Ambulatory blood pressure as a predictor of cardiovascular risk

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Abstract

Hypertension is one of the most common primary diagnoses and a known risk factor for cardiovascular disease, stroke and kidney disease. Like many other physiological variables, blood pressure is characterized by long- and short-term variability. Thus, blood pressure measured over extended periods of time, i.e. ambulatory monitoring, is more representative of the actual value than a single office reading. In longitudinal studies, ambulatory blood pressure (ABP) is found to predict future cardiovascular risk better than conventional blood pressure. Not only blood pressure values but also the pattern predicts cardiovascular risk on ABP measurement. Non-dipping blood pressure pattern, i.e. night-time/daytime pressure greater than 0.9, is an independent risk factor for cardiovascular events. Ambulatory blood pressure is vital for identifying specific conditions such as white coat hypertension, masked hypertension, and apparent drug resistance. Recognizing these conditions is important considering the fact that they have significantly different prognosis than predicted from conventional office readings in each condition.

Key words: ambulatory hypertension, white coat effect, masked hypertension, cardiovascular risk, resistant hypertension.

Introduction

Hypertension is a known modifiable risk factor for cardiovascular disease, stroke and kidney disease [1]. There is convincing evidence that maintaining blood pressure in the normotensive range reduces the cardiovascular risk [2]. Till now blood pressure measurement in the clinic setting using a sphygmomanometer is the most widely used method of diagnosing and monitoring hypertension. Though there is a good correlation between office blood pressure and cardiovascular events, this snapshot might not capture the true picture. Some patients may receive unnecessary and/or aggressive therapy (white coat effect) while some true hypertensives would be missed (masked hypertension).

Prevalence of hypertension, white coat hypertension and masked hypertension

Hypertension is the most common primary diagnosis in the United States. As per the National Health and Nutrition Examination survey of 2005-06, it is estimated that about 29% of Americans older than

18 years suffer from Hypertension. Another 37% had pre-hypertension defined by systolic blood pressure 120-139 and diastolic blood pressure 80-89 mm Hg but no use of antihypertensive medications [3]. The prevalence of hypertension increases steadily with age, as about 67% of Americans aged 60 years or older are affected. Interestingly, about 7% of patients were diagnosed as hypertensive during this survey who were never told by their health care provider that they were hypertensive [3]. Of note, this survey was based on an average of up to three brachial readings obtained during a single examination.

The prevalence of white coat hypertension varies from 9 to 25% in different studies [4, 5]. Two possible factors responsible for these variations are mean age of the sample and the clinical settings, i.e. population-based studies [4, 6] vs. clinic-based studies [5]. A meta-analysis of four population-based studies, three from Europe and one from Japan, found that about 10.9% of the population had white coat hypertension [7].

In the same meta-analysis, which enrolled more than 7000 subjects from the general population, about 14.6% of individuals were found to be suffering from masked hypertension.

Normal variations in blood pressure

In humans, like many other physiological variables, blood pressure is characterized by both short- and long-term variability. In fifteen normal lean healthy subjects with mean age of 29.9 ±6 years blood pressure was measured in the lower limbs using two microphones and an automated blood pressure recorder for 12-24 h [8]. Mean arterial pressure dropped markedly immediately after subjects went to bed, followed by a second dip during the hyperemic blood flow phase. There was a gradual increase in blood pressure during the later part of the night, followed by an abrupt increase during the change from supine to upright position the next day.

Blood pressure and heart rate variability over a 24-h period were examined by Mancia *et al.* in 89 subjects by intra-arterial monitoring using the Oxford technique [9]. Each subject showed marked short-term and long-term blood pressure and heart rate variability. But, in average analysis of all the subjects, the only long-term variation which was systemically found was reduction in blood pressure during sleep. Though absolute blood pressure variability was higher in the hypertensive subjects, the percentage change was similar in the two groups.

Dippers versus non-dippers

A decline of 10% or more from the daytime blood pressure during sleep or nighttime has been used in various studies to classify dippers [10]. Conversely, subjects with less than 10% decline during sleep or nighttime from their daytime or awake blood pressure are called non-dippers. Non-dippers have been found to be at increased risk for blood pressure related complications.

