Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: October 31, 2022

Citation: Izzo JL, 2022. Blood Pressure Variability: Mechanisms, Measurement, Subtypes, and Clinical Implications, Medical Research Archives, [online] 10(10). https://doi.org/10.18103/mra.v10i10.3174

DOI
https://doi.org/10.18103/mra.v10i10.3174

ISSN: 2375-1924

RESEARCH ARTICLE

Blood Pressure Variability: Mechanisms, Measurement, Subtypes, and Clinical Implications

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ABSTRACT

The complex topic of short- and long-term blood pressure (BP) variability confounds the diagnosis, classification, and management of hypertension. True pathophysiologic BP variation (systematic and non-systematic deviations between- and within-individuals) is related to heart rate, respiration, complex responses of the sympathetic nervous system, vascular reactivity, and arterial stiffness. Measurement errors (systematic biases and random error) further compound the analysis. Most studies use serial clinic BP values, 24-hour ambulatory BP recordings, or home BP values with standard statistical indicators (standard deviation, variance, or coefficient of variation) or absolute real variability (mean difference of successive values). Clinical impact in retrospective secondary analyses includes a modest increase in cardiovascular disease (CVD) risk (equivalent to a few mmHg in mean systolic BP) yet questions remain whether adjustment for mean BP is needed. BP variability is reduced to a small degree by calcium antagonists and increased by ACE inhibitors, beta-blockers, and alpha-blockers but no interventional trial has addressed the question of whether reducing BP variability confers CVD risk protection. BP variability is not specifically discussed in practice guidelines but it is tacitly acknowledged by recommendations to repeat BP measurements, standardize technique, and confirm the hypertension diagnosis by home or ambulatory BP measurements to account for the "white coat effect." There is no formal consensus on how to quantitate or manage BP variability despite a real-world need for better diagnostic and therapeutic guidance. Practitioners should thus focus on control of (mean) BP using combinations of agents that improve CVD outcomes. Future consensus guidance should directly address BP variability and should include educational materials for physicians, patient-contact staff, and patients.

Keywords: blood pressure, blood pressure variability, hypertension

INTRODUCTION

Within individuals, intrinsic variation in blood pressure (BP) is beneficial in allowing vigorous responses to acute physiologic stressors while conserving energy and limiting unnecessary strain on target organs during rest. At the same time, BP variability poses a significant challenge to the accurate diagnosis, classification, and management of hypertension. Between individuals in the general population, traditional office systolic BP values are distributed almost normally over a roughly 3-fold range and within an individual during 24-hour ambulatory BP monitoring (ABPM), the range often reaches 2-fold. BP variability can be divided broadly into 2 categories: 1) true pathophysiologic variability (between- and within-subjects) and 2) BP measurement uncertainties due to technique biases and random measurement error. CVD risk is modestly elevated when BP variability is high but it is not yet clear that BP variability should be added to risk stratification algorithms or that it can or should be treated. Clinical uncertainty is further amplified by divergence among international guidelines about recommended measurement techniques, hypertension classifications, and therapeutic goals. This review will discuss major factors contributing to BP variability and the resulting clinical uncertainties it causes. It also offers limited commentary regarding practical approaches to BP variation in everyday medical practice.

MECHANISMS OF BP REACTIVITY AND VARIABILITY

The pathophysiology and temporal classifications of BP variability patterns have been covered in previous expert reviews[1,2] but critical factors in the underlying pathophysiology are briefly recapitulated here to provide relevant scientific background.

Heart rate and respiration

Systolic BP varies by heartbeat in resting individuals but this form of BP variability may not have the same impact as other forms of BP variability that will be discussed subsequently.[3-7] Beat-to-beat variation in systolic BP or pulse pressure (PP) is principally reflective of the underlying variation in cardiac stroke volume and its dependence on cardiac preload (cardiac filling time and central venous pressure). When heart rate is low (and RR interval is high), greater atrial filling allows cardiac Starling forces to increase stroke volume; systolic BP increases immediately for that heartbeat. Neither stroke volume nor heart rate variation is the dominant component of overall BP variability, accounting for about 10% and 30% of total 24-hour BP variability, respectively.[8] In more extreme conditions such as atrial fibrillation, PP and systolic BP can vary from nil (a pulseless beat) to 100 mmHg depending on the prior RR interval (Izzo, unpublished observations). Obligatory systolic BP variation is also linked to respiration and breathing patterns (rate and depth) via changes in intrathoracic pressure and cardiac preload. The clinical manifestation of respiratory variation in BP is "pulsus pardoxus," which is always present to some degree but systolic BP can easily vary by 20 mmHg or more if there are extreme fluctuations in intrapleural pressure. All of this can occur without any changes in sympathetic nervous activity or systemic vascular resistance. Respiration-linked changes in BP typically lag by a few heartbeats (2-3 seconds) because of the time it takes to transfer the preload-dependent changes in right heart output to the left heart.[9,10]

Sympathetic nervous system (SNS)

Most aspects of BP variability, from moment-to-moment BP fluctuation (a few seconds) to long-term BP changes (decades) are dependent on the underlying activity of the SNS.[11] The SNS is activated by various external and internal stressors but also plays a role in homeostasis.[11] The basal "firing rate" of peripheral SNS neurons is about 0.1 Hz (every 6 seconds) but under major stress, the neuronal firing rate and amplitude can increase dramatically, along with the amount of norepinephrine released per nerve burst. The SNS control centers in the ventrolateral medulla oblongata regulate the constriction of peripheral arteries and veins via neurons in the intermediolateral columns in the spinal cord and post-ganglionic peripheral sympathetic nerves. Separately, the SNS regulates heart rate via vagal cardiac efferent neurons to the sino-atrial node. Variation of BP during normal daily activities is a reflection of activation and deactivation of the SNS; this includes sleep-waking cycles, ambient temperature and postural adaptation, cognitive and emotional responses, and physical exertion. SNS activity can be organ-specific or generalized. SNS control centers are modulated by complex afferent and neuro-modulatory signals from cortical nuclei, the hypothalamus, basal ganglia, circumventricular control centers, baroreflexes, and excitatory metaboreceptors in muscle and kidney. Negative feedback via aorto-carotid baroreflexes is familiar to most physicians but less well known is the role of cardiopulmonary baroreflexes, where

stretch fibers in the atria and central veins sense changes in cardiac preload and central blood volume and relay this information to the SNS control centers.[12]

