REVIEW ARTICLE

VARIABILITY: THE HALLMARK OF BLOOD PRESSURE MEASUREMENT – TYPES, ASSESSMENT AND PROGNOSTIC SIGNIFICANCE

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Abstract: Systemic blood pressure, recorded by various parameters, always shows variation. This is known as 'variability', an entity not assessed routinely. Research has shown greater prognostic importance of it than routine parameters. Various intrinsic and extrinsic factors modulate it. Depending on the interval of successive readings, blood pressure variability is of five types, with different non-invasive methods utilized for recording. It is calculated by various statistical parameters, the most common being standard deviation, but average real variability is the most accurate and easily applied. Clinical evidence is increasing rapidly, indicating variability as a prognostic marker for stroke, ischemic heart disease, renal failure, cognitive dysfunction, heart failure, and mortality. Therapeutic measures for the control of variability have also been forwarded. The paucity of clinical application of blood pressure variability is the stimulus to narrate this review, especially for physicians managing hypertensive patients.

Keywords: Blood pressure variability, types, statistical measures, prognosis

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INTRODUCTION

Blood pressure (BP), not a constant number in any individual, varies from beat to beat. Variation occurs due to several factors emanating from person, environment, atmosphere, time of day, and season. BP variability (BPV) has been noted in both normotensive and hypertensive subjects, especially in the latter. Frattola et al., for the first time, reported the prognostic importance of BPV.[1]

All parameters of BP are associated with sub-clinical organ damage culminating in end-organ dysfunction, either acutely or chronically. Most prognostic studies utilized absolute and mean BP values as indicative of target organ damage (TOD), with BPV not given due importance, probably due to the non-availability of a standardized method for its assessment. Lately, many observational studies and analysis of clinical trial data (post-hoc) have shown prognostic importance.[2]

BPV can be 'physiological', enabling an individual to cope with the stresses of daily life, or 'pathological', being a harbinger of diseases. No matter what time interval is taken for BP measurements, readings differ, at times, substantially. Different devices can record this variation. Initially, BPV was assessed intra-arterially, not applicable in routine practice. Non-invasively, beat-to-beat variability is measured by finger plethysmograph – an oscillometric method. Ambulatory blood pressure monitor (ABPM) and time-triggered home blood pressure monitor are used for 24-hour BP monitoring, whereas digital, mercurial, and aneroid BP monitors are utilized for day-to-day, i.e., home and visit-to-visit BP monitoring.

Depending on the duration of successive measurements, BPV is of five types: very short-term (beat-to-beat), short-term (within a day), mid-term (within a week), long-term (visit-to-visit), and very long-term (visit-to-visit > five years).[3] A difference in the prognostic impact of these BPVs has been noted.[4]

In a systematic review of 33 studies (over one million subjects), Stevens SL et al. examined the association of three types of BPVs (short-, mid- and long-term) with various endpoints. They concluded: "Long-term variability in SBP was associated with risk of all-cause mortality (HR 1.15, 95% CI 1.09 to 1.22), CVD mortality (HR1.18, 95%CI 1.09 to 1.28), CVD events (HR 1.18, 95% CI 1.07 to 1.30), CHD (HR 1.10, 95% CI 1.04 to 1.16), and stroke (HR 1.15, 95% CI 1.04 to 1.27). Mid-term and short-term variability in daytime SBP were also associated with all-cause mortality (HR 1.15, 95% CI 1.06 to 1.26 and HR 1.10, 95% CI 1.04 to 1.16, respectively)".[5] The hazard ratio for BP variability with respect to cardiovascular disease (CVD) mortality has been found to be 1.18.

In a similar meta-analysis (41 cohorts), Diaz KM et al found modest association of visit-to-visit BPV with various endpoints, "for each 5 mmHg higher SD of SBP, the pooled hazard ratios for stroke across seven cohorts was 1.17 (95% CI:1.07–1.28), for CHD across

four cohorts was 1.27 (95% CI:1.07–1.51), for CVD across five cohorts was 1.12 (95% CI:0.98– 1.28), for CVD mortality across five cohorts was 1.22 (95% CI:1.09–1.35), and for all-cause mortality across four cohorts was 1.20 (95% CI:1.05–1.36)".[6]

The prognostic impact of BPV has been noted in normotensives also. Liu M et al. studied 7065 patients with optimal systolic blood pressure (SBP) for MACE (major adverse cardiac events), which was higher by 21% in subjects with the highest SBP variability (quartile 4) as compared to those with the lowest (quartile 1) (HR 1.21; 95% CI, 1.09–1.35).[7]

For the assessment of BPV without any loss of prognostic information, at least 48 readings are needed.[8]

Various statistical parameters assess the variability of BP, the foremost being 'standard deviation (SD)', a measure of the dispersion of BP readings around a central mean value. The number of readings obtained during day and nighttime are sometimes different, and 'dipping' in nighttime BP is also noted. Many researchers have used another measure of ' weighted SD ' to remove bias created by these two factors. To obviate the total dependency of BPV on the mean value, the 'coefficient of variation (CV)', calculated by dividing SD with the mean value, was advocated by some researchers, but this also did not totally remove the effect of mean BP. 'Variation independent of mean (VIM)' and 'average real variability (ARV)' obviate the effect of mean maximally. In VIM, SD is divided by mean BP raised to the power of x, which nullifies the correlation between these two. In ARV, the sum of differences between successive BP measurements is divided by the number of total readings minus one and has been shown to provide the best estimate of BPV.[9]

The therapeutic impact of BPV is yet to be established. However, certain studies have shown that Calcium channel blockers decrease, whereas beta-blockers and diuretics are inferior in this regards.[10]

Awareness of BPV amongst physicians could be better, as shown by Setia S et al. in a survey of 60 Singaporean physicians. Approximately 82% of physicians had no training for BPV.[11]

Although the literature is loaded with evidence for BPV, basic knowledge (definition, types, acquisition methods, advantages, and drawbacks along with prognostic information – total or differential), has not yet been detailed for a busy clinician. To remove this paucity, it is entirely rational to narrate a text where the subject has been explained in an understandable manner. Due to the very low application of this important phenotype of BP, the main objective of this review is to apprise the treating physician of the applicability of BPV in routine clinical practice, making the management of BP in the long term more stringent.

