Curr Atheroscler Rep (2013) 15:317
DOI 10.1007/s11883-013-0317-9

CORONARY HEART DISEASE (JA FARMER, SECTION EDITOR)

Ambulatory Blood Pressure Improves Prediction of Cardiovascular Risk: Implications for Better Antihypertensive Management

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Published online: 20 February 2013

Abstract Accurate measurement of arterial pressure is necessary for diagnosis of hypertension and for assessment of its therapy. The development and growing application of ambulatory blood pressure monitoring (ABPM) furthers these goals. Use of ABPM has defined white coat hypertension (WCH) and masked hypertension (MH), important prognostic diagnoses. ABPM categorizes blood pressure in several ways that increase accuracy for diagnosis and prediction of cardiovascular risk. Measurements of blood pressure throughout the day, at night during sleep, during the morning surge, and, in some instances selected intervals can be especially valuable for both research and clinical management. ABPM is being explored for its value in measuring pulse pressure and a derived index of arterial stiffness. ABPM has also shown to be valuable for defining the effects of antihypertensive drugs therapy. Results of such studies are crucial for advancing antihypertensive management. This review will summarize the important and emerging role of ABPM in defining risk for cardiovascular disease.

Keywords Ambulatory blood pressure monitoring · White coat hypertension · Masked hypertension · Dipper · Non-dipper · Morning surge · Pulse pressure · Arterial stiffness index · Hypertension · Cardiovascular risk · Cost-effectiveness

Introduction

The introduction of a non-invasive, portable recording device for measuring arterial blood pressure outside of the clinic was initiated in the late 1960s [1]. The first study using such a device for evaluating the prognosis of hypertensive patients in comparison with clinic pressures was published in 1983. It was clearly shown in this prospective study, that out of office pressures were superior to clinic pressures for predicting future cardiovascular events [2]. In the past 30 years, ambulatory blood pressure monitoring (ABPM) has become the gold standard for defining arterial pressure in relation to both prognosis and the effects of antihypertensive therapy. There have been major improvements in technology, methods of analysis, diagnostic precision, and application, so that one national health care system has already recommended that ABPM be widely applied to classify hypertension in community-wide screening [3••, 4]. Other national or international guideline writing groups are giving ABPM substantial emphasis [5••, 6]. This review will focus on how the application of ABPM can improve the prediction of future cardiovascular and renal disease in comparison with clinic or office measurement.

What Information Does ABPM Provide?

ABPM is comprised of several elements: 1) devices that are portable, non-invasive and use an upper arm cuff with an enclosed sensor to detect arterial pressure; 2) a pump in the device inflates and deflates the cuff on a defined schedule; 3) software in the device to adjusts cuff pressures and record measurements; 4) a connection to a desktop computer for storing and analyzing measurements; and 5) computer software for data processing, reporting and, in research settings, transmission to central computers. Devices are programmed to record arterial pressure throughout the waking day and at night, during sleep, then during and after reawakening for completion of the 24-hour cycle [7]. Analysis of the recordings (see Table 1, top half) allows calculation of: 1) the entire 24-hour averages

This article is part of the Topical Collection on *Coronary Heart Disease*

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for systolic pressure, diastolic pressure, mean arterial pressure, pulse pressure and heart rate; 2) average daytime measurements; 3) average nighttime measurements; 4) sleep time measurements; 5) measurements during the morning surge; and 6) selected intervals of interest. For example, measurements can be chosen for specific conditions or behaviors, such as angina episodes [8]. Any or all of these measurements have been used for longitudinal surveys of outcomes for cardiovascular disease [9–15, 16•].

The hemodynamic pattern for arterial pressure throughout the day has been characterized. At night, when pressure falls, there is a disproportionate reduction in cardiac output and substantial increase in peripheral resistance. The morning surge, when pressure increases to daytime levels is characterized by a large increase in cardiac output [17].

Classification of Blood Pressure by ABPM

Based on clinic blood pressures alone, populations can be divided into a few categories: optimal blood pressure < 120/80 mmHg, normal blood pressure 120–129/80–85 mmHg , high-normal, pressure 130–139/80–89 mmHg , and hypertension ≥ 140/≥ 90 mmHg [18]. The US Seventh Joint National Committee on High Blood Pressure (JNC 7) uses the term "prehypertension" to overlap normal and high-normal to include all of the above so that pre-hypertension is defined as 120–139/80–89 mmHg [19]. This approach is based on the well-founded expectation that most of those in the pre-hypertensive range will eventually become hypertensive [20].

