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CONTEMPORARY REVIEW

Blood Pressure Variability in Clinical Practice: Past, Present and the Future

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ABSTRACT: Recent advances in wearable technology through convenient and cuffless systems will enable continuous, noninvasive monitoring of blood pressure (BP), heart rate, and heart rhythm on both longitudinal 24-hour measurement scales and high-frequency beat-to-beat BP variability and synchronous heart rate variability and changes in underlying heart rhythm. Clinically, BP variability is classified into 4 main types on the basis of the duration of monitoring time: very-short-term (beat to beat), short-term (within 24 hours), medium-term (within days), and long-term (over months and years). BP variability is a strong risk factor for cardiovascular diseases, chronic kidney disease, cognitive decline, and mental illness. The diagnostic and therapeutic value of measuring and controlling BP variability may offer critical targets in addition to lowering mean BP in hypertensive populations.

Key Words: blood pressure ■ blood pressure variability ■ digital cardiovascular health ■ hypertension ■ noninvasive blood pressure monitoring ■ photoplethysmography ■ smart wearable devices

While it is broadly accepted that blood pressure (BP) measurements are critical in the diagnosis and management of hypertension and heart failure, the potential importance of BP variability (BPV), alone or in tandem with heart rate variability (HRV), has not been assessed due to a lack of convenient, wearable, continuous BP monitors. Continuous, noninvasive, wearable BP monitors may improve and assist hypertension and heart failure management by informing healthy and unhealthy ranges of and variance in 24-hour ambulatory pressures and, importantly, the beat-to-beat oscillations that govern tissue perfusion that may contribute to morbidity and mortality of heart failure syndromes.

Clinic-based BP measures are a guiding parameter in the treatment of hypertension and heart failure, both with reduced ejection fraction and preserved ejection fraction. Traditional BP management depends on serial office-based BP (OBP) measurements or intermittent home monitoring, often inferring the association of high or low BP with underlying signs or symptoms, inferring associations to changes in heart rate or rhythm, and monitoring responses to therapeutic interventions. However, BP is a continuous variable that constantly fluctuates in response to various factors, including physical and mental activities; associated heart rate and rhythm; posture; sleep disturbances; AND autonomic, humoral, mechanical, and environmental stimuli. Several studies have shown strong evidence that assessment and quantification of BPV, in addition to traditional BP, can provide important pathophysiological and prognostic information.[1] For instance, BPV has been shown to be an independent risk factor for dementia, stroke, end-stage renal disease, cardiovascular events, and mortality.[2,3] These findings point to the potential importance of BPV for congestive heart failure management, but this area remains underexplored. The application of ambulatory, continuous

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Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
ARV	average real variability
BPV	blood pressure variability
CoV	coefficient of variation
HBP	home blood pressure
HRV	heart rate variability
OBP	office-based blood pressure
PTT	pulse transit time
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
VALUE	Valsartan Antihypertensive Long-term Use Evaluation

measures to congestive heart failure populations may further inform therapeutics and give critical insights into which heart failure populations are at risk of congestion versus hypertension during abrupt changes in circulating volume.

Relying solely on OBP can often lead to missed identification of those at risk (white coat hypertension or masked hypertension), resulting in mis/overdiagnosis and suboptimal treatment. White-coat hypertension or isolated OBP is defined as elevated OBP but normal ambulatory BPor home BP (HBP), possibly due to anxiety or anticipatory sympathetic response to the clinical setting. Masked hypertension, on the other hand, is characterized by normal OBP with elevated ambulatory BP or HBP. Taking the environment into consideration as a BP-influencing factor, the updated clinical guidelines for the management of hypertension strongly recommend the use of HBP or ambulatory BP monitoring (ABPM) to supplement OBP for the diagnosis and monitoring of patients with hypertension.[4,5] The goal of ABPM is to empower patients, improve compliance, and allow more frequent and accurate BP measurements. This rising interest in the use of ABPM, combined with recent advancements in technology, has led to strong efforts in the development of more ergonomic and user-friendly ways to measure BP continuously and longitudinally. Advances in technology have resulted in numerous compact electronic devices, such as wearable wristwatches, that allow noninvasive radial BP monitoring. Such devices provide new opportunities for patient-focused telemedicine by relaying relevant daily medical information electronically to the health care professional to optimize the management of BP and other cardiovascular risk factors (such as arrhythmias).[4,5] The use of OBP to guide therapy in heart failure is similarly limited by the inability to readily capture 24-hour and ambulatory BP ranges and beat-to-beat oscillations in BP.

Based on these potentially paradigm-shifting advances in data capture available through the use of medical technologies, the purpose of this review is to provide an overview of BP regulation, advances in BP monitoring, BPV, and its theragnostic implications.

BLOOD PRESSURE REGULATION

The main determinant of arterial BP is the stretch on the walls of the artery by the volume of blood it contains. This pressure increases during systole (due to an increased inflow of blood into the arterial system) and decreases after the peak of ejection (diastole). These dynamic and cyclical changes in the blood volume entering the aorta are reflected as cyclic changes in the aortic BP waveform. The elastic aortic compliance buffers changes in stroke volume, while autonomic and hormonal influences govern the tone of the muscular peripheral artery, which regulates arterial BP essential for maintaining adequate perfusion to meet the metabolic.

The relationship between arterial wall compliance and arterial volume is curvilinear (aortic volume–pressure relationship). Due to this curvilinear relationship, the change in arterial pressure associated with the change in volume is greater at a higher initial volume; that is, a higher pulse pressure will be produced even with a similar stroke volume if the initial arterial volume is higher. The initial higher volume elicits a greater arterial tone and therefore lowers the buffering capacity. Conditions affecting aortic compliance, such as premature or advanced aortic stiffening or reduced aortic compliance (related to aging, chronic hypertension, arteriosclerosis, diabetes, chronic obstructive pulmonary disease, rheumatoid arthritis, or heart failure) may blunt the aortic capacity to regulate and maintain an optimal BP and increase BPV toward unhealthy levels.[6]

During aerobic exercise in a healthy adult, the cardiac output can increase nearly 5-fold by changes in venous capacitance (the total volume contained at a given pressure in the venous system), by contraction or relaxation of venous smooth muscle, leading to increased cardiac venous return (also called preload reserve). Heart failure is characterized by a lowered venous capacitance (impaired storage capacity of the splanchnic vascular compartment and increased sympathetic activity leading to an increase in cardiac preload).[7] Given the relationship between arterial compliance and venous/splanchnic capacitance in the regulation of BP, measuring BPV may offer new insights into beat-to-beat changes in venous/splanchnic capacitance in populations with different arterial compliance. This interconnecting dynamic may be seminal in understanding how some populations with dysfunctional arterial compliance manifest congestion

and others hypertension crisis when challenged with sympathetic mediated venous/splanchnic capacitance changes. Even respiratory changes in ventricular filling may provide insight into individual patient arterial compliance. There are various well-known mechanisms (neural, hormonal, and local autoregulatory) involved in this complex control of BP (Figure 1).

