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REVIEW

Understanding short-term blood-pressure-variability phenotypes: from concept to clinical practice

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Abstract: Clinic blood pressure (BP) is recognized as the gold standard for the screening, diagnosis, and management of hypertension. However, optimal diagnosis and successful management of hypertension cannot be achieved exclusively by a handful of conventionally acquired BP readings. It is critical to estimate the magnitude of BP variability by estimating and quantifying each individual patient's specific BP variations. Short-term BP variability or exaggerated circadian BP variations that occur within a day are associated with increased cardiovascular events, mortality and target-organ damage. Popular concepts of BP variability, including "white-coat hypertension" and "masked hypertension", are well recognized in clinical practice. However, nocturnal hypertension, morning surge, and morning hypertension are also important phenotypes of short-term BP variability that warrant attention, especially in the primary-care setting. In this review, we try to theorize and explain these phenotypes to ensure they are better understood and recognized in day-to-day clinical practice.

Keywords: hypertension, BPV, HBPM, ABPM, morning surge, nocturnal dipping

Background

Hypertension, one of the most important preventable causes of death globally, accounts for more than 12.8% of all deaths annually.[1,2] Elevated blood pressure (BP) is one of the major modifiable contributing factors to cardiovascular risk; however, there is often uncertainty as to the "true underlying BP", as patients often present with discrepant BP readings.[3] This is because BP is a continuous variable that fluctuates constantly in response to various changes in physical and mental activities, sleep, and autonomic, humoral, mechanical, myogenic and environmental stimuli.[4] It is characterized by marked spontaneous oscillations over short- and long-term periods.[5] As such, clinic BP or home BP (HBP) in an individual at one time can be considerably different from his/her average day and nighttime BP.[4] This presents a challenge in diagnosing and prescribing treatments for patients correctly.

Physiology of relationship between sleep and BP regulation

Sleep usually involves calmness and detachment from the external environment, and hence generally causes a reduction in BP at night.[6] This decrease does not occur under conditions of total sleep deprivation. Sleep disturbances, including sleep restriction, sleep apnea, insomnia, and shift work, have also been found to induce stress on the cardiovascular system and play a role in the development of cardiovascular disorders.[7] The sleep-dependent changes in BP are specific to each sleep state, and

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result from the integration between cardiovascular reflexes (which modulate heart rate in response to changes in BP) and central autonomic commands to heart and resistance vessels.[6,8] The pathophysiological mechanisms behind these clinical associations probably alter the integration of these cardiovascular reflexes and central autonomic commands.[6] A positive beneficial association has been found between "close relationships" and BP dipping, while posttraumatic stress disorder and obstructive sleep apnea have been associated with diminished nocturnal BP fall.[9–11]

Blood-pressure variability

Even though average clinic BP values remain the gold standard for the diagnosis and treatment of hypertension, recent studies in hypertensive subjects have demonstrated that the assessment and quantification of BP variability (BPV) in addition to normal BP values, is of both physiopathological and prognostic importance.[2,12] For instance, there is strong evidence to show that increased BPV is independently associated with higher risk of target-organ damage, cardiovascular events, and mortality.[2,5,13] It follows that controlling BPV in addition to reducing absolute BP levels may contribute to optimal cardiovascular protection in hypertensive patients.[14]

Continuous intra-arterial BP recordings are used to assess very short-term beat-to-beat changes in BPV, whereas continuous monitoring systems, such as ambulatory BP monitoring (ABPM), are used for assessing short-term BP fluctuations within a day (24 hours). On the other hand, home BP monitoring (HBPM) or office BP monitoring (OBPM) over lengthy time periods are used to detect long-term changes in BP stretching over days or visits.[2,15]

Some studies have observed that the extent of BPV is directly proportional to mean BP values, and hence BPV is generally higher in hypertensive subjects compared to normotensive subjects.[16] It is also noted that a reduction in mean BP values leads to a proportional reduction in BPV, and thus it has been suggested that employment of longer-acting BP-lowering drugs might be particularly beneficial in controlling BPV in addition to BP control.[16] However, setting the optimal therapeutic target for BPV control with antihypertensive therapy remains a challenge.[14]

Different types of BPV

Popular concepts of BPV, such as "white-coat hypertension" and "masked hypertension", are well recognized in clinical practice, and have been studied extensively for their prognostic relevance.[13] White-coat hypertension or isolated office hypertension is characterized by elevated office BP (OBP) with normal ambulatory BP (ABP) or HBP, and might be caused by anxiety or in response to an unusual clinical setting.[17,18] Masked hypertension, on the other hand, is characterized by normal OBP, even though ABP or HBP levels are elevated.[19] However, it is important to recognize that BPV is a complex phenomenon that expands beyond such popular concepts, and is influenced by fluctuations in both the short term, ranging from seconds to hours, and the long term, ranging from days to months.[2,5,14] In general, BPV can be divided into three different types, based on the time frame it occurs: very short-term BPV, short-term BPV and long-term BPV.[2,15] Depending on the method and time interval considered for its assessment, the clinical significance and prognostic implications of a given measure of BPV differ.[2,14]