Cross-sectional studies have found an association between end-organ damage and non-dipping blood pressure pattern. A study evaluating asymptomatic cerebrovascular disease with magnetic resonance imaging (MRI) found a significant association between a lower fall in nocturnal blood pressure and silent cerebrovascular disease [11]. A comparative study of patients with Binswanger and lacunar dementia with normal controls derived a similar conclusion [12]. Left ventricular mass/hypertrophy has been found to be more closely associated with the non-dipping pattern even after adjustment for age, sex, and daytime blood pressure [13].

The findings of cross-sectional studies have been confirmed in prospective studies involving hypertensive and normotensive subjects. Verdecchia *et al.* prospectively followed 1187 hypertensive subjects and 205 healthy volunteers who underwent baseline 24 h ambulatory blood pressures measurement for a mean of 3.2 years. In this cohort cardiovascular morbidity, i.e. combined fatal and nonfatal cardiovascular events, was significantly higher in non-dippers as compared to dippers [14]. Similarly, a community-based Japanese study followed 1542 residents over 40 years of age for a mean of 5.1 years after a baseline ambulatory blood pressure (ABP) recordings [15]. In this study, non-dippers had significantly higher cardiovascular mortality as compared to dippers. But, the highest mortality was observed in the subjects who had increased nighttime blood pressure, defined as inverted dippers.

Technique

Ambulatory blood pressure monitors are used to measure blood pressure while the patients go about performing their daily activities. It involves a monitoring device of size of about 4 by 3 by 1 inch and about 2 kg (kilograms) in weight. It can be easily worn on a belt by the patient. This monitor is connected to an appropriate size blood pressure cuff worn on the upper arm through a plastic tube.

At the start of monitoring the monitor is attached and the cuff is placed on the non-dominant upper arm. It is recommended that a series of calibration readings be taken by an experienced technician to ensure that the device is within 5 mm Hg of a standard mercury sphygmomanometer [10]. During a typical monitoring blood pressure is measured every 15-30 min over a 24-h period.

Patients should be instructed to hold the arm still by their side while the device is monitoring

blood pressure. A diary of daily activities can be helpful for correlation especially in terms of sleeping, awake and post-exertional blood pressure readings. Also, a normal working day is preferred for 24-h monitoring.

A total of about 50 to 100 readings are taken and stored in the device. This data can be downloaded into a computer using device-specific software. A report of mean value and the trend of both systolic and diastolic blood pressures during specific, i.e. daytime, nighttime and 24-h period, can be synthesized from raw data. The most commonly used outputs for clinical use include absolute level of mean daytime, nighttime and 24-h blood pressure.

Normal values for ambulatory blood pressure

Currently suggested normal values of ABP are mostly based on the distribution of ABP in a normotensive reference population [16, 17] and comparison of ABP level that corresponds to office or conventional office blood pressure (CBP) of 140/90 mm Hg [10]. This values are presented in Table I. It is worth mentioning that these cut-off values are predominantly derived statistically and not based on outcome studies. Data from an outcome driven population based study suggests that a lower threshold should be used than proposed by current guidelines [18].

Ambulatory versus conventional blood pressure

Prognostic superiority of ABP was evident as early as 1983 in the study done by Perloff *et al*. [19]. They followed 1076 hypertensive subjects after initial measurement of both ambulatory and office blood pressure. An estimated ABP was calculated for each subject using his or her office blood pressure by linear regression. The difference between estimated and observed ABP was analyzed using the life-table method. It was found to be significantly associated with fatal and nonfatal cardiovascular events. This finding was confirmed by the same investigators in 761 hypertensive patients using the Cox proportional hazard model [20].

In a Danish population-based study involving patients free of any major cardiovascular disease at baseline investigators found that every 10/5 mm Hg rise in systolic/diastolic ABP was associated with significantly higher risk of common end-point of cardiovascular mortality, stroke and ischemic heart disease [21].