BP VARIABILITY

BPV is defined as a change in the value of arterial blood pressure over a defined period of time. The complex underlying physiology of BPV relies on interactions between hemodynamic neuronal, humoral, behavioral factors (anxiety, postural changes, lifestyle), environmental factors (atmospheric pressure, climate), and the interaction of aortic compliance and systemic capacitance and is complicated by concurrent antihypertensive and heart failure medical therapies.[8]

Multiple studies have shown that BPV is a strong and independent risk factor for cardiovascular diseases (CVDs), chronic kidney disease, dementia, and stroke, as well as hypertension-related morbidity and mortality.[9] The underlying mechanism is not fully understood, but it is postulated that BPV is associated with the development of target-organ damage through increased large artery stiffness, vascular remodeling in the microcirculation (increase in media/lumen ratio, decreased lumen diameter, compromised vasodilation), activation of the inflammatory cascade, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, and so on[10] (Figure 2).

BPV Indices

It is crucial to differentiate "background noise" observed during BP measurement from BPV. In an effort to do so, various indices for BPV assessment have been proposed, including SD, coefficient of variation (CoV), average real variability (ARV), residual BPV, weighted 24-hour SD, and variability independent of the mean. These indices can better quantify the extreme changes in BP measurements and may offer an advantage over mean values.[11] For instance, although CoV (SD divided by the corresponding mean) provides a good estimate of intraindividual BPV, however, it does not take into account the order of measurements.[12] In comparison, ARV is an average of the absolute differences between consecutive BP measurements. It is more sensitive to the individual BP measurement sequence and may be a better index to represent short-term, reading-to-reading changes. For instance, a steady change (eg, 140, 130, 120, 110) versus a more chaotic change (140, 120, 130, 110) in BP will have the same mean, SD, and CoV but different ARV. Therefore, ARV-based BPV measurements may offer an advantage, especially in the assessment of very-short-term and short-term BPV. Weighted 24-hour SD is an average of daytime and nighttime BP. The majority of studies on BPV have

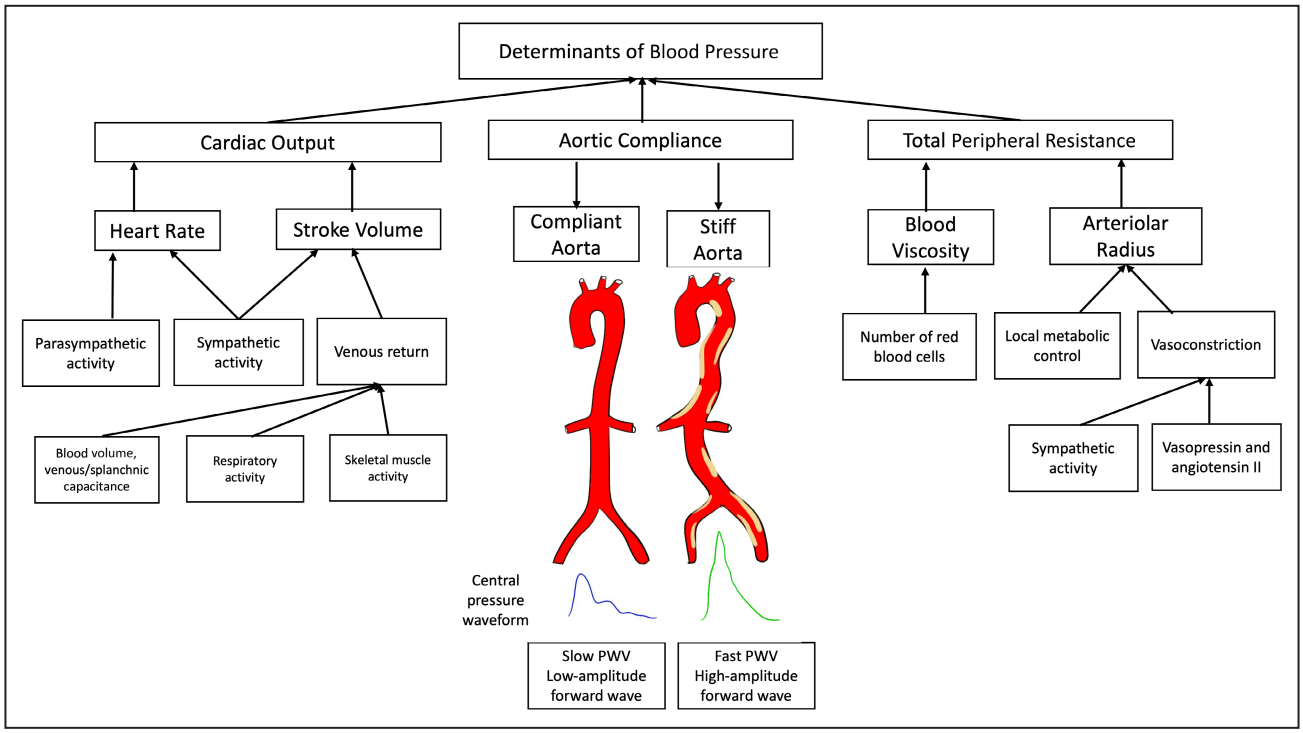

Figure 1. Determinant of blood pressure.
PWV indicates pulse wave velocity.

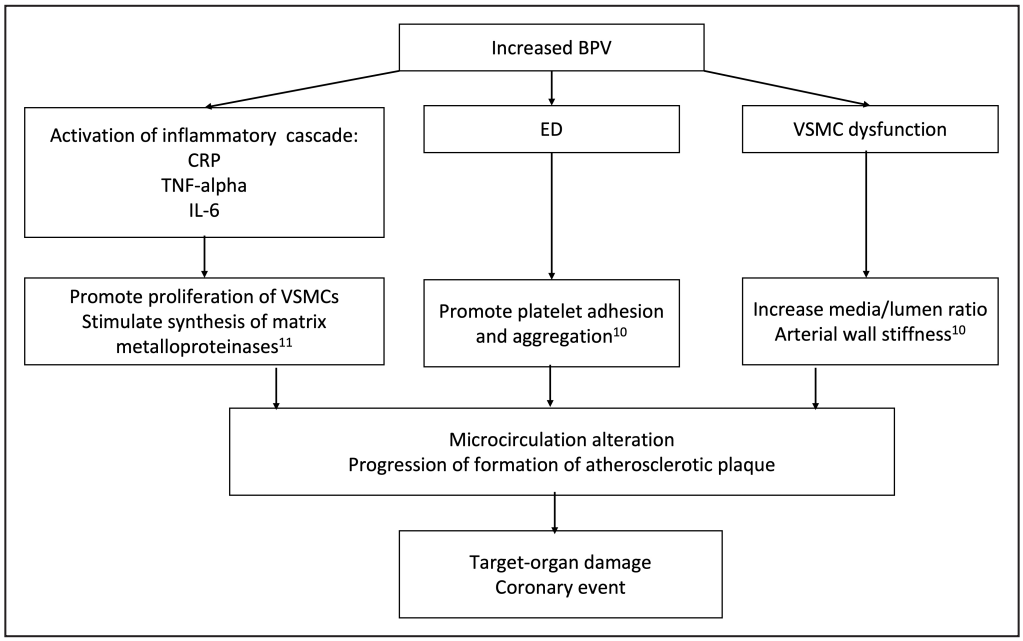

Figure 2. Potential mechanism of impact of blood pressure variability (BPV) on microcirculation and target organ damage.
CRP indicates C-reactive protein; ED, endothelial dysfunction; IL-6, interleukin-6; TNF-alpha, tumor necrosis factor-alpha; and VSMC, vascular smooth muscle cell.

only included a limited number of these parameters, with 24-hour BP being the most commonly reported.[13] Some authors have suggested that since various BPV indices and mean BP are correlated (ie, change in one affects the other), therefore making independent prognostic models based on BPV alone challenging.[14] To avoid this overlap, a new BPV index has been proposed, variability independent of the mean, which is a new statistical measure to allow the measurement of BPV uncorrelated to the mean.

