

## REVIEW ARTICLE

# PROGNOSTIC SIGNIFICANCE AND LIMITATION OF VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY IN PATIENTS WITH REDUCED EJECTION FRACTION: A MINI-REVIEW

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**Havyarimana Juvenal, Chengkun Kou, Ekhlas Mahmoud Al-hashedi, Jing Yu**

DEPARTMENT OF CARDIOLOGY, LANZHOU UNIVERSITY SECOND HOSPITAL, LANZHOU, PEOPLE'S REPUBLIC OF CHINA

**ABSTRACT**

Visit-to-visit variability (VTV) of blood pressure (BP) can facilitate in predicting future reduced ejection fractions cases. In the recent past, the prognostic significance of visit-to-visit variability of BP has been examined widely in patients with a high risk of cardiovascular disease. The findings of numerous investigations have indicated that increased visit-to-visit variability of blood pressure can lead to better estimation or proper treatments that can minimize blood pressure variability and associated risks while enhancing clinical outcomes. However, inconsistent data of the visit-to-visit hypothesis in the post-hoc analysis have also been explored. Therefore, this review discusses recent analysis, background, and reports of the limitations of visit-to-visit blood pressure variability (VTV-BP) and the prognostic significance of visit-to-visit blood pressure variability in populations at high risk of reduced ejection fractions in predictions of future vascular diseases. The role of the antihypertensive drugs is highlighted while describing the clinical implications and future research directions.

**KEY WORDS:** VTV of BP, antihypertensive drugs, cardiovascular disease, systolic heart failure

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**INTRODUCTION**

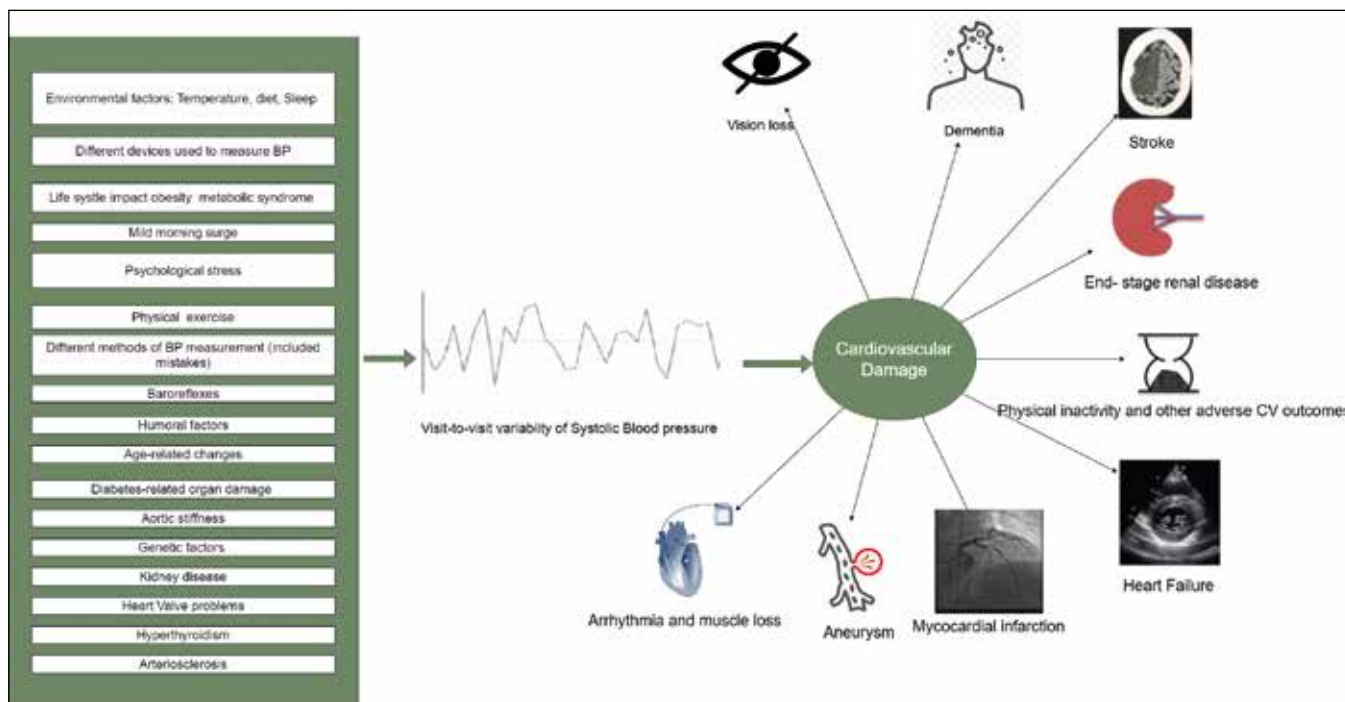
Multiple visit-to-visit variabilities of blood pressure have been evaluated concerning mortality and reduced ejection fractions outcomes in various researches, including several patient populations [1–8]. There is a high reduction in associated cardiovascular deaths due to cardiovascular risk detection and management advancements. However, elevated blood pressure has been investigated as a significant risk factor for heart-related diseases. Few controversial studies have claimed that it is not yet well understood whether variation in blood pressure can accurately predict future heart complications and other associated diseases [9]. In addition, current researches indicate that various outcomes in populations with stroke or with systolic heart-elevation myocardial infarction are independently related to VTV of BP [10, 11].

