

Doubts and difficulties in studying blood pressure variability

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Abstract. – The blood pressure (BP) fluctuation was first noticed in the 18th century. However, its clinical significance did not get attention until recent years. The increase in BP variability (BPV) is possibly more valuable than the increase in BP level for predicting damages in target organs. Moreover, attenuating BPV is more important than decreasing the BP level. However, the concept of BPV was not used in any related guideline for diagnosing, defining, and grading the risk of hypertension, which is due to the understanding of BPV is not profound, and blind areas and misunderstanding still exist in the definition, features, and classification of BPV. In this paper, the doubts and difficulties in studying BPV are analyzed, which may conduce to understand BPV and thus help for the clinical diagnosis and treatment of hypertension.

Key Words:

Blood pressure, Blood pressure variability, Doubts and difficulties, Cardiovascular disease.

Introduction

According to a considerable number of studies, BPV increase is a risk factor of cardiovascular and cerebrovascular diseases, which is independent from the mean BP level. Some researchers^{1,2} found that BPV had a greater value than the mean BP level in predicting cardiovascular and cerebrovascular diseases. Therefore, clinical research of BPV has become a hotspot. BPV is complex and includes many types, such as very short-term BPV (beat-to-beat), short-term BPV (minute-to-minute, reading-to-reading within a 24 h period), mid-term BPV (day-to-day), and

long-term BPV (visit-to-visit and seasonal). The factors affecting these BPV types also vary along with many BPV metrics, such as the standard deviation of systolic and diastolic blood pressure or pulse pressure; coefficient of variation; and variability uncorrelated with mean BP. These metrics have their own advantages and disadvantages. The lack of a generally accepted metric with a clear-value range results in difficulties in the in-depth study, reasonable explanation, and accurate clinical application. Given the problems above mentioned, the doubts and difficulties in studying BPV are reviewed and analyzed from a multidisciplinary perspective.

Similarities and Differences of the Factors Affecting the BPV Types

Many internal and external factors are involved in the regulation of BP, such as neuroendocrine, vessel wall elasticity, environment, emotion, posture, and motion. These factors affect the long-term and short-term regulation of BP to varied degrees, so they are bound to influence the variation of different time-interval BPV¹⁻³. Most factors simultaneously affect the short-term and long-term variation of BPV and differ only in degree. Some factors mainly affect the transient and short-term BPV, such as sympathetic nerve tension; reflection function of artery, heart and lung; respiration; levels and activity of endocrine hormones (angiotensin II, bradykinin, endothelin-1, insulin, nitric oxide, etc.); inflammatory factors (C-reactive protein); hemorheology; emotion or psychological stress; sleep; active state; and posture¹⁻³. On the other hands, some factors primarily influence long-term BPV, such as the application of antihypertensive drugs, the frequency and accuracy of

BP measurement, the elasticity of arterial wall³⁻⁵, climate changes⁶, the day and night types of BP⁷. In addition, BP level, hypertension course, comorbidities (e.g., diabetes mellitus), pathological changes in target organs (such as apoplexia, myocardial infarction, heart failure, idiopathic sudden sensorineural hearing loss and renal failure) are related to BPV at different timescales⁸⁻⁷⁶. However, their cause-and-effect relation with BPV remains unclear, and related studies are inconsistent. For example, recent studies of home blood pressure variability as captured by the variability independent of the mean (VIM) failed to demonstrate that BPV substantially refines risk profiling beyond BP levels^{14,15}. Therefore, considering variability indexes for risk stratification is less meaningful¹⁶. As shown in Table I, a post-hoc analysis of data from the European Lacidipine Study on Atherosclerosis showed that visit-to-visit variability (VVV) was neither associated with progression of organ damage nor with cardiovascular outcomes¹⁷.