International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcome (IDACO) investigators conducted a meta-analysis of 7030 patients from four countries to evaluate the prognostic superiority of daytime ABP over CBP measurement in

Table I. Suggested values for ambulatory blood pressure

	Optimal [mm Hg]	Normal [mm Hg]	Abnormal [mm Hg]
Daytime	< 130/80	< 135/85	> 140/90
Nighttime	< 115/65	< 120/70	> 125/75
24-h	< 125/75	< 130/80	> 135/85

predicting fatal and nonfatal cardiovascular events [7]. In a multivariate fully-adjusted analysis including both CBP and ABP, CBP lost its prognostic significance whereas ABP retained its predictive value with the exception of diastolic ABP as a predictor of cardiac and coronary events.

Prognostic significance of ABP has also been evaluated in hypertensive patients already taking antihypertensive agents. In a study of 1963 treated hypertensive patients, higher ABP was found to significantly predict cardiovascular events even after adjusting for age, sex, smoking status, diabetes mellitus, cholesterol level, body mass index, use of lipid-lowering drugs, history of cardiovascular events and even office blood pressure measurements [22]. In contrast, a randomized trial of placebo versus antihypertensive medications in about 800 patients older than 60 years suffering from isolated systolic hypertension failed to show a statistically significant association between ABP and cardiovascular events after adjusting for CBP [23]. Interestingly, in the same study placebo group ABP predicted cardiovascular risk over and above CBP in controls. Though the exact reason for the difference in outcome is not well understood, possible causes are differences in age and baseline characteristics of the two populations, inclusion criterion based on diastolic blood pressure in the former versus isolated systolic blood pressure in the latter, and intention to treat analysis in the latter versus no loss to follow-up in the former.

Not only is high ABP associated with higher cardiovascular event rate but treatment with well controlled ABP actually might decrease the cardiovascular risk over CBP. This was evident in a *post-hoc* analysis of a study of 790 patients with essential hypertension who underwent ABP monitoring at baseline [24]. During a mean follow-up of 3.7 years, 37.3% achieved adequately controlled ABP. ABP control was associated with lower risk of cardiovascular event even after adjusting for age, diabetes and left ventricular hypertrophy, whereas CBP predicted a statistically insignificant lower risk.

Despite these possible advantages ABP is not currently used for routine risk assessment in the general population. Current recommendations from the seventh report of the Joint National Committee [25] and Task Force of the European Society of Hypertension and European Society of Cardiology [26] on ABP measurement are presented in Table II and Table III respectively.

Table II. Situations in which ABP monitoring may be helpful*

• Suspected white coat hypertension without end-organ damage
• Apparent drug resistance
• Hypotensive symptoms of antihypertensive medications
• Episodic hypertension
• Autonomic dysfunction

Seventh report of Joint National Committee

Table III. Ambulatory blood pressure monitoring should be considered in the following clinical situations: when...*

• Considerable variability of office BP is found over the same or different visits
• High office BP is measured in subjects otherwise at low cardiovascular risk
• There is a marked discrepancy between BP values measured in the office and at home
• Resistance to drug treatment is suspected
• Hypotensive episodes are suspected, particularly in elderly and diabetic patients
• Office BP is suspected in pregnant women and pre-eclampsia is suspected

Task Force for the management of Arterial Hypertension of the European Society of Hypertension and European Society of Cardiology

A few special clinical situations relevant to ABP monitoring are discussed below.

White coat hypertension

A persistently elevated clinic blood pressure greater than 140/90 but an average ABP less than 135/85 is a commonly used definition of white coat hypertension (WCH) [10, 25, 26]. White coat hypertension has been recognized for long and found to be associated with fear or anxiety related to the medical environment and physicians [10, 25]. The role of the physician in white coat hypertension was evident in a large study in which blood pressure was measured by physicians and a nurse in the same subjects [27]. Nurses recorded significantly lower mean systolic and diastolic blood pressure despite no difference in technique. It is important to recognize this phenomenon as this may lead to erroneous labeling of patients as hypertensive and institution of therapy. This was exemplified in a meta-analysis done by IDACO investigators, which showed that about 39% of patients with white coat hypertension were on antihypertensive treatment [7].