Some studies have noted that systolic BPV (versus diastolic BPV) has a better correlation with arterial stiffness.[15] This may suggest different underlying pathophysiology of systolic BPV and diastolic BPV, with systolic BPV reflecting the dynamic interplay between cardiac output and primarily vascular stiffness, endothelial dysfunction (which may play a role in arterial stiffening), and aging, while diastolic BPV may be more related to the passive arterial recoil and autonomic dysfunction (increased sympathetic activity).[16] This hypothesis supports the findings from studies showing that the relationship between BPV and outcomes can be different on the basis of which BPV indices are used. In systemic analysis, short-term systolic BPV has been noted to be a good indicator of clinical outcome, but short-term diastolic BPV seems to be even better. This contrasts with the elderly population, in which short-term systolic BPV was found to be a better indicator of clinical outcomes than diastolic BPV.

In addition, heterogeneity in BPV study designs, including target populations and types of BPV indices, make direct comparison and assessment for BPV indices challenging. The optimal BPV indices for the measurement of BPV remain an area of active research.

BPV Classification Based on Monitoring Duration

Clinically, BPV is classified into 4 main types on the basis of the duration of monitoring time: very-short-term (beat-to-beat), short-term (within 24 hours), medium-term (within days), and long-term (over months and years). Various potential determinants of BPV are summarized in the Table.[17]

Very-Short-Term BPV

Defined as beat-to-beat variability in BP, very-short-term BP is due to the interaction between baroreceptor reflexes, nitric oxide, renin-angiotensin-aldosterone system, the sympathetic system, and behavioral and emotional factors.[18] Webb et al[19] have postulated that beat-to-beat BPV is associated with physiological phenotype, including increased arterial stiffness, aortic pulsatility, reduced baroreceptor gain, and increased cardiovascular reactivity to stress. They also postulated beat-to-beat BPV to be a composite measure of multiple physiological processes, including irregular episodic components and rhythmic

Table. Blood Pressure Variability, Characteristics, Indives if Assessment, and Determinants of Different Types of BPV

Type of BPV	Measurement methods	Indices	Determinants
Very-short-term (beat-to-beat)	Continuous BP measurement	SD CoV ARV Spectral analysis	Neurohormonal factors (baroreceptor reflex, sympathetic activation) Environmental Behavioral and emotional
Short-term (within 24-h)	ABPM HBPM	SD CoV ARV Spectral analysis 24-h weighted SD 24-h VIM	Neurohormonal factors (baroreceptor reflex, sympathetic activation) Environmental Behavioral & emotional Circadian rhythm Nocturnal dipping
Medium-term (day-to-day)		SD CoV ARV VIM	Adherence to antihypertensive therapy Choice of antihypertensive therapy Vascular factors (endothelial damage, arterial compliance) Age
Long-term (visit-to-visit)	ABPM HBPM OBPM		Adherence to antihypertensive therapy Choice of antihypertensive therapy Vascular factors (endothelial damage, arterial compliance) Age Seasonal changes

ABPM indicates ambulatory blood pressure monitoring; ARV, average real variability; CoV, coefficient of variation; HBPM, home blood pressure monitoring; OBPM, office-based blood pressure monitoring; and VIM, variability independent of the mean;

SD=square root of the sum of squared differences from the mean divided by the size of the data set; CoV=SD/mean; ARV=average of absolute difference between consecutive BP measurements; VIM=computed as fitting a curve of the for *y*=Kxp through a plot of SD-SBP (*y* axis) against mean SBP (*x* axis); transformation of SD uncorrelated to the mean BP; residual BPV=computed in the frequency domain through spectral analysis of BP fluctuations over time; SV=square root of the average difference between consecutive BP measurements; AUC=evaluated by magnitude and duration of BP outside target ranges; Weighted 24-h SD=weighted average of daytime and nighttime BP SD for duration of the day and nighttime periods and by averaging the SD of these 2 subperiods.

components related to breathing and underlying autonomic rhythms (low-frequency oscillations at 0.04–0.15 Hz), and its prognostic significance may also reflect multiple pathophysiological processes. Given the novelty of the concept, there is limited information on the determinants and clinical characteristics of patients with increased beat-to-beat BPV. In one study, the author noted a U-shaped relationship between body mass index and beat-to-beat systolic BPV in women, that is, increased systolic BP (SBP) variability in women with both a reduced and increased body mass index compared with normal body mass index. The author suggested that increased autonomic instability, sympathetic overactivity, and inflammatory cascade (causing endothelial dysfunction and increased arterial stiffness) seen in patients with increased body mass index may explain the underlying pathophysiology. The study also noted no significant association between age and beat-to-beat SBP variability (after adjustment for pulse wave velocity).

It was traditionally measured using invasive intra-arterial methods, which have been supplanted by the Penaz method, using photoplethysmography-based finger sensors.[20] SD values obtained from spectral analyses at various frequency bands are used as the main indices for assessing very-short-term BPV.[2] According to 1 study, a rapid 5-minute assessment of beat-to-beat BPV showed similar prognostic significance as HBP monitoring.

Short-Term BPV

Defined as BP variations over a 24-hour period. It is characterized by circadian variability with typical nocturnal physiological reductions and morning rise of systolic and diastolic BP (DBP).[21] A similar circadian pattern has been observed in HRV, with a nocturnal increase in cardiac parasympathetic modulation (high-frequency HRV) and a morning increase in sympathovagal activity (low-frequency HRV).[22] Currently, it can be measured using cuff-based, noninvasive 24-hour ABPM, which measures BP every 15–30 minutes. Various indices, including SD, CoV, ARV, residual BPV, and weighted 24-hour SD, have been used to evaluate short-term variability[23] (Table). Some authors have suggested that SD and CoV values can be affected by stressors and day-night differences (night dipping and morning surge) and therefore have proposed the use of other indices, such as ARV and weighted 24-hour SD, as a better measure of short-term variability as well as a predictor of target-organ damage and cardiovascular risk.[17,23,24] Unfortunately, short-term BPV cannot identify the respiratory variation of BP and may be unable to identify postural changes in BP, depending on the

timing of cuff measurements coinciding with postural changes.

BP generally dips by 10% to 20% during sleep in normotensive individuals. These sleep-dependent changes in BP result from the interactions between cardiovascular reflexes (which modulate BP changes in response to changes in heart rate) and central autonomic commands.[24] In patients with and without hypertension, a varied nocturnal BP trend can be seen: extreme dippers (those who dip >20% at night compared with their daytime BP), dippers (normal dipping profile of 10%–20%), nondippers (those who dip <10%), and reverse dippers (those for whom BP increases at night compared with daytime BP).[3,4] Similarly, there is a surge in BP in the morning in normotensive individuals, but this response may be exaggerated in patients with hypertension.

Medium-Term BPV

Defined as day-to-day variability in BP, medium-term BPV is primarily due to behavioral and environmental (temperature, altitude, etc.) factors and can be influenced by compliance with antihypertensive therapy.[18] Medium-term BPV may represent a convenient data set made available by home daily automatic measuring devices but is particularly susceptible to nonstandardized daily measuring conditions.