Kobalava et al. reported little relation between VTV of BP and reduced ejection fractions. VTV of BP was recorded between 2.3 and 20 mmHg in a total of 47 endpoints in 37 patients [2]. The findings demonstrated that the populations with endpoints possessed maximum systolic VTV of BP between (11.2±4.0 vs. 9.5±3.5 mmHg), which was considerably higher. In addition, the logistic regression analysis suggested that the risk of reduced ejection fraction outcomes did not correlate with adverse results in persons with stable reduced ejection records. More analysis on chronic heart failure data with reduced ejection fraction (HFrEF) provided empirical evidence that HFrEF is recognized as a condition of “paradoxical epidemiology”

whereby higher blood pressure is connected with the more beneficial outcomes [11–13]. Partly, their results can be sustained by the understanding that in chronic heart failure (CHF), higher blood pressure is indicated probable improved cardiac output [14].

Conducted research on blood pressure variability (BPV) in patients with CHF proposed that data taken during a limited period, especially short-term BPV monitored within 24-hours with low BP and the level of NTproBNP recorded in 24-hours were associated with more severe heart failure cases and showed minimal prognostic significance [15]. For a better treatment of hypertension, it is recommended that “usual blood pressure” determined as the mean of the total blood pressure records over multiple occasions should be constantly monitored because it accounts for several risks of cardiovascular and associated events. Moreover, it is used to settle antihypertensive drugs to administer [16].

Hypertension is classified among the independent risk factor for various fatal or nonfatal heart failure cases such as vision loss, dementia, stroke, heart failure, renal disease, and myocardial infarction (Fig. 1). A meta-analysis of patient's data for one million adult populations in more than 61 potential research has determined that elevated systolic blood pressure (SBP) up to 20 mm Hg or 10 mmHg of diastolic blood pressure (DBP) from 115 to 75 mmHg is related with an advanced risk of cardiovascular disease or cardiovascular-related deaths as well as other multiple risk factors as shown in Figure 1 [18]. Supportive meta-analysis



**Fig. 1.** Several causes of VVV of BP and the related organ damage. Information adapted from [17] with minimum modifications.

studies recommended that minimizing systolic blood pressure below 130 mmHg can notably lower cardiovascular disease risk [17]. The use of antihypertensive drugs was also recommended in patients at high risk of heart failure disease [19, 20].

The novelty of this review includes combining together the significance and limitations of VVV of BP in an attempt to provide clinicians and researchers with a combined assessment that might find solutions to overcome challenges associated with blood pressure variability in patients with high-risk systolic heart failure, such as the implementation of research results data into proper health measures and policy; identifying an accurate VVV of BP that causes a greater risk of suspicious cardiovascular events; determining the recommended time and number of visits to measure blood pressure and establishing long-term BP variability clinical relevance. Moreover, our review has discussed the recommended behavior and medications for populations at high risk of cardiovascular disease.

**METHODOLOGY**

This study literature search was conducted in the PubMed, Embase, and Google Scholar databases. Our search terms were: visit-to-visit variability of blood pressure (VVV of BP), heart diseases, heart failure, cardiovascular disease, reduced ejection fractions, coronary heart disease, BP, hypertension. Our search was limited on the importance of BP-VVV and the shortcomings discussed in previous studies. Several articles assessing these mentioned keywords were identified. The studies with relevant data were retrieved and discussed in this review.