CRITICAL OVERVIEW OF LITERATURE

The appreciable spurt of clinical evidence has been noted for BPV. A PubMed search for this term fetched only three articles in 1948. Since then, the number of studies has constantly risen, reflected by 2754 studies last year and 1537 this year till this manuscript was written.

1. TYPES OF BLOOD PRESSURE VARIABILITY (PHENOTYPES)

Variability in BP is time-constrained and has been divided into five classes, as shown in Figures 1 (Ultra short-term and mid-term) and 2 (mid-term and long-term) with intervals for measurements mentioned in Table 1. Devices used for measurement of different types of variability and the advantages/disadvantages of each are shown in Table 1.

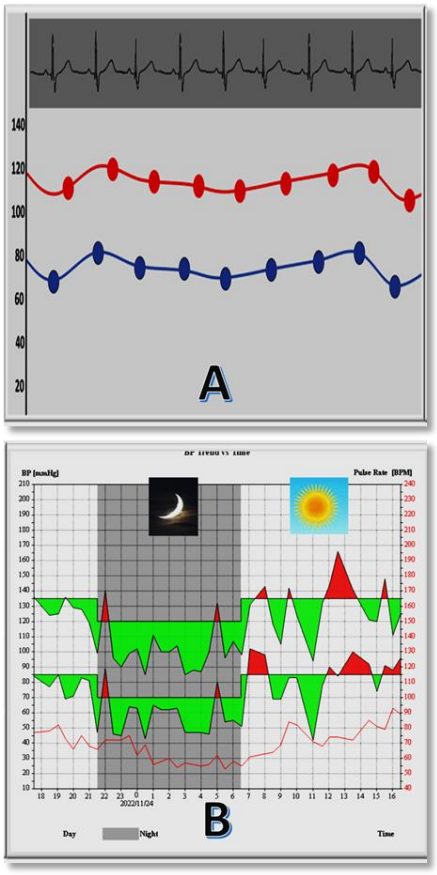

Figure 1: A- Ultra short-term BP variability. The red line is for systolic BP, and the blue line is for diastolic BP,

with dots representing BP values. B- Short-term variability recorded by 24-hour ABPM

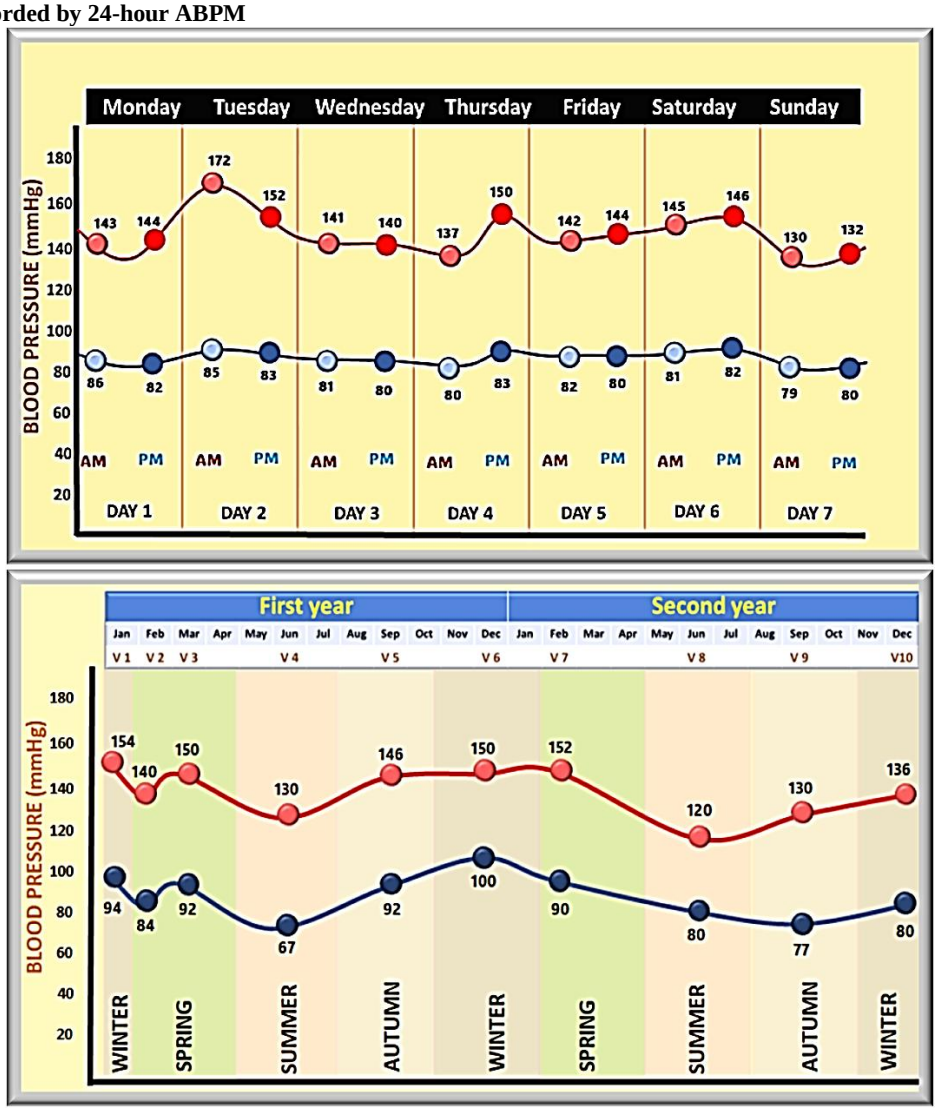

Figure 2: Upper panel: Mid-term variability recorded by HBPM. Lower panel: Long-term BP variability recorded by data on visit-to-visit basis, at least 3-10 records are needed for meaningful analysis. If record is available for more than five years in the same fashion, very long-term variability can be assessed