From a hemodynamic perspective, peripheral sympathetic nerves control central blood volume and cardiac preload via peripheral venoconstriction; they also modulate cardiac afterload via arteriolar constriction. Within an individual, variations in cardiac stroke volume and HR contribute about 40% of the observed BP variability throughout the day, while 60% is attributable to the underlying variation in systemic vascular resistance.[8] In population studies, however, 24-hour mean HR and BP are almost completely decoupled in both normotensive and hypertensive populations.[13] Aorto-carotid and cardiopulmonary baroreflexes are subject to resetting and blunting, allowing SNS activity and BP to increase with aging.[14,15]

Vasoreactivity

The contractile response of a peripheral artery or vein to a given stimulus (e.g. sympathetic nerve discharge) is modulated by local factors, particularly vascular structure and endothelial function. The impact of an SNS discharge on the percentage decrease in lumenal cross-sectional area and the corresponding percentage increase in systemic vascular resistance and BP is highly dependent on caliber of the arteriole and its wall-to-lumen ratio. Thus, smaller arterial diameter (as occurs in people with shorter stature and women) or the presence of arteriolar smooth muscle hypertrophy (as occurs with long-standing hypertension) will cause a greater increase in systemic vascular resistance and BP in response to a "standard" SNS discharge.[16] Another aspect of vasoreactivity is the role of the endothelium and local nitric oxide production in blunting vasoconstrictive responses.[17] Substances such as angiotensin II contribute to endothelial dysfunction by promoting local superoxide radical generation; enhanced vasoreactivity and atherogenesis are also promoted by cholesterol oxidation products.[18,19] We have found that individuals with high cholesterol exhibit enhanced BP reactivity to mental stress and demonstrated improvement following cholesterol-lowering medication.[20] We identified the same pattern in individuals with insulin resistance, whose BP hyper-reactivity was ameliorated by an insulin-sensitizing agent.[21] In a similar vein, a higher healthy lifestyle composite score (1 point each for never smoking, adhering to a healthy diet, performing moderate or intense physical activity, keeping body mass index <25 kg/m2, maintaining total cholesterol <200 mg/dl, a glycated hemoglobin <5.7%, and conventional BP <120/80 mm Hg) has been associated with lower BP variability.[22] Participation in a cardiac rehabilitation program has been reported to decrease BP variability but exercise training alone does not.[23,24]

Arterial stiffness

Pulse pressure and systolic BP increase inexorably as arteries stiffen with age. Arterial stiffness is directly correlated with higher pulse pressure and systolic BP but there is ongoing debate whether systolic hypertension precedes or results from arterial stiffening.(19-22) The most useful model is that aging, arterial stiffening, and systolic hypertension are inter-related components of a long-term "vicious cycle".[25] Arterial stiffening universally increases the variability of systolic BP; this can be described mathematically as an increase in the exponent (β) of the non-linear pressure-volume relationship within an arterial region;[25] β actually represents the curvature of an artery's pressure-volume curve. Said differently, there is greater sensitivity of PP and systolic BP to any change in pulse volume, hence greater BP variability. Based on this relationship, we proposed use of the "pulse stiffening ratio" (PSR), which is simply [standard deviation of systolic BP] / [standard deviation of diastolic BP].[25] Because arterial stiffness always depends to a degree on arterial pressure, effective long-term antihypertensive therapy will passively reduce arterial stiffness to a small degree (probably< 10%). Any reduction in stiffness that is attributable to true arterial remodeling, however, will require several months owing to the slow turnover of collagen in vascular walls. Accordingly, effective antihypertensive therapy may reduce BP variation but to a very limited degree. There is no true "anti-stiffness" medication at this time.[26,27]

MEASURING BP VARIABILITY

Methods

The most common approach to the quantitation of BP variability is to analyze a sample of several BP readings using traditional statistical indicators such as range, variance, standard deviation (SD), and standard error. All reflect the dispersion of measurements around the mean and although they are mathematically independent of the mean, their interpretation is not. Range is biased toward the most extreme values, while the other statistical variables more closely reflect the central tendencies

of the distribution and are strongly affected by the number of measurements. Other approaches, including using coefficient of variation (standard deviation/mean), inter-quartile range, or "average real variability" (ARV, the mean of the absolute changes in BP between consecutive readings over a period of time) [28] have been used; the last is least dependent on the number of measurements used.

Short-term BP variability is most often studied using 24-hour ambulatory BP monitoring (ABPM), with BP values obtained every 20-30 minutes throughout the day. In a normal day, BP is subject to a wide variety of physiological changes, including sleep-waking cycles ("nocturnal dipping"), supine and upright posture, arm position, physical activity, emotional responses, environmental temperature changes, and meals as well as drug pharmacodynamics.

Multiple time intervals and detection techniques have been used, including visit-to-visit clinic BP variability (VVV) and home BP monitoring (HBPM).[29-32] [33] These methods use relatively few individual measurements and often differ greatly in the time period studied. HBPM is usually performed twice a day for 5 days but VVV data represent variable numbers of observations over months to years. There are few studies that compare techniques; one suggested that beat-to-beat and day-to-day SBP variability were similar in their correlations with a variety of vascular function indicators but 24-hour ABPM were not.[4] In a very small series, between-subjects variance of mean BP was 1/3 greater with clinic readings than ABPM, except in isolated systolic hypertension (ISH); this finding has direct implications for sample sizes in clinical trials.[34]

BP reactivity vs BP variability

BP reactivity (maximum response – baseline) is relatively convenient to measure in a clinical laboratory but reactivity is not synonymous with variability and reactivity can be misleading as an indicator of SNS activity. For example, SNS and BP responses to exercise stress vary widely between individuals and peak responses or % change are not automatically proportional to the pre-stress SNS output or BP level but the magnitude of the systolic BP response to exercise is linked to future hypertension and hypertensive target-organ damage, including ventricular hypertrophy and arterial stiffness.[35-37] Cardiovascular fitness can reduce the magnitude of the BP response to exercise and to mental stress but cardiovascular fitness is not correlated with BP variability and BP variability is not reduced by exercise conditioning.[37-40] Responses to cold stress are similar to patterns observed for exercise in that basal conditions and stress responses are not necessarily proportional; chronic exposure to low temperatures correlates with higher resting BP but in these individuals, BP reactivity to a cold pressor test is reduced.[41] Responsiveness to mental stress varies widely within and between individuals and studies are not always reproducible within-individuals due to learning and habituation and to difficulties in achieving and maintaining baseline and background conditions. The actual strength of stimulus is particularly hard to quantitate and extraneous emotional and cognitive factors often influence responses to stress.[42]

SUBTYPES OF BP VARIABILITY

BP variability can be divided into 2 broad categories: 1) measurement error, both random and systematic, and 2) true pathophysiologic variation, both within and between individuals. Each can contribute substantially to apparent BP variability.

