Ambulatory Blood Pressure Monitoring in the Diagnosis and Management of Hypertension

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Hypertension (HTN) is a major risk factor for cardiovascular morbidity and mortality, especially in patients with diabetes mellitus (1). The classic definition of HTN is based on office blood pressure (BP) measurements, and most data relating HTN to cardiovascular morbidity and mortality are derived from office measurements (2). Yet, the measurements in the office may not reflect the true BP levels. They may be elevated when the true BP is normal (white coat effect), or they may be normal when the true BP is elevated (masked HTN). Office measurements also do not reflect the diurnal variation and nocturnal BP levels. Twenty-four-hour ambulatory BP monitoring (ABPM) is a precise method to quantify BP levels and diagnose HTN. Recent studies showed that 24-h ABPM is more accurate than office BP measurements in predicting cardiovascular morbidity and mortality (3–6). The present review will summarize the advantages of 24-h ABPM over office measurements and will recommend when and how to use 24-h ABPM in the diagnosis of HTN in diabetic patients.

Ambulatory BP measurements

The use of 24-h ABPM was introduced in the late 1970s. In the beginning, the devices were large, heavy, and cumbersome, but today the devices are lightweight and nearly all of them use an oscillometric measurement method to compute BP levels. This method eliminates observer bias and provides information on BP levels and heart rate throughout the day. The large numbers of readings obtained during the patient's daily activities provide a superior assessment of the true BP and can be used for the diagnosis of HTN. Additionally, 24-h ABPM provides information on BP variability, circadian changes, and the effects of environmental and emotional conditions on BP levels. Several studies that compared ABPM with intra-arterial measurements and mercury column sphygmomanometers demonstrated the accuracy of ABPM (7). However, since many new devices have appeared in the market, it is necessary to validate each device according the criteria proposed by the national committees. It is recommended to perform the 24-h monitoring on a typical working weekday and to obtain a diary or log of activities, wake and sleep times, time of medication administration, meals, and any occurrence of symptoms. Excessive heavy physical activity during measurements should be avoided.

Advantages of ambulatory BP measurements over office measurements

Prediction of cardiovascular events.
Several studies showed that 24-h ABPM better correlates with cardiovascular outcome than clinic BP levels (5,6). In a substudy of the Systolic Hypertension in Europe (Syst-Eur) Trial, Staessen et al. (6) showed that in elderly subjects with untreated isolated systolic HTN, ambulatory systolic BP was a significant predictor of cardiovascular risk over and above clinical BP values. In a prospective cohort study that included 1,464 subjects who were followed for 6.4 years, Ohkubo et al. (5) showed that ambulatory BPs were significantly better related to stroke risk than were screening office BP levels. Recently, Hara et al. (3) showed in 1,007 subjects that 24-h daytime and nighttime ambulatory BP values were closely associated with the risk of silent cerebrovascular lesions detected by brain magnetic resonance imaging, whereas the clinic BP values were not associated with subclinical cerebrovascular events. Of the ambulatory BP values, nighttime BP was the strongest predictor of silent cerebrovascular events.

Comparison of ambulatory BP measurements with home measurements.
Home BP monitoring (HBPM) offers an attractive alternative to 24-h ABPM. Several studies have reported that target organ damage and cardiovascular outcomes are more strongly correlated with HBPM than with clinic BP measurements (8–10). HBPM provides measurements over a much longer period, is cheaper, more widely available, more convenient for patients (particularly for repeated measurements), and has been shown to improve patients' compliance with treatment and HTN control (11). However, unlike ABPM it does not allow the assessment of BP during sleep or at work or the quantification of short-term BP variability. In addition, the recommendation to measure BP at home may induce anxiety that leads to excessive measurements and treatment changes made on the basis of erroneous measurements. A recent meta-analysis showed that HBPM and clinic BP measurements have insufficient sensitivity and specificity compared with 24-h ABPM to be used as a single test for diagnosing HTN in adults (12). It seems that HBPM should be used in conjunction with ABPM as a complementary method of BP assessment. When there is a concordance between the methods, HBPM may be appropriate for long-term follow-up of treated HTN patients.