Table 1: Variability types, devices used for recording, advantages, and disadvantages

S. No.	Type of variability	Time interval and duration	Device used	Advantages	Disadvantages
1	Ultra short-term	Beat to beat	Beat-to-beat monitor	Measures indices of autonomic CV modulation	Research object and not available usually. Marred by artifacts, readings may not correspond with out-of-office BP.
2	Short-term	BP is recorded every 15- 30 minutes for 24-48 hours.	ABPM/Time-triggered HBPM	Gold standard. Moderate acceptability. Provides many phenotypes of BP. Low cost. Plethora of clinical studies available.	Repeated use is not possible. Disturbance during sleep may not depict night readings perfectly.
3	Mid-term	BP is recorded in the morning and evening for 7 days.	HBPM	Low cost and well accepted.	Provides BP reading during awaking and not during work/stress Requires training and medical supervision.

4	Long-term	BP recorded every visit.	Visit to visit BP measurement-digitally or manually	Seasonal effects are best recorded. Done under direct medical supervision.	White coat effect. Provision of validated devices may not be possible. Personnel expertise during different time frames may include bias.
5	Very long-term	BP recorded every visit with data available for more than 5 years.	Same as above	Well suited for the long term as more than 20 years of follow-up reported.	Patient migration and physician switching may not allow such long records to be maintained.

2. PARAMETERS TO MEASURE BLOOD PRESSURE VARIABILITY

Initially, the standard deviation (SD) of BP records was taken as the criterion of variability. It is a measure of the dispersion of BP measurements around a central mean value, Figure 3A. Many drawbacks have been noted for SD as a measure of variability. Since SD and mean BP are correlated, both cannot be used in multivariate analysis simultaneously. SD gives one average value of the whole dataset, disregarding the sequence of change in variability.

In a 24-hour study of BP records, more measurements are obtained during daytime compared to nighttime. This preponderance of daytime readings has a biased effect on the 24-hour mean value (and any derived measurement). Nocturnal dipping of BP also creates bias. To obviate these confounders, another method has been introduced in which the measurements of day and nighttime are weighted according to their numbers, and the SD derived is known as weighted SD (wSD), Figure 3B.[12]

Another method to remove the dependency on the mean is the coefficient of variation, in which SD is divided by mean BP and expressed as a percentage, Figure 3C. Being a proportion, data recorded in different units can be compared by this parameter.

During routine chores, BP sometimes varies so abruptly that transient changes go unnoticed, which causes more target organ damage than steady state higher BP values. To catch these transient changes, another parameter came into vogue, 'time rate of BP variation (TRBP)' by Zakopoulos.[13] In this, the mean of absolute ratios in the difference of successive BP readings and time between them are noted.

Two measures of assessment of BPV known as 'variation independent of the mean (VIM)' and 'average real variability (ARV)' totally disregard the mean BP, hence providing a better estimate of variability. VIM is derived by dividing SD with the mean, which has been raised to the power of x (derived from a fitting curve obtained by plotting mean SD against mean BP), rendering the correlation between the two almost zero, Figure 3D.

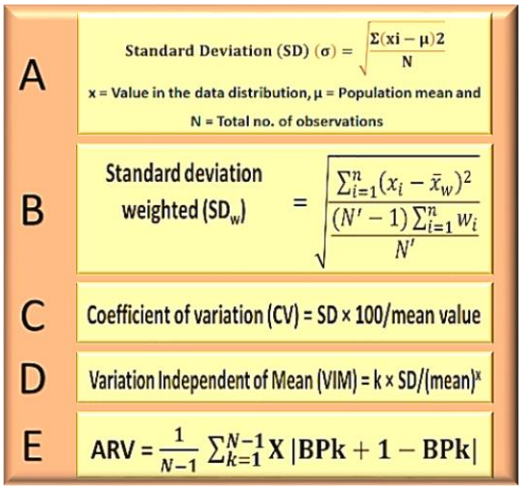

Figure 3: Statistical parameters used to assess BP variability

The ARV provides a better estimate of BP dispersion and therapeutic measures. It has shown greater predictive power for subclinical organ damage, mortality, and non-fatal events. ARV is the preferred index for very short-term and short-term variability assessment. Absolute differences between successive BP readings are summed up and divided by the total number of BP readings minus one, Figure 3E.

Although derived from the same data, the prognostic information obtained by these parameters differs. This has been explicitly shown by Mena LJ et al. in their remarkable meta-analysis of 19 studies comparing the predictive powers of these indexes.[14]

3. FACTORS AFFECTING BLOOD PRESSURE VARIABILITY

Many intrinsic and extrinsic factors affect BPV, varying with type. However, most specifically affects short-term variability, as shown in Figure 4 (blue ovals). Behavioral and environmental factors affect both types of variability (white margins), and drugs or inappropriate estimation of blood pressure (yellow margins) affect long-term variability more often.

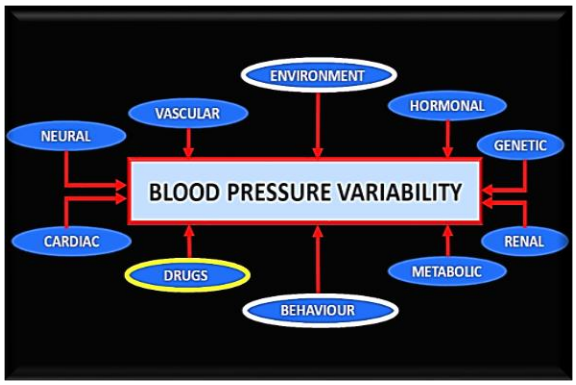

Figure 4: Factors affecting BP variability

Eating causes a slight rise in BP, which usually falls 1 hour later due to vasodilation in viscera and is seen especially after carbohydrate intake in elderly and hypertensive subjects.