Measurement uncertainties

Random measurement error. BP variability statistics always depend to a degree on the accuracy and repeatability of the measurement itself. Accuracy standards for BP measurement devices are remarkably loose, in part because typical validation studies and device comparisons conflate random measurement error with true physiologic variability. The current AAMI/ESH/ISO guideline states that a BP measurement device is considered acceptably accurate if there is at least an 85% probability that the measurement error is ≤10 mmHg. In practice, two criteria must be met: (1) the mean difference between the test device and the reference standard must be ≤5 mmHg and (2) the standard deviation for systolic and diastolic BP measurements must be ≤ 8 mmHg. Despite the minimal nature of these standards, they have not been applied to all available devices.[43] Error attributable to observer and technique is another major factor that diminishes the accuracy and repeatability of traditional cuff BP measurements. Most of these errors arise because the observer has not followed recommended protocols, including failure to allow time for patient equilibration (at least 5 minutes undisturbed), wrong cuff size, cuff looseness, excessive rates of cuff deflation, and inability of the observer to match pulse sounds to the BP scale on the device.[44] In a small study, there was greater variability with nurse readings than physician readings, likely due in part to reporting BP values to the nearest 10 rather than 2 mmHg.[6,45]

There is also excessive random error with BP watches and other cuffless devices and they should not be used clinically.[46-48]

Systematic (device and technique) measurement error. Systematic biases are introduced by differences intrinsic to the technique or device employed. For example, cuff systolic BP taken at the wrist will be higher than that of the upper arm due to the phenomenon of pulse pressure amplification, which is variable between individuals.[47] Thus, wrist devices are not recommended in current guidelines. Failure to regularly calibrate a BP cuff can also lead to a substantial systematic error. Poor measurement technique may also represent systematic error. For example, some health professionals still take BP with the arm elevated, while others leave the arm dangling; the differences attributable to arm position can easily change BP by 10 mmHg due to differences in hydrostatic pressure. More complex measurement inaccuracy (within-individual and between-individual error and bias) occurs when BP is obtained with legs dangling and back unsupported (about 6 mmHg higher on average).

True BP variation

Within-individual BP variability. BP varies widely throughout the day in response to the physiologic needs of the organisms. Many different physiological stressors cause short-term SNS-mediated increases in BP as already discussed. A well-recognized subtype of stress-response is the "*white coat effect* (WCE)," which confounds hypertension diagnosis and management based on clinic BP readings. WCE is triggered by the presence of an observer in close proximity to a patient ("in their space") during the measurement of BP. WCE has been called an "alerting reaction" similar to a Pavlovian conditioned stress response. It is also a situation-specific conditioned response. The presence of WCE is not an indicator of generalized hyperresponsiveness to all stressors or situations and if present, the magnitude of the response varies widely within and between individuals.[49] There are varying numerical cutoffs for WCE but in practice, the term has been applied to a consistent difference between average clinic and non-clinic systolic BP (variably 10-20 mmHg).[50-53] Technically, the term *white coat hypertension* refers to a much narrower population, individuals with clinic systolic BP $\geq$140 mmHg and non-clinic (daytime ABPM or HBPM) < 135 mmHg.[50,51,53] In common parlance, the distinction between WCE and white coat hypertension is often lost, however.

Alternative BP office measurement methods have been developed to minimize WCE, the most important being automated office BP measurement (AOBP).[54,55] AOBP devices operate with no observer in the room; the patient activates the recording BP cuff, which takes several BP measurements (often 4 at 1 minute intervals); the mean of the last 2 readings is taken as the BP for that determination. The bias between standard clinic BP and AOBP varies with the individual clinic but seems to range from 5-10 mmHg. AOBP is significantly but variably lower than daytime ABPM (by as much as 12$\pm$14 mmHg, $p<0.001$ yet major guidelines suggest that daytime ABPM, HBPM, and AOBP values are equal and that the diagnosis of hypertension can be confirmed by a systolic BP of at least 135 mmHg from either HBPM or daytime ABPM.[50-53] More recent data suggest that the first AOBP measurement is closest to ABPM daytime mean systolic BP.[55]

The opposite pattern of variability to WCE is *masked hypertension*. Those with masked hypertension have higher daytime mean ambulatory BP than the BP values observed while sitting in a medical office.[56] Relatively little is known about the cause of masked hypertension. One explanation is that people with masked hypertension have higher physical activity and emotional stress levels in routine daily life than in a medical office but people with increased systolic BP reactivity to low-level bicycle exercise are more likely to have masked hypertension.[57]

BP variability over a longer period also exists. For example, there is seasonal variation in BP (up to about 10 mmHg), especially in rural areas in northern latitudes, associated with winter-time systemic vasoconstriction, activation of the SNS and renin-angiotensin systems, and increased plasma aldosterone.[58-60] Other long-term BP trends are associated with comorbidities such as weight gain and insulin resistance, which further exacerbate SNS overactivity and increase BP.[61,62] The longest-term increase in SNS activity and BP is that related to age, as already discussed.[11,14]

Between-individual (population) BP variability. Population variation in BP is, in essence, the epidemiology of essential hypertension. BP is relatively normally distributed in the general population with some rightward skew. This shape is not consistent with a single genetic cause and worldwide collaborative efforts have now defined 535 genetic loci associated with BP.[63] The sheer number of these candidate genes far exceeds the number of possible contributing pathophysiologic mechanisms for hypertension and even more

problematic is the fact all of these loci account for only 5.7% of the population distribution of systolic BP.[63] Random error in the form of within-subjects BP variability and poorly representative and inaccurate BP measurements almost certainly contribute to this limited association but there are also systematic biases, such as those between individual clinics and even between countries.[64,65] Overwhelmingly, it is more likely that population variation in BP is more closely related to environmental and acquired characteristics, including systematic biases such as age and individual characteristics such as obesity.

ANTIHYPERTENSIVE DRUGS

Within-individual variability.

Drug pharmacodynamic differences contribute to within- (and between-) individuals BP variability. Peak-to-trough ratio has been a standard measure of duration of an antihypertensive drug effect and trough values are important in establishing drug dosing frequencies and labelling. In general, long-acting agents such as dihydropyridine calcium antagonists and non-loop diuretics (thiazide-type or aldosterone antagonists) have a peak-to-trough ratio close to 1. Another way to measure homogeneity of effect is the smoothness index, which relates the 24 hour mean BP and SD to the weighted hourly BP mean and SD).[66] The smoothest and most consistent effects are observed with thiazide diuretics and dihydropyridine calcium antagonists.[67] Short duration of acting is one reason why oral clonidine, labetalol, and hydralazine are not considered to be preferred first-line antihypertensive drugs.[50-53] These drugs also have no major studies demonstrating positive CVD outcomes but this is not surprising given the era in which they were developed. Another solution to a short pharmacodynamic half-life is the development of a timed-release formulation of the short-acting agent, as has been done for drugs such as metoprolol, nifedipine and clonidine.