Very short-term BPV

Very short-term BPV refers to beat-to-beat fluctuations in BP due to the interplay of different cardiovascular control systems, such as the baroreceptor reflex, the renin–angiotensin system, the vascular myogenic response, and the release of nitric oxide from the endothelium, as well as changes in behavioral and emotional mechanisms.[2,5,20] It is usually assessed in a laboratory via intra-arterial recording or under ambulatory conditions by noninvasive finger cuffs that continuously track finger-BP levels through infrared photoplethysmography.[2,15] Standard deviations of BP values or fluctuations in BP obtained from spectral analyses at various frequency bands are often used as the main indices for assessing very short-term BPV.[2]

Even though its usefulness and reliability in practical usage is questionable, very short-term BPV has been used as a tool in diagnosing and treating patients with cardiovascular disease, as well as to study the mechanism of action of antihypertensive drugs.[2,20–22] Detecting changes in beat-to-beat BPV can also help in rationally selecting antihypertensive drugs.[5] For instance, hypertensive patients with elevated low-frequency BPV may present with enhanced sympathetic modulation of vascular tone, and hence may respond well to sympatholytic antihypertensive drugs.[20]

Short-term BPV

Short-term BPV refers to the BP changes that occur within a day (24 hours), and is characterized by normal circadian variations, such as nocturnal BP dipping and morning BP surge.[2,14,15,23] It is mainly influenced by central neural factors, reflex autonomic modulation, and changes in the elastic properties of arteries and humoral systems and rheological and mechanical factors.[15,24–29] However, all these factors are

often inextricably intertwined with each other.[14] Various studies have demonstrated that higher 24-hour BPV independently of mean BP values is clinically important, as this can increase cardiovascular (CV) events, mortality, and target-organ damage.[30–37]

Short-term BPV can be measured in two ways: using either ABPM to measure BP every 15–30 minutes over a 24-hour period or special HBPM devices that can measure BP while sleeping.[2,14,38,39] Some common indices of measurement for short-term BPV include standard standard deviation (SD) of BP values measured over the whole 24-hour period, waking hours, or sleeping hours.[2] Other indices include coefficient of variation (CoV), 24-hour weighted SD, and average real variability (ARV).[2,40–42] These indices are covered in detail in "Understanding indices of short-term BPV" section. The main advantages of short-term BPV monitoring are that it can provide extensive information on BP changes over a day and detect important circadian BP changes, such as morning BP surge and nocturnal dipping, that may have important prognostic implications.[43–47]

Long-term BPV

Long-term BPV refers to day-to-day, visit-to-visit, and season-to-season BP changes.[2,15] Factors contributing to long-term BPV remain relatively unclear.[2] Long-term BPV could be a consequence of poor BP control in treated patients, such as inadequate treatment by the physician, poor patient adherence, or improper BP-measurement methods.[2,15] It may also be influenced by behavioral changes in an individual, as well as environmental factors, such as outdoor temperature and daylight-hour differences between different seasons.[2,4,15] For instance, BPV was found to be greater during winter than in summer, possibly due to increased sodium retention and vascular resistance caused by augmented sympathetic activity.[4] Some studies have also suggested that increased arterial stiffness contributes to the pathogenesis of long-term BPV.[5,48]

Day-to-day BPV can be assessed by ABPM over 48 hours or HBPM data collected over several days, weeks, or months, while visit-to-visit BPV is usually assessed by ABPM or OBPM that is usually spaced by visits over weeks, months, and years.[2,15] However, the reliability of using OBPM to assess long-term BPV has been questioned, as it does not take into account the patient's normal activities and requires frequent visits to the physician for BP measurements.[2,15] A recent single-center cross-sectional study showed significant differences between single OBPM and means of consecutive BP measurements.[49] In-office measurements are also sometimes inaccurate, mainly because of the white-coat effect, inadequate or uncalibrated devices, and suboptimal measurement techniques (eg, incorrect cuff size, no rest before measurement).[50,51] Although a large number of recommendations on correct OBPM techniques have been published (Table 1), these guidelines are generally not translated into primary-care practice.[51,52]

There is strong evidence to suggest that increased long-term BPV is associated with higher risk of stroke, cardiovascular events, and mortality, including all-cause mortality.[53–57] Therefore, measuring long-term BPV might be clinically important, as it can provide useful insights into the long-term control of the patient's BP and effectiveness of the patient's current antihypertensive therapy.[2]