Identification of white coat HTN

The term white coat HTN (WCH) was originally used to describe subjects who are not receiving antihypertension treatment and have elevated office BP but normal 24-h ABPM (13). More recently, the term WCH is erroneously used with regard to patients who receive antihypertension treatment. The cardiovascular risk of patients with WCH is relatively low, and many studies have shown that the risk of these patients is very similar to the risk of normotensive subjects. It has been shown that in patients with WCH, antihypertensive treatment does not lower ambulatory BP levels (14) and has no effect on cardiovascular morbidity and mortality (15). Many studies showed that WCH carries a more benign prognosis than sustained HTN, even in diabetic patients (16,17). However, in some studies the risk of diabetic patients with WCH was significantly higher than the risk in normotensive subjects (18). This may be related to the high risk of developing true HTN in patients with WCH (19). Therefore, repeated 24-h ABPM should be done in subjects with WCH. A recent study suggests confirmation of a white coat effect with repeated 24-h ABPM within 3 months (20). In those with confirmed white coat effect, a 24-h ABPM follow-up should be done every 6–12 months depending on the BP values recorded during the ABPM. When office BP levels are elevated, 24-h ABPM should be done to confirm the diagnosis of HTN. When the subject is not medicated and the ABPM is normal, a diagnosis of WCH can be made. When the patient is medically treated and the ABPM is normal, the best definition is "treated normalized HTN" (21). When office BP is elevated and ABPM levels are less elevated than office levels, the best term is white coat effect. When office and ABPM are elevated to the same extent, a diagnosis of true HTN should be made (Fig. 1). WCH is also associated with a long-term greater progression of blood glucose abnormalities and an increased risk of developing diabetes and may represent increased susceptibility to future weight gain and dyslipidemia (22,23). This is largely accounted for by the metabolic abnormalities that are frequent components of this condition. WCH may be present in as many as 20% of subjects who appear to have HTN according to office measurements. WCH seems to be less frequent in the context of type 2 diabetes, and its impact on cardiovascular complications remains controversial (24). However, in a recent large study WCH was present in 33% of the diabetic patients (25). These subjects may receive long-term unnecessary and expensive drug treatment (26). Thus, the only way to prevent overdiagnosis of HTN is to confirm it by 24-h ABPM.

Identification of masked HTN. Masked HTN is defined when office BP levels are normal in an untreated subject and ABPM levels are elevated. This condition is present in ~10–20% of subjects who are considered to be normotensive according to office BP measurements (27). Masked HTN is more common in diabetic patients (24), and it may be present in one of two subjects with type 2 diabetes and apparently normal office BP (28). Several studies have shown that the cardiovascular risk in patients with masked HTN is elevated and similar to the risk in patients with sustained HTN (29,30). This condition should be identified and treated adequately to control BP. Yet, it is not practical to perform ABPM in all normotensive subjects to reveal masked HTN. Therefore, ABPM should be done only in normotensive subjects who are likely to have masked HTN, such as those with evidence of target organ damage (left ventricular hypertrophy, renal failure, and microalbuminuria), those with occasional elevated BP readings, and those with exaggerated BP response to exercise (31,32).

Nocturnal BP. Physiologically, BP falls by >10% during nighttime (asleep). When BP falls by <10% during nighttime, it is defined as nondipping (31). Nocturnal nondipping is associated with increased risk of stroke, end-organ damage, and cardiovascular events including death (33,34). Nondipping is common in diabetic patients and may reach a prevalence of ~30% (34,35). What are the mechanisms for the attenuated BP decline during sleep in diabetic patients? Subjects with type 2 diabetes are more likely to have obesity-associated obstructive sleep apnea, a recognized cause for nondipping. Orthostatic hypotension, which is more common in diabetic patients owing to autonomic neuropathy, is also associated with nondipping (36). Diabetic nephropathy, heart failure, and perhaps a more general form of salt retention might dampen the BP reductions expected during sleep-related sympathetic withdrawal. For diagnosis of nondipping, it is important to relate nighttime readings with the patients' diary to confirm their reliability. A decrease in heart rate, which is typical in sleep time, may indicate that the patient was asleep. Extreme fall of >20% in BP during sleep time is known as extreme dipping. This pattern is not necessarily benign, since it may be associated with mild cognitive impairment in the elderly (37).