**REVIEW AND DISCUSSION**

**THE SIGNIFICANCE OF INCREASED VVV OF BP IN PATIENTS WITH A HIGH RISK OF CARDIOVASCULAR DISEASE**

Considerable evidence has been collected on the significance of increased VVV of BP as a significant risk in patients with a high risk of myocardial infarction. Worrying patterns of blood pressure were reported with increasing age. Studies found that systolic blood pressure (SBP) progresses to vary with increasing age. In contrast, diastolic blood pressure (DBP) rises at the age of 50 and reduces after one decade and, in most cases, remains at the same level throughout life [21]. DBP and SBP prevail in patients of age 50 and above. Studies have shown that DBP has a great influence as a cardiovascular risk factor than SBP [21, 22]. Clinical trials have shown that managing SBP can minimize death cases associated with SBP, stroke, and heart failure cases [23]. Clinical trials, as well as observational trial data, might result in poor systolic blood pressure, which causes low rates of blood pressure. However, more findings show that poor SBP also correlates with the physician’s antihypertensive and lipid-lowering treatment. Attack trial (ALLHAT) and verapamil to understand more about cardiovascular end points (CONVINCE) Trial treatments show both treatments can effectively control DBP at a 90% rate. In comparison, SBP was controlled between 60-70%. More studies are needed to understand how to manage systolic hypertension, especially in this aging world population (Fig. 1).

Ajs and Pm investigated the effect of hypertension in end-organ damage and its correlation in causing other vascular events [24]. It is widely accepted that high BP

is the cause of all BP-associated risk of vascular events. Therefore, the importance of drugs that reduce high blood pressure and other safety guidelines on diagnosis and better hypertension treatments should be properly implemented. For better treatment, it is advised that various informative measures such as VVV of BP in clinics should not be neglected. More attention should be given to understand the long-term effects of antihypertensive drugs. Even though clinical guidelines suggest that episodic hypertension is not treatable, it can be monitored and regulated. The possible risks of residual variability in a patient with hypertensive risks should be carefully monitored [25]. The recently documented BPV over several hours by ambulatory BP morning (ABPM) showed

standard deviations between 10-15 mmHg during day-time and 5-10 mmHg at night. Nevertheless, numerous analyses of the prognostic value of 24-hours ABPM have determined mean blood pressures, or at day-night dissimilarity in mean level, and it was noticed that patients with higher night-time mean BP than the one found at night time are more exposed to experience target organ damage, vascular death, vascular events, however, the definite correlation is inaccurate, reverse dippers incline to be greater, several times is more observed in diabetic patients with a record of a previous vascular occurrence.

More studies by Mehlum et al. highlighted BPV and risk of heart failure events and deaths in populations with hypertension risks and various established baseline conditions at different risk levels [16]. To understand if an associated risk of valsartan antihypertensive long-term use combined with amlodipine affects BPV, patients with hypertensive risk of various cardiovascular events were investigated. The timeline for the experiment was 4.2 years. The systolic VVV of BP mean standard deviation was calculated from six-month visits on the ward in patients who showed up at least  $\geq 3$  visits and showed no cases during the first six months of a visit to the hospital. Comparing the highest and lowest quintile of normal blood pressure variability using cox regression of 13803 patients, 1557 (11,3%) had a cardiovascular event, and 1087 (7,9%) deaths were reported as BP-related cases. Patients with the highest VVV of SBP had the highest risk of cardiovascular cases. The calculated hazard ratio of 2.1, 95% confidence interval (95% CI) 1.7-2.4;  $p < 0.0001$ ], the valsartan of 5 mmHG augmented in SD of systolic blood pressure which had correlation with a 10% rise in death risk (HR 1.10, 95% CI 1.04-1.17;  $p = 0.02$ ). The correlations were particularly higher among younger adult patients and populations with minimum SBP. The association was also recorded in patients with various baseline risks except for a higher death risk in patients with well-determined cardiovascular disease. Therefore, it was established that higher VVV systolic blood pressure is related to elevated cardiovascular disease risk in populations with hypertension and other cardiovascular events [26].