Sodium causes an elevation in BP more at nighttime, especially in salt-sensitive patients, as excretion of this mineral also shows diurnal variation.[15] Physiology of other minerals like potassium, magnesium, and calcium is exactly the opposite as they lower BP.

Neurohormonal factors in the form of sympathetic activation and baro-receptor reflexes play an important role in very short-term and short-term BPV. G Mancia et al. have elaborated on it in their study of 82 patients.[16]

Hormones also have a role in the modulation of BPV. Catecholamines, Insulin, and Angiotensin II have been studied clinically. Vasodilators like bradykinin, nitric oxide, and endothelins cause an effect on BPV. These agents mostly affect very short-term and short-term BPV.

Seasonal alteration by sympathetic modulation mainly affects both short-term and long-term variability as higher blood pressures are recorded in winter, especially in the elderly.[17]

Each 1-degree centigrade fall in temperature results in a 1% increase in mortality due to alteration in BP. A seasonal variation in SBP of 2.9/3.4 mmHg and 1.4/0.9 mmHg in the Northern/Southern hemispheres has been reported, respectively, from data across three continents and 24 studies (cross-sectional).[18]

A working group of the European Society of Hypertension issued a consensus statement on seasonal variation in BP, mentioning the evidence and recommendations for clinical practice.[19]

Behavioral factors, especially mental stress, physical activity, and postural changes, by producing changes in sympathetic activity, volume status, and cardiac output, affect both short- and long-term BPV.

Adherence to medical treatment and restriction of social habits (smoking and alcohol consumption) ensure effective control of BPV.

4. BLOOD PRESSURE VARIABILITY AS A PROGNOSTIC MARKER

The prognostic significance of BPV has been shown in a large number of studies. This has varied from individual target organs to cumulative evidence of damage, as demonstrated by all phenotypes. Intra-phenotypic comparison has also been done for various endpoints, showing mixed results. BPV has demonstrated clear superiority over other BP parameters like SBP, DBP, and mean BP.

- **Target organ damage:** Clinical evidence for target organ damage (TOD) has been noted in earlier studies. Gianfranco H et al. studied 108 hypertensive patients by intra-arterial 24-hour BP measurement.[20] Parameters for LVH (ECG), cardiac volume (CXR), ocular fundi (Keith-Wegner classification), heart failure, cerebral and peripheral vascular insufficiency (clinical measures), and renal dysfunction (BUN, creatinine, and proteinuria) were scored for TOD. Short-term and long-term variabilities were assessed within half-hour SD and among half-hour SD of mean BP. High BPV, both short- and long-term ($p < 0.05$ and < 0.01), respectively, were found to have significant prognostic values for TOD.

  The association of increased incidence of stroke due to arterial stiffness and carotid intima malformation with short- and mid-term BPV has been studied. Zhou TL et al., in 1671 patients, demonstrated that an increase of 1-SD in BPV (derived from a composite of short-, mid-and long-term BP record) increases carotid-femoral pulse wave velocity [0.10 m/s (95% CI, 0.01–0.20)], carotid circumferential wall tension (0.84 dyne/cm [0.51–1.17]), circumferential wall stress [0.79 kPa (0.031–1.27)], and intima-media thickness [8.6 µm (1.0–16.3)], but not carotid distensibility [-0.033×10^{-3}/kPa (-0.255 to 0.190)].[21] This shows carotid maladaptation, which can result in stroke.
  An increase in left ventricular mass is one of the targets of high blood pressure. Mustafa et al. demonstrated a significant association of short-term variability (by ABPM record) of nocturnal diastolic BPV (SD) with increased LV mass and hypertrophy.[22] Similar associations were noted

for 24-hour ARV and nocturnal diastolic ARV. An increase in LV mass is a harbinger of many cardiovascular complications.

- **Major adverse cardiovascular events:** In a retrospective study of 42482 patients, Ebinger JE et al. searched for an association of BPV with multiple endpoints (MI, stroke, heart failure, and death), individually and cumulatively, over a period of six years.[23] Data was obtained from digital health records corresponding to the real-life methods of BP recording and not the stringent confines of a robust clinical trial. The investigators obtained a significant correlation of VIM, SBP (HR, 1.22; 95% CI 1.17−1.28), and DBP (HR, 1.24: 95% CI 1.19−1.30) with endpoints. VIM was chosen as a reference parameter as other measures depend highly on mean BP. In this study, the association of BPV with clinical endpoints was demonstrated, and the utility of routinely obtained BP measurements was emphasized.

- **Mortality:** Sierra ADL, in a Spanish study of 249 elderly in-hospital patients (>80 years of age), studied the relation of various parameters on 24-hour ABPM like arm and central BP (aortic), BP and heart rate variabilities, ratio of systolic and diastolic BP variabilities and aortic pulse wave velocity with 1-year mortality.[24] Considering only BP variabilities, they found that a 1% increase in SBP variability raised the mortality rate by 38% (HR: 1.38; 95%; CI: 1.06–1.80). Brachial BPV was also associated with mortality significantly (HR: 1.31; 1.06–1.62). The researchers recommended a cautious approach in the administration of short-acting antihypertensive medicines to these hospitalized patients as variation in BP would be further enhanced.