Preferred long-acting antihypertensive drugs have minimal effects on within-subjects BP variability (generally <10%)[68] but there are modest divergences among different drug classes: ACE inhibitors, alpha blockers, and beta-blockers tend to increase BP variability slightly, while dihydropyridine calcium antagonists tend to reduce it.[6,68,69] The effects of diuretics on BP variability is not clear. In one meta-analysis, thiazides (and beta blockers) increased VVV and the risk of atherosclerotic endpoints[70] while in another study, "non-loop diuretics" improved BP variance and stroke risk.[69] We have reported that the within-subjects 24-hour ambulatory SD of heart rate is lower with equi-depressor doses of beta blocker (carvedilol) compared to angiotensin receptor blocker (valsartan) but there were no differences between these drugs in the SD or coefficient of variation of systolic or diastolic BP.[71]

Similarly, BP reactivity is generally not affected substantially by antihypertensive agents, which are more powerful in lowering baseline BP than the BP response to physical or mental stress. For example, we have found that the BP response to low-level bicycle exercise is not reduced by standard antihypertensive drugs, including beta-blockers.[72-75] We have also demonstrated this principle for mental stress[72]. These observations have led to a model that fully separates baseline BP from BP stress responses; in this model, the highest tier of CVD risk is represented by individuals with both high baseline BP and high BP reactivity.[76,77]

Between-individual variability.

As a heterogeneous syndrome with multiple interacting contributory factors within and between individuals, no single mechanism is sufficient to explain essential hypertension, which has been described in the past as a "mosaic." It follows that no single antihypertensive drug class, each of which is relatively specific for a given mechanism, can control BP in the entire population. Clinical including neurohormonal assessment (e.g. stratification by plasma renin activity) is expensive and not useful clinically in part because the mechanisms that control BP counter-regulate each other continuously (e.g. diuretics reduce extracellular fluid volume, which causes a reflex increase in plasma renin activity). BP responses to antihypertensive drug classes are quite heterogeneous; each class of antihypertensive drugs causes a clinically significant drop in BP in about half the population. With certain classes, the antihypertensive effect is highly complementary to certain other drug classes;[78] This is the rationale for preferred combinations such as a renin-angiotensin blocker (ACE inhibitor or angiotensin receptor blocker or beta-blocker) plus a diuretic or calcium antagonist.[50,51,53,79].

BP VARIABILITY AND CARDIOVASCULAR DISEASE RISK

There is a relatively large observational experience from secondary analyses of clinical trials that reveals a general trend toward modestly increased cardiovascular disease (CVD) risk in individuals with high BP variability.[28,30,33,80-84] Risk attendant to exaggerated VVV has been found to persist whether or not patients remain adherent to

antihypertensive therapy.[30,69,85] Studies using VVV seem to demonstrate more robust associations with CVD risk than those based on 24-hour ABPM[30,82] but this statement may be confounded in part by the use of ARV rather than SD. There have also been negative studies.[86,87] The absence of a standard definition of exaggerated BP variability, divergences among measurement and statistical methods, and variations in results suggest that the association of CVD risk with exaggerated BP variability is not extremely robust, at least as defined by current methods. Assessment methods also strongly affect the associations of variability and risk. For example, when populations are dichotomized into low and high variability groups, the apparent risk appears to be relatively modest. One "low resolution" meta-analysis dichotomized BP variability (low vs. high) and found that high BP variability was associated with a 15% increase in all-cause mortality, 18% in CVD mortality, 10% in ischemic heart disease, and 15% for stroke.[84] This study is problematic for several reasons, including co-mingling of VVV with ABPM methods, use of varying time periods and numbers of readings, and reporting data outside of strict inclusion criteria. Another meta-analysis of dichotomized BP variability found modest increases in total and cardiovascular mortality (11 and 16%, respectively) with high ARV on ABPM but in this study, adjustment for mean 24-hour BP diminished the contribution of BP variability to <1% of the overall predictive power.[82] The risk of high BP variability appears to be much higher when the highest decile of BP variability is compared to the lowest; in the Australian National BP Study, after adjusting for sex, age, treatment, and average on-treatment SBP, CVD event rates in the highest decile of BP variability were: first fatal/nonfatal cardiovascular event 218%, stroke 278%, myocardial infarction 411% and heart failure 479% higher.[83] In the SHEP program, higher VVV was associated with a higher CVD mortality but these investigators did not adjust for mean BP.[86] An ABPM study reported that each 5 mmHg increase in night-time (but not daytime) BP variability was associated with an 80% increase in stroke incidence but not other CVD events.[80] A secondary analysis of the SPRINT study found no significant association between VVV and combined fatal and non-fatal CVD events.[87] They reported coefficient of variation of systolic BP over 4 visits (12 months) and observed 324 events in 7879 participants (a 4% event rate). The hazard ratio for high BP variability was not significant (HR 1.20; 95% CI 0.85,1.69) but had they studied a higher risk population, increased the observation period, used a more robust indicator of variability, or increased the sample size, statistical significance might well have been achieved.

It is difficult to directly compare the risks attributable to BP variation to those attributable to chronic BP elevation. Current data strongly suggest that the risk associated with persistent BP elevation (i.e. the BP burden or lifetime mean BP or area under the lifetime BP curve) remains paramount.[87,88] The robustness of the relationship between BP burden and risk is most persuasively demonstrated by the work of the Prospective Study Collaborators, who constructed a worldwide meta-regression based on age and mean BP in nearly 1 million adults studied for 12 years.[88] They found an extremely precise relationship of weighted 12-year mean systolic BP (12-year systolic BP burden) and cardiovascular mortality, where each 20 mmHg increment in mean systolic BP increased the CVD mortality risk by 100% over the range of 115-185 mmHg. In comparison, in the largest meta-analysis of BP variability, high *relative* systolic BP variability increased relative CVD mortality risk by about 18%.[84] This would be the equivalent of an increase in systolic BP of about 4.5 mmHg but it must also be remembered that adjustment for systolic BP burden may largely eliminate the risk attributed to systolic BP variability. [82,88]

CLINICAL IMPLICATIONS

BP variability exerts a subtle but important influence on all aspects of hypertension care, from diagnosis to classification, risk assessment, and treatment. At present, the potential role of BP variability in the pathogenesis of CVD remains unresolved, as are questions regarding clinical impact and appropriate clinical care and patient education. The lack of a clear definition and classification scheme and standardized methods for assessing BP variability are barriers to further progress.

