Blood Pressure Variability: Assessment, Prognostic Significance and Management

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Abstract
Interest in blood pressure variability (BPV) as a cardiovascular risk factor has gained focus in recent times. Increased BPV places added strain on the cardiovascular (CV) system unrelated to its average value, leading to increased risk of target organ damage (TOD) and CV events. Recent data suggests that there is inter-drug variation in efficacy with calcium channel blockers (CCBs) such as Amlodipine proving superior to other drugs in reducing BPV. Addition of CCBs to other antihypertensive agents significantly reduces BPV; however the reverse is not true.

Introduction
Office blood pressure (BP) has been found to be clinically significant due to its independent continuous relationship with the incidence of several cardiovascular (CV) events, mainly stroke, myocardial infarction (MI), sudden death, heart failure (HF) and peripheral artery disease (PAD) in addition to end-stage renal disease (ESRD). This association remains true across all age and ethnic groups.

Interest in blood pressure variability (BPV) as a cardiovascular risk factor has gained focus in recent times due to evidence which suggests that increased BPV places added strain on the CV system unrelated to its average value, leading to increased risk of target organ damage (TOD) and CV events. BP values undergo spontaneous variations due to various reasons. Short-term variations may occur within the 24 hours due to day-night changes, and also among hours, minutes, and even adjacent beats. Long-term variations may occur due to differences among days, months and seasons. Additionally systolic BP (SBP) increases with age and diastolic BP (DBP) exhibits an age-related biphasic change. Treatment with antihypertensive medications might help in reducing BPV, in addition to obtaining mean BP control, conferring optimal CV protection. To this end, understanding the basics of BPV might prove valuable.

Types of BPV and Mechanisms

Very Short-term BPV
The beat-to-beat changes in BP occur due to interaction between several CV regulatory systems such as the baroreceptor reflex, the renin-angiotensin system (RAS), the vascular myogenic response and the release of nitric oxide (NO) from the endothelium. The identification of these BPV influencers can be done by power spectral analysis and may provide important information on individual BP control mechanisms.

Very Short-term BPV or beat-to-beat variability is measured by non-invasive continuous monitoring of BP through finger-cuffs equipped with an infrared photoplethysmograph and technology-based quantification of finger blood pressure levels. Several newer non-invasive devices are also being developed. However, since most recordings are done under laboratory settings, its reliability outside of the controlled environment is suspect.

Short-term or 24-hr BPV
24-hr BPV occurs due to several factors such physical activity, sleep and emotional stimuli. Day and night changes may be influenced by signals initiated by the brain. BPV also occurs due to mechanical forces generated by ventilation and due to humoral and local vasomotor phenomena. These BP changes are regulated largely via the baroreflex, and also to some extent through the sympathetic nervous system (SNS) and certain non-neural mediators (Figure 1).

Night-time BP (sleep) is on an average 10-20% lower than that during daytime (waking hours). However, in hypertensive patients the 24-hr BP patterns might be diverse. Some show >20% or <10% decrease in BP at night and some may even show a rise in night-time BP as compared to daytime values. Depending on their SBP values, these patients are usually categorised as extreme dippers (night–day BP ratio ≤0.8), dippers
in patients with higher VVV BPV aortic distensibility were observed arterial elasticity and reduced contribute to long-term BPV. Lower that arterial stiffness may also Atherosclerosis (MESA) showed Data from the Multiethnic Study of Long-term BPV volume overload. Sodium handling and nocturnal sensitivity, sleep apnea, abnormal dysfunction, disturbed baroreflex night include nocturnal autonomic proposed reasons for this BP rise at out outcomes than dippers and theReverse dippers seem to present with worse reasons than dippers and the proposed reasons for this BP rise at night include nocturnal autonomic dysfunction, disturbed baroreflex sensitivity, sleep apnea, abnormal sodium handling and nocturnal volume overload.

### Long-term BPV

Long-term BPV includes day-to-day, visit-to-visit (VVV) and seasonal variations. Behavioural changes play a major role in long-term BPV as suggested by the clear differences observed in ambulatory BP (ABP) values during weekdays and weekends. Inadequate BP treatment due to poor treatment compliance by the patient or improper dosing/titration of the antihypertensive medication by the physician might also influence long-term BPV. BP measurement errors play a major role in VVV BPVs. Lastly, BP levels vary between summer and winter indicating the influence of temperature and daylight hours brought about by seasonal changes.