Understanding short-term BP variability

Nocturnal dipping and nocturnal hypertension

BP generally dips about 10%–20% during sleep in normotensive patients, due to a phenomenon known as nocturnal dipping.[14,15] However, in hypertensive patients, the extent of BP dipping can differ significantly, and individuals can be categorized into four groups based on the extent of fall in nighttime BP. These include extreme dippers, dippers, nondippers, and reverse dippers.[15] In general, individuals whose BP falls in the range of 10%–20% are known as dippers.[58] Those who dip >20% are known as extreme dippers, while those exhibit <10% dip in BP are called nondippers. On the other hand, those who have an increase in nocturnal BP, instead of a fall, are known as "risers" or "reverse dippers".[58] Various causes for the absence of dipping have been proposed including sleep disturbance, depression, obesity, obstructive sleep apnea, orthostatic hypotension, autonomic dysfunction, chronic kidney disease, diabetic neuropathy, and old age.[23,59–61]

There is strong evidence indicating that such circadian variations have prognostic significance in both hypertensive and normotensive patients. For instance, blunted or reverse nocturnal BP dipping and exaggerated morning BP surge are independently associated with increased cardiovascular events, stroke, and target-organ damage.[4,37,43,62–77] These circadian variations within 24 hours can also give rise to other phenotypes of short-term BP variations, such as nocturnal hypertension and morning hypertension.[78,79]

Nocturnal hypertension is defined as having an average of nocturnal BP values of ≥ 120/70 mmHg and is generally caused by a failure in nocturnal dipping and hence usually observed in nondippers or reverse dippers.[59] It is especially important to control nocturnal BP, as it is more likely to

Table 1 Recommendations for OBP monitoring from key guidelines on hypertension

	JSH 2014[39]	NICE 2011[142]	ESH/ESC 2013[94]	CHEP 2015[143]	AHA 2017[105]
Measurement devices	Auscultation using mercury/aneroid sphygmomanometry should be used. Electronic sphygmomanometry may also be used. Measuring devices should be properly validated, maintained, and regularly recalibrated. Cuff sizes appropriate for the patient's arm circumference should be used.	Direct auscultation over the brachial artery using mercury/aneroid sphygmomanometry should be used. Aneroid sphygmomanometry may be less accurate than mercury-operated sphygmomanometry. Automated devices may also be used, except if there is pulse irregularity. Measuring devices should be properly validated, maintained, and regularly recalibrated. Cuff sizes appropriate for the patient's arm circumference should be used.	Auscultatory/oscillometric semiautomatic sphygmomanometry is recommended, since mercury sphygmomanometry is no longer used in European countries. Measuring devices should be properly validated, maintained, and regularly recalibrated. Bladder dimensions should be suited to the arm circumference of the patient. An automated recording of clinic BP readings with the patient seated alone in an isolated room (AOBP) might produce more reliable readings than traditional OBP readings.	Measurements should be taken with electronic sphygmomanometry. If not available, a recently calibrated aneroid device may be used. Measuring devices should be properly validated, maintained, and regularly recalibrated. Choose a cuff with an appropriate bladder size. An automated recording of clinic BP readings with the patient seated alone in an isolated room (AOBP) is preferred over traditional OBP.	A validated and recently calibrated BP-measurement device should be used. Appropriate cuff size, such that the bladder covers 80% of the arm circumference, should be used.
Measurement conditions	BP should be measured in a quiet environment at room temperature after resting for a few minutes in a seated position on a chair with support for the back with the legs uncrossed. Talking during measurement should be avoided. Smoking and alcohol/caffeine consumption should be avoided before measurement. The arm cuff should be maintained at the heart level of the patient. The cuff should not be placed over thick clothing or on the elbow. Avoid tight compression of the measuring arm by folded sleeves.	A quiet and comfortable environment at normal room temperature is ideal. The patient should not have the need to pass urine or have eaten recently. Smoking or consumption of caffeine or exercise should be avoided prior to the measurement. Patient should be allowed to rest for at least 5 minutes before measurement. It is recommended that measurements be taken while seated. The patient's arm should be out-stretched and rested on a table level with their heart and in line with their midsternum.	The patient should be allowed to sit for 3–5 minutes before BP measurements. The cuff should be at the heart level, regardless of the position of the patient. BP to be measured in both arms initially to spot possible variability between arms, after which the arm with the higher BP reading should be used.	The patient should be allowed to rest for about 5 minutes before the measurement. Patient should be in a seated position with back support with legs uncrossed. The measuring arm should be bare and supported at the heart level. The lower edge of the cuff should be 3 cm above the elbow crease and centered over the brachial artery. There should be no talking during the measurement.	The patient should be relaxed and seated in a chair with feet on floor and back supported for >5 min. Ensure that the patient has emptied his/her bladder. Avoid consumption of caffeine, physical activity, and smoking for at least 30 minutes before measurement. Patient and observer should not talk during the measurement. Patient's measuring arm should be supported on a table. The location of cuff placement on the arm should have all clothing or covering removed. The middle of the cuff should be placed on the patient's upper arm at the level of the midpoint of the sternum.