Is WCH a cardiovascular risk factor? There have been a number of studies which have looked at long-term cardiovascular risk in patients with WCH. Most studies have found that WCH has significantly lower risk for cardiovascular events as compared to essential or sustained hypertension [28, 29]. In a meta-analysis of seven studies with a total sample size of 11 502 subjects evaluating the relative risk of cardiovascular events in WCH, normotension, masked hypertension (MH) and sustained hypertension, the incidence of cardiovascular events was twice in sustained hypertension as compared to WCH [30]. Importantly, there was a 12% increase in cardiovascular events in WCH as compared to normotension which was statistically insignificant. In addition to combined cardiovascular events, there have been studies which have looked at a specific association between stroke and WCH. A meta-analysis of four such studies concluded that WCH is not definitely associated with increased risk of stroke during the 6-year follow-up period [31]. But, before discarding WCH as a benign condition it is important to mention that the hazard curve of WCH crossed that of ambulatory hypertension by the 9th year of follow-up [31]. Also, in a 10-year follow-up study of 420 newly diagnosed hypertensive patient and 146 controls, WCH was found to be associated with significantly higher incidence of fatal and non-fatal events than normotensive subjects [32]. Thus the benign nature of WCH in long-term follow-up is not well established. Now there is evidence that cardiovascular risk increases linearly from blood pressure as low as 115/75 mm Hg [1]. Therefore, it is possible that this unproven higher risk of cardiovascular events in WCH in long-term follow-up is related to the fact that WCH subjects have higher mean out-of-office blood pressure than the normotensive population as evident in a meta-analysis of seven studies [30].

Suspected WCH is the only current indication for ABP monitoring which qualifies for Medicare reimbursement [25]. However, it is difficult to predict which hypertensive patients in the clinic are suffering from WCH. But, WCH is more common in grade 1 hypertensive females, at older ages, in non-smokers, in recent-onset hypertension and a limited number of office blood pressure measurements [26].

Current recommendations from the European Society of Hypertension/European Society of Cardiology (ESH/ECC) are as follows. The identification of WCH should be followed by a search for other metabolic risk factors and evidence of end-organ damage. Drug treatment should be started if there is evidence of end-organ damage or high cardiovascular risk. Lifestyle changes and close follow-up are recommended in all patients who are not started on medications.

Masked hypertension

It is the reverse of WCH, defined as normal blood pressure (< 140/90) in the clinic but an elevated home or ambulatory blood pressure. Therefore, this is

a condition which cannot be diagnosed in the clinic [25, 26]. As noted above the prevalence of masked hypertension (MH) ranges from 9 to 17% depending upon the clinical setting and selection criterion [30]; a meta-analysis of four large population-based studies estimated it to be about 14.6% [7]. Many clinical studies have reported higher cardiovascular risk in MH as compared to normotension. A large meta-analysis done by IDACO investigators found that the adjusted hazard ratio for MH was 1.8 (1.59-2.03, p < 0.0001) for a combined outcome of fatal and non-fatal cardiovascular events [7]. Another meta-analysis included two primary care and one specialist clinic-based studies, in addition to the above-mentioned four population-based studies. The total sample size amounted to 11,502 participants. The adjusted hazard risk for MH was 2.00 (1.58-2.52, p < 0.0001) for an endpoint of fatal and non-fatal cardiovascular events [30].

Thus, MH is an important cardiovascular risk factor which is missed by routine clinic blood pressure monitoring. Currently, there is insufficient evidence to recommend screening for MH in the general or specific patient population. But on the basis of cross-sectional studies screening of MH in two groups may prove cost-effective. The first group comprises a patient population known to have high prevalence of MH; it includes subjects with transiently high clinic blood pressure or high normal clinic blood pressure [33]. The second group includes patients with high cardiovascular risk such as diabetic patients or patients with chronic kidney disease and high cardiovascular risk profile or evidence of end-organ damage [26, 34].