Data from the Multiethnic Study of Atherosclerosis (MESA) showed that arterial stiffness may also contribute to long-term BPV. Lower arterial elasticity and reduced aortic distensibility were observed in patients with higher VVV BPV.

### Methods of BPV Measurement

The various methods of obtaining BPV measures include continuous beat-to-beat BP recordings, repeated office BP measurement (OBPM), 24-hr ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) over long periods of time.

The key index of short-term BPV is standard deviation (SD) of the 24-hr average ABP values. Since night-time fall in BP might interfere with accurate BPV assessment, it has been proposed that 24-hr SD can be alternatively expressed as the weighted mean of daytime and night-time values. The average SD of BP can also be divided by the corresponding mean BP and multiplied by 100 to express a normalized measure of BPV as a coefficient of variation (CoV). Another BPV index is average real variability or ARV. It denotes the average of the absolute differences between consecutive BP measurements and has been found to be a more reliable prognostic indicator than SD.

Day-to-day BPV can be assessed by ABPM for over 48 hrs which may not be tolerated by all patients. The alternative is use of HBPM which can accumulate data over several days. Availability of day-to-day BPV data might help the physician streamline the hypertensive treatment earlier as compared to VVV BP measurement.

VVV BPV can be assessed by ABPM or OBPM. However, OBPM is an imperfect tool to assess VVV BPV since it might not reflect the BP burden during the patient’s normal activities and requires consistent visits to the physician’s office. Since ABPM cannot be repeated frequently, it can be an inefficient tool to measure VVV BPV. On the other hand, HBPM seems ideally suited for this assessment without the presence of the “white-coat effect” and can be obtained under fairly constant conditions.

Table 1 offers a quick review of the various parameters associated with BPV.

### BPV: A Novel Predictor of TOD and CV Events Across Patient Subgroups

The prognostic importance of both short and long-term BPV as outlined in some key studies are discussed below.

#### Short-term BPV

Mancia G et al. conducted one of earliest studies where the relationship between 24-hr BPV and BP mean was assessed by intra-arterial BP measurement over 24 hours. Results showed that BPV (SD of the 24 hours, day and night mean BPs) increased in patients with hypertension compared to normotensive individuals. The degree of BPV was generally linked to the mean BP values. It follows that reduction of mean BP by antihypertensive medications also results in BPV reduction.