Measurement method	At least two BP measurements should be taken at 1- to 2-minute intervals in one clinic visit and the average value of the readings recognized as the OBP value. If the two measurements differ significantly, additional measurement should be performed. Hypertension should be diagnosed based only on the BP values measured over at least two different visits.	BP readings should be taken in both arms initially, and the arm with the higher reading should be selected for subsequent measurements. It is recommended to take two BP readings: one at the beginning and the other at the end of the visit.	Take at least two BP measurements in the sitting position with 1- to 2-minute intervals. If the first two readings are significantly different, take additional readings. Taking the average of these BP readings should be considered if deemed appropriate. Take repeated measurements in patients with arrhythmias, such as atrial fibrillation, for better assessment.	BP readings should be recorded to the closest 2 mmHg on the manometer or 1 mmHg on electronic devices. BP should be measured initially in both arms for at least one visit, and the arm with the higher pressure should be subsequently used for measurement. Seated BP should be used to diagnose and monitor treatment decisions, while standing BP should be used to monitor for presence of postural hypotension. In patients with arrhythmia, additional readings should be taken via auscultation to estimate average BP. When using AOBP, the first measurement should be taken by a health professional to verify cuff position and validity of the measurement. After this, the patient should be left alone for subsequent readings to be taken by an automatic device. When using traditional OBP, at least three readings to be measured in the same arm. The first reading should be discarded and the latter two averaged. To avoid venous congestion, it is recommended to space the readings at-least one minute apart.	BP should be measured in both arms initially to spot possible variability between arms, after which the arm with the higher BP reading should be used for subsequent readings. Repeated measurements should be taken only after at least 1–2 minutes. An average of at least two or more readings obtained on at least two or more visits should be used to estimate the individual's BP.

Abbreviations: OBP, office blood pressure; JSH, Japanese Society of Hypertension; NICE, National Institute for Health and Care Excellence; ESH, European Society of Hypertension; ESC, European Society of Cardiology; CHEP, Canadian Hypertension Education Program; AHA, American Heart Association; OBPM, OBP monitoring; AOBP, automated OBP.

represent the patient's actual BP more closely, as it is often not influenced by the pressor effects of physical, emotional, and other environmental factors that occur during the day.[14] Moreover, patients with nocturnal hypertension have been found to be at significantly higher risk of organ damage and cardiovascular events, independently of OBP or morning BP values.[59,64,80–82] Nocturnal BP has also been found to be a superior predictor of cardiovascular disease than daytime BP.[45,83] Previously, nocturnal hypertension was able to be detected only by ABPM. However, development of novel semiautomatic HBPM devices that can intermittently measure BP during sleep have allowed HBPM to monitor nocturnal BP accurately.[59,84–87] Nocturnal HBP values obtained by such devices are comparable to nocturnal BP values obtained by traditional ABPM.[59,85]

Morning surge and morning hypertension

BP tends to surge higher in the morning, and this is considered a normal physiological process, but exaggerated morning BP surge has been observed in some hypertensive patients.[23] Early-morning BP is also viewed as a missed therapeutic target, since the timing of the trough plasma-drug level and the lowest pharmacological effect may coincide with early-morning rise in BP, especially for antihypertensives taken once daily in the morning.[88]

Morning hypertension is diagnosed if morning BP values are ≥135/85 mmHg using out-of-office BP monitoring or ≥140/90 mmHg using OBPM in the morning.[89] It can also be defined as having a morning–evening BP difference of >15 mmHg or a morning–nocturnal BP difference of >35–55 mmHg.[59,90] It is recommended to take two to three BP readings every morning for 5–7 days, and the average of these BP readings should be used for evaluation.[89] There are two types of morning hypertension that can be detected by HBPM: one is caused by extreme morning BP surge, whereas the other is caused by prolonged nocturnal hypertension that extends into the morning.[59,66,79,91] In the latter case, persistent nocturnal hypertension overlaps partially with morning hypertension, and it is often observed in patients with nondipping or reverse nocturnal dipping patterns.[78,91]

The morning surge observed by ABPM has been found to be unreproducible.[90] Also, a threshold above which the morning surge in BP becomes pathological remains elusive, and there is still no consensus on a clear definition and assessment of this parameter.[14,23] Morning BP, however, may be regarded as a therapeutic target for preventing target-organ damage and subsequent cardiovascular events in hypertension. Morning hypertension is best monitored through HBPM under fixed conditions at the same time in the morning and evening (or during sleep if possible) over a long period.[78] Japanese Society of Hypertension guidelines recommend morning HBP be measured within 1 hour of waking and after urination, but before medications or meals, while evening HBP should be measured just before going to bed (Figure 1).[92,93]