- **Ischemic heart disease:** Groove JS et al. studied 1433 men of the Honolulu heart program for a 10-year period, recording their blood pressures at four different times approximately three years apart.[25] They studied the variation of SBP as a cause of coronary heart disease for a subsequent 11.3 years and found a significant correlation ($p<0.001$). This group demonstrated the variability of blood pressure with cardiac events.
  Soh MS et al. studied 343 post-PCI patients for long-term BPV for a median period of 76 months.[26] Systolic BPV was 13.2 ± 7.6 mmHg and diastolic BPV was 8.9 ± 4.4 mmHg. Subjects were divided into two groups (high BPV >12.3 mmHg and low BPV < 12.3 mmHg) based on systolic BPV. They found a significant association only in the high BPV group for MACE, whereas no difference was noted for other study endpoints (recurrent MI, target vessel revascularization, and all-cause mortality), and neither an association was noted for diastolic BPV with any of the endpoints.

  Weasel CL et al. studied 471 post-angioplasty patients (10 BP measurements in a span of 3-60 months), correlating visit-to-visit BPV (SD and largest change) with MACE (myocardial infarction, cerebrovascular accident, death, and all-cause hospitalization).[27] Systolic BPV was significantly higher in patients who died or were re-admitted by both parameters, whereas diastolic BPV was significantly higher in subjects showing large change only.

- **Stroke:** BPV affects the prognosis of patients after neurological insult markedly, especially in the early phase of acute ischemia/infarction. Higher BPV is associated with more significant residual disability. Control of mean BP and variability at this stage will lead to better neurological outcomes.

  Naito H et al. studied short-term BP (by 24-hour ABPM) variability parameters (SD and CV of SBP, DBP, and morning surge) with functional status in acute ischemic stroke patients.[28] Total cohort comprised of 626 subjects with 497 subjects analyzed at three months by modified Rankin score (mRS) for disability status. SD and CV of 24-hour SBP and DBP, along with morning surge and non-dipping pattern, were significantly associated with a worse mRS.

  Han X et al., in a study of 137 patients with acute ischemic pontine infarct, found worse outcomes (assessed by modified Rankin score) in subjects with high BPV (assessed by CV of systolic and diastolic pressure on 24-hour ABPM record), paramedian location of infarct and higher National Institute of Health Stroke Score (NIHSS).[29]

  Chang JY et al. studied 90 patients who had undergone successful endovascular thrombectomy but had poor collateral circulation and found that BPV (assessed by SD, CV, and VIM of SBP and mean PR) during the first 24 hours after recanalization had a greater impact on functional outcome (assessed by early neurological recovery on day one and mRS at three months) in patients with poor collateral

circulation.[30] This necessitates adequate control of BPV for effective functional recovery.

Neurological and cardiac insults in their earlier stages demand stricter control of BPV as these patients show fluctuation in BP levels more often in the first seven days. Control at this time makes recovery smooth and better for long-term functional recovery.

- **Cognitive function and dementia:** Chiu TJ et al., in a systemic review of 20 cohort studies (7 924 168 persons), found SBP variation assessed by CV and SD was associated with a higher risk of dementia of all causes, especially during shorter follow-ups in elderly subjects (> 65 years).[31]

  Haverkamp RA et al., in a study of 279 elderly patients, assessed the risk of mortality with cognitive decline and BP variability by 7-day HBPM record.[32] No correlation was found for day-to-day variability irrespective of the mean (VIM) for mortality and cognitive decline, but a significant association was noted for morning systolic BP VIM and mortality (adjusted HR: 1.09, 95%-CI 1.01–1.18, p = 0.033).

  Dementia and cognitive decline are associated with small cerebrovascular disease (sCVD). This entity is identified on MRI by white matter hyperintensities, microbleeds, lacunes, and perivascular spaces' enlargement. In a study of 82 middle-aged hypertensive patients, an association of BPV with sCVD was evaluated by de Heus RA et al. by HBPM.[33] Significant association of systolic BPV and evening SBP was noted with sCVD. Association for DBP, mean BP, or morning BP was not significant.

  In 3511 Chinese patients comprised of two groups [45-59 years (mid to old life) and 60 years or more (old to old life)], Xu et al. found a significant negative association between SBP variability and various parameters of cognitive function like orientation, language, recall, and total (assessed by Mini-mental state exam-MMSE).[34] For every one-unit increase in SBP variability, the MMSE score decreased by 9.5 points. No such correlation was noted for DBP and pulse pressure variability. A significant association was stated only in the older group, emphasizing better control of SBP in this group to reduce cognitive dysfunction.

- **Heart failure:** Admission BP and variability in cases of heart failure have shown prognostic value with regard to mortality. A higher admission blood pressure is associated with a better prognosis, but a higher BPV in heart failure showed an adverse prognosis.[35] Wei FF et al., in 1006 patients with acute decompensated heart failure (preserved ejection fraction), assessed mean admission BP, SD, and CV of BP during multiple hospitalizations for a median follow-up of 1.54 years.[36] For every 1% increment in SD and CV of SBP, the risk of all-cause mortality increased by 10% and 11%, respectively (SD: HR, 1.10, 95%CI, 1.01-1.21, P=0.029, CV: HR, 1.11, 95%CI, 1.02-1.21, P=0.017), which further increased to 18% and 19% after adjusting confounders.

  Similarly, patients with heart failure with reduced ejection fraction (HFrEF) also showed poorer prognosis regarding mortality and heart failure re-hospitalizations. Rossignol P et al. studied 3834 patients of HFrEF for 6.8 years divided into two groups receiving low (50 mgs) and high (150 mgs) doses of Losartan and assessed by visit-to-visit variability of blood pressure by SD, CV, and ARV. All parameters showed increased hazard ratios (HR: 1.023, 95% CI 1.013- 1.034, P < 0.0001) for outcome irrespective of dose of Losartan.[37]

- **Endocrinology:** Bisogni V et al., in their study of 23 patients of Pheochromocytoma and paraganglioma (PPGL), assessed short-term BPV parameters. Removal of PPGL showed "a significant decrease in 24-h systolic BP ARV (8.8 ± 1.6 vs. 7.6 ± 1.3 mmHg, p < 0.001), in 24-h diastolic BP ARV (7.5 ± 1.6 vs. 6.9 ± 1.4 mmHg, p = 0.031), and wSD of 24-h diastolic BP (9.7 ± 2.0 vs 8.8 ± 2.1 mmHg, p = 0.050) compared to baseline measurements."[38]

  In a large Swedish study of 9855 diabetic patients followed up for a median of 4 years, the correlation of BPV (by SD, CV, and VIM) with cardiovascular and all-cause mortality was studied with no change in hypertension treatment.[39] No significant association was noted for the entire group, but in the subset of patients not taking any antihypertensive medicine (n=2949), an association was noted for all-cause mortality with only a small increase in discrimination when this variable was added to other measures. This study doesn't support the use of BPV in this group of patients as a marker of mortality.