The clinical classification of hypertension is clearly impacted by true BP variability and BP measurement uncertainties. Because the BP distribution is continuous in the population, the definitions of essential hypertension and its subcategories (stages or grades) are intrinsically arbitrary. Current guidelines make accommodations for BP variability in their requirements for multiple BP measurements and the confirmation of the diagnosis of hypertension with non-office BP readings. Yet the current classifications schemes include categories whose "band widths" are 10/5 mmHg. The most recent U.S. hypertension guideline

identifies normal BP as <120/80, elevated 120-129/80, stage 1 hypertension 130-139/80-89, and stage 2 hypertension as ≥ 140/90 mmHg. The most recent European guideline lists optimal BP as <120/80 mmHg, normal 120-129/80-84, elevated 130-139/85-84, Grade 1 hypertension 140-159/90-99, Grade 2 hypertension 160-179/100-109, and Grade 3 hypertension as >180/110 mmHg) and the International Society of Hypertension identifies normal BP (<130/85 mmHg), high normal (130-139/85-89 mmHg), Grade 1 hypertension (140-159/90-99 mmHg) and Grade 2 hypertension (≥160/100 mmHg).[50-53] Within each of these current guidelines, all of which use different terminology and thresholds, there is at least one category where the range of values is 10/5 mmHg. This makes little sense for patients with exaggerated BP variability who may have BP readings that span 2 or 3 categories within a single visit. For example, a patient with high BP variability and a mean systolic BP in the mid-130s ("high-normal BP" 130-139/85-89 mmHg in the International Hypertension Society classification system)[53] may easily have normal, high-normal, and hypertensive BP readings within the same visit. These narrow categories and arbitrary thresholds tend to obfuscate common degrees of BP variability, sometimes causing unnecessary anguish among caregivers and patients. Further confusion is caused by the divergent categories apparent in current guidelines. For reference, a calculated feature of the JNC7 guideline was a classification system with band widths of at least 20/10 mmHg.[89] This was not accidental; not only did this system minimize unnecessary category shifts, it allowed simple risk stratification consistent with the "20/10 mmHg rule" of risk doubling identified in the Prospective studies analysis.[88]

The principal justification for hypertension treatment is to reduce cardiovascular morbidity and mortality.[50-53] In general practice and in regulatory policies, hypertension is considered a true surrogate for CVD risk. As such, no outcome studies are required to market an antihypertensive drug, simply the demonstration of safety and efficacy, generally a significant reduction in BP (about 5 mmHg more than placebo) in two competent trials or an approved matrix design. Hypertension differs from conditions such as heart failure, where approval is based on safety and efficacy in 2 or more favorable outcome trials. In contrast, the trend toward increased CVD risk associated with exaggerated BP variability is still not unequivocal and there are no prospective interventional studies designed to answer the question of whether reducing BP variability proportionally reduces adverse CVD outcomes; if there were such trials, it is conceivable that BP variability could be used as an independent CVD risk factor in a multiple-factor algorithm or even as a treatment target. It is highly unlikely, however, that the robustness of BP variability as a risk factor is more than a fraction of that attributable to BP burden. Given the improbability of funding for a long-term outcome trial, it is unrealistic to think that BP variability will be widely adopted in clinical guidelines or clinical practice in the foreseeable future.

Problems caused by BP variability are very much a reality of everyday clinical practice. Patients and clinical staff routinely experience anguish and uncertainty regarding whether a BP "spike" is meaningful or dangerous. All too often, patients are sent to emergency facilities for elevated BP values that do not require immediate treatment. One area of reasonably close agreement among guidelines is the approach to hypertensive urgencies and emergencies: relatively sudden but sustained increases in BP over weeks to months in the clinic or home setting. An "urgency" is a markedly elevated BP (generally >180/110 mmHg) that is asymptomatic or accompanied by relatively mild symptoms such as headache but without acute target organ damage. In this setting, combinations of 2 or 3 antihypertensive drugs should be started (or restarted for patients with poor medication adherence) in the ambulatory setting, with follow-up within a few days. A hypertensive crisis or emergency signifies the presence of a high BP plus acute target organ damage, which necessitates hospitalization and immediate BP-lowering (minutes to hours).

At present, there is no educational guidance for practitioners or patients. As such, it remains the responsibility of individual practitioners to educate themselves, their staffs, and their patients on the available facts about BP variability. It is hoped that the information provided in this review will offer sufficient perspective for the interested clinician to formulate a practical but science-based approach to BP variability. All practitioners responsible for BP care should be able to provide accurate and useful information on BP variability to patients, including guidance on what can and cannot be treated. Perhaps even more important is the responsibility of the physician to educate nursing and office staff so that popular myths and misconceptions can be minimized.

SUMMARY AND CONCLUSIONS

BP variability is caused by true pathophysiologic BP variation (systematic and non-systematic between- and within-individuals) and measurement errors (systematic biases and random error). Clinical impact in retrospective secondary analyses includes an apparent, modest increase in cardiovascular disease (CVD) risk equivalent to a few mmHg in mean systolic BP. Antihypertensive drugs have relatively little impact on BP variability but it is decreased slightly by dihydropyridine calcium antagonists and increased slightly by ACE inhibitors, beta-blockers, and alpha-blockers. No interventional trial has addressed the question of whether reducing BP variability confers CVD risk protection. There is no formal consensus on how to quantitate or manage BP variability. Practitioners should focus on control of (mean) BP using combinations of agents that improve CVD outcomes. Future consensus guidance should directly address BP variability and should include educational materials for physicians, patient-contact staff, and patients.

ACKNOWLEDGEMENTS

This work was unfunded. The author has no conflicts of interest regarding this manuscript.

REFERENCES

1. Parati G, Stergiou GS, Dolan E, Bilo G. Blood pressure variability: clinical relevance and application. *The Journal of Clinical Hypertension*. 2018;20(7):1133-1137. doi:https://doi.org/10.1111/jch.13304

2. Rosei EA, Chiarini G, Rizzoni D. How important is blood pressure variability? *European Heart Journal Supplements*. 2020;22:E1-E6. doi:10.1093/eurheartj/suaa061

3. Gunstad J, Cohen RA, Tate DF, et al. Blood pressure variability and white matter hyperintensities in older adults with cardiovascular disease. Research Support, N.I.H., Extramural. *Blood pressure*. 2005;14(6):353-8.