Measurement of short-term BPV

There is increasing evidence to show that conventional OBPM to diagnose and monitor a patient's response to antihypertensive treatment may not be effective.[14,23,49] OBP measurements have some serious limitations, such as their inability to assess the dynamic characteristics of BP and collect data in the patient's usual daily setting.[14] They also rely heavily on the technique of the operator, and thus may give rise to observer bias.[14] Lastly, white-coat hypertension and masked hypertension are also commonly associated with BP readings taken in a clinical setting, which may lead to an inaccurate diagnosis of hypertension.[2,14,18] HBPM and ABPM, on the other hand, are recommended in clinical practice to diagnose white-coat hypertension and masked hypertension and can estimate increased BPV, since they are able to detect various changes in BP associated with such conditions.[23,94]

A major advantage of out-of-office BP monitoring is that it can provide a large number of BP measurements away from the medical environment. Evidence is growing that such out-of-office measurements can also have better prognostic values for cardiovascular events, and these are now widely considered as significantly superior to OBPM readings.[14,23,73,95–100] As such, out-of-office measurements, such as ABPM and HBPM, are increasingly recommended by major guidelines to complement conventional OBP measurements in clinical practice (Table 2).[101–104]

HBPM is defined as regular measurement of BP at home by the patient outside any clinical setting.[3] Despite the widespread use of HBPM, there is no standardized protocol for its measurement, and this might result in an inaccurate assessment of BP. Therefore, it is vital to adopt a standardized protocol that has been validated.[3] HBPM is recommended to be measured as such:

- BP measurement should be taken in a quiet room in a seated position using a validated automatic BP device with correct arm-cuff size[3,103,105]
- the patient should be seated with their back supported and feet flat on the floor with legs uncrossed, while the measuring arm should be relaxed and supported at heart level[3,105]

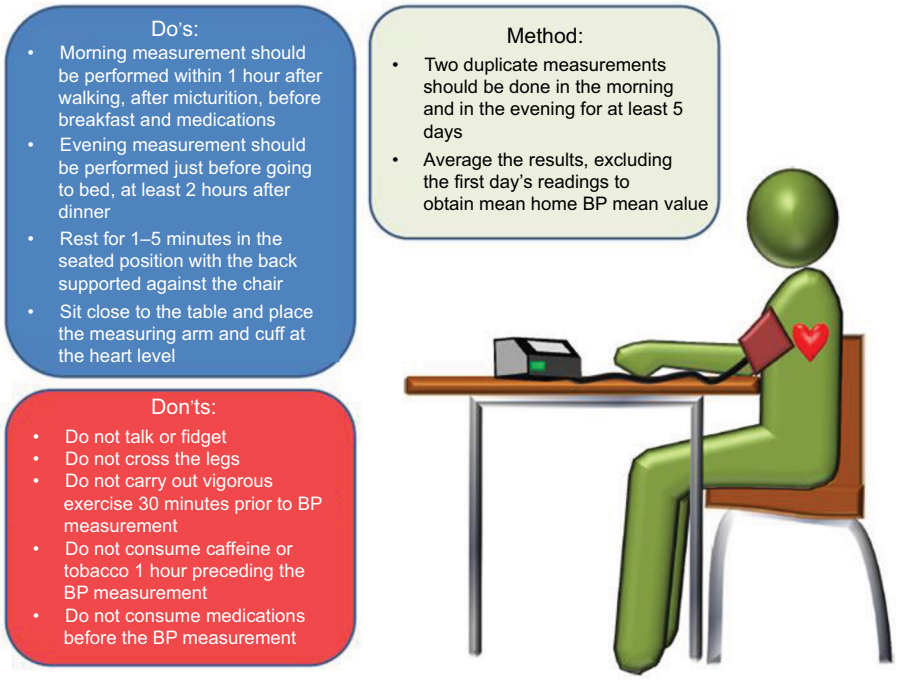

Figure 1 Measurement of home blood pressure (BP).
Note: Image created as per recommendations from JSH[39] and NICE[142] guidelines.
Abbreviations: JSH, Japanese Society of Hypertension; NICE, National Institute for Health and Care Excellence.