Microalbuminuria and kidney disease

Cardiovascular disease is the major cause of mortality in patients with diabetes. Hypertension frequently coexists with diabetes as compared to the general population [35]. It has recently been recognized that microalbuminuria, which is highly prevalent in the diabetic and hypertensive population, is an independent predictor of cardiovascular risk [36]. Even after using a lower threshold for office-based blood pressure or CBP, i.e. 130/80 mm Hg, older studies have suggested that nephropathy precedes the development of hypertension [37]. In a prospective observational study of 75 type 1 diabetics with more than 5 years of disease, but without any evidence of microalbuminuria or hypertension, ABP was measured at baseline and at 2 years. These patients were followed for development of microalbuminuria by measurement of urinary albumin every three months [38]. Fourteen patients developed microalbuminuria during the mean follow-up of 63 ±9.3 months; these patients had significantly higher mean systolic pressure during sleep. A ratio of 0.9 or lower between nighttime systolic to daytime systolic pressure had 91% negative predictive value for development of microalbuminuria. Therefore, a loss of normal fall in blood pressure during sleep may select the patients who are at increased risk of microalbuminuria and might benefit from early therapy with ACE inhibitors or at least closer follow-up. High nocturnal blood pressure has also been found to be a predictor of progression of nephropathy in type 2 diabetic populations [39].

Chronic kidney disease represents another cohort which has exceptionally high cardiovascular risk over the general population [40]. Non-dipping pattern of blood pressure on ambulatory monitoring has been found to predict a decline in renal function after adjusting for other factors [41]. Hemodialysis patients represent a unique challenge for blood pressure measurement with conventional means, as there are marked changes in intravascular volume associated with dialysis. A study evaluating the prognostic significance of 24-h ABP in non-diabetic hemodialysis patients found that the ratio of night to daytime systolic blood pressure was the sole blood pressure variable which predicted cardiovascular mortality in addition to left ventricular hypertrophy (LVH) [42]. In multivariate analysis LVH lost its predictive significance but the ratio of night/daytime pressure still had marginal statistical significance.

Orthostatic hypotension

Orthostatic hypotension (OH) is defined as drop of greater than 20 mm Hg in systolic pressure or 10 mm Hg in diastolic pressure from a sitting to standing position [25]. The normal response to a change in posture from sitting to standing is a slight increase in diastolic pressure and a slight drop in systolic pressure. The common clinical practice of measuring blood pressure in a sitting position precludes the diagnosis of OH in the clinic. Important causes of OH include diabetes, hemodialysis and Parkinsonism in addition to volume depletion, baroreflex dysfunction and other dysautonomias [25]. The recognition of OH is becoming more important due to the fact that it is frequently encountered in the elderly with isolated systolic hypertension [43]. The presence of OH has been found to be an independent predictor of all-cause and cardiovascular mortality [25]. To complicate the situation further, these patients may have high blood pressure in the supine position, especially during the night or sleep [44]. Treatment of these patients with antihypertensive agents such as α-blockers, nitrates and diuretics can aggravate OH.

Thus 24-h blood pressure monitoring can not only be used to correlate symptoms such as dizziness and light headedness with OH in

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the target population, but also to optimize the blood pressure control and to decrease their risk of falls.

Resistant hypertension

Resistant hypertension is defined as failure to achieve blood pressure goals in patients who are on the full dose of an appropriate three-drug regimen including a diuretic [25]. While resistant hypertension can be secondary to important causes such as volume overload or drug induced, an exaggerated white coat effect is responsible for high clinic pressure in a fraction of these patients. Prospective studies have shown that a subgroup of treated hypertensive patients with normal ABP are at significantly lower risk for cardiovascular events than true resistant hypertensive patients [45, 46]. Thus, 24-h ABP monitoring can be used to identify patients with relatively benign prognosis and prevent further work-up or additional treatment.

Conclusions

Normal variations in blood pressure make conventional office reading less representative of true blood pressure in an individual than ABP measurement. Furthermore, ABP correlates better with long-term cardiovascular risk than conventional or office blood pressure. Not only values but also diurnal pattern of blood pressure can help in predicting cardiovascular risk. Also, non-dipping blood pressure pattern is an important risk factor for cardiovascular events. Ambulatory blood pressure can be used to recognize a subset of patients with white coat hypertension and masked hypertension, which have significantly different prognosis than suggested by their office blood pressure. Ambulatory blood pressure may also help in managing patients with apparent drug-resistant and orthostatic hypotension.

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