Long-Term BPV

Long-term BPV is defined as visit-to-visit variability in BP over months and years. Like medium-term variability, it is primarily due to behavioral, environmental (temperature, light cycles, altitude, etc.), and compliance to antihypertensive therapy. For instance, studies have noted a greater degree of BPV in winter months compared with that in summer, potentially due to increased sympathetic activity leading to an increase in vascular resistance and sodium retention.[24] Multiple studies have also noted a strong correlation between long-term BPV and cardiovascular events, stroke, kidney damage, and all-cause mortality.[25,26] Some authors have also pointed out that identification of long-term BPV at an early age may assist in predicting cardiovascular and kidney disease risk in later life.[27] In addition, it has been postulated that increased arterial stiffness may be a contributory factor in the development of long-term BPV.[28]

It is also important to highlight that, as discussed above, various physiological processes, including exercise, respiration, and circadian rhythm (night dipping and morning surge), cause BPV. Regular physical exercise can reduce BP (chronically but not acutely) and is recommended by the current American and European hypertension guidelines.[29] Interestingly, studies have shown that BPV (SD and ARV of SBP, DBP, mean arterial BP) decreased after an acute session but not chronically.[30] The underlying reasons for the lack of long-term effect of exercise on BPV remain unclear.[29]

BPV Based on Site of Measurement

It is worth noting that arterial blood pressure is not the same throughout the arterial tree. However, no clinical studies have been conducted to measure and classify BPV on the basis of the site of measurement, including central (aorta), peripheral (brachial), and arteriolar (fingertip). When moving distally from central to peripheral arteries, systolic arterial pressure is often amplified depending on the level of compliance mismatch between the central and peripheral arteries (as arterial pressure waves travel from the more elastic central aorta to stiffer peripheral arteries like the brachial artery, the systolic peak of the waveform becomes narrower and taller). In comparison, DBP and mean BP remain relatively constant.[31] This SBP amplification from the brachial to radial arteries is termed the Popeye phenomenon (named after “Popeye the Sailorman” cartoon character, with a disproportionately high muscle girth in the forearm below the elbow, compared with the shoulder and upper arm).[32]

Studies have shown that central BP (central aortic pressure) is a better cardiovascular risk indicator than peripheral BP (brachial BP).[33,34] Central BP is a more accurate representation of the continuous column of pressure to which the target organs (brain, eyes, heart, and kidneys) are exposed.[35] Various noninvasive methods are available for the estimation of central BP.[36] However, current guidelines for the management of hypertension are based on brachial cuff BP measurements only.[37] The issue of site selection when measuring BP is of critical importance, as it is widely acknowledged that BP is not the same throughout the body at a given time, and one site’s BP measurements cannot be substituted or used to infer results from a different site.[38]

Most of the cuffless devices, as discussed below, rely on pulse wave analysis for analysis and estimation of BP. In addition, it has been reported that some studies attempting to validate brachial cuff-based BP measurement devices have used intra-arterial radial SBP as their reference standard.[39] Given this lack of concordance between BP measurements at different sites, it stands to reason that the same site BP measurement must be used as a reference standard for validating BP measurement devices. In addition, extrapolation of brachial BP from BP measurements made at the wrist or fingertip using newer BP measurement devices may be inherently inaccurate compared with brachial measures and provide different biological insights into pathology and treatments.

MEASUREMENT OF BP AND BPV–ROLE OF TECHNOLOGY

The direct method of measuring beat-to-beat BP requires an invasive (arterial catheter, using a transducer that converts information of mechanical motion resulting from the flow of blood within the catheter into electrical signals, which in turn is transmitted to the monitor) technique, which is predominantly used in the intensive care unit setting or in particular research scenarios. Noninvasive BP measurement using a mercury-based sphygmomanometer was first introduced in 1896, and it remained the gold standard for BP measurement up until recent decades. It provided an easily performed standardization in BP measurement, allowing BP measurement in clinical practice, and set cutoffs for diagnosis and therapeutic interventions. Due to the risk of mercury toxicity, the mercury-based sphygmomanometer has mainly been replaced by a broad range of cuff-based (sphygmomanometer cuff; based on auscultatory or oscillometry measurements) to cuffless devices (based on photoplethysmography measurements, analysis of pulse waveform features; and pulse transit time [PTT] or pulse arrival time) for BP measurement both inside and outside of office settings. These devices can be described as either manual (eg, inflation of cuff), automated, or semiautomated. It is worth noting that while available to purchase, many of these newer automated and semiautomated devices have not yet been validated for clinical use and may lack the precision/accuracy of measurement seen in mercury-based sphygmomanometers.

Hypertension is a well-known risk factor for stroke, CVD, heart failure, and chronic kidney disease and accounts for 12.8% of deaths annually worldwide.[2] It is estimated that by 2025, the number of people living with hypertension will reach 1.5 billion.[40] Management of hypertension remains a daunting task for health care systems worldwide. Early detection and intervention are essential for the optimal management of hypertension and associated complications.

Diagnosis of hypertension was traditionally based on clinic-based BP measurement. Over the past few decades, various studies have noted a significant difference in BP obtained during routine clinic settings versus those obtained using 24-hour ABPM or HBP monitoring by ≈5 to 10 mm Hg.[41] Studies have also noted that ABPM and HBP monitoring were better than OBP in predicting total and cardiovascular morbidity in patients with hypertension.[42] The clinical application of ABPM allows the clinician to identify and differentiate masked hypertension and white-coat hypertension from office hypertension.

Based on these considerations, ABPM is now the recommended reference standard for the diagnosis and management of patients with hypertension.[43] The 2017 American College of Cardiology/American Heart Association hypertension guidelines also recommend out-of-office BP measurements (HBP monitoring is considered an acceptable alternative to ABPM) to confirm the diagnosis of hypertension and for titration of antihypertensive medications.

The opportunity to easily make continuous noninvasive BP measurements migrates traditional BP recordings from intermittent, hourly, daily, or annual measures to continuous beat-to-beat changes and will challenge the clinical system to rapidly standardize techniques, reporting, interpretation, and gather meaningful epidemiologic data to guide clinical decision making.[44]

Cuff-Based Devices

Cuff-based devices measure BP by using 1 of 2 main techniques, the auscultatory method, and the oscillometry method. In the auscultatory method, the clinician listens to Korotkoff sounds over the brachial artery using a stethoscope to estimate SBP and DBP. The auscultatory gap (silent gap) is characterized by diminished/absence of Korotkoff sounds during auscultation. It is caused by reduced peripheral blood flow due to changes in the pulse wave. Incorrect interpretation of the auscultatory gap can lead to inaccurate BP measurement. The potential problem of an auscultatory gap can be avoided by initial estimation of the SBP by palpation to feel for the presence of a pulse.[45] The volume clamp method is based on the Penaz method, which involves an inflatable cuff combined with a photodiode. The photodiode measures the diameter of the artery in the finger as the pressure of the cuff changes to keep the diameter of the artery constant. These pressure changes in the cuff are then used to calculate arterial BP. In the oscillometric-based method, an electronic pressure sensor records the pressure oscillations produced through the arterial wall. The device constructs an oscillogram from upper and lower values of these oscillations as cuff pressure varies from above SBP to below DBP. Then proprietary algorithms are used to calculate the mean, systolic, and diastolic pressures from the oscillogram[46] (Figure 3).