Several studies have established the impact of short-term BPV on TOD and CV events in hypertensive patients. Parati G et al. studied 108 hospitalized subjects with mild-severe hypertension and found that lower 24-hr BPV was associated with significantly lower prevalence and severity of TOD compared
Table 1: Types of BPV: Methods of measurement, prognostic relevance, and proposed mechanisms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Very short-term BPV (beat-by-beat)</th>
<th>Short-term BPV (within 24-hr)</th>
<th>Long-term BPV (day-by-day)</th>
<th>Long-term BPV (VVV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP measurement method</td>
<td>Continuous BP recordings in a laboratory setting or under ambulatory conditions</td>
<td>ABPM</td>
<td>ABPM over ≥ 48 h</td>
<td>ABPM</td>
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<td></td>
<td></td>
<td></td>
<td>HBPM</td>
<td>OBPM</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>HBPM</td>
</tr>
<tr>
<td>Time intervals</td>
<td>Beat-to-beat over variable recording periods (1 min to 24 h)</td>
<td>Every 15–20 min over 24 h</td>
<td>Day-by-day, over several days, weeks or months</td>
<td>Spaced by visit over weeks, months and years</td>
</tr>
<tr>
<td>Pros</td>
<td>Assessment of indices of autonomic CV regulation</td>
<td>24-hr BP profile recorded effectively alongwith detection of circadian rhythms of BPV</td>
<td>Ideal for long-term monitoring</td>
<td>Ideal for long-term monitoring</td>
</tr>
<tr>
<td>Cons†</td>
<td>Stability of measurements might not be guaranteed outside controlled environment</td>
<td>Repetition difficult</td>
<td>HBPM: patient training and involvement required</td>
<td>OBPM and HBPM: data on BP profiles not extensive</td>
</tr>
<tr>
<td>Indices of BPV SD</td>
<td>Indices of autonomic modulation can be calculated (via spectral analysis)</td>
<td>24 h, daytime, and night-time SD and CoV</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 h weighted SD</td>
<td>CoV</td>
<td>CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day-to-night BP changes</td>
<td>†Subclinical organ damage‡</td>
<td>†Subclinical organ damage‡</td>
</tr>
<tr>
<td>Proposed</td>
<td>Enhanced central sympathetic drive</td>
<td>Enhanced central sympathetic drive</td>
<td>Diminished arterial compliance</td>
<td>Inappropriate dosing/titration of AHT</td>
</tr>
<tr>
<td>mechanisms</td>
<td>Decreased arterial/ cardiopulmonary reflex</td>
<td>Decreased arterial/ cardiopulmonary reflex</td>
<td>Inappropriate AHT dosing/ titration</td>
<td>Decreased AHT adherence</td>
</tr>
<tr>
<td></td>
<td>Humoral and rheological factors</td>
<td>Humoral and rheological factors Behavioural and emotional factors Activity/sleep Ventilation</td>
<td>Decreased AHT adherence BP measurement errors</td>
<td>BP measurement errors</td>
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<td></td>
<td>Behavioural/ emotional factors Activity/sleep Ventilation</td>
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</tr>
<tr>
<td>Prognostic</td>
<td>Subclinical organ damage† Cardiovascular events and mortality? Cardiovascular events and mortality</td>
<td>Subclinical organ damage† Cardiovascular events and mortality</td>
<td>↑ Subclinical organ damage†</td>
<td>↑ Subclinical organ damage†</td>
</tr>
<tr>
<td>relevance for cardiac and renal outcomes</td>
<td>All-cause mortality Progression of microalbuminuria, proteinuria ®eGFR, progression to ESRD</td>
<td>↑ All-cause mortality</td>
<td>↑ Microalbuminuria</td>
<td>↑ Microalbuminuria and proteinuria</td>
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<tr>
<td></td>
<td></td>
<td>↓eGFR</td>
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</tbody>
</table>

*Adapted from Parati et al†
†Stability of measurements might not be guaranteed outside the laboratory setting; Cannot be repeated frequently; Patient training and involvement is required for HBPM; ABPM over 48 h is neither always well tolerated or accepted by patients; OBPM and HBPM provide limited information on BP profiles

Abbreviations: VVV, visit-to-visit variability; ABPM, ambulatory blood pressure monitoring; AHT, antihypertensive treatment; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; CoV, coefficient of variation; HBPM, home blood pressure monitoring; OBPM, office blood pressure measurement, ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate. ‡cardiac, vascular, and renal subclinical organ damage; ?BPV on a beat-to-beat basis has not been routinely measured in population studies.

to those with higher 24-hr BPV (p<0.05). Cardiac structural and vascular alterations have also been attributed to 24-hr BPV, making it an independent predictor for CV events. A study conducted on 73 hypertensive patients followed up for an average of 7.4 yrs showed that the severity of TOD, especially increase in left ventricular mass index, was related to baseline 24-hr BPV. CV complications of hypertension may thus depend on the degree of 24-hr BPV.15

In a study by Sander D et al16 the progression of carotid intima-media thickness (IMT), a marker for atherosclerosis, was significantly greater in the patients with increased SBPV during 3.3 yrs of follow-up. Kaplan-Meier survival analysis (Figure 2) showed a significantly higher rate of CV morbidity events with increased BPV. Consequently, the relative risk of CV events was also significantly increased in these patients, even after adjusting for other risk factors.

The Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) Study evaluated the
ability of 24-hr BPV to predict long-term risk of death over a period of 12 yrs. Results showed that CV mortality was inversely correlated to the day/night BP difference. Conversely, higher residual BP variability [day and night erratic DBP changes detected by eliminating the cyclic components (nocturnal and postprandial BP falls) assessed via Fournier spectral analysis] resulted in higher risk for fatal CV events. This study reaffirmed that BPV, especially erratic BPV, has prognostic value in hypertension over and above that of mean BP values.17

Diurnal changes in BP have also been shown to be predictors of CV risk in hypertensive patients with/without CV disease at baseline. A meta-analysis conducted on the significance of the night-time ABP in 3468 hypertensive patients without history of major CV disease showed that reverse dippers were at higher risk for CV disease than dippers. Also, all-cause mortality was found to be lower in extreme dippers than in dippers, independent of mean 24-hr BP values and other variables. In another analysis conducted amongst 302 patients with CV disease at baseline, significantly increased all-cause mortality and incidence of CV events was observed in reverse dippers compared to dippers, both before and after adjustment for 24-hr BP values.8

Long-term BPV

The prognostic value of variability in day-by-day HBPM was assessed by Kikuya M et al18 amongst 2455 residents of Ohasama, Japan. Over a follow-up period of 12 yrs, day-to-day BP and heart rate (HR) variability (measured as within-subject SDs of home measurements) were predictors of CV mortality, after adjusting for several risk factors. SDs of SBP and HR were significantly and independently linked to CV mortality. Specifically, SD of SBP foretold risk of stroke and cerebral infarction.

In the Finn-Home study, Johansson JK et al19 evaluated the prognostic value of BPV via HBPM and HR measured for 7 consecutive days in a sample of 1866 Finnish adults. After a follow-up of 7.8 yrs, higher variability of morning-evening and morning day-by-day home BP, and corresponding HR values predicted CV events after adjusting for several relevant risk factors.

Results from the Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm (ASCOT-BPLA) trial also showed that patients with good control of mean BP but greater residual SBPV had a 5 times higher risk of stroke than those with lower variability values, establishing VVV BPV as a key predictor of the long-term risk of stroke after TIA.20

Data from The National Health and Nutrition Examination Survey (NHANES) III conducted on 956 subjects demonstrated that SD of VVV SBPV >4.80 mmHg was associated with a 57% increase in overall mortality.21 Another meta-analysis involving 77,299 patients over 6.3 yrs showed that VVV SBPV can predict all-cause and CV mortality and stroke, independent of age and mean SBP.22

The impact of long-term BPV on mortality risk was assessed in a study by Hastie CE et al23 amongst 522 hypertensive patients followed-up for four periods of time after the first visit: year 1, years 2 to 5, years 5 to 10 and years >10. Results showed that both SBPV and DBPV for the 1 to 4 yrs and 5-9 yrs time frame were predictive of mortality irrespective of the mean BP values. Moreover, this association held true for all-cause, CV and non-CV mortality.

Data from 58,228 postmenopausal women involved in the Women’s Health Initiative followed up for 5.4 yrs showed higher annual VVV SBPV was correlated with an increased stroke risk after adjusting for several factors.24

In a study conducted on 2161 type 2 diabetes patients over 5.5 yrs, VVV BPV significantly predicted all-cause mortality, irrespective of mean BP values.25 Ushigome E et al26 evaluated the correlation between day-by-day variability in HBP on 14 consecutive days and macroalbuminuria in 858 Japanese patients with type 2 diabetes. They
found that CoVs of morning and evening SBP were significantly higher in macroalbuminuric patients compared to those without macroalbuminuria. After adjusting for several factors, further analyses showed that CoVs of morning SBP and DBP as well as those of evening SBP were independently linked with the logarithm of urinary albumin excretion (UAE). CoV of HBP was thus a novel factor correlated with macroalbuminuria, after accounting for known risk factors in patients with type 2 diabetes.