BPV Metrics and Their Relation

BPV was mainly expressed using standard deviation (SD) of systolic blood pressure (SBP), diastolic blood pressure (DBP), and/or pulse pressure (PP) and coefficient of variation (CV). BPV was further assessed using VIM (1) (VIM is a measure of variability uncorrelated with mean BP, given by $VIM = SD/means$, where x is estimated from the power curve of SBP SD plotted against mean SBP), the difference between maximum and minimum BP¹⁸, and the average real variability (ARV)¹⁹. ARV attempts to correct the limitations of the commonly used SD, which accounts only for the dispersion of values around the mean and not for the order of the BP readings. Furthermore, BPV can be intuitively grasped to some extent through successive variation (SV), range, maximum, peak size, and trough size of SBP and DBP²⁰. Also, two different approaches have been used to assess the ability of a given treatment to induce a smooth reduction of BP over 24 h, leading to reduced 24 h BPV, assessment of trough/peak ratio, and estimation of the smoothness index (SI)²¹.

The correlation among SD, CV, and VIM has been reported to be very high ($r_s > 0.90$), which is suggestive of having identical information²². In the TROPHY study population, Levitan et al²⁰ found that all of the VVV metrics were significantly correlated with one another, and correlations were strongest among SD, VIM, CV, and range, as well as between ARV and SV.

Relation and Differences Among BPVs at Different Timescales

Poor or over cardiovascular response is the primary pathological and physiological mechanisms of the increase in BP level and BPV. Short-term BPV reflects that cardiovascular system copes with unexpected events, whereas long-term BPV reflects that the cardiovascular system chronically adapts to long-term internal and external environmental stress. Therefore, the etiology, pathogenesis, and prognosis of BPV over these different timescales and methods are likely to vary considerably^{22,23}. The causes are as follows. Firstly, the factors affecting BPV over different timescales vary. Secondly, the BPV readings are influenced by the measurement frequency of BP, which is significantly less in long-term BPV than in short-term BPV in most cases. Thirdly, different BP measurement methods lead to deviation in the results. For instance, home blood pressure monitoring (HBPM) can eliminate physical and spiritual influences, while office blood pressure monitoring (OBPM) can be affected by white coat hypertension. The effect of environmental and daily activities on ambulatory blood pressure monitoring (ABPM) cannot be avoided as well^{3,24}. Fourthly, the observation deviation of observers and instrument error also lead to deviation in the results. Therefore, VVV may differ even in the same individual in different timescales^{25,26}. Lastly, the repeatability of BPV measurement methods is theoretically linked, and the methods cannot be essentially repeated. However, considering the differences in the affecting factors, HBPM is more stable and repeatable than ABPM and OBPM. Accordingly, the metrics above are not consistent when comparing BPV in the same period or the drug effects on BPV^{2,3}. Several studies have reported a low correlation between VVV of BP and 24 h BPV^{1,27,28}, ranging only from 0.15 to 0.26 on ABPM. Mancia et al¹⁷ found that intra-individual VVV assessed by 24 h ABPM is lower than BP values measured in an office of a physician. A study suggested that while accounting for BP level, associations of target organ damage with BPV were readily detectable in beat-to-beat recordings but least noticeable in home recording, with 24 h ambulatory monitoring being informative only for pulse-wave velocity¹⁸.

What is Time-Frequency Analysis of BPV?

Short-term, mid-term, and long-term BPVs reflect BP changes at different time intervals and

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Table I. Types of BPV: measurement methods and intervals, evaluating indices, influencing factors, and advantages and disadvantages.