ABPM greatly expands options for classification in two ways, as indicated in Table 1 (bottom half). By describing blood pressure throughout the 24-hour period, norms for the entire period, daytime, nighttime, sleep intervals and the morning surge can be assigned. Furthermore, comparison between clinic pressures and ABPM has led to recognition of white coat hypertension (WCH) WCH (Clinic pressure elevated and ABPM normal [21–23]) and masked hypertension (MH) (Clinic Pressure normal and ABPM elevated [24••]). The pattern of blood pressure throughout the day has also given rise to the clinic diagnoses of 'dipper', 'non-

Table 1 Classification of blood pressure by ambulatory blood pressure monitoring (ABPM)

Measurement	Normal range [18, 78]	Comments
24-hour pressure	< 130/80 mm Hg	No adjustment for older age groups.
Daytime blood pressure	< 135/85 mm HG	No adjustment for older age groups.
Nighttime or Sleep Pressure	< 120/80 mm Hg	No adjustment for older age groups.
Sleep awake ratio %	Sleep/average daytime pressure	Generally accepted
Dipper pattern	10–20 % reduction from daytime to sleep	Generally accepted
Non dipper pattern	Fall in pressure during sleep is 0–9 % below daytime average.	Generally accepted
Reverse Dipper	Sleep/daytime > 1.0	Generally accepted
Extreme Dipper	Sleep/average daytime > 20 %	Generally accepted
Morning surge	Increase in post-awakening pressure from lowest sleep pressure for pre-awakening pressure [16•]. No normal range defined by consensus.	Less well documented
Diagnosis	Definition	
White Coat Hypertension	Untreated. 24-hour average pressure is normal, and clinic pressure is elevated.	
White Coat Effect in treated patients	On treatment. 24-hour average pressure is normal, and clinic pressure is elevated.	Similar to pseudo-resistant hypertension.
Masked Hypertension	Untreated. 24-hour average pressure is elevated. Clinic pressure is normal.	
Masked Effect in treated patients	On treatment. 24-hour average pressure is elevated. Clinic pressure is normal.	This may be a variant of resistant hypertension.
Sustained hypertension	Both clinic pressure and ABPM pressures are in the hypertensive range.	Sometimes called out-of-office hypertension.
True resistant hypertension	Treated with several medications.[a] Both clinic and ABPM are elevated.	
Pseudo-resistant Hypertension	Treated with several medications.[a] Clinic pressures are elevated. ABPM is normal.	

[a] Definitions of resistant hypertension vary. Most definitions list three or more drugs, with one being a diuretic; all at maximum or maximally tolerated doses [79]

dipper', 'reverse dipper', 'extreme dipper'. The increase in blood pressure from sleep to awakening or 'morning surge' has also been recognized. The relationship of these terms to prognosis of future cardiovascular and renal disease in modifying risk prediction will be described in the next section.

ABPM Components and Risk Prediction

ABPM is valuable for more accurate prognosis of future disease, compared to clinic pressure alone. First, ABPM accumulates multiple measurement of blood pressure by a device, eliminating observer bias. Most ABPM studies record pressure every 15–20 min during daytime and every 30 min at night. By contrast, clinic measurements are few, subject to bias [25] and made in the artificial environment of the clinic. The small number of clinic measurements, even when bias-free, may give rise to inaccuracy through regression-dilution [26, 27]. ABPM pressures are averaged with sufficient numbers for estimates of variability (standard deviation) and, if desired, confidence limits [28]. The statistical advantage of ABPM is robust.

Each of the several types of measurement that ABPM provides can be assessed in prospective surveys to determine which are helpful, compared to clinic pressures, for reclassifying patients regarding long-term risk. In general, the strongest relationships are between either 24-hour systolic pressure or nighttime systolic pressure for prediction of total mortality, cardiovascular mortality and stroke, as shown in Table 2. Daytime systolic pressure is also well correlated with these events. Compared to clinic pressures, 24-hour diastolic pressure and daytime diastolic pressure are less consistently related to accurate prediction [9, 15].