- the patient should be in a comfortable and calm state while the measurement is made, and should have at least 1–5 minutes of seated rest before the measurement[39,105,106]
- measurement should be taken before medication, food, or vigorous exercise and after micturition[3,105,107–110]
- stimulants containing such products as coffee and cigarettes should not be consumed for 30 minutes before BP measurement.[3,105]

Two measurements should be conducted, 1 minute apart, in the morning, as well as in the evening, for a total of 7 days (at least 5 days).[94,105,111–113] Measurements should be taken at around the same time while maintaining similar conditions throughout the measuring period to minimize the BPV around the true mean BP value.[114] HBP is then calculated by averaging systolic and diastolic BP recorded over the period after excluding the first day's readings.[3] In general, HBP higher than 135/85 mmHg is accepted as the criterion for diagnosis of hypertension by various guidelines (Table 3).[3,92,93,101,103,104,115] However, it has been found that many physicians may not follow this BP-cutoff point for diagnosis of hypertension, but instead use a higher BP cutoff (>140/90 mmHg) to diagnose hypertension based on HBPM recordings.[116–118]

The consensus target HBP for antihypertensive treatment remains controversial. The recent American Heart Association guidelines now recommend HBP of 135/85 mmHg as target for treatment in hypertensive patients and 130/80 mmHg in high-risk patients.[115] Japanese Society of Hypertension guidelines, on the other hand, recommend HBP of 125/80 mmHg as target for treatment in young and middle-aged persons and 135/85 mmHg in the elderly.[93,119]

ABPM is defined as the method of measuring BP readings noninvasively at short intervals over a 24-hour period with the aid of an automated BP device while the patient is going about their daily routine.[39,105,120] An ABPM device automatically takes BP readings every 15 minutes during the day and 30 minutes at night over a 24-hour period.[23] Daytime for ABPM is defined as 9:00–21:00 while the patient is normally awake. On the other hand, nighttime is defined as 1:00–6:00 while the patient is asleep. A total of at least 20 valid readings when awake and seven valid readings while asleep (about 70% of total readings) are needed to confirm the results at the end of the 24-hour ABPM. The ABPM device automatically provides the user with unique data, such as 24-hour average BP, daytime (awake hours) BP, nighttime (sleeping) BP, dipping status, early-morning BP surge, BP load, trough:peak ratio, and smoothness index. The actual diagnosis of hypertension depends on the time frame of ABPM used.[23,94] In general, patients with greater-than-average BP of 130/80 mmHg measured over a 24-hour

Table 2 Recommendations on out-of-office BP measurements from key international guidelines on hypertension

Indications	JSH 2014[39]	NICE 2011[142]	ESH/ESC 2013[94]	CHEP 2015[143]	AHA 2017[105]
Confirmatory diagnosis of hypertension	If OBP is ≥140/90 mmHg, first offer HBPM to confirm the diagnosis of hypertension. Offer ABPM if confirmatory diagnosis of hypertension with HBPM is difficult, such as when HBP fluctuates around high-normal values of 125/80–134/84 mmHg.	If OBP is ≥140/90 mmHg, offer ABPM or HBPM (if the patient is unable to tolerate ABPM) to confirm the diagnosis of hypertension. However, if the patient has severe hypertension (ie, BP ≥180/110 mmHg), start antihypertensive treatment immediately without waiting for the results of ABPM or HBPM.	Out-of-office BP should be considered to confirm the diagnosis of hypertension. It is recommended to confirm borderline or abnormal findings on HBPM with ABPM.	If first-visit mean AOBP is ≥135/85–109 mmHg or the mean non-AOBP is ≥140/90 mmHg, ABPM or HBPM should be performed before the second visit. If during the first visit, mean AOBP or non-AOBP SBP is ≥180/110 mmHg, hypertension is diagnosed without the need for out-of-office BP measurements.	Diagnosis of hypertension for patients with OBP of ≥130/80 mmHg should be confirmed with corresponding HBPM or ABPM values.
Identification and management of white-coat hypertension	If OBP is ≥140/90 mmHg, first offer HBPM to detect white-coat hypertension. When a definitive diagnosis of white-coat hypertension cannot be made based on the HBP level, offer ABPM.	When an untreated patient has persistently elevated OBP readings, but has normal HBP or ABP values of <135/85 mmHg, white-coat hypertension may be present. When a hypertensive patient has disproportionately higher OBPM readings than HBPM or ABPM readings, a white-coat effect may be present.	HBPM or ABPM is recommended to detect white-coat hypertension in untreated individuals with grade I hypertension without the presence of asymptomatic organ damage and at low total CV risk. HBPM or ABPM should also be used in identification of the white-coat effect in hypertensive patients.	ABPM is the gold standard for diagnosis of white-coat hypertension. HBPM can also be used to diagnose white-coat hypertension, but it should be confirmed by repeated HBPM or ABPM. The use of HBPM on a regular basis is recommended for hypertensive patients who have previously demonstrated a white-coat effect.	In untreated patients with OBP ≥130/80 mmHg but <160/100 mmHg despite 3 months of lifestyle modification, offer ABPM or HBPM to screen for white-coat hypertension. In treated patients with OBP ≥5–10 mmHg above target BP despite use of three or more antihypertensive agents, offer HBPM or ABPM to detect white-coat hypertension.
Identification and management of masked hypertension	If OBP is <140/90 mmHg, first offer HBPM to detect masked hypertension. When a definitive diagnosis of masked hypertension cannot be made based on the HBP level, offer ABPM.	When a patient has normal OBP readings of <140/90 mmHg but elevated daytime ABPM and/or HBPM measurements of ≥135/85 mmHg, masked hypertension may be present.	HBPM or ABPM is recommended to detect masked hypertension in patients with high-normal OBP and/or normal OBP with asymptomatic organ damage or high total CV risk.	HBPM is useful for the diagnosis of masked hypertension, and its use on a regular basis should be considered for hypertensive patients who have previously demonstrated masked hypertension.	In untreated patients with OBP systolic BP 120–129 mmHg and diastolic BP <80 mmHg despite 3 months of lifestyle modification, offer ABPM or HBPM to screen for masked hypertension. In treated patients who are meeting OBP goal but at increased CVD risk or target-organ damage, offer HBPM or ABPM to detect masked hypertension.
Assessment and management of short-term BPV	Out-of-office BP measurements, such as HBPM and ABPM, should be used to monitor short-term BP changes, such as nocturnal dipping and early-morning BP surge to maximize CV-risk reduction.	Not discussed	ABPM is recommended to assess nocturnal dipping status and nocturnal hypertension or in cases where absence of dipping is suspected, such as in patients with sleep apnea, CKD, or diabetes.	The magnitude of changes in nocturnal BP should be taken into account in any decision to prescribe or withhold drug therapy based on ABPM results.	Not discussed