It has been established that non-controlled BP increases cardiovascular risk, despite the type of medication used. To understand the influence of verapamil SR-trandolapril

on the consistency of blood pressure and whether there is any adverse outcome closely related to taking that treatment, 22576 patients with known hypertension and coronary artery complications were separated into four groups depending on the number of visits at the hospital for blood pressure record as well as the consistency of their BP ( $<140/90$  mmHg):  $<25\%$ ,  $25\%$  to  $<50\%$ ,  $50\%$  to  $<75\%$ , and  $>75\%$ . Several primary cardiovascular outcomes were registered (nonfatal stroke, nonfatal myocardial infarction, first incidence of mortality, myocardial infarction, and reduced stroke). It was observed that from the group of  $<25\%$  BP to the group of  $<75\%$  BP, the number of strokes was reduced progressively. More findings showed that the risk of primary outcomes such as nonfatal stroke (heart rate:0.50;95% CI:0.37 TO 0.67) was minimal in the group with  $>75\%$  with BP under control in comparison with the group with  $<25\%$  of the visit of BP, nonfatal myocardial infarction (heart rate:0.58;95% CI:0.48 TO 0.70), the first occurrence of death, myocardial infarction and stroke was reduced significantly in  $<25\%$  BP to the group of  $<75\%$  BP. It was demonstrated that baseline of blood pressure could not predict the risk of primary outcomes. However, comparing the proportion of visits with blood pressure control, they were related to the mean follow-up systolic blood pressure ( $r^2=0.64$ ), and both independently associated with the outcomes.

In contrast, in cases where the proportion of visits with blood pressure reduces the rise, a steep depletion in heart diseases was reported associated with independent of baseline characteristics and mean on-treatment blood pressure. Reports show that consistency of blood pressure control could provide additional information during treatment using protective antihypertensive treatment. It is recommended that doctors or types of medications should be altered when blood pressure is not controlled at each visit [27].

Ferrari and Fox reviewed the importance of heart rate reduction in decreasing the risk of myocardial ischemia [28]. Understanding how elevated rates affect cardiovascular disease can provide critical information in the reduction of cases. It has been established that a high heart rate can stimulate myocardial ischemia in patients with known CAD. Among the preventive measures to minimize myocardial ischemia and other chronic heart failures (HF) include the use of the antianginal effect of  $\beta$ -blockers (bisoprolol and metoprolol) and other calcium blockers (diltiazem and verapamil) that reduce heart rate. Reducing heart rate is an established method to ease prognosis in patients with heart failure conditions. Comparative analysis between SHIFT AND SIGNIFY indicated different results, whereby SHIFT findings showed that reducing heart rate enhances prognosis while SIGNIFY findings argue that heart rate variability is a non-modifiable risk factor in patients with cardiovascular disease (CAD). However, further studies showed that heart rate reduced blood flow in coronary arteries and played a significant role in determining cardiac arrhythmias, while low heart rate can be correlated with atrial [29, 30]

Masugata et al. explored the relationship between systolic blood pressure (SBP) variability and cardiac infarction in hypertensive patients [22]. Their study directly contrasted VVV in systolic BP and left ventricular (LV) diastolic dysfunction to understand their correlation with the mean SBP value and other cardiac parameters in patients under various treatments. For one year, forty treated patients with hypertensive conditions ( $69 \pm 9$  years of age) recorded their BP every one or two months at the outpatient clinics. Their findings showed that the standard deviation of systolic blood pressure demonstrated some critical difference between the high and low SBP, especially during the assessed VVV period. The mean of SBP was also analyzed despite the limitation (Table 1). Left ventricular diastolic function was analyzed using (E/A) ratio of early (E), early diastolic mitral annular velocity ( $\dot{e}$ ), and late (A) diastolic transmittal flows. The ratio (E/ $\dot{e}$ ) of E to  $\dot{e}$  employing echocardiography/A was only associated with the standard deviation of systolic blood pressure ( $r = -0.327$ ,  $p = 0.040$ ), on the contrary, it was associated with a standard deviation of systolic blood pressure ( $r = -0.496$ ,  $p = 0.001$ ) and maximum-minimum SBP difference ( $r = -0.490$ ,  $p = 0.001$ ). E/ $\dot{e}$  correlated with a standard deviation of SBP ( $r = 0.384$ ,  $p = 0.014$ ), the recorded high-low SBP difference was between ( $r = 0.410$ ,  $p = 0.009$ ), and the mean value of SBP ( $r = 0.349$ ,  $p = 0.028$ ). Multiple regression calculation determined that only the maximum-minimum SBP difference independently correlated with E/ $\dot{e}$  ( $\beta = 0.410$ ,  $p = 0.009$ ). Therefore, it was concluded that VVV of SBP demonstrated a better association with left ventricular diastolic dysfunction than the mean values of SBP. Elevated VVV was lined with left ventricular diastolic dysfunction and may thus, present high damage for diastolic heart failure in patients with the hypertensive condition. These results correlated with the findings from different studies that visit-to-visit variability in systolic blood pressure can predict stroke occurrence [7, 17].