Table 2 Relationship between ambulatory blood pressure monitoring (ABPM) parameters and future risk. Results from two large prospective surveys comparing ABPM with clinic blood pressures. For each study, ABPM results were adjusted for clinic pressures to arrive at the added value for each measurement

Measurement	Total Mortality	Cardiovascular Mortality	Stroke
24-hour systolic	***/***	***/***	***/***
Daytime systolic	**/**	**/***	***/**
Nighttime systolic	***/***	***/***	***/***
24-hour diastolic	**/*	NS/**	**/*
Daytime diastolic	NS/NS	NS/NS	*/NS
Nighttime diastolic	***/***	**/***	**/***

Significance of hazard ratios *** $p < 0.001$; ** $P < 0.01$, > 0.001; * $P < 0.05$, > 0.01; *NS* not significant, $p > 0.05$

Left side results from Fagard et al. [15]; Right side results from Dolan et al. [9]

The following sections will assess the specific kinds of information that can be derived from ABPM for modifying risk of cardiovascular disease.

Implications for Risk Modification by ABPM

The effect of ABPM on risk modification compared to clinic pressures is of the greatest relevance for diagnosis of white coat hypertension, the white coat effect and masked hypertension. Making the correct diagnosis is crucial for appropriate treatment and for cost-effectiveness in best uses of resources for health care [29, 30••].

White Coat Hypertension

White coat hypertension may be found in 18–30 % of those thought to be hypertensive by screening in clinics or other screening sites [31]. Prevalence of WCH increases with age [32], and may be higher in women compared to men. In general, the likelihood of future cardiovascular disease in WCH is nearly that of normal or high normal blood pressure for several years, but may increase with longer observation periods [10, 12, 33]. The rate of conversion from WCH to sustained hypertension is not well defined, but aging, being overweight, weight gain and a high salt diet are likely to increase conversion rates. When WCH is found, antihypertensive drug treatment is not immediately necessary, but long-term surveillance is required. It is reasonable to recommend life style improvement for those with WCH and all those at higher risk for future cardiovascular disease, due to smoking, overweight, pre-diabetes, or adverse lipid patterns. However, the lack of need for antihypertensive drug treatment for WCH is the basis for the cost-effectiveness of this strategy [30••] and the decision by the UK advisory group, NICE, to recommend ABPM for all recently detected hypertensives [3••]. When WCH is found, annual surveillance by ABPM (or home blood pressure monitoring) is a reasonable approach and may be cost-effective as well [29].

Masked Hypertension

The diagnosis of masked hypertension can only be made through the use of ABPM or home blood pressure monitoring [24••]. Those most likely to have MH have high-normal clinic pressures and may also have features of the metabolic syndrome or diabetes [34, 35•]. MH is associated with increased target organ pathology, compared with normal ABPM pressures [36]. Effective control of hypertension is necessary for masked hypertension, as it may have same cardiovascular risk as sustained hypertension [12, 37].

Because clinic pressures give a misleading picture, control of MH requires out of the office blood pressure recording, either ABPM or home blood pressure monitoring.

Resistant and Pseudo-Resistant Hypertension

Use of ABPM for treated hypertensive patients may also be helpful for defining risk, especially for those thought to have resistant hypertension. It has been clearly shown that a significant fraction of those with above goal clinic pressures on multiple medications, have normal or well controlled blood pressure defined by ABPM, indicating a large white coat effect [38–41]. These patients may be considered as having "pseudo-resistant" hypertension [42•]. There is no need for intensification of antihypertensive drug treatment in these patients. ABPM in resistant hypertension may also reveal a lack of normal dipping at night suggestive of the sleep apnea syndrome [43], a condition that requires specific treatment to normalize nocturnal respiration.

Nocturnal Hypertension

For those with a normal day–night pattern of behavior and normal diurnal control of blood pressure, there is a reduction of 10–20 % in pressure at night, during sleep, "dipper" status. This pattern may also be observed in many hypertensives with or without antihypertensive medication. However, dippers need not have a normal blood pressure at night. Elevated nocturnal blood pressure can only be measured by ABPM and may be the most highly predictive pressure for future cardiovascular disease [9, 15]. It is possible to adjust medication schedules so that the peak effect of antihypertensive medications occur at night [44•], but it is not known if selective treatment of nocturnal hypertension is beneficial [45•]. Even less is known about the value of treatment of isolated nocturnal hypertension for the occasional 'reverse dipper' who has normal daytime pressure, but elevated pressures at night.