Characteristic	Very short-term BPV	Short-term BPV (within 24 h)	Mid-term BPV (day-to-day)	Long-term BPV (visit-to-visit)
BP method	Continuous BP recordings in a laboratory setting or under ambulatory	ABPM	ABPM over ≥ 48 h HBPM	ABPM OBPM HBPM
Measurement intervals	Beat-to-beat over variable recording periods (1 min to 24 h)	Every 15 min to 1 h over 24 h	Day-to-day, over several days, weeks, or months	Spaced by visit over weeks, months, and years
BPV indices	SD Indices of autonomic modulation can be calculated (spectral analysis) Time domain and frequency domain analysis through time intervals of beat-to-beat	SD, weighted SD, CV, VIM, ARV, and MMD of 24 h, daytime and night-time	SD, CV, VIM, SV, and ARV Range, maximum, peak size, and trough size of BP	SD, CV, VIM, SV, and ARV Range, maximum, peak size, and trough size of BP
Influencing factors	Sympathetic tone, arterial and cardiopulmonary reflex, elasticity of arterial wall, breathing, levels and activity of some endocrine hormones (such as angiotensin II, bradykinin, endothelin-1, insulin, nitric oxide, etc.), inflammation factors (such as C-reactive protein), hemorheology, emotional or psychological stress, sleep, activity, and posture	Sympathetic tone, arterial and cardiopulmonary reflex, elasticity of arterial wall, breathing, levels and activity of some endocrine hormones (such as angiotensin II, bradykinin, endothelin-1, insulin, nitric oxide, etc.), inflammation factors (such as C-reactive protein), hemorheology, emotional or psychological stress, sleep, activity, posture, and dosing/titration of AHT	Elasticity of arterial wall, frequency and accuracy of blood pressure measurement, climate change, and dosing/titration of AHT	Elasticity of arterial wall, frequency and accuracy of blood pressure measurement, climate change, and dosing/titration of AHT
Advantage	Assessment of indices of autonomic cardiovascular modulation Usually only a very short period of time nonlinear analysis can be performed	Extensive information on 24 h BP profile identification of patterns of circadian BP variation	Appropriate for long-term monitoring	Appropriate for long-term monitoring
Disadvantage	Some data of blood pressure wave might be lost in the monitoring process The stability and accuracy of the data will be disturbed by some noise if monitoring time was extended Stability of measurements might not be guaranteed outside the laboratory setting	Stability of blood pressure can be affected by too many factors cannot be frequently repeated	Patient training and involvement required for HBPM and ABPM over 48 h are neither always well tolerated nor accepted by patients Easily lost	OBPM and HBPM provide limited information on BP profiles

Abbreviation: ABPM, ambulatory blood pressure monitoring; AHT, antihypertensive treatment; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; CV, coefficient of variation; HBPM, home blood pressure monitoring; OBPM, office blood pressure measurement; MMD, difference between maximum and minimum; SV, successive variation; VIM, variability independent of the mean.

are, thus, regarded as indexes to evaluate BP stability. The timescale and frequency scale of BPV are applicable only to beat-to-beat BPV and usually conducted with HRV time-frequency analysis²⁹. In particular, the analysis of BPV frequency

scale reflects the transient variation velocity of BP, which requires Fourier transform to change the beat-to-beat time series. BPV occurrence was first described at the beginning of the 18th century by Stephen Hales (1733), but BPV assessment

in the clinical setting was only made possible toward the end of the 19th century thanks to the sphygmomanometer technique invented by the Italian scientist Scipione Riva-Rocci³⁰. In the 1960s, the development of the intra-arterial Oxford system allowed continuous ambulatory BP monitoring³¹ and represented a further step forward in BPV assessment in humans. The beat-to-beat BPV analysis is still a general statistical analysis based on the beat-to-beat blood pressure value, which shows the stability of transient variation. The invasive measurement of arterial blood pressure greatly limits the development of transient BPV studies. The time frequency of HRV is always studied as the heartbeat interval, and pulse waves (including pressure, velocity, and diameter waves) are relatively consistent in a time period^{29,32}. Nevertheless, electrocardio signal is an electrophysiological phenomenon, and pulse wave is an electro-mechanical-separated phenomenon^{29,32}. Although similar in terms of pathological and physiological significances, they greatly differ in many aspects^{26,33}. Some slight differences unavoidably exist between the heartbeat and pulse wave intervals, hence the differences in the time frequency analysis of HRV and BPV. With regard to signal amplitude, the band energy figure can be drawn, and HRV and BPV can describe the time frequency features of electrocardio signal and BP signal at different physiological states with different significances. Accurate measurement of the pulse wave interval is difficult to obtain, thereby causing difficulty in conducting time-frequency analysis of transient BPV. A noninvasive technique for continuous 24 h ABPM at the finger level was established in 1993³⁴, in which the study of transient BPV was valued. The time frequency analysis of BPV was simpler, more accurate, and feasible. Currently, as indicated by the frequency spectrum analysis of instantaneous BPV^{4,33}, the fluctuation pattern of BP can be divided into the following: (1) high frequency (HF) band (0.15-0.5 Hz), which stands for the rapid fluctuation of blood pressure, as a quantitative indicator of vagus nerve function; (2) low frequency (LF) band (0.05-0.15 Hz), which stands for low BPV, resulting from the sympathetic nerve and pressure reflection, and the frequency increases as the activity of sympathetic nerve rises; the LF band is an indicator of sympathetic nerve function; and (3) extremely low frequency band (0.025-0.05), which stands for a lower variation component and may be associated with local temperature regulation, ren-