In addition, more convincing evidence in a meta-analysis of 77299 patients has confirmed that VVV of SBP, regardless of age, could be used to alert cardiovascular, mortality, and stroke. The meta-analysis study of 13 potential types of research was performed to assess the prognostic significance of VVV of SBP by various parameters in 77299 patients with a mean follow-up of 6.3 years. The findings showed that the pooled age and mean SBP-recorded hazard ratios (HRs) for all-cause of fatality rate were 1.03 (95% confidence interval [CI], 1.02-1.04;  $\leq 0.010$ ) per 1-mmHg, while the SBP standard deviation (SD) was 1.04 (1.02-1.06,  $p \leq 0.001$ ) per 1% SBP coefficient of variation, the associated values of heart failure mortality were 1.10 (1.02-1.17,  $p \leq 0.001$ ). The results showed that an increase of 1 mmHg in SD was related to the occurrence of stroke. Therefore, the above clinical analysis demonstrated that VVV of SBP could be used to estimate the future occurrence of cardiovascular events [31].

#### LIMITATION OF VISIT-TO-VISIT VARIABILITY OF BLOOD PRESSURE HYPOTHESIS

Rossignol et al. examined the limitations of the VVV of BP hypothesis in various patients [32]. They highlighted

the significance of the normal BP variability in anticipating the future occurrence of cardiovascular cases. Their investigations used HEAAL (Angiotensin II Antagonist Losartan), whereby 3834 patients with underlying heart failure records and reduced ejection fraction were given 150 mg or 50 mg of losartan daily in a double-blind, supervised, and randomized trial. The patients were monitored for up to 6.8 years during a randomized experiment, and their blood pressure was taken at least three times points in the first year and at a semi-annual visit in the years afterward. During the patients' three-time visit to the hospital, their VVV of BP standard deviation was calculated. The average absolute for each patient visit-to-visit variation and the coefficient of variation. Their study used cox proportional hazard models to understand the associations between variation in SBP, time to death, heart failure cases, hospitalization, and baseline covariates. In a complete multivariate analysis which correlated with BP baseline, the subjects with relatively higher VVV of BP showed adverse consequences; their average absolute variation in systolic blood pressure in mmHg was 1.023 (95% CI (1.013, 1.034),  $P = 0.0001$ , these results were separate of the administered extra dose of losartan which was considered enhancing the outcomes. The above assessment concludes that in chronic myocardial infarction patients with reduced ejection fraction, there was an elevated VVV of BP. This is highly confirming some reported cases of more inadequate cardiovascular events; therefore, more clarifications and analysis should be prioritized in patients with congestive cardiac failure diseases to minimize CHF cases and increase testing prevention strategies.

Similar studies by Muntner et al. seek to analyze whether the VVV of BP was associated with coronary heart diseases, stroke, mortality, or heart failure [33]. Their assessment monitored 1194 fatal chronic heart diseases or nonfatal myocardial infarction, 1948 deaths, 921 heart failure cases, and 606 strokes. Their study conducted a multivariable analysis whereby the mean of systolic blood pressure, the ratio was recorded comparing the highest against the lowest quantile of participated patients of SD of SBP ( $\geq 14.4$  mmHg vs.  $\leq 6.5$  mmHg) was found to be 1.30 (95% CI, 1.06 to 1.59) for fatal chronic heart diseases or nonfatal myocardial infarction, 1.58 (CI, 1.32 to 1.90) for all-cause mortality, 1.46 (CI, 1.06 to 2.01) for stroke, and 1.25 (CI, 0.97 to 1.61) for heart failure. The results showed that the higher VVV diastolic BP highly correlated with chronic vascular diseases cases and mortality. However, their study has not assessed the long-term impact. Their study recommended that future studies should determine whether reducing VVV of BP lowers the BP events.