- **Chronic kidney disease:** The role of BPV in assessing CKD patients is taken with care as

volume and pressure status vary significantly due to interventions (dialysis, etc.). However, in certain areas, BPV plays a significant prognostic role.

Hsieh MY et al., in their study of 1011 patients on regular dialysis, found BPV was associated with an increased risk of access thrombosis [HR= 1.27, 95% CI, 1.18–1.44, /SD increase in BPV].[40] The risk in patients was 2.45 times in the highest BPV quartile.

In the HEMO trial comprising 1844 patients on regular hemodialysis, Chang TI et al. studied the association of BPV (by CV and ARV) with all-cause and cardiovascular mortality.[41] They found an 18% higher risk of death from any cause with every 10% rise in BPV by CV, and ARV also showed a similar association. "Black race, a history of heart failure and diabetes mellitus, catheter use, and having more frequent intradialytic hypotension are associated with higher visit-to-visit blood pressure variability."

Chia YC et al., in their long (15 years) retrospective study of 874 patients, studied the relation of BPV with a decline in eGFR.[42] A significant negative correlation was noted (SD: $r=0.16$, $p<0.001$; CV: $r=0.14$, $p<0.001$). They found that an SD of 13.5 mmHg and CV of 9.74% were associated with the onset of chronic kidney disease.

Wang G et al., in their study of 245 non-dialyzed patients of renal failure (grade 1-4), found a correlation of high BPV (assessed by SD, CV, and VIM) with the progression of renal disease (seen only in unadjusted model and not in fully adjusted model) and cardiovascular disease but not with total mortality.[43] They found hyperkalemia, LV end-diastolic diameter, hypertension, and BMI as markers of high BPV.

Kumanan T et al., in their one-year study of long-term blood pressure variability of 406 patients, found that female sex ($p=0.023$), DM ($p=0.013$), CKD ($p=0.007$), and the tendency for developing OSA ($p=0.004$) were associated with significant variability.[9] A median value of 11.69 differentiated low and high variability groups. In multivariate analysis, only DM and CKD were significantly associated with high variability.

- **Obstructive sleep apnea:** Obstructive sleep apnea (OSA) is associated with hypertension. Steinhorst has studied the association of BPV and OSA, AP et al. in 107 patients.[44] A significantly higher BPV has been noted in patients with apnea-hypopnea index ≥ 10.

Damage to targets of high blood pressure is accrued by every component of it (SBP, DBP, and mean BP), but the narration mentioned above shows clinical evidence of a higher damaging role of blood pressure variability, emphasizing its recognition and effective control.

5. TARGETING BP VARIABILITY THERAPEUTICALLY

Although the position of BPV as a prognostic marker has been clearly established, there are clinical lacunae in its implementation as a therapeutic target. First, there is no clear demarcation for normality at present; secondly, pharmacological trials especially directed against BPV, need to be improved. However, evidence is accumulating from earlier large-scale trials (ALLHAT trial) that calcium channel blockers reduce BPV significantly more than ACE inhibitors (lisinopril). In a retrospective analysis of MRC trial and ASCOT-BPLA trials, beta-blockers proved inferior to diuretics (Chlorthalidone) and calcium channel blockers (Amlodipine).[45] Combinations of antihypertensive agents, including calcium channel blockers, are better at reducing BPV than combinations lacking this agent (COPE trial).[46] The superiority of calcium channel blockers for modulation of BPV extends to all types of it and combination with ACEI/ARB, outperforming other combinations, especially those involving beta blockers. However, more dedicated research is still needed in this regard.

6. DIFFERENTIAL PROGNOSIS OF BLOOD PRESSURE VARIABILITY PHENOTYPES

The prognostic impact of the different phenotypes of BPV differs, as demonstrated by comparative clinical studies.

Tahir ZA studied 152 hypertensive patients retrospectively, comparing short-term (ABPM record) and long-term (home BP record) BPVs for a period of 10 years. The endpoints of the study were “acute coronary syndrome (ACS), chronic ischemic heart disease (IHD), heart failure (HF), or stroke”. Systolic BPV of day (OR=1.94; 95% CI=1.09–3.45; $p=0.025$) and nighttime (OR=1.23; 95% CI=1.00–1.51; $p=0.048$) showed significant association with IHD, whereas SD of visit-to-visit BPV was significantly associated with ACS (OR=1.10; 95% CI=1.01–1.21; $p=0.04$).[47]

In another comparative study (n = 508) of long-term (visit-to-visit BPV) vs. short-term (24-hour BPV) for mortality in treated hypertensive patients (age > 65 years), Chowdhury EK et al. also showed differential results.[48] SD of daytime SBP and SDw of 24-hour SBP were more significantly associated with mortality, whereas SD of visit-to-visit SBP was not. The low association of VV BPV with endpoint was attributed to a small number of patients by the researchers, as other studies have shown an association in this regard.