4. Webb AJ, Rothwell PM. Physiological correlates of beat-to-beat, ambulatory, and day-to-day home blood pressure variability after transient ischemic attack or minor stroke. *Stroke*. Feb 2014;45(2):533-8. doi:10.1161/strokeaha.113.003321

5. Asayama K, Wei FF, Liu YP, et al. Does blood pressure variability contribute to risk stratification? Methodological issues and a review of outcome studies based on home blood pressure. *Hypertension research : official journal of the Japanese Society of Hypertension*. Feb 2015;38(2):97-101. doi:10.1038/hr.2014.153

6. Del Giorno R, Balestra L, Heiniger PS, Gabutti L. Blood pressure variability with different measurement methods: Reliability and predictors. A proof of concept cross sectional study in elderly hypertensive hospitalized patients. *Medicine*. 2019;98(28):e16347.

7. Parati G, Torlasco C, Pengo M, et al. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertension Research*. 2020/07/01 2020;43(7):609-620. doi:10.1038/s41440-020-0421-5

8. Izzo J, Nagpal S, Mukhopadhyay D, et al. Variation in mean arterial pressure and its hemodynamic components during 24-hour ambulatory pulse wave analysis: impact of age, race, and gender. *Journal of hypertension*. 2022;40(Suppl 1):e116-e117.

9. Parati G, Izzo JL, Jr., Gavish B. Respiration and blood pressure. In: Izzo JL, Jr, Sica DA, Black HR, eds. *Hypertension Primer*. American Heart Association; 2008:136-8:chap A43.

10. Teboul JL, Monnet X, Chemla D, Michard F. Arterial Pulse Pressure Variation with Mechanical Ventilation. *Am J Respir Crit Care Med*. 2019;199(1):22-31. doi:10.1164/rccm.201801-0088CI

11. Izzo JL, Jr. The sympathetic nervous system in acute and chronic blood pressure elevation. In: Oparil S, Weber MA, eds. *Hypertension: Companion to Brenner and Rector's The Kidney*. Second ed. Elsevier-Saunders; 2005:60-76:chap 6.

12. Izzo JL, Jr., Sander E, Larrabee PS. Effect of postural stimulation on systemic hemodynamics and sympathetic nervous activity in systemic hypertension. *Am J Cardiol*. 1990 1990;65:339-342.

13. Izzo JL, Anwar MA, Elango K, et al. Decoupling of Heart Rate and Blood Pressure: Hemodynamic Counter-regulatory Mechanisms and their Implications. *Artery Research*. 2019/12/24 2019;25(3-4):87-94. doi:https://doi.org/10.2991/artres.k.191210.001

14. Izzo JL, Jr., Smith RJ, Larrabee PS, Kallay MC. Plasma norepinephrine and age as determinants of systemic hemodynamics in men with established essential hypertension. *Hypertension (Dallas, Tex : 1979)*. 1987 1987;9:415-419.

15. Izzo JL, Taylor AA. The sympathetic nervous system and baroreflexes in hypertension and hypotension. journal article. *Curr Hypertens Rep*. 1999;1(3):254-263. doi:10.1007/s11906-999-0030-9

16. Folkow B. Structural factors: the vascular wall. Consequences of treatment. *Hypertension (Dallas, Tex : 1979)*. Sep-Oct 1983;5(5 Pt 2):Iii58-62. doi:10.1161/01.hyp.5.5_pt_2.iii58

17. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation*. Mar 13 2007;115(10):1285-95. doi:10.1161/circulationaha.106.652859

18. Harrison DG. Endothelial function and oxidant stress. *Clin Cardiol*. Nov 1997;20(11 Suppl 2):Ii-11-7.

19. Mitra S, Goyal T, Mehta JL. Oxidized LDL, LOX-1 and atherosclerosis. *Cardiovasc Drugs Ther*. Oct 2011;25(5):419-29. doi:10.1007/s10557-011-6341-5

20. Sung BH, Izzo JL, Jr., Wilson MF. Effects of cholesterol reduction on BP response to mental stress in patients with high cholesterol. *AmJHypertens*. 1997 1997;10(6):592-599.

21. Sung BH, Izzo JL, Jr., Dandona P, Wilson MF. Vasodilatory effects of troglitazone improve blood pressure at rest and during mental stress in type 2 diabetes mellitus. *Hypertension (Dallas, Tex : 1979)*. 1999;34(1):83-8.