For accurate BP measurement, the patient should be appropriately prepared and properly positioned, the BP devices need to be properly calibrated, an appropriate cuff size must be used, and multiple readings (≥3 sequential measurements) must be recorded. In manual BP measurement, personnel should be adequately trained. The most commonly noted causes of BP measurement errors are related to insufficient rest time, incorrect body position, inappropriate cuff size, and talking during the measurement.[47]

In a validation study on Omron HEM-6410T-ZM or Omron HEM-6410T-ZL (Omron Healthcare, Kyoto, Japan), watch-type wearable BP monitors with a

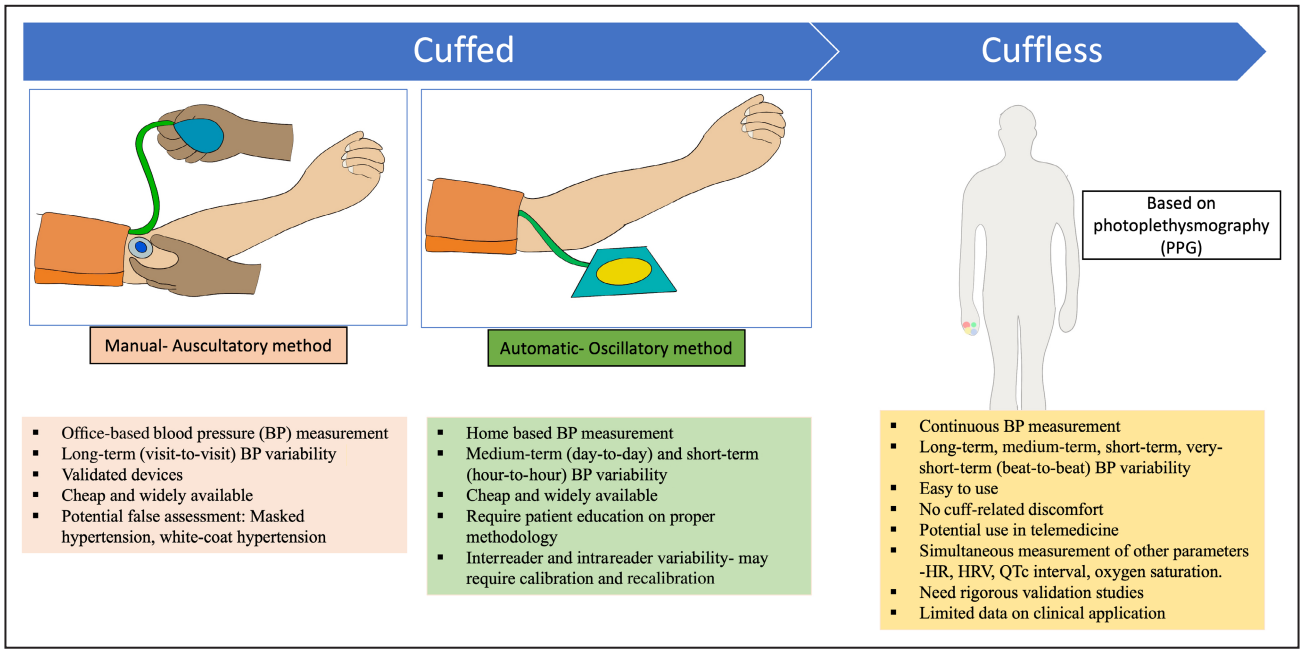

Figure 3. Methods for measurement of blood pressure variability.
BP indicates blood pressure; HR heart rate; and HRV, heart rate variability.

cuff-oscillometric–based automatic BP measurement function, fulfilled validation criteria of the American National Standards Institute/Advancement of Medical Instrumentation/International Organization for Standardization 81060-2:2013 guidelines when used in the sitting position with the wrist at heart level. Mean differences between reference BP values and HEM-6410T-ZM readings were −0.9±7.6/−1.1±6.1 mm Hg for SBP/DBP for criterion 1 (American National Standards Institute/Advancement of Medical Instrumentation/International Organization for Standardization 81060-2:2013 guidelines), and −0.9±6.8/−1.1±5.5 mm Hg for criterion 2 (American National Standards Institute/Advancement of Medical Instrumentation /International Organization for Standardization 81060-2:2013 guidelines); corresponding differences for HEM-6410T-ZL readings were 2.4±7.3/0.7±7.0 and 2.4±6.5/0.7±6.5 mm Hg. However, the study noted a significant difference in BP measurement on the basis of body or palm position, which may limit its real-world applications.[48]

In an outpatient setting, mean differences between reference BP values (measured using an ambulatory BP monitoring device) and HEM-6410T-ZM (both devices were worn on the same arm), the mean difference in systolic BP readings were 3.2±17.0 mm Hg (P<0.001).[49] Although in another mixed-effects model analysis, no significant difference was noted between the 2 devices in BP temporal trends.[50]

Cuff-based devices can also cause cuff-inflation hypertension. It is characterized by a marked rise in BP caused by cuff inflation during self-measurement, potentially from physical exertion required to inflate the cuff (it can be resolved by using the automated device) or from anticipatory anxiety (its effect can be minimized by taking multiple sequential measurements and discarding the first reading).

Cuffless Devices

These devices include all methods of BP measurement without using a cuff. There are distinct potential advantages of cuffless BP measurement, including being more convenient for the patient (no pain or anxiety associated with cuff inflation or waking of the patient during the night during cuff inflations), user friendly (by avoiding the complex pressurization mechanism), and maybe wearable (smartwatch), which may provide continuous BP monitoring, giving thousands of pressure measurements over 24 hours compared with the ≈36 currently acquired from ABPM systems. As a result, there is significant clinical and commercial interest in the development and validation of these devices.

The most commonly used cuffless devices are based on the analysis of photoplethysmography (pulse waveform features, pulse transit time, oscillatory method, transdermal optical imaging). Photoplethysmography is an optical method for measuring the amount of light that is absorbed or reflected by blood vessels in living tissue (Figure 3). A potential limitation of the photoplethysmography-based system includes inaccuracies stemming from the difference in skin tones, motion artifacts, and significant interdevice variability (due to the use of proprietary machine-learning algorithms used by different manufacturers).[51] The amount

of light absorbed or reflected in photoplethysmography depends on the amount of blood in the optical path. Therefore, readings from photoplethysmography can be used to measure changes in the blood volume in the microvascular bed of tissue (Figure 4). The pulsatile component of a photoplethysmography signal measures the intra-arterial changes in blood volume, and the nonpulsating component of the photoplethysmography signal corresponds to basic blood volume, respiration, and thermoregulation.[52] Light absorption by hemoglobin in the blood is maximized when the vessel is fully expanded during systole and minimized during diastole.[53] The photoplethysmography signal is used to construct pulsatile waveform features such as pulse width, the slope of the initial upstroke, height, and time between pulse arrival at different locations on the body (PTT). A machine learning–based pulse wave analysis algorithm is then applied to calculate SBP and DBP.[53] The major limitation of this method is that prediction accuracy depends on the size and diversity of the training data set of learning algorithms.