Abnormal Diurnal Blood Pressure Rhythm and Risk

The normal reduction of arterial pressure at night, during sleep, of 10–20 % may be absent due to a less than normal fall (non-dipper), an increase in pressure at night (reverse dipper), or a greater than normal fall (extreme dipper). Each of these abnormal patterns has been associated with greater risk for future cardiovascular disease, including heart failure [10, 46] [47] [48]. The non-dipper pattern tends to increase with age, perhaps due to impaired autonomic reflex performance. Diabetics are more likely to have the non-dipper pattern, a reflection of diabetic autonomic neuropathy [48]. Sleep apnea is another cause of non-dipper or even reverse dipper status [43, 49]. The non-dipper pattern has also been associated with the Metabolic Syndrome [50•].

Giving some antihypertensive medications at night may change the non-dipper to dipper pattern, as mentioned above in relation to treatment of nocturnal hypertension. Treatment of the sleep apnea syndrome by improved nocturnal ventilation can significantly lower blood pressure as a treatment for this form of identifiable hypertension [49, 51]. It is not known whether treatment strategies to change non-dipper to dipper status are beneficial for prevention of cardiovascular disease.

Hypertension due to several adrenal disorders, including primary aldosteronsim, Cushings Syndrome and pheochromocytoma, is associated with non-dipper status [52, 53]. Non-dipper status is also found in chronic renal disease and associated with a less favorable prognosis for loss of renal function, when compared to dipper status [54].

Extreme dippers have > 20 % reduction of nocturnal pressure from daytime levels. As previously noted, this condition may be associated with greater risk of cerebrovascular disease, as defined by stroke or the occurrence of silent cerebrovascular lesions on magnetic resonance imaging [46]. Extreme dipping of nocturnal blood pressure has also been linked to several types of ocular disease, including 'normal pressure' glaucoma [55, 56].

The Morning Surge and Risk

During a 24-hour daytime cycle, blood pressure rises from its lowest level during sleep to a much higher level after awakening, the morning surge. Because the morning surge of blood pressure is associated with increased risk of cardiovascular events, antihypertensive drugs that have delayed release for greater effect after awakening, have been developed to be taken at night. A delayed release form of verapamil, verapamil COER, has been compared to a morning schedule of atenolol and hydrochlorothiazide in the CONVINCE trial. Outcomes were similar for the two groups, with no superiority for the delayed release ("anti-surge") strategy [57].

Episodic Fluctuations in Blood Pressure

Unusual or unpredicted fluctuations in blood pressure may be detected by scanning the data record of ABPM recordings. Artifacts can usually be excluded due their having abnormally narrow pulse pressures. However, spikes in pressure may be associated with symptoms, as in the panic-disorder syndrome [58] or bursts of catecholamine

secretion in pheochromocytoma [59, 60]. Abnormal spectral analysis of the diurnal blood pressure pattern has also been correlated with the diagnosis of pheochromocytoma [61].

Analysis of ABPM records for hypotensive episodes has been performed in patients with known coronary heart disease and angina pectoris occurring during antihypertensive treatment. Cardiac ischemia monitoring was conducted on the same day as the ABPM. Both symptomatic and non-symptomatic ischemic events were preceded by significant reductions in diastolic pressure [8]. This was a small study and should be expanded for confirmation, as it implies that overly aggressive antihypertensive therapy may be harmful in those advanced coronary artery disease. A small study using ABPM of patients with systolic heart failure undergoing treatment with multiple neuromodulating agents found that increased diastolic hypotensive events were associated with more re-admissions to hospital and a trend to increased mortality [62].

ABPM Pulse Pressure and Risk

The pulse pressure, systolic-diastolic pressure, has been studied as a possible independent risk factor for cardiovascular disease. The pulse pressure reflects, in part, stiffness of the large arteries. In age-related widening of the pulse pressure, systolic pressure increases and diastolic pressure tends to fall. In the Framingham longitudinal study of risk factors for prediction of cardiovascular disease, clinic pulse pressure was found to be a significant component of risk in several statistical models [63•]. Pulse pressures calculated from ABPM may also have some degree of predictive value in resistant hypertension [41] and the elderly [64••].