22. Maseli A, Aeschbacher S, Schoen T, et al. Healthy Lifestyle and Blood Pressure Variability in

Young Adults. *American journal of hypertension*. Jul 1 2017;30(7):690-699. doi:10.1093/ajh/hpx034
23. Ishida T, Miura S, Fujimi K, et al. Visit-to-Visit Variability and Reduction in Blood Pressure After a 3-Month Cardiac Rehabilitation Program in Patients With Cardiovascular Disease. *Int Heart J*. Sep 28 2016;57(5):607-14. doi:10.1536/ihj.16-026
24. Pagonas N, Dimeo F, Bauer F, et al. The impact of aerobic exercise on blood pressure variability. *Journal of human hypertension*. Jun 2014;28(6):367-71. doi:10.1038/jhh.2013.121
25. Gavish B, Izzo JL. Arterial Stiffness: Going a Step Beyond. *American journal of hypertension*. November 1, 2016 2016;29(11):1223-1233. doi:10.1093/ajh/hpw061
26. Mackenzie IS, McEniery CM, Dhakam Z, et al. Comparison of the effects of antihypertensive agents on central blood pressure and arterial stiffness in isolated systolic hypertension. *Hypertension (Dallas, Tex : 1979)*. Aug 2009;54(2):409-13. doi:10.1161/hypertensionaha.109.133801
27. Schwartz JE, Feig PU, Izzo JL, Jr. Pulse Wave Velocities Derived From Cuff Ambulatory Pulse Wave Analysis. *Hypertension (Dallas, Tex : 1979)*. Jul 2019;74(1):111-116. doi:10.1161/hypertensionaha.119.12756
28. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-Hour Blood Pressure Variability Assessed by Average Real Variability: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association*. 2017;6(10):e006895. doi:doi:10.1161/JAHA.117.006895
29. Kario K, Shimbo D, Hoshide S, et al. Emergence of Home Blood Pressure-Guided Management of Hypertension Based on Global Evidence. *Hypertension (Dallas, Tex : 1979)*. 2019;74(2):229-236. doi:doi:10.1161/HYPERTENSIONAHA.119.12630
30. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet (London, England)*. Mar 13 2010;375(9718):895-905.
31. Muntner P, Joyce C, Levitan EB, et al. Reproducibility of visit-to-visit variability of blood pressure measured as part of routine clinical care. *Journal of hypertension*. Dec 2011;29(12):2332-8. doi:10.1097/HJH.0b013e32834cf213
32. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation*. 2012;126(5):569-78.
33. Asayama K, Kikuya M, Schutte R, et al. Home blood pressure variability as cardiovascular risk factor in the population of Ohasama. Research Support, Non-U.S. Gov't. *Hypertension (Dallas, Tex : 1979)*. 2013;61(1):61-9.
34. Silagy CA, McNeil JJ, Farish S, et al. Components of blood pressure variability in the elderly and effects on sample size calculations for clinical trials. *American journal of hypertension*. Jul 1992;5(7):449-58. doi:10.1093/ajh/5.7.449
35. Fazio S, Palmieri EA, Izzo R, et al. An exaggerated systolic blood pressure response to exercise is associated with cardiovascular remodeling in subjects with prehypertension. Comparative Study. *Italian Heart Journal: Official Journal of the Italian Federation of Cardiology*. Nov 2005;6(11):886-92.
36. Wilson NV, Meyer BM. Early prediction of hypertension using exercise blood pressure. *PreventativeMed*. 1981 1981;10:62-68.
37. Schultz MG, La Gerche A, Sharman JE. Blood Pressure Response to Exercise and Cardiovascular Disease. *Curr Hypertens Rep*. Oct 18 2017;19(11):89. doi:10.1007/s11906-017-0787-1
38. Uusitalo AL, Laitinen T, Väisänen SB, et al. Physical training and heart rate and blood pressure variability: a 5-yr randomized trial. *American journal of physiology Heart and circulatory physiology*. May 2004;286(5):H1821-6. doi:10.1152/ajpheart.00600.2003
39. Lin GM, Tsai KZ, Lin CS, Han CL. Physical Fitness and Long-term Blood Pressure Variability in Young Male Military Personnel. *Current hypertension reviews*. 2020;16(2):156-160. doi:10.2174/1573402115666191023111351
40. Hamer M, Jones J, Boutcher SH. Acute exercise reduces vascular reactivity to mental challenge in offspring of hypertensive families. *Journal of hypertension*. 2006;24(2):315-20.
41. Postolache T, Gautier S, Laloux B, et al. Positive correlation between the blood pressure and heart rate response to the cold pressor test and the environmental temperature in older hypertensives. *American Journal of Hypertension*. 1993;6(5 Pt 1):376-81.
42. Maier KJ, Waldstein SR, Synowski SJ. Relation of cognitive appraisal to cardiovascular reactivity, affect, and task engagement. *Ann Behav Med*. Aug 2003;26(1):32-41. doi:10.1207/s15324796abm2601_05
43. Stergiou GS, Alpert B, Mieke S, et al. A Universal Standard for the Validation of Blood Pressure Measuring Devices. *Hypertension (Dallas,*

Tex : 1979). 2018;71(3):368-374. doi:doi:10.1161/HYPERTENSIONAHA.117.10237

44. Sewell K, Halanych J H, Russell L B, et al. Blood Pressure Measurement Biases in Clinical Settings, Alabama, 2010–2011. . *Prev Chronic Dis* 2016;13:150348.

45. Morcos RN, Carter KJ, Castro F, et al. Sources of Error in Office Blood Pressure Measurement. *The Journal of the American Board of Family Medicine*. 2019;32(5):732-738. doi:10.3122/jabfm.2019.05.190085

46. Westhoff TH, Schmidt S, Meissner R, et al. The impact of pulse pressure on the accuracy of wrist blood pressure measurement. *Journal of human hypertension*. 2009/06/01 2009;23(6):391-395. doi:10.1038/jhh.2008.150

47. Casiglia E, Tikhonoff V, Albertini F, Palatini P. Poor Reliability of Wrist Blood Pressure Self-Measurement at Home. *Hypertension (Dallas, Tex : 1979)*. 2016;68(4):896-903. doi:doi:10.1161/HYPERTENSIONAHA.116.07961

48. Mukkamala R, Yavarimanesh M, Natarajan K, et al. Evaluation of the Accuracy of Cuffless Blood Pressure Measurement Devices: Challenges and Proposals. *Hypertension (Dallas, Tex : 1979)*. 2021;78(5):1161-1167. doi:doi:10.1161/HYPERTENSIONAHA.121.17747

49. Pickering TG, Gerin W, Schwartz AR. What is the white-coat effect and how should it be measured? *Blood Press Monit*. Dec 2002;7(6):293-300. doi:10.1097/00126097-200212000-00001

50. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. 10.1161/HYP.0000000000000065. *Journal of the American College of Cardiology*. 2018;71:e127-e248.

51. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Journal of hypertension*. 2018;36(10):1953-2041. doi:10.1097/hjh.0000000000001940

52. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. *Canadian Journal of Cardiology*. 2020/05/01/ 2020;36(5):596-624. doi:https://doi.org/10.1016/j.cjca.2020.02.086

53. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension (Dallas, Tex : 1979)*. 2020;75(6):1334-1357. doi:doi:10.1161/HYPERTENSIONAHA.120.15026

54. Roerecke M, Kaczorowski J, Myers MG. Comparing Automated Office Blood Pressure Readings With Other Methods of Blood Pressure Measurement for Identifying Patients With Possible Hypertension: A Systematic Review and Meta-analysis. *JAMA Internal Medicine*. 2019;179(3):351-362. doi:10.1001/jamainternmed.2018.6551

55. Tobe S, Dubrofsky L, Nasser D, et al. Randomized Controlled Trial Comparing Automated Office Blood Pressure Readings After Zero or Five Minutes of Rest. *Hypertension (Dallas, Tex : 1979)*. 06/28 2021;78doi:10.1161/HYPERTENSIONAHA.121.17319

56. Asayama K, Thijs L, Li Y, et al. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. *Hypertension (Dallas, Tex : 1979)*. 2014;64(5):935-42.

57. Schultz MG, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked hypertension is "unmasked" by low-intensity exercise blood pressure. Research Support, Non-U.S. Gov't. *Blood pressure*. Oct 2011;20(5):284-9.

58. Stergiou GS, Palatini P, Modesti PA, et al. Seasonal variation in blood pressure: Evidence, consensus and recommendations for clinical practice. Consensus statement by the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. *Journal of hypertension*. Jul 2020;38(7):1235-1243. doi:10.1097/hjh.0000000000002341

59. Radke KJ, Izzo JL, Jr. Seasonal variation in haemodynamics and blood pressure-regulating hormones. Research Support, Non-U.S. Gov't. *Journal of human hypertension*. Jun 2010;24(6):410-6.