PTT-Based BP Measurement

PTT-based BP measurement requires at least 2 sensors for simultaneous collection of the photoplethysmography signal and heartbeat (phonocardiogram, seismocardiogram) to collect features of PTT.[54] Therefore, the accuracy of PTT-based BP measurements is dependent on the calibration quality and may require frequent recalibration of the devices.[55] The use of an equation to further estimate the systolic and diastolic pressures is required and can be a further source of inaccuracy.

Photoplethysmography-Based Oscillometric Method

A simultaneous collection of the photoplethysmography signal and oscillatory signal (pressure sensor) by using a camera (photoplethysmography signal) and pressure sensor (external sensor, Chandrasekhar et al[56]; touch pressure-sensitive phone screen- the iCare Health Monitor, iCareFit Studio [http://www.icarefit.com/]) can potentially allow a cuffless oscillometric method for BP measurement. The touch-based pressure-sensitive phone screen method is also identified as a source of inaccuracy and operator dependency.

Transdermal Optical Imaging

In this video camera–based photoplethysmography method, the transdermal optical imaging (multiple regions of the face), blood flow data are collected using

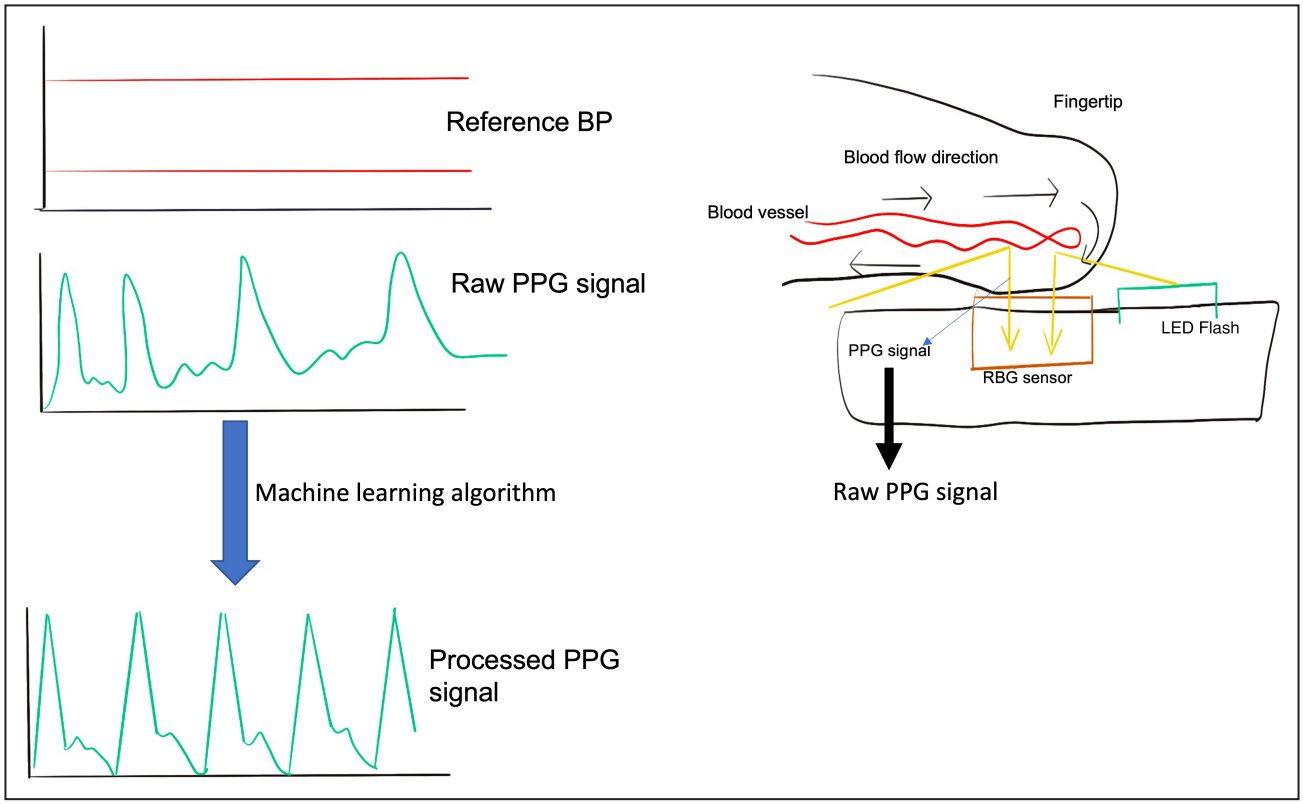

Figure 4. Principle of photoplethysmography (PPG).
Data generated from volumetric blood flow changes due to light passing through the fingertip into the RBG sensor (red, blue, and green light sensor). The raw PPG data is fed into a machine learning algorithm for PPG feature extractions. BP indicates blood pressure.

a video camera. A machine learning algorithm extracts hemoglobin-rich signals and discards melanin-rich signals from each image of the video sequence.[57] This set of images is then used to extract data on features of pulse waves to calculate BP.[58] In doing so, the system measures the blood flow waveform oscillations from the video (eg, in the face) but does not have a means to accurately calibrate the waveforms due to the inability to measure BP in such regions.

Transdermal Ultrasound Imaging

An array of ultrasound crystals applied to the skin overlying a superficial artery, for example, using embedded adhesive skin patches, can measure the time-dependent dimension of beat-to-beat changes in artery diameter or volume and continuously transmit the images to smartphones or central servers. A machine learning algorithm supports the adequate focus of the crystals on the artery, and the signal can be calibrated with arterial pressures obtained from either indwelling artery measurements or manometric blood pressures. This technique is applicable to any artery within reach of the ultrasound imaging crystals, allowing calculation of continuous brachial pressure as well as central artery pressure observed at the carotid artery.

A number of companies have launched wearable devices and smartphone applications for BP measurement with Food and Drug Administration clearance, including BioBeat (Petach Tikva, Israel) (BB-613WP) and Omron (Kyoto, Japan) (HeartGuide).[59] However, it is worth noting that some of these Food and Drug Administration–cleared devices may not be accurate enough for clinical use. For instance, in a study on Samsung Galaxy Watch Active 2, the author demonstrated a show a systematic bias toward a calibration point, overestimating low BPs and underestimating high BPs, when investigated in both normotensive and hypertensive patients.[60]

Food and Drug Administration clearance of these noninvasive BP devices requires that the manufacturer demonstrate that a new BP device is approximately as safe and effective as similar devices on the market, also called "substantial equivalence." Therefore, these devices do not need to meet the more stringent accuracy of measurement criteria for validation protocols set forth by various medical associations, including the British and Irish Hypertension Society, Association for the Advancement of Medical Instrumentation, American National Standards Institute, and European Society of Hypertension international protocol.[61] To address this shortcoming, device registries containing a peer-reviewed listing of validated devices, such as the Dabl (http://www.dableducational.org) independent site created by DABL educational trust; the Medaval (http://medaval.ie/) independent site created by a nonprofit organization, the American Medical Association (https://www.validatebp.org), and the Japanese Society of Hypertension device listing, have been created to inform consumers and health care providers on which devices have been validated and the criteria used for their validation.[47,62] Some of these device registries lack independent scientific oversight (Dabl, Medval) when compared with registries created and maintained by professional hypertension societies.