Arterial Stiffness Index and Risk

Li and colleagues suggested that an index of arterial stiffness could be derived from ABPM measurements of systolic and diastolic pressure. They calculated the linear slope of the relationship for diastolic pressure as a function of systolic pressure; this slope tended to be smaller with increased arterial stiffness, as correlated with another index, the carotid-femoral pulse wave velocity. The arterial stiffness index was defined as 1-slope. [65•]. The arterial stiffness index has been calculated from a large registry of ABPM and is related to outcomes over a follow-up interval of 5 years. This index was superior to pulse pressure for prediction of cardiovascular mortality and stroke mortality. Neither pulse pressure nor the stiffness index was a significant predictor of cardiac mortality [66•]. In a longitudinal study of older persons with diabetes, the arterial stiffness index added significantly to prediction of all-cause mortality [67]. A meta-analysis summarizing the arterial stiffness index reports a highly significant association between this index and either cardiovascular events or stroke [68]. The relationship between changes in the arterial stiffness index and another index of arterial stiffness, the carotid flow velocity, are inconsistent during treatment of hypertension [69]. It is not yet clear how the arterial stiffness index will be useful for decisions in treatment of hypertension.

ABPM and Therapeutic Trials of Hypertension

ABPM has been used in clinical trials of therapy for hypertension. This technology has objective and statistical advantages for minimizing the placebo effect and reducing the size of trials by increasing power for detection of differences in pressure [70, 71]. Despite these advantages, most trials rely on clinic pressures for entry criteria and for follow-up during conduct of the trial. For the larger and very large trials, ABPM has been limited to a small selected sample of the whole [72•]. In general, changes in blood pressure are larger and more variable for clinic measurements than for ABPM, as demonstrated in a clinical trial of renal denervation for hypertension [73••]. It seems likely that clinical trials that include blood pressure as an important measure will require ABPM as the "gold standard" for this purpose. The increased cost per patient for including ABPM will, in well-planned studies, be offset by the reduced numbers of participants required for adequate power to detect differences.

Limitations of ABPM

ABPM is a sophisticated technology. For its implementation, appropriate resources and well-trained personnel are needed. Quality control to assure accurate measurement is a must. There are several devices and computer software now available for ABPM. Equipment costs for setting up ABPM are in range of $4,000 and upward, depending on the number of devices needed. Personal computers needed for processing data and reports now cost less than $1,000. Not all health care systems will be able to sustain these costs, so that implementation of ABPM in those nations with limited resources for health care may not be feasible.

ABPM measures blood pressure throughout a single day in most studies. 48-hour monitoring has been used in a few research studies [44•]. For out of office blood pressure over many days, weeks or months, home blood pressure monitoring may also convey important information and is also becoming more widely accepted [74, 75•]. The cost of devices for home blood pressure monitoring is $100 or less. Home blood pressures can be transmitted via telemetry to provider sites for data review and decision making so that fewer visits to clinics are needed. This may be important for populations who live in rural areas that are remote from

medical clinics. Home blood pressures have been incorporated into selfcare strategies in which participants adjust their own medication and are monitored via telemetry [76••]. Home monitoring of cardiovascular risk factors with telemedicine may become a necessary strategy even for some developed nations, as primary care providers become less available [77]. Nonetheless, it needs reemphasis that only ABPM can provide measurements of blood pressure throughout the entire day and nighttime, which may be most important for prognosis [9, 15].

Summary and Conclusions

Arterial blood pressure varies throughout the day, so that many measurements are necessary to characterize this crucial physiologic parameter and cardiovascular risk factor. ABPM has emerged as a powerful non-invasive improvement for assessing blood pressure in clinical medicine and research. The technology is now widely available and well standardized. The recognition that total day average blood pressure and especially, nocturnal blood pressure, are far more accurate in predicting future cardiovascular disease compared to clinic pressure has led to widespread acceptance of ABPM for clinical application in improving risk prediction for patients. It can be expected that greater use of ABPM will identify more patients with white coat hypertension and masked hypertension as well. Appropriate treatment of those with these diagnoses should lead to better allocation of resources for blood pressure control. Thus, broader application of ABPM will be effective for prevention of cardiovascular disease and will be cost-effective as well.

For the time being, the most valuable measurements provided by ABPM are average daytime and nighttime systolic and diastolic pressure. The potential added value of pulse pressure and indirect indices of arterial stiffness are in the early phases of exploration, but may prove useful.

Conflicts of interest Lawrence R. Krakoff declares that he has no conflicts of interest.

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- • Of importance
- •• Of major importance

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