60. Lewington S, Li L, Sherliker P, et al. Seasonal variation in blood pressure and its relationship with outdoor temperature in 10 diverse regions of China: the China Kadoorie Biobank. *Journal of hypertension*. Jul 2012;30(7):1383-91. doi:10.1097/HJH.0b013e32835465b5

61. Daly PA, Landsberg L. Hypertension in obesity and NIDDM. Role of insulin and sympathetic

nervous system. *Diabetes Care*. 1991 1991;14(3):240-248.
62. Izzo JL, Jr. Prehypertension: demographics, pathophysiology, and treatment. Review. *Curr Hypertens Rep*. Aug 2007;9(4):264-8.
63. Evangelou E, Warren HR, Mosen-Ansorena D, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nature genetics*. Oct 2018;50(10):1412-1425. doi:10.1038/s41588-018-0205-x
64. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. Apr 2020;16(4):223-237. doi:10.1038/s41581-019-0244-2
65. Agarwal R. Implications of Blood Pressure Measurement Technique for Implementation of Systolic Blood Pressure Intervention Trial (SPRINT). *J Am Heart Assoc*. Feb 3 2017;6(2)doi:10.1161/jaha.116.004536
66. Parati G, Schumacher H. Blood pressure variability over 24 h: prognostic implications and treatment perspectives. An assessment using the smoothness index with telmisartan–amlodipine monotherapy and combination. *Hypertension Research*. 2014/03/01 2014;37(3):187-193. doi:10.1038/hr.2013.145
67. Parati G. Blood pressure variability: its measurement and significance in hypertension. *Journal of Hypertension Supplement*. 2005;23(1)
68. Smith TR, Drozda JP, Jr., Vanslette JA, Hoeffken AS, Nicholson RA. Medication class effects on visit-to-visit variability of blood pressure measurements: analysis of electronic health record data in the "real world". *Journal of clinical hypertension (Greenwich, Conn)*. Sep 2013;15(9):655-62. doi:10.1111/jch.12165
69. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet (London, England)*. Mar 13 2010;375(9718):906-15.
70. Basson MD, Newman WE, Klug MG. Correlations Among Visit-to-Visit Blood Pressure Variability and Treatment With Antihypertensive Medication With Long-Term Adverse Outcomes in a Large Veteran Cohort. *American journal of hypertension*. Oct 27 2021;34(10):1092-1099. doi:10.1093/ajh/hpab087
71. Izzo JL, Jr., Yedlapati SH, Faheem SM, et al. Differences in mean and variability of heart rate and ambulatory rate-pressure product when valsartan or carvedilol is added to lisinopril. *Journal of the American Society of Hypertension : JASH*. Nov-Dec 2012;6(6):399-404. doi:10.1016/j.jash.2012.08.007
72. Allen K, Shykoff BE, Izzo JL, Jr. Pet ownership, but not ACE inhibitor therapy, blunts home blood pressure responses to mental stress. *Hypertension*. 2001;38(4):815-20.
73. Schulte W, Neus H, Thönes M, von Eiff AW. Basal blood pressure variability and reactivity of blood pressure to emotional stress in essential hypertension. *Basic Research in Cardiology*. 1984/01/01 1984;79(1):9-16. doi:10.1007/BF01935802
74. Drummond PD. Cardiovascular Reactivity in Borderline Hypertensives during Behavioural and Orthostatic Stress. *Psychophysiology*. 1985;22(6):621-628. doi:https://doi.org/10.1111/j.1469-8986.1985.tb01656.x
75. Izzo JL, Jr., Rajpal M, Karan S, et al. Hemodynamic and central blood pressure differences between carvedilol and valsartan added to lisinopril at rest and during exercise stress. *Journal of the American Society of Hypertension*. 2011;6(2):117-123. doi:10.1016/j.jash.2011.12.001
76. Pickering TG. Blood pressure variability and ambulatory monitoring. *Current Opinion in Nephrology & Hypertension*. 1993;2(3):380-5.
77. Izzo JL, Jr. Blood pressure variability and reactivity. In: Izzo JL, Jr., Sica DA, Black HR, eds. *Hypertension Primer*. Fourth ed. Wolters Kluwer Health/Lippincott, Williams and Wilkins; 2008:177-180:chap A56.
78. Izzo JL, Jr., Jia Y, Zappe DH. Influence of Age and Race on 24-Hour Ambulatory Blood Pressure Responses to Valsartan, Hydrochlorothiazide, and Their Combination: Implications for Clinical Practice. *Journal of clinical hypertension (Greenwich, Conn)*. Feb 2017;19(2):143-150. doi:10.1111/jch.12891
79. Feldman RD, Zou GY, Vandervoort MK, et al. A Simplified Approach to the Treatment of Uncomplicated Hypertension: A Cluster Randomized, Controlled Trial. *Hypertension (Dallas, Tex : 1979)*. April 1, 2009 2009;53(4):646-653. doi:10.1161/hypertensionaha.108.123455
80. Pringle E, Phillips C, Thijs L, et al. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *Journal of hypertension*. 2003;21(12):2251-7.
81. Verdecchia P, Angeli F, Gattobigio R, et al. Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension.

American journal of hypertension. 2007;20(2):154-61.

82. Hansen TW, Thijs L, Li Y, et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations.[Erratum appears in Hypertension. *Hypertension (Dallas, Tex : 1979)*. 2010;55(4):1049-57.

83. Chowdhury EK, Owen A, Krum H, et al. Systolic blood pressure variability is an important predictor of cardiovascular outcomes in elderly hypertensive patients.
Journal of hypertension. 2014;32(3):525-33.

84. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2016;354:i4098-i4098. doi:10.1136/bmj.i4098

85. Kronish IM, Lynch AI, Oparil S, et al. The Association Between Antihypertensive Medication Nonadherence and Visit-to-Visit Variability of Blood Pressure. *Hypertension (Dallas, Tex : 1979)*. 2016;68(1):39-45. doi:doi:10.1161/HYPERTENSIONAHA.115.06960

86. Kostis JB, Sedjro JE, Cabrera J, et al. Visit-to-visit blood pressure variability and cardiovascular death in the Systolic Hypertension in the Elderly Program. *Journal of Clinical Hypertension*. 2014;16(1):34-40.

87. Chang TI, Reboussin DM, Chertow GM, et al. Visit-to-Visit Office Blood Pressure Variability and Cardiovascular Outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertension (Dallas, Tex : 1979)*. Oct 2017;70(4):751-758. doi:10.1161/hypertensionaha.117.09788

88. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet (London, England)*. Dec 14 2002;360(9349):1903-13.

89. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: JNC 7 Express. *Jama*. 2003;289(19):2560-72.