Assessment and management of hypertension treatment	HBPM is recommended for evaluation of effectiveness of current treatment, as well as to assess patient's adherence to treatment.	For patients identified as having a white-coat effect, consider ABPM or HBPM as an adjunct to OBPM measurements to monitor their response to treatment.	Out-of-office measurements should always be used together with office measurements to evaluate treatment targets, despite the current lack of direct evidence on BP targets for HBPM or ABPM.	HBPM should be used to monitor and improve compliance if a patient is suspected of non-adherence to treatment. ABPM should be used to monitor patients who are below their target BP, despite receiving appropriate chronic antihypertensive therapy.	HBPM and/or ABPM measurements are recommended in treatment evaluation, such as titration of BP-lowering medication in conjunction with telehealth counseling or clinical interventions.

Abbreviations: BP, blood pressure; JSH, Japanese Society of Hypertension; NICE, National Institute for Health and Care Excellence; ESH, European Society of Hypertension; ESC, European Society of Cardiology; CHEP, Canadian Hypertension Education Program; AHA, American Heart Association; BPV, BP variability; OBP, office BP; OBPM, office BP monitoring; HBP, home BP; HBPM, HBP monitoring; ABP, ambulatory BP; ABPM, ABP monitoring; AOBP, automated OBP; CV, cardiovascular; CVD, cardiovascular disease; CKD, chronic kidney disease.

period are considered hypertensive.[94] In addition, a daytime average >135/85 mmHg or a nighttime average >120/70 mmHg are also considered hypertensive.[94]

Understanding indices of short-term BPV

There are a few different methods to represent short-term BPV.[15] SD of 24-hour average ABP values is one of the most commonly used parameters in measuring short-term BPV, but it is sometimes expressed as the weighted mean of daytime and nighttime BP levels to take into account the fall in BP during sleep.[15,41,121] However, the validity of SD has been questioned as an appropriate index of short-term BPV, considering that it reflects only the dispersion of values around the mean, does not account for the order in which BP measurements are obtained, and is sensitive to the low sampling frequency of ABPM.[122]

Therefore, other indices, eg, 24-hour weighted SD, CoV, and ARV, are also used to overcome the limitations of traditional SD values and provide more accurate assessment better to predict target-organ damage and cardiovascular risk:[2,40–42]

- 24-hour SD can also be divided by the corresponding mean BP and multiplied by 100 to be expressed as a CoV;[2] CoV has been observed to have greater prognostic ability than SD, as it can pinpoint individuals whose BPV falls outside its anticipated range[4]
- 24-hour weighted SD is the average of daytime and nighttime BP that has been adjusted for the duration of the day and night period to account for day–night BP changes.[41]
- ARV is another index that is the average of the absolute differences between consecutive BP measurements, and some studies have shown it to be more reliable prognostic indicator compared to SD, as it is more sensitive to the individual BP-measurement sequence and less sensitive to low sampling frequency.[4,2,40,123]

ABPM vs HBPM for assessment of short-term BPV

ABPM monitors changes in BP at many time points throughout the day in an unrestricted manner, whereas HBPM detects BP fluctuations under standardized conditions over a longer period.[78] Multiple readings of ABPM obtained within 24 hours allow for more detailed analyses of both night- and daytime readings, making ABPM more suitable than HBPM for monitoring of intraday BP fluctuations.[14,23] As such, ABPM may provide several advantages over HBPM in providing more extensive information on BP changes throughout the day.[23]