Despite these challenges, these newer wearable devices offer a number of potential benefits, including (1) continuous BP monitoring over days and months, providing a more accurate BP profile and measurement of BPV, with theragnostic potential; (2) convenience for the patient, ease of use (small wearable, no pushing of button or inflation of cuff), less discomfort (related to cuff-inflation), and low cost; (3) changing paradigm for patient-focused telemedicine—these devices provide a platform for the transfer of health care data between the patient and health care professionals and can be potentially used as a telemonitoring tool for guiding management and monitoring treatment response in the future; (4) simultaneous measurement of other clinically relevant information, such as heart rate, HRV, arrhythmias, cardiac output, systolic volume, corrected QT interval analysis, oxygen saturation, sleep stages, and changes in electrolyte abnormalities[63]; and (5) continuous measurement of brachial or central BPs.

CLINICAL APPLICATIONS OF BPV–THERAGNOSTIC IMPLICATIONS

The degree of hypertension is a well-established predictor of target-organ damage and a determinant of prognosis.[64] However, until recently, very limited data were available on the prognostic impact of BPV. Data available from various studies and meta-analyses have shown that BPV is an independent risk factor (even after adjusting for the increased risk attributable to the elevation of mean BP levels) for cardiovascular events, a decline in renal function, subclinical brain small-vessel disease, dementia, and end-organ damage.[16,28,65,66]

The exact underlying mechanism responsible for target-organ damage due to BPV is not known. However, the literature suggests that the adverse effects of increased BPV can be related to a traumatic effect of wider BP swings on the vessel wall integrity, causing microcirculation dysfunction and eventually leading to target-organ damage.[16] While the use of BPV as a clinical tool to predict outcomes has been used effectively in patients with hypertension, the application of such a prognostic tool in patients with heart failure requires an entirely different data set to understand the outcome and potentially inform more tailored treatment.

A number of animal studies have been conducted to evaluate the effect of BPV on end-organ damage. For instance, in a Wistar rat model with chronic kidney disease, the increased BPV was induced by sino-aortic denervation and was associated with a higher level of glomerulosclerosis and cardiac and renal hypertrophy.[67] In another rat model-based (spontaneously hypertensive rats) study, discontinuous treatment with valsartan induced a significant increase in day-to-day BPV, short-term BPV, diastolic BPV, and increase in pulse wave velocity despite a similar decrease in SBP and no changes in elastin/collagen ratio or aortic thickness, as compared with continuous treatment with valsartan.[68] This study highlights the potential role of BPV independent of SBP in the development of aortic stiffness.

Cardiovascular Disease

Variability of the mean BP, particularly medium- to long-term BPV (visit-to-visit), is an independent risk factor for cardiovascular events and death.[69,70] For instance, data from the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) trial, involving ≈14 000 middle-aged and older patients with hypertension, showed a 15% increase in the risk of cardiovascular events and a 10% increase in the risk of death for a 5-mm Hg increase in SD of within-visit and visit-to-visit systolic BPV, respectively.[69] Another study noted a 37% and 33% increase in the risk of cardiovascular events per SD of beat-to-beat BPV and day-to-day BPV, respectively.

BPV is a strong predictor of coronary artery disease.[71] Various studies have found a higher incidence of myocardial infarction in patients with higher long-term BPV. In contrast, other studies have shown short-term BPV to be a better predictor of CVD mortality.[72,73] However, a number of studies have shown that both long- and short-term BPV have a similar correlation with all-cause mortality.[69,73] To better understand the underlying pathophysiology associated with different types of BPV and their correlation with various risk factors, further clinical research is needed.

While the majority of literature describes the role of BPV in hypertension, some limited studies have also shown BPV to be a positive predictor of heart failure and its outcome.[74] In addition, a study conducted by Wei et al[75] on 3184 patients with heart failure with preserved ejection fraction (ejection fraction ≥45%) enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial found greater short-term systolic and diastolic BPV to be independently (of baseline BP level) associated with adverse health outcomes. Furthermore, medium-term visit-to-visit systolic BPV has been shown to be an independent risk factor for new-onset atrial fibrillation.[76]

Literature has suggested that a potential increase in sympathetic activity related to an increase in BPV may induce pathological changes in the heart, including excitation of ion channels in cardiomyocytes leading to atrial fibrillation and cardiac remodeling leading to heart failure.[77] In addition, some studies have also suggested a positive correlation between BPV and coronary plaque formation and impaired coronary perfusion, which may further explain the increased risk of heart failure and myocardial infarction in patients with higher BPV.[78]

In addition, the increase in CVD risk associated with BPV is higher in high-risk patients, that is, in patients with high baseline risk.[26] Younger patients are more susceptible to the impact of BPV, despite a higher BPV and higher absolute risk that is seen in older patients. This could be due to the overshadowing of the negative effect of BPV by other risk factors in older patients (compared with younger adults with fewer risk factors) or survivor bias (individuals with high BPV who survive to older age may have a higher tolerance to the effect of BPV compared with younger patients).[69,79]

Autonomic dysfunction is a common chronic complication of diabetes and is characterized by impairment of the autonomic nerve fibers regulating heart rate, myocardial contractility, cardiac output, and vasoconstriction, with a potentially life-threatening outcome. Studies have noted that the degree of loss in short-term BPV (the day-night rhythm of BP) potentially due to underlying cardiac autonomic neuropathy is a risk factor for cardiovascular accidents in patients with diabetes.[80]

Quantification of this cardiac autonomic dysfunction characterized by blunting of circadian BPV with an increase in nocturnal sympathetic activity (increase in heart rate, BP) may help provide important prognostic and therapeutic response markers for antisympathetic or volume regulation strategies in patients with diabetic autonomic neuropathy.[81]

Chronic Kidney Disease

Hypertension is a known risk factor for CKD.[82] Studies have shown that an increase in BPV is also a poor prognostic factor for the development, progression, and severity of renal outcomes in CKD and in patients undergoing hemodialysis.[67] The suggested underlying pathophysiology of BPV is similar to that described in the development of cardiovascular disease, which is a combination of fluctuations in renal blood flow, changes in aortic hypertrophy and remodeling, endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, and inflammatory cytokines.[83]

Wang et al[27] studied the long-term effect of visit-to-visit BPV on kidney disease using data from an

ongoing Hanzhong Adolescent Hypertension study involving 1771 participants (children and adolescents aged 6–18 years at baseline with no chronic disease) that were followed over a 30-year period (6 visits). They found that higher systolic and diastolic BPV (SD, ARV) were associated with a higher risk of subclinical kidney damage and albuminuria in adulthood.