ABPM guiding management of HTN. ABPM may guide management of HTN. Progressive decrease in sleep BP in nondipping patients reduces cardiovascular morbidity and mortality and therefore should be a therapeutic target (38).
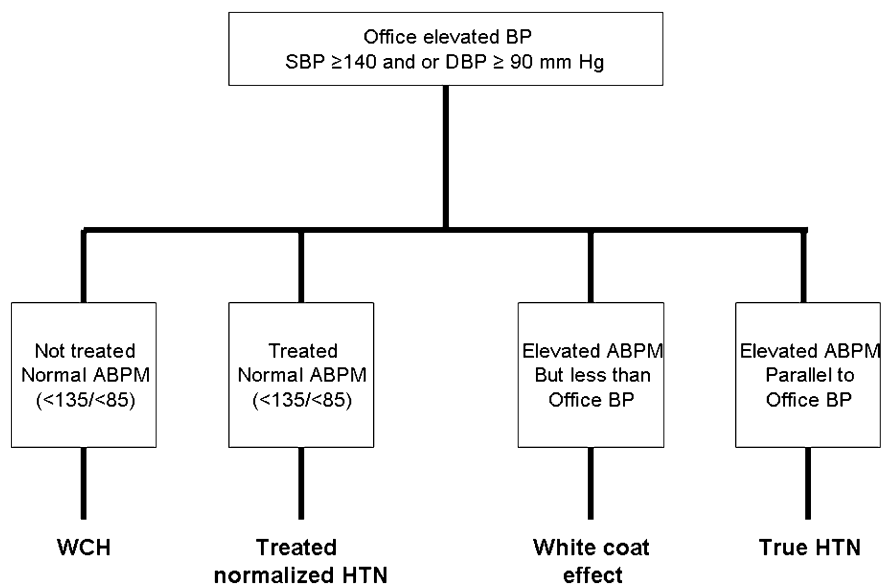

Figure 1—*Possible diagnosis of patients with elevated office BP levels according to ABPM. SBP, systolic BP; DBP, diastolic BP.*

Achieving this target requires proper patient evaluation by 24-h ABPM. Bedtime treatment will be clearly indicated in patients with a nondipping pattern, whereas in extreme dippers evening dosing should be avoided.

ABPM may also identify patients with morning BP surge. Several studies showed an association between morning BP surge and cardiovascular morbidity and mortality (39–41). Indeed, in one study the morning BP surge was associated with decreased mortality in nondipping HTN patients (42). However, a recent meta-analysis showed that exaggerated increase in morning BP is associated with increased cardiovascular risk (43). Treatment that controlled BP throughout the early morning hours is desirable, since it reduces the risk associated with the morning BP surge (44). Using antihypertension agents with long-lasting effect in combination with short-acting agents given at bedtime may be suitable for nondipping patients with morning BP surge. Drugs that are given once daily in the morning but do not provide adequate BP control during the night and early morning may be less protective than drugs providing 24-h BP control. Among the β-blockers, atenolol once daily does not provide adequate BP control during the nighttime and early-morning periods (45). Sarafidis et al. (46) showed that atenolol was less effective in sustaining 24-h and early-morning BP reductions compared with metoprolol succinate in HTN patients treated with once-daily hydrochlorothiazide. It is possible that differences in outcome between atenolol-based and other therapies may be the result of inadequate dosing of atenolol, a medication that may not be effective for the entire 24-h period. An alternative approach to lower night BP and the morning surge is to administer treatment at night. Recently, it has been suggested that administration of at least one antihypertension agent at bedtime may improve BP control (47). In a prospective study, Hermida et al. (47) showed that in HTN patients with type 2 diabetes, bedtime treatment with at least one antihypertension agent improved 24-h ABPM control and reduced cardiovascular morbidity and mortality.

Additional information derived from ABPM. ABPM may help to identify secondary HTN. Lack of nocturnal fall in BP may suggest the existence of sleep apnea (48). Performing ABPM is indicated in all patients with resistant HTN to exclude white coat effect as a cause of apparent

resistance (49). It has been shown that 20–30% of patients with apparent resistant HTN have normal BP levels according to 24-h ABPM (50). Data derived from 24-h ABPM can be useful to diagnose the cause of syncope. It is useful to document fluctuating BP in patients with orthostatic hypotension, autonomic failure, or asymptomatic postprandial hypotension. The incidence of these pathologies is especially high in elderly patients with type 2 diabetes (51,52). Ambulatory BP measurements also provide information on heart rate throughout the day, which may be helpful in choosing the right antihypertension treatment. In young patients with fast heart rate, β-blockers may be effective, whereas in those with slow heart rate β-blockers should be avoided. Adjustment of antihypertension therapy based on 24-h ABPM provides the same BP control as treatment based on office measurements but with less intensive therapy (53). ABPM may also be used to ensure BP control throughout the 24 h (54). In addition, ABPM provides information on short-term BP variability derived from the SD of daytime and nighttime readings. This parameter has been correlated with risk of end organ damage and cardiovascular mortality (55,56). It has been shown that calcium antagonists are more effective than β-blockers in reducing BP variability (57).