CONCLUSION

Blood pressure variability, a parameter of great prognostic importance, is yet to gain widespread clinical acceptance in daily practice. Long-term variability can be gauged easily by serial BP measurements obtained from patients' medical records. The application needs the knowledge of the treating physician in this regard, which is the primary purpose of this manuscript. Short-term variability assessment needs some sophisticated measures (home BP measurement or ABPM), which are now becoming more readily available with advancements in medical care. The medical community must refrain from showing inertia in using these gadgets and apply all the available parameters to ensure better health care. Reasonable control of BPV in acute phases of vascular events ensures better survival and limited damage in the long term.

Similarly, encouraging results can be obtained if this parameter is closely observed in cognitive and renal dysfunction areas. No specific therapeutic agent is available at present for BPV normalization, but there are clues from large-scale studies showing the efficacy of certain agents (calcium channel blockers). This area needs special attention for better clinical outcomes in the future. BPV phenotypes differ regarding prognostic capability in different clinical conditions, and variability of various blood pressure parameters also show prognostic differences for clinical endpoints. A thorough knowledge of these subtleties of blood pressure management will ensure high-quality care for hypertensive patients

AUTHORS' CONTRIBUTION

IH: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. IH: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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REFERENCES

1. Frattola A, Parati G, Cuspidi C, Albini F, Mancia G. Prognostic value of 24-hour blood pressure variability. J Hypertens. 1993;11(10):1133-7.
2. Dolan E, O'Brien E. Is it daily, monthly, or yearly blood pressure variability that enhances cardiovascular risk? Curr Cardiol Rep. 2015;17:1-5
3. Parati G, Torlasco C, Pengo M, Bilo G, Ochoa JE. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. Hypertension Res. 2020;43(7):609-20.
4. Rosei EA, Chiarini G, Rizzoni D. How important is blood pressure variability? Eur Heart J Supplements. 2020;22(Supplement_E):E1-6.
5. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ. 2016;9:354.
6. Diaz KM, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D, et al. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. Hypertension. 2014;64(5):965-82.
7. Liu M, Chen X, Zhang S, Lin J, Wang L, Liao X, et al. Assessment of Visit-to-Visit Blood Pressure Variability in Adults With Optimal Blood Pressure: A New Player in the Evaluation of Residual Cardiovascular Risk? J Am Heart Assoc. 2022;11(9):e022716.
8. Mena LJ, Maestre GE, Hansen TW, Thijs L, Liu Y, Boggia J, et al. How many measurements are needed to estimate blood pressure variability without loss of prognostic information? Am J Hypertens. 2014;27(1):46-55.
9. Kumanan T, Sujanitha V, Guruparan M, Rajeshkannan N. Factors associated with visit-to-visit variability of blood pressure measured as part of routine clinical care among patients attending cardiology outpatient department of a tertiary care centre in Northern Sri Lanka. Int J Hypertens. 2019;2019:6450281.
10. Nishioka R, Kinoshita S, Shiibashi M, Shimazu T, Nakazato Y, Yamamoto T, et al. Evaluation of the differences in the effects of antihypertensive drugs on blood pressure variability by 24-hour ambulatory blood pressure monitoring in chronic cerebrovascular disease. J Stroke Cerebrovasc Dis. 2015;24(8):1848-54.
11. Setia S, Subramaniam K, Tay JC, Teo BW. Hypertension and blood pressure variability management practices among physicians in Singapore. Vasc Health Risk Manag. 2017;13:275-85.
12. Bisogni V, Petramala L, Oliviero G, Bonvicini M, Mezzadri M, Olmati F, et al. Analysis of short-term blood pressure variability in pheochromocytoma/paraganglioma patients. Cancers. 2019;11(5):658.
13. Zakopoulos NA, Tsivgoulis G, Barlas G, Papamichael C, Spengos K, Manios E, et al. Time rate of blood pressure variation is associated with increased common carotid artery intima-media thickness. Hypertension. 2005;45:505-12.
14. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis. J Am Heart Assoc. 2017;6(10):e006895.
15. Kawano Y. Diurnal blood pressure variation and related behavioral factors. Hypertens Res. 2011;34(3):281-5.
16. Mancia G, Parati G, Pomidossi G, Casadei R, Di Rienzo M, Zanchetti A. Arterial baroreflexes and blood pressure and heart rate variabilities in humans. Hypertension. 1986;8(2):147-53.
17. Jehn M, Appel LJ, Sacks FM, Miller ER. 3rd; DASH Collaborative Research Group. The effect of ambient temperature