One meta-analysis showed that patients with higher systolic BPV had a 5% higher risk of CKD for each 1 mm Hg increase in SD compared with patients with lower systolic BPV.[67] The study also found that both systolic and diastolic BPV showed a positive correlation with an increase in the risk of CKD, and the effect was augmented when both variabilities were present together.[84] Visit-to-visit BPV was also noted to be an independent predictor of early renal impairment. It is worth noting that CKD is also an important risk factor for CVD, infection, and cognitive impairment.[85] This may explain the increase in overall and cardiovascular mortality noted in patients with CKD and increased systolic BPV.[86]

Cerebrovascular Diseases and Dementia

Stroke is one of the leading causes of death globally, accounting for 11.1% of all-cause mortality. Elevated systolic BPV (visit-to-visit) is an independent risk factor for stroke.[87] The suggested underlying mechanism of BPV in stroke is similar to that proposed for the development of CVD and CKD, and other target-organ damage.[88] A systemic review noted elevated systolic BPV to be associated with a higher rate of death and disability after stroke.[89] Some studies have noted an increase in infarct growth with higher BPV, which may, in part, explain worse stroke outcomes in patients with elevated BPV.[90] In a study by Webb et al, they noted beat-to-beat BPV to be a predictor of recurrent stroke and cardiovascular events, independently of mean systolic BP and risk factors. They noted a 47% and 24% increase in the risk of stroke per SD of beat-to-beat BPV and day-to-day BPV, respectively. Interestingly, they did not notice any correlation between short-term BPV and the risk of recurrent stroke and cardiovascular events.[91]

Multiple studies have also noted a correlation between BP elevation and markers of both cerebral amyloidosis and tau-mediated neurodegeneration (hyperphosphorylated tau; including Alzheimer disease) in cerebrospinal fluid and positron emission tomography markers.[92] Similar robust studies on the relationship between BPV and dementia are lacking. However, data from a limited number of studies suggest a positive correlation between elevated BPV (both systolic and diastolic) (visit-to-visit) to be an independent (of average BP levels) predictor of cerebrovascular disease and cognitive decline.[93,94] Although the underlying mechanism remains unclear, some studies have suggested that vascular dysfunction, increased risk of cerebrovascular diseases, and decline in cerebral perfusion may play a role in the development of Alzheimer disease and vascular dementia.[95] This is supported by findings from the study by Sible et al,[96] which noted a positive relationship between elevated BPV and longitudinal tau accumulation.

CVD is the most common cause of death in patients with mental illnesses (such as anxiety, depression, and bipolar disorder). This has led to a hypothesis that patients with mental illness may have higher BPV, which may be the underlying mechanism causing increased cardiovascular risk and target-organ damage. A systemic review including 12 studies found that people with mental illness were significantly associated with an increased BPV, regardless of age. The author also suggested that since mental illness may lead to deterioration of autonomic function (heart rate and BPV), early therapeutic intervention in a mental illness may prevent diseases associated with autonomic dysregulation (eg, BPV) and reduce the likelihood of negative cardiac outcomes.[97]

Therapeutic Implications of BPV

BPV is a significant risk factor for heart failure, myocardial infarction, atrial fibrillation, CKD, stroke, and dementia.[16,28,65,98] These seemingly disparate conditions may share similar underlying pathophysiological mechanisms related to BPV.

Given the novelty of the BPV concept, the absence of established threshold levels to discriminate pathological from physiological BPV, and the lack of adequate clinical data, the standardized management guidelines have not yet been updated to include BPV as a potential therapeutic target. Data from various studies have demonstrated that a reduction in BPV may lead to a reduction in the risk of cardiovascular events.[66] Various BPV indices, ranging from beat-to-beat BPV (very short term) to visit-to-visit (long term), have shown significant predictors of recurrent stroke and cardiovascular events, independently of mean SBP and other risk factors.

A post hoc analysis of 2 large-scale studies showed that the use of amlodipine (calcium channel blocker) to stabilize BPV led to a decrease in the incidence of coronary events.[99] In a systemic review on the effect of the antihypertensive drug on the management of BPV, long-acting calcium channel blockers (CCBs) (dihydropyridine calcium antagonists) were noted to be the most effective treatment for BPV control.[99] The study Heart also noted that monotherapy or, in combination, CCBs had been associated with the most effective long-term BPV lowering. Liu et al[100] noted that CCBs were most effective in reducing BPV and related organ damage in hypertensive rat models.

Another study has shown that calcium antagonists or diuretics have the most significant effects on the control of BPV.[101] In contrast, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers may even lead to an increase in BPV. Another study compared responses in patients with hypertension to valsartan versus amlodipine. The author reported that compared with patients in the valsartan group, the amlodipine group showed a higher decline (by 1.4 mm Hg) in visit-to-visit systolic BPV.[69] It is important to note that patients with the highest visit-to-visit BPV and more cardiovascular risk factors were more often treated with valsartan compared with amlodipine. It is crucial to note that drugs acting at the renin-angiotensin system, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, have been shown to offer superior protection against cardiovascular events than CCBs.[102] This may suggest a combination therapy with CCB (better control on BPV) and drugs acting at the renin-angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers [better control of cardiovascular remodeling and mortality benefits]) may offer superior outcomes to monotherapy with CCB or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

The underlying mechanisms responsible for the effects of CCBs on BPV are not fully understood. According to 1 of the suggested mechanisms, arterial vasodilatory effects of CCBs may improve arterial compliance and baroreceptor function, which in turn may lead to improvement in BPV.[66] Long-acting drugs seem to buffer excessive BPV over a 24-hour period. It is also important to note that adherence to antihypertensive therapy has been shown to have a buffering effect on medium- to long-term BPV.[103]

Whereas HRV has been used to assess autonomic influences, BPV may capture the relation between changes in preload reserve associated with respiration or posture and the ability of central aortic compliance. For example, reduced BPV during respiration may reflect either defective preload reserve or healthy aortic compliance.

Future Directions

Continuous, noninvasive BP monitoring is challenging the traditional view of hypertension management through convenient systems that allow 24-hour continuous BP monitoring with beat-to-beat time frames. Continuous BP monitoring provides an opportunity for a better understanding of the underlying physiology of BP regulation, including BPV and its implication on cardiovascular conditions such as hypertension, heart failure, and arrhythmias. However, recent clinical studies have shown the potential role of BPV as a prognostic tool in various disease processes. However, it is still unclear whether BPV in itself is responsible for target-organ damage or is just a prognostic marker of other pathological processes like autonomic dysfunction, vascular stiffness, or endothelial dysfunction. Future research clarifying the role of various BPV determinants is needed to better understand the underlying pathophysiology of target-organ damage and BPV. In addition, future studies are needed to define and validate the physiologic and pathologic ranges of BPV. Integration of continuous BP monitoring and BPV in future clinical trials may help address some critical knowledge gaps, including the impact of sleep, body posture, and physical activity on BPV; the effect of dosing regimen (dosing and frequency) on BP and BPV; the impact of diseases on BPV; the effect of medications on BPV; and correlation between heart rhythms, rhythm-related symptoms, drugs, BP, and BPV. Critical information from these clinical trials may help identify new baseline strategies, reduce the variability of treatment end points, and enable the assessment of treatment response (including noncompliance).

Integration of BPV with HRV and pulse arrival time will allow discrimination of the autonomic contributions versus the contributions of vascular capacitance/compliance toBP to better inform treatment options in the future. Importantly, studies validating the accuracy and establishing a platform for reporting and analysis of the vast data obtained by these devices will impact our understanding and management of these diseases.

CONCLUSIONS

BPV is an independent risk factor for cardiovascular events, dementia, stroke, a decline in renal function, and mortality. Continuous, noninvasive BP monitoring is challenging the traditional view of hypertension management through convenient systems that allow 24-hour continuous BP monitoring with beat-to-beat time frames. Studies validating the accuracy and establishing a platform for reporting and analysis of the vast data obtained by these devices will impact our understanding and management of these diseases. The current guidelines do not include the use of BPV as a target in hypertension or heart failure management. However, given the potential beneficial role of BPV management in reducing CVD outcomes, controlling BPV should be considered a new goal standard.

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