In a study by Vishram et al., 8505 patients were subjected to losartan and atenolol medicament in the LIFE study, and their blood pressure was monitored over 24,6,12,18 months [34]. It was found that antihypertensive treatment is associated with the mean value of BP measurements. Nevertheless, it is unknown whether high VVV of BP is beneficial or detrimental in patients with complications in the left ventricular hypertrophy (LVH).

**Table I.** Experienced limitations encountered during different visit-to-visit blood pressure variability researches.

Limitations	Explanations	Reference
<p>Inaccurate recordings, substandard peripheral circulation, elevated ectopy, or atrial fibrillation during the measurement.</p> <p>Statistical strength to understand various restrictions of BPV was limited by the minimum cases of repetitive vascular events.</p> <p>BPV was assessed after the inception of administering antihypertensive drugs, which may influence BPV and its relationship with repetitive events.</p> <p>Repeated assessments for estimation of repetitive conditions were conducted after the commencement of treatment.</p>	<p>This indicates the weakness of the investigation; however, it might also show the robustness of the investigation, which include a continuously enrolled, random old population with acute events.</p> <p>The investigation is among the broadest investigation of the prognostic effect of visit-to-visit SBP fluctuation in patients with stroke .</p> <p>This, however, basically eliminates the perplexing impacts of deficient mean BP control.</p> <p>This is required to cause a disparage of reproducibility.</p>	<p>[35]</p>
<p>A post hoc investigation of the TOPCAT trial, incomplete variables, and residual confounding factors can affect the outcome.</p> <p>Various point characteristics were self-declared and may therefore get disqualified due to some bias.</p> <p>Data on using BP-lowering medication on top of which the drug survey can be provided was not obtainable.</p> <p>An extensive investigation of the TOPCAT publications research did not describe precise effectiveness in controlling BP measurements in the TOPCAT trial.</p> <p>The number of people who participated in clinical trials was limited by the need to examine the validity of the observations in comparison with data from the community.</p>	<p>The use of antihypertensive drugs and other medications as a time-dependent co-variable.</p> <p>The assumption can fairly have made that the BP records in TOPCAT, a trial concentrated on HFpEF, were of clinical grade. Despite the evidence that the BP readings in TOPCAT were sub-optimally standardized across centers, this has diminished the study's strength and correlations between different difficulties regarding BP level and variability.</p> <p>Future studies should focus on the same topic.</p>	<p>[13]</p>
<p>The study was post-hoc and exploratory.</p> <p>Their results outcome was delivered from patients with HFrEF, and light symptoms and generalized to different patients with cardiovascular failure was not possible.</p> <p>The mechanisms behind the connection between SBP-CoV and results (particularly for the relationship between low SBP-CoV and worse results) were not perceived, and a threshold SBP value was utilized to decide to participate in the trial which could affect SBP-CoV results partially</p> <p>Due to the multi-centric design of the investigation that incorporated endpoints not centered around BP records, various devices for BP measurement were utilized</p> <p>These results were for hypothesis testing only, as various interactions tests are statistically unsatisfactory, and these records were not aligned for multiplicity</p>	<p>Information was extracted from an enormous randomized controlled trial, allowing adequate statistical capacity to assess the connections between SBP-CoV and risk.</p> <p>Further studies were recommended.</p> <p>All BP estimations were made utilizing approved semi-robotized BP machines with alignment records checked during each clinical exploration monitoring visit. Besides, having various devices decrease the likelihood of a systematic error occurring, reinforcing the relationship validity because they were not involved by random vacillations in the estimation measurements</p>	<p>[36]</p>
<p>This was a post-hoc exploratory analysis</p>	<p>Patients were not exposed to randomization. All things considered, the huge survey data and the thorough analysis of HR and SBP information data give the statistical backup to permit an accurate investigation of the associations to risk. These results might have clinical significance because they demonstrate that doctors that low SBP variation and low HR variation over several medical checkups indicate significant clinical data on future predictions in HF patients. It has to be established that this information is useful to HF with systolic dysfunction; on the contrary, in the HF population with preserved ejection fraction, no information was accessible</p>	<p>[37]</p>
<p>Their results could not represent all types of HF. For instance, a low pacing rate could be destructive in patients with extreme or decompensated HF, just as in serious heart failure problems</p> <p>Since the majority of the medical cases were registered with biventricular pacing (during the two pacing time frames), direct impacts of ventricular resynchronization as indicated by various pacing rates were not barred</p>		<p>[38]</p>