nin-angiotensin system, and body fluid changes. Moreover, pulse wave parameters have been successfully applied to the clinical measurement of arterial pressure in recent years, and the time frequency of pulse transit time variability (PTTV) can be used to investigate some time-frequency features of instantaneous BPV. A study showed that PTTV has a significant coherence (> 0.5) with HRV and BPV under all physiological conditions at HF. However, the coherence became insignificant at LF immediately after the exercise (≤ 5 min after exercise) and the coherence would increase at the time of 9 min after the exercise³⁵. The coherence of time-frequency analysis of PTTV, HRV, and BPV is not stable, and their differences and significances in explaining physiological and pathological states require further studies.

Is BPV Bound to Increase as BP Level Grows?

The BPV of hypertensive patients is greater than that of healthy people. BPV grows to varied degrees as the BP level increases^{8,10,36}. However, two randomized controlled studies^{37,38} found that calcium channel blockers (CCBs) decreased the VVV of SBP in hypertensive patients, whereas β blockers increased the VVV of SBP. However, no significant difference was found in the BP level decrease between the two drugs. β -blockers decreased the BP level but increased BPV, which is possibly related to its effects on reducing heart rate and increasing peripheral vascular tension. The four types of day and night BPV are dipper, non-dipper, ultra-dipper, and reverse-dipper. The dipper type is the ideal one. However, numerous studies have currently shown that the incidence of hypertension complications, such as left ventricular hypertrophy or stroke in patients with dipper blood pressure is higher than that in patients with non-dippers³⁹⁻⁴¹. With the SD of BP value as the indicator of BPV, the short-term BPV of dippers came from 24 h ABPM, which is theoretically greater than that of the non-dippers. Thus, lesser values lead to more significant differences. Current studies have proven that hypertensive individuals with high BPV also have a higher risk of cardiovascular events^{8,10,36}. A previous analysis indicated that dippers have a higher risk of cardiovascular events than non-dippers, but some analyses show contradicting results. Therefore, the correlation between BP level and BPV is not always consistent.

Consideration of Normal Reference Value of BPV

An exact consensus of the normal reference value of BPV is currently not available. Thus, BPV is not included in guidelines all over the world as a risk factor and diagnostic stratification basis of hypertension and targeted organs. BP is not a definite value as it changes all the time to guarantee blood supply for tissues and organs and maintain energy metabolism. From the aspect of nonlinear biological dynamics, all vital phenomena are non-quasiperiodic oscillatory occurrences, such as heartbeat⁴², brain wave⁴³, respiration⁴⁴, and hormone secretion⁴⁵. Then, BP fluctuation is also non-quasiperiodic. Consequently, BPV metrics should be an interval between normal upper and lower limits regardless of their type. A normal BPV reference interval statistically requires many individual BPV values. Acquiring accurate individual BPV values has two conditions. First, multiple BP measurements should be under the normal distribution. Second, multiple BP measurements should follow a time sequence. These two conditions are difficult to satisfy. Thus, most current studies that utilized SD as the major indicator to evaluate BPV are not very accurate and cannot truly reflect BP dispersion. Other BPV metrics such as VIM and ARV are also based on SD. Although these metrics can overcome some SD limits, no fundamental changes have been found. Therefore, the use of BPV metrics is lack of reliability. Considering that BPV measurement is affected by more many factors than BP measurement, obtaining a suitable, accurate, and feasible BPV reference interval requires more many prospective randomized controlled studies. Moreover, the definition and measurement methods of BPV should be revised and unified^{3,46}, which is a long-term and arduous task.