Table 3 Recommendations from key international guidelines on diagnosis of hypertension using OBP and out-of-office BP monitoring

	JSH 2014[39]	NICE 2011[142]	ESH/ESC 2013[94]	CHEP 2015[143]	AHA 2017[105]
OBP	≥140/90 mmHg	≥140/90 mmHg	≥140/90 mmHg	AOBP ≥135/85 mmHg or non-AOBP ≥140/90 mmHg	OBP ≥130/80 mmHg with estimated 10-yr CV risk ≥10%
Home BP	≥135/85 mmHg	≥135/85 mmHg	≥135/85 mmHg	≥135/85 mmHg	≥130/80 mmHg with estimated 10-yr CV risk ≥10%
Ambulatory daytime[a] BP	≥135/85 mmHg	≥135/85 mmHg	≥135/85 mmHg	≥135/85 mmHg	≥130/80 mmHg with estimated 10-yr CV risk ≥10%
Ambulatory nighttime[b] BP	≥120/70 mmHg	–	≥120/70 mmHg	–	≥110/65 mmHg with estimated 10-yr CV risk ≥10%
Ambulatory 24-hour[c] BP	≥130/80 mmHg	–	≥130/80 mmHg	≥130/80 mmHg	≥125/75 mmHg with estimated 10-yr CV risk ≥10%

Notes: [a]Average of BP readings taken while patient is awake; [b]average of BP readings taken while patient is asleep; [c]average of BP readings taken over a whole day (24 hours). **Abbreviations:** OBP, office blood pressure; JSH, Japanese Society of Hypertension; NICE, National Institute for Health and Care Excellence; ESH, European Society of Hypertension; ESC, European Society of Cardiology; CHEP, Canadian Hypertension Education Program; AHA, American Heart Association; AOBP, automated OBP; CV, cardiovascular.

Even though ABPM can provide extensive information, such as average day and night readings, BPV, morning BP surge, and BP load, ABPM still faces many issues regarding practicality, reproducibility, and long-term usage.[2,3,23,78,124] Previously, only ABPM had the ability to record nocturnal BP values, which are superior to daytime values in predicting mortality.[43,77,83,124–126] With recent developments and newer HBPM devices with the ability to record accurate nocturnal recordings, HBPM might offer a reliable alternative to ABPM for monitoring short-term BPV within a day.[95]

HBPM is also highly practical and more affordable and accessible to patients compared with ABPM.[127] HBPM can also be easily repeated over prolonged periods (days to months) in the patient's own environment, making it more suitable for the monitoring of longer-term BPV in day-to-day or visit-to-visit parameters.[2,23,95,104,128,129] As such, HBPM was found to be the more common tool used by physicians to diagnose hypertension, even though ABPM was ranked the more valuable tool for assessing hypertension.[78,116] Moreover, mean BP values from HBPM are stable and highly reproducible, since they are obtained under fixed conditions and not easily influenced by changes in daily activities.[78] In addition, HBPM is easily available to the general public, and can thus be used in both normotensive and hypertensive individuals.[78,130]

HBPM can also provide instant feedback directly to the health-care professional regarding the diagnosis and treatment of hypertension, while there is usually a delay in ABPM in relaying the information.[78,131–134] However, HBPM is prone to patient-recording errors and improper BP-recording techniques, which may compromise the accuracy and reliability of the data.[78,135,136] Therefore, it is useful to use a device with integrated memory, and patients should be properly trained on the method for its use.[2,23,78,105,137–139] On balance, HBPM has been suggested as the method of choice to monitor BPV over the long term in clinical practice by many guidelines, even though it may not provide insights as extensive as ABPM.[2,58,92,93,103,104,140,141]

Conclusion

Short-term BPV within 24-hours is heavily influenced by circadian variations, resulting in many important phenotypes, such as morning BP surge, morning hypertension, nocturnal dipping, and nocturnal hypertension. Such variations in short-term BPV are only captured and reflected through out-of-office BP measurements like 24-hour ABPM or HBPM. As such, it is important to have a good understanding of proper use of these out-of-office measurements in a clinically validated manner. Both physicians and patients should be strongly encouraged to use ABPM and/or HBPM for monitoring BP, as a reduction in nocturnal hypertension and exaggerated morning BP surge are vital for the effective management of hypertension, rather than simply controlling average BP levels.

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Author contributions

All authors were involved in the conception, design, and analysis and interpretation of data. All authors were also involved in preparation of the manuscript, revising it for scientific content and final approval before its submission for publication.

Disclosure

KS and SS are employees of Pfizer. MTY underwent indirect patient-care pharmacy training for 3 months at Pfizer, Singapore. The other authors report no conflicts of interest in this work.

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