It is widely recorded that patients with causal hypertension in the clinic are at high risk of experiencing a transient ischemic attack or recurrent attack regardless of careful control of mean blood pressure [24]. A study by Webb et al. assessed whether regular BPV could determine whether they will be an increased risk of the cardiovascular case [35]. However, it has some limitations: it can only reflect one type of VVV of BP, requires continuous monitoring to provide accurate results, requires a particular statistical analyst, needs validation from other cohorts, requires normative values and thresholds for pathological BPV. Webb et al. used 520 patients, 22 patients with atrial fibrillation and 26 patients with an irregular beat-to-beat history. Among 520 patients, 400 of them had consistency in all kinds of monitoring. In six weeks of the regular transient ischemic attack, BPV was recorded every 5 minutes, day-to-day for one week on home follow-up with at least three readings per day with a sphygmomanometer and measuring awake ambulatory blood pressure. It was found that beat-to-beat BP predicted recurrent stroke and cardiovascular cases with no correlation with mean SBP. Therefore, beat-to-beat BPV should be considered as an essential predictor of cardiovascular events. In addition, more data analysis of VVV in SBP patients, conducted to understand its relationship with the rise in the number of deaths in the general population, has concluded that VVV for DBP is not associated with mortality. However, VVV of SBP can be found in clinical practice, which is assumed to be the effect of measurement error [7, 21].

The relationship of elevated VVV of SBP in comparison with variability and all-cause of death were also assessed using medical records on the US adult population of > 20 years of age from the 3<sup>rd</sup> National Health and Nutrition Examination Study. The survey used three consecutive BP records registered during three different regular checks up from 1988 to 1994. According to the mean results of the second and third evaluations from the medical checkup, the VVV of BP for every patient was determined using the coefficient of variation and standard deviation between visits. The mortality rate was evaluated on the 31<sup>st</sup> December 2006 (the median follow-up was 14 years while the n=240 deaths). The findings showed that the mean, standard deviation for systolic blood pressure registered in-between visits was 7.7 mmHg. However, more analysis of multivariable adjustment such as female gender, older age, the records of myocardial infarction, elevated mean SBP, utilizing angiotensin-converting enzyme inhibitors, and pulse pressure were closely related with maximum standard deviation in SBP. The assessment found that the multivariable aligned hazard ratios for all-cause mortality correlated with a 4.80 to 8.34 and 8.35 mmHg systolic blood pressure, and the standard deviation were 1.57(95% CI, 1.07 to 2.18), and 1.50 (95% CI, 1.03 TO 2.18) respectively (Table I) [7].

## CONCLUSION

Elevated VVV of BP is one of the causes of cardiovascular diseases. The researchers have inconsistently associated the

increased blood pressure variability hypothesis with the epidemiology of hypertension, kidney, and stroke, and their clinical uses are still arguable, especially in patients with high BPV. However, there is some conclusive research on the role of blood pressure variability in increasing the risk of organ damage and stimulating cardiovascular events. Therefore, the prognostic significance of VVV of BP outweighs the limitations. The current hypothesis should be confirmed in future research to understand the cause, the mechanism, consequences, and the proper medication to regulate variability in blood pressure. In addition, future research should also focus more on verifiable predictions that can facilitate the treatment process of VVV of BP. Medical doctors and practitioners should be careful of the prognostic effect of VVV on BP and the effect of using the drugs recommended to control VVV of BP.

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**ORCID and contribution:**

Havyarimana Juvenal: 0000-0001-6819-4217<sup>A,B,D,F</sup>

Chengkun Kou: 0000-0002-7887-0087<sup>E</sup>

Ekhlash Mahmoud Al-hashedi: 0000-0002-8692-505X<sup>E</sup>

Jing Yu: 0000-0003-2809-3547<sup>F</sup>

**Conflict of interest:**

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**CORRESPONDING AUTHOR**

**Jing Yu**

Department of Cardiology,  
Lanzhou University Second Hospital  
82 Cuiyingmen St, Lanzhou, 730030, Gansu,  
People's Republic of China Lanzhou  
e-mail: yujing2304@126.com

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