ABPM in diabetic patients. ABPM is particularly important for the management of HTN in diabetic patients, since HTN is a major risk factor for cardiovascular disease in these patients. Diabetic patients are more likely to be nondippers, and therefore office BP measurements do not reflect the real cardiovascular risk (25). WCH seems to be less frequent, and masked HTN is more frequent in diabetic patients and seems to be associated with increased organ damage (24). Since HTN is particularly devastating in diabetic patients, it seems prudent to perform ABPM in all diabetic patients with high-normal BP levels (1). In patients with normal office BP levels and elevated ambulatory BP levels, antihypertension treatment should be initiated and the response should be evaluated by repeated ambulatory BP measurements. Abnormalities in systolic BP, particularly during the night, could be linked with the excess of BP-related cardiovascular risk of diabetes. A wider use of ABPM in diabetic patients would identify more patients with masked HTN and patients with nocturnal HTN and would help to improve BP control.

Device validation and analysis of ABPM data

For achievement of valid data from 24-h ABPM, it is important to use only devices that were approved by international standards (58,59). It is essential to choose the correct cuff size because BP obtained from oscillometric devices may vary, depending on cuff size and cuff-arm compliance (60). The ABPM should be done on a normal workday rather than a rest day to obtain a typical BP profile.

The readings should be taken every 20–30 min during the day and every 30–60 min at night to avoid interfering with activity or sleep. However, measurements can be made more frequently. To be considered successful, at least 85% of readings should be suitable for analysis. ABPM profiles should be interpreted with reference to activity and sleep patterns. Ambulatory BP readings may not be accurate when taken during exercise, movement, or driving or when cardiac rhythm is irregular (e.g., atrial fibrillation). Using the device for ABPM is safe and not usually associated with complications, but occasionally petechiae of the upper arm or bruising under the inflating cuff may occur, and there may be sleep disturbances. Discomfort and sleep disturbance should be taken into account when interpreting the readings (including the presence or absence of nocturnal dipping) acquired by 24-h ABPM.

Normal ambulatory BP values

A recent large study that included 8,575 patients assessed the ambulatory BP equivalents to clinic BP thresholds for diagnosis and treatment of HTN (61). Average clinic measurements by trained staff were 6/3 mmHg higher than daytime ambulatory BP and 10/5 mmHg higher than 24-h BP. Daytime ambulatory equivalents were 4/3 mmHg less than the 140/90 mmHg clinic threshold, 2/2 mmHg less than the 130/80 mmHg threshold, and 1/1 mmHg less than the 125/75 mmHg threshold. Equivalents were 1/2 mmHg lower for women and 3/1 mmHg lower in older people compared with the whole group. Based on this study, it has been suggested that HTN should be defined according to 24-h ABPM when one or more of these criteria exist; the 24-h average BP is >130/80 mmHg and the daytime average >135/85 mmHg and/or nighttime average >120/70 mmHg (31). Target BP in HTN patients depends on the associated diseases and target organ damage. In uncomplicated HTN, the ABPM equivalent to office BP of 140/90 mmHg

is an average daytime BP of 136/87 mmHg. In diabetic patients or patients with coronary artery disease or chronic kidney disease, ABPM equivalent to office BP of 130/80 mmHg is average daytime BP of 128/78 mmHg, and in HTN patients with proteinuria >1 g per day the ABPM equivalent to office BP of 125/75 mmHg is average daytime BP of 124/74 mmHg (31).

Summary and conclusions

Several studies have shown that ABPM predicts cardiovascular events better than office BP levels (62). Eguchi et al. (63) demonstrated in diabetic patients that elevated ambulatory systolic BP while awake and asleep predicts increased risk of cardiovascular disease more accurately than clinic BP. ABPM may help to diagnose WCH and white coat effect, masked HTN, and nocturnal HTN.

The most recent recommendations from the National Institute for Health and Clinical Excellence on the management of HTN suggest using ABPM to confirm the diagnosis of HTN when clinic BP is ≥140/90 mmHg (64). This strategy is cost-effective and would reduce misdiagnosis and save costs. In a recent analysis, Lovibond et al. (65) developed a Markov model to assess the cost-effectiveness of three diagnostic strategies for HTN after a raised initial clinic BP reading. ABPM was the most cost-effective strategy for the diagnosis of HTN for men and women of all ages. It also resulted in more quality-adjusted life-years for men and women older than 50 years. It has been shown that additional costs from ambulatory monitoring are counterbalanced by cost savings from better targeted treatment. Thus, it seems that we should change our traditional practice to diagnose and manage BP according to office measurements and more broadly use 24-h ABPM, particularly in diabetic patients, to optimize BP control.

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