and barometric pressure on ambulatory blood pressure variability. Am J Hypertens 2002;15(11):941-5.
18. Alperovitch A, Lacombe JM, Hanon O, Dartigues JF, Ritchie K, Ducimetie`re P, et al. Relationship between blood pressure and outdoor temperature in a large sample of elderly individuals: the Three-City study. Arch Int Med. 2009;169(1):75-80.
19. Stergiou GS, Palatini P, Modesti PA, Asayama K, Asmar R, Bilo G, 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. J Hypertens. 2020;38(7):1235-43.
20. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia Ge. Relationship of 24-Hour Blood Pressure Mean and Variability to Severity of Target-Organ Damage in Hypertension. J Hypertens. 1987;5(1):93-8.
21. Zhou TL, Henry RM, Stehouwer CD, van Sloten TT, Reesink KD, Kroon AA. Blood pressure variability, arterial stiffness, and arterial remodeling: the Maastricht Study. Hypertension. 2018;72(4):1002-10.
22. Mustufal ER, Istrătoaie O, Musetescu R. Blood pressure variability and left ventricular mass in hypertensive patients. Current health sciences journal. 2016;42(1):47-50.
23. Ebinger JE, Driver M, Ouyang D, Botting P, Ji H, Rashid MA, et al. Variability independent of mean blood pressure as a real-world measure of cardiovascular risk. EClinicalMedicine. 2022;48:101442.
24. de la Sierra A, Sierra C, Murillo M, Aiello TF, Mateu A, Almagro P. Pulse Wave Velocity and Blood Pressure Variability as Prognostic Indicators in Very Elderly Patients. J Clin Med. 2023;12(4):1510.
25. Grove JS, Reed DM, Yano K, Hwang LJ. Variability in systolic blood pressure—a risk factor for coronary heart disease? Am J Epidemiol. 1997;145(9):771-6.
26. Soh MS, Park JS, Seo KW, Yang HM, Lim HS, Choi BJ, et al. Visit-to-visit systolic blood pressure variability in patients with ST-elevation myocardial infarction predicts long-term cardiovascular outcomes. J Hum Hypertens. 2019;33(4):259-66.
27. Weisel CL, Dyke CM, Klug MG, Haldis TA, Basson MD. Day-to-day blood pressure variability predicts poor outcomes following percutaneous coronary intervention: A retrospective study. World J Cardiol. 2022;14(5):307-18.
28. Naito H, Hosomi N, Kuzume D, Nezu T, Aoki S, Morimoto Y, et al. Increased blood pressure variability during the subacute phase of ischemic stroke is associated with poor functional outcomes at 3 months. Sci Rep. 2020;10(1):811.
29. Han X, Zhang G, Liu N, Zhang H, Xu J, Han M, et al. Blood Pressure Variability and Severity of Early Prognosis in Patients with Acute Pontine Infarction. Int J Hypertens. 2020;2020:1203546.
30. Chang JY, Jeon SB, Jung C, Gwak DS, Han MK. Postreperfusion blood pressure variability after endovascular thrombectomy affects outcomes in acute ischemic stroke patients with poor collateral circulation. Front Neurol. 2019;10:346.
31. Chiu TJ, Yeh JT, Huang CJ, Chiang CE, Sung SH, Chen CH, et al. Blood pressure variability and cognitive dysfunction: A systematic review and meta-analysis of longitudinal cohort studies. J Clin Hypertens. 2021;23(8):1463-82.
32. Haverkamp RA, Melis RJ, Claassen JA, de Heus RA. Day-To-Day Home Blood Pressure Variability and All-Cause Mortality in a Memory Clinic Population. J Alzheimer's Dis. 2022;85(3):1219-31.
33. de Heus RA, Reumers SF, van der Have A, Tumelaire M, Tully PJ, Claassen JA. Day-to-day home blood pressure variability is associated with cerebral small vessel disease burden in a memory clinic population. J Alzheimer's Dis. 2020;74(2):463-72.
34. Xu L, Yang Y, Cui D. Association between blood pressure control status, visit-to-visit blood pressure variability, and cognitive function in elderly Chinese: A nationwide study. Front Public Health. 2022;10:877192.
35. Raphael CE, Whinnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH, et al. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. Heart. 2009;95(1):56-62.
36. Wei FF, Chen SL, Chen C, Yu ZP, Zhou YY, Xu TY, et al. Associations of all-cause mortality with admission blood pressure variability during multiple hospitalizations in acute decompensated heart failure. Zhonghua Xin Xue Guan Bing Za Zhi. 2023;51(4):377-83.
37. Rossignol P, Girerd N, Gregory D, Massaro J, Konstam MA, Zannad F. Increased visit-to-visit blood pressure variability is associated with worse cardiovascular outcomes in low ejection fraction heart failure patients: Insights from the HEAAL study. Int J Cardiol. 2015;187:183-9.
38. Bisogni V, Petramala L, Oliviero G, Bonvicini M, Mezzadri M, Olmati F et al. Analysis of short-term blood pressure variability in pheochromocytoma/paraganglioma patients. Cancers. 2019;11(5):658.
39. Bell KJL, Azizi L, Nilsson PM, Hayen A, Irwig L, O¨stgren CJ, et al. Prognostic impact of systolic blood pressure variability in people with diabetes. PLoS One. 2018;13(4):e0194084
40. Hsieh MY, Cheng CH, Chen CH, Liou MT, Lin CC, Yang TF, et al. The association of long-term blood pressure variability with hemodialysis access thrombosis. Front Cardiovasc Med. 2022;9:881454.
41. Chang TI, Flythe JE, Brunelli SM, Muntner P, Greene T, Cheung AK, et al. Visit-to-visit systolic blood pressure variability and outcomes in hemodialysis. J Hum Hypertens. 2014;28(1):18-24.
42. Chia YC, Lim HM, Ching SM. Long-term visit-to-visit blood pressure variability and renal function decline in patients with hypertension over 15 years. J Am Heart Assoc. 2016;5(11):e003825.
43. Wang G, Ma K, Ma Z, Guo X, Wang Y, Ma L, Qi C, et al. Short-term blood pressure variability and outcomes in non-dialysis chronic kidney disease. Front Med. 2022;9:911205.
44. Steinhorst AP, Gonçalves SC, Oliveira AT, Massierer D, Gus M, Fuchs SC, et al. Influence of sleep apnea severity on blood pressure variability of patients with hypertension. Sleep Breath. 2014;18(2):397-401.
45. Nardin C, Rattazzi M, Pauletto P. Blood pressure variability and therapeutic implications in hypertension and cardiovascular diseases. High Blood Press Cardiovasc Prev. 2019;26(5):353-9.
46. Umemoto S, Ogihara T, Matsuzaki M, Rakugi H, Ohashi Y, Saruta T. Effects of calcium channel blocker-based combinations on intra-individual blood pressure variability: post hoc analysis of the COPE trial. Hypertens Res. 2015;39(1):46-53.
47. Taher ZA, Khayyat WW, Balubaid MM, Tashkandi MY, Khayyat HA, Kinsara AJ. The effect of blood pressure variability on the prognosis of hypertensive patients. Anatol J Cardiol. 2019;22(3):112-6.
48. Chowdhury EK, Wing LM, Jennings GL, Beilin LJ, Reid CM. Visit-to-visit (long-term) and ambulatory (short-term) blood pressure variability to predict mortality in an elderly hypertensive population. J Hypertens. 2018;36(5):1059-67.

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