Effects of Antihypertensive Drugs on BP Level and BPV

The effects of all antihypertensive drugs on BPV are based on their influences on BP levels, despite the correlation is not being always consistent³⁴. No study has shown that antihypertensive drugs can only reduce BPV while not change BP levels³⁴. A considerable number of researches^{5,37,38,46,47} indicated that the effects of different antihypertensive drugs on BPV differed significantly while slightly on BP levels. Among the five types of first-line antihypertensive drugs, CCBs can decrease inter-individual and intra-individual VVVs of BP in hypertensive patients;

diuretics can also reduce VVV of BP, but the effect of the latter is less significant than that of CCBs^{37,38}. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β blockers can increase the VVV of BP to varied degrees^{37,38,47}. Some authors^{5,48-51} found that all first-line antihypertensive drugs can decrease BP and 24 h short-term BPV to varied degrees. Therefore, the effects of drugs on BPV at different timescales should be considered in combined treatment to evaluate further their benefits and shortcomings.

Hypertension is a systemic disease. Pathological damages such as vascular endothelial injury, small artery hyalinization, microvascular occlusion rarefaction, carotid intima thickening, and large artery atherosclerosis appear as BP increases⁵²⁻⁵⁴, along with the involvement of other organs. The new guideline⁵⁵ says that the major risk factor of atherosclerotic cardiovascular disease (ASCVD) is hypertension. Accordingly, the prevention and treatment of ASCVD should start from preventing hypertension. The heart and brain are always the targeted damaged organs of hypertension, and the disability rate and mortality of cardiovascular and cerebrovascular diseases are very high. Therefore, most researches still focus on the relationship between BP and the cardiovascular and cerebrovascular diseases, rather than the BP level or BPV recently.

Several papers^{56,57} have shown that BPV is correlated with carotid intima-media thickness, left ventricular hypertrophy, kidney trouble, ischemic cardiovascular disease and stroke. Particularly worth mentioning is the closest relation between BPV and stroke. Hence, high-risk stroke patients can benefit the most from decreasing BPV. A meta-analysis³⁸ found that the decrease in myocardial infarction risk for hypertensive patients is mainly caused by the decreased average SBP and has minimal relation with BPV. This finding is the reason why β blockers can defer coronary atherosclerosis and decrease the mortality of cardiovascular diseases⁵⁸ but increase the risk of stroke⁵⁹. As a result, the BP level and BPV should be decreased when treating people with high risk of stroke, and CCBs are the first-choice drug⁷⁷. The BP level, burden from drugs, and heart protection need to be considered for individuals with high risk of coronary diseases. If no contraindication is present, β -blockers should be the first choice. As for individuals with risk of cardiovascular diseases, a combined use of drugs can complement one another.

Differences in Antihypertensive Drug Effects on BPV Intra- and Inter-Individual Variation

Rothwell et al^{1,37} showed that about 50% of SD of SBP groups during any follow-up is a result of within-individual VVV rather than the differences among individuals in underlying mean SBP. Moreover, given the extent of reported within-individual VVV^{1,37}, trials are unlikely to be the result of reductions in the inter-individual differences in mean SBP, particularly without any difference in mean SBP overall. In ASCOT-BPLA, group SD of SBP was lower in the amlodipine group than in the atenolol group at all follow-up visits ($p < 0.0001$), mainly because of lower within-individual VVV^{1,37,60}. The previous study indicates that CCBs have a broader spectrum of antihypertensive effects, whereas the antihypertensive effect of β blocks is selective. The findings are consistent with the pathological and physical mechanisms of hypertension and these drugs' antihypertensive mechanisms. The pressure from peripheral blood vessel resistance is a major part of arterial BP, whereas the pressure from blood volume related to heart rate covers a much less proportion. During the occurrence and development of hypertension, almost all hypertension patients have increased peripheral blood vessel resistance to varied degrees, while not all patients have the sympathetic active state⁵²⁻⁵⁴. Therefore, the hypertension patients without sympathetic active state are not suggested to take β -blocks as first-line antihypertensive drugs⁵⁹. CCBs has antihypertensive effects on all hypertension patients to varied degrees, especially for patients those with slight hypertension⁶¹. CCBs is associated with lowered average BP level and BPV, particularly in young hypertension patients¹. Accordingly, CCB should be considered as the first choice in the treatment of young people with high stroke risk.

