

Clinicians who have availability of ABPM can utilize the recorders to establish their dipping profile, especially in those populations at highest risk of having an abnormal circadian pattern (the very elderly, those with chronic kidney and heart disease, and autonomic dysfunction syndromes). The use of chronotherapy, switching

**FIGURE 3.** Morning blood pressure surge as defined by ambulatory blood pressure monitoring. From [46].

the administration of at least one full dose medication to a bedtime dose, should be considered in those patients with a documented nondipping profile to reduce cardiovascular risk and improve overall 24-h BP control.

**THE MORNING SURGE OF BLOOD PRESSURE**

As part of the normal circadian rhythm, both BP and heart rate rise in the early morning, particularly postawakening (fig. 3) [46]. On the basis of data from the IDACO [47], a relatively normal rise in systolic BP is less than 20 mmHg. A rise in morning BP exceeding 20 mmHg has been shown to be an excessive ‘surge’ in morning BP. Morning blood pressure surge (MBPS) is associated with increased cardiovascular risk in some populations. Early studies evaluating the impact of the MBPS demonstrated increased risk of myocardial infarction, stroke [48] and sudden cardiac death [49]. Japanese researchers found that every 10 mmHg increase in the MBPS resulted in a 22% increased risk of ischemic stroke [50]. In a recent study of elderly patients with well-controlled 24 h BP, the morning surge BP was an independent predictor of fatal and nonfatal stroke, myocardial infarction (MI), peripheral arterial disease and development of heart failure [51].

Cost, large sample size and the time necessary to adequately study the potential benefit from attenuating the morning surge BP have been substantial impediments. As such, there are no large randomized data demonstrating benefit from drug therapy targeted at reducing the rise in morning BP. There are data showing the effectiveness of treating morning surge BP with a-blockers at bedtime [52] or with long-acting renin–angiotensin system blockade [53,54]. Targeting morning surge BP is reasonable given the data available demonstrating the risk it seems to carry. Utilizing chronotherapy to blunt the morning surge or long-acting agents that maintain
their efficacy throughout the 24-h period could be considered as a clinical management tool.

ROLE OF AMBULATORY BLOOD PRESSURE MONITOR IN SPECIAL CONDITIONS

Ambulatory BP monitoring has applications beyond the diagnosis and management of primary hypertension. The technology offers a unique perspective for the evaluation of both orthostatic hypotension and resistant hypertension.

ORTHOSTATIC HYPOTENSION

A blunting of the normal circadian BP rhythm has been demonstrated in patients with orthostatic hypotension and those with autonomic dysfunction (type 1 and 2 diabetic neuropathy, neurodegenerative disorders and autoimmune diseases). These patients may have an inverse nocturnal dipping profile (i.e. riser). Their clinical syndrome may be characterized by profound orthostatic hypotension and supine hypertension. The exaggerated rise in nocturnal BP places these patients at increased cardiovascular risk [55]. Furthermore, marked postural hypotension leads to fall risk, syncope and poor quality of life due to dizziness and confinement to wheelchairs with disease progression. Following a diagnosis of nocturnal supine hypertension using ABPM, very short-acting antihypertensive medications administered at bedtime are often effective in reducing nocturnal BP, while having little impact on their upright daytime BPs.

RESISTANT HYPERTENSION

Defined as a failure to achieve target BP goals with a minimum of 3–4 drugs regimen, including a diuretic, resistant hypertension is a not an uncommon dilemma for clinicians. Ambulatory BP assessment provides clinicians with an opportunity to evaluate these treatment-resistant patients and potentially adjust their regimens. Most importantly, ABPM can differentiate between those patients who are truly resistant and those with a severe WCE. Several studies have demonstrated that as many as 50% of patients deemed resistant based on office BP readings alone are in fact well controlled by ABPM measurements [56,57]. Furthermore, studies have shown lower cardiovascular risk in patients with pseudo resistance [58] with findings that ABPM can stratify patients with resistant hypertension into low-risk, medium-risk and high-risk groups [59]. In addition, ambulatory monitoring can prevent unnecessary titration of medication in pseudo-resistant patients and can offer guidance on when additional medications may be beneficial.

CONCLUSION

Ambulatory BP monitoring has long been recognized as the most accurate and reproducible method for the diagnosis of hypertension. Decades of data have demonstrated the prognostic superiority of ABPM. However, data supporting the clinical benefits of treating hypertension based on the various BP profiles described by ABPM are lacking. Clinical research has shown that chronotherapy can be used to safely normalize the circadian rhythm, blunt the most detrimental rises in BP and maintain well-controlled 24-h BPs. Two decades ago, the effectiveness of utilizing ABPM to reduce the number of medications in treated hypertensive patients without adversely affecting the control of BP, or exerting detrimental effects on LV mass was reported [60]. It is not likely that randomized trials evaluating the effectiveness of managing hypertension based on 24-h ambulatory versus doctor’s office BPs will ever be performed because of the enormity of the study size, duration required to ascertain differences and the cost of such a trial. Nevertheless, nearly all studies in hypertension today use ambulatory BP as either the primary or coprimary endpoint to determine the efficacy of new cardiovascular drugs or safety of noncardiac drugs felt to have a possible BP safety signal during development. As recommended by the US Preventive Services Task Force report in 2015 [7], the quality of data from the past 40 years strongly supports using ambulatory BP monitoring to evaluate and treat patients with any form of newly diagnosed hypertension with the exception of those with severely elevated BP and/or the presence of hypertensive target organ involvement.

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Conflicts of Interest

There are no conflicts of interest with respect to the information presented in this article.
REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

12. cuspidi c, rescaldani m, tadic m, et al. White-coat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: a meta-analysis. J Hypertens 2014; 32:24–32.
14. The first study to demonstrate the deleterious effects of WCH on the right ventricle.
16. This is a recent meta-analysis of current studies that evaluated the cardiovascular significance of WCH.
25. A large prospective observational study to determine the prevalence of masked hypertension in a population of reportedly well-controlled hypertensive patients. A total of 2500 patients were followed for 5 years to determine the prevalence and impact of MUCH.
28. The recent large population-based study that evaluated the prevalence and impact of masked hypertension in African Americans. This study demonstrated a higher prevalence of MH in the black population and increased cardiovascular risk from MH.
30. A recent population-based study demonstrating the relatively high incidence of MH in a population of nearly 900 healthy patients. Highlights the importance of ABPM for routine screening for MH, especially in those with borderline or prehypertensive clinic readings.