Value of SBP or DBP Variability in Predicting the Targeted Organ Damage

The increase of DBP marks the start of hypertension. In 1977, JNC1⁶² stated that treatment is considered when DBP is 90-104 mmHg, while DBP > 105 mmHg could be diagnosed as hypertension and should be treated. Three years later, in JNC2⁶³, increases of DBP were further classified as follows: mild hypertension (90-104 mmHg), moderate hypertension (105-114 mmHg), and severe hypertension (> 115 mmHg). In 1984, SBP was included into the diagnosis cri-

teria of hypertension for the first time in JNC3⁶⁴. As the clinical evidence and the understanding of hypertension increased, people found that the effects of high SBP on targeted organ damage are more important than high DBP, especially in patients older than 50 years⁶⁵. Different cardiovascular disease risks can be predicted based on the level of SBP and DBP⁶⁶. In 1993, JNC5⁶⁷ considered SBP to be an important indicator for cardiovascular diseases and took SBP ≥ 140 mmHg as an essential basis of diagnosing hypertension for the first time. Based on current researches, early primary hypertension is shown as the increase of DBP. However, DBP gradually decreases and SBP increases as patients age⁶⁸⁻⁷¹. Therefore, elderly hypertension patients mainly are characterized by an increase in SBP. The changing tendency of SBP and DBP variability are related to age. Studies^{8,56} also demonstrate that SBP variability gradually increases, whereas DBP variability has no such tendency as patients age. Therefore, BPV in hypertension patients increases along with the increase of BP level¹⁻⁴. Thus, SBP variability is a good indicator to predict targeted organ damage in the elderly⁸. By contrast, for young patients in early hypertension stage with increased DBP, DBP variability is more significant. However, the results of the study on the hypertension of all age groups (middle age and older) indicate that the correlation between DBP variability and targeted organ damage is unclear⁵⁶. More researches are needed.

Conclusions

Considerable works have been conducted to understand the pathological and physiological mechanisms of hypertension. The development of evidence-based medicine made progress in the clinical treatment of hypertension. However, hypertension seems to become a stubborn illness as the incidence remains high⁷². The newest JNC8 report shows that the goal of systolic pressure control is increased to 150 mmHg⁷³. In some countries, the goal of hypertension control seems to be improved^{73,74}. However, the risk of cardiovascular diseases caused by hypertension remains high, while the risk of stroke caused by hypertension increased much more markedly. This increase in risk is not only related to the blood pressure level but also to the insufficient understanding of hypertension fluctuation and the absence of corresponding timely treatment.

Current studies show that BPV is of greater significance than simple BP level in determining organ damage, and the increase in BPV is more harmful to targeted organs than the increase in BP level. Therefore, to prevent and control hypertension, an in-depth understanding of BPV is needed. Furthermore, clinical treatment for BPV needs to be improved. Guidelines from the European Society of Hypertension and the National Institute for Health Care and Excellence emphasized the importance of BPV in hypertension control⁷⁴. Recently, guidelines for the management of hypertension have largely ignored the role of BPV in the selection of antihypertensive therapy⁷⁵. In this paper, some doubts and difficulties in studying BPV have been explained and analyzed, which may conduce to the in-depth understanding of hypertension and thus guide the clinical treatment of hypertension.

Acknowledgements

This review was funded by the National Twelfth Five-year Major Projects (2012ZX091011105), Shandong Provincial Natural Science Foundation, China (ZR2011LH021 and ZR2015HM024), IIFSDU (2010JC016), SRF for ROCS, SEM and the seed Fund of the 2nd Hospital of Shandong University.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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