Patients on hemodialysis with left ventricular hypertrophy formed the treatment population in The Fosinopril in Dialysis (FOSIDIAL) Study which evaluated the safety and efficacy of long-term fosinopril treatment versus placebo on CV clinical outcomes. Further analysis of data on 388 FOSIDIAL patients showed that VVV SBP and DBP was strongly predictive of CV events in this group. In fact, event-free survival was lowest in the patients with highest CoV-SBP (co-efficient of variation of SBP) (Figure 3).27

An analysis of chronic kidney disease (CKD) subjects from the African American Study of Kidney Disease (AASK) trial showed that VVV SBP was associated with increased overall and CV mortality.28

**BPV Management: Protection Offered by Antihypertensive Drugs**

Since both short-term and long-term BPV contribute to TOD and CV events in patients with hypertension or diabetes, appropriate antihypertensive treatment which reduces this variability, in addition to reducing mean BP, might prove to be a beneficial target for CV prevention. Recent data suggests that there is inter-drug variation in efficacy with calcium channel blockers (CCBs) such as Amlodipine proving superior to other drugs in reducing BPV.29

A *post hoc* analysis of the ASCOT-BPLA and the Medical Research Council (MRC) trial was conducted to study the differential impact of β-blockers and CCBs on BPV and stroke risk. ASCOT-BPLA compared Atenolol-based regimens with Amlodipine-based regimens in 19,257 patients with hypertension and other vascular risk factors, while the MRC trial compared Atenolol-based and diuretic-based regimens versus placebo in 4396 hypertensive patients.20

In ASCOT-BPLA, within-visit, VVV and ABPM BPV were all reduced by Amlodipine-based treatment, irrespective of its effect on mean BP, whereas BPV increased with Atenolol-based regimen. The reduced event rates with Amlodipine-based regimen was explained by its beneficial effect on VVV BPV. In the MRC trial, SBPV was increased in the Atenolol group compared to placebo as well as diuretic group and stroke risk was allied with the effect on BPV. Optimal prevention of stroke would thus occur with a drug which effectively reduces mean BP without increasing BPV, ideally reducing both.

A meta-analysis of 389 trials showed that there were differential effects of antihypertensive drugs on BPV. CCBs and non-loop diuretic drugs reduced inter-individual SBPV, whereas angiotensin converting enzyme inhibitors (ACEIs), angiotensin-2-receptor blockers (ARBs) and β blockers increased it, with CCBs showing maximal effect vs placebo (Figure 4). This aspect might be the key reason for the differences in effects of antihypertensive drugs on stroke risk.30 Addition of CCBs to other antihypertensive agents significantly reduced VVV BPV; however the reverse was not true.4

The influence of antihypertensive...
treatment with Candesartan, Indapamide sustained release or Amlodipine on SD of 24-hour ABPM in 577 patients was assessed in the Indapamide versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study. After 3 months, Amlodipine significantly decreased daytime, night-time and 24-hrs SBPV; whereas Indapamide SR significantly decreased SBPV in the daytime and 24 hours. Conversely, Candesartan did not reduce SBPV significantly in any time frame (Figure 5). Even after adjustment for mean BP, only Indapamide was efficacious across all time-frames.4,31

A secondary analysis of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) calculated effect of Amlodipine, Chlorthalidone and Lisinopril on VVV BPV across a period of 6-28 months. Results showed that even after adjusting for mean BP, Amlodipine and Chlorthalidone reduced VVV BPV to a greater extent than Lisinopril.32

Combination of antihypertensive drugs have also proven effective in reducing BPV. In a study by Hoshino A et al on 31 hypertensive patients, the combination of Amlodipine and Olmesartan given at bedtime reduced the morning BP surge effectively, corrected the nocturnal BP fall and improved UAE.33

In another study by Levi-Marpillat N et al4 the efficacy of mono and combination therapy on short-term BPV was assessed on 2780 hypertensive patients. CCBs, followed by diuretics, were correlated with lower short-term BPV compared to ARBs, ACEIs and β-blockers. Also, the combination of CCBs and diuretics resulted in lowest short-term BPV compared to other combinations.

**Conclusion**

The impact of BPV on TOD and CV events across hypertensive, diabetic and kidney disease patients is well-established. Recent data suggests that some antihypertensive drugs are capable of reducing BPV in addition to their efficacy in reducing mean BP values. Amongst the available antihypertensive agents, CCBs such as Amlodipine, have been found to be most effective in reducing BPV, either as monotherapy or in combination with other molecules. Use of Amlodipine and its combinations to attenuate BPV might be a step in the right direction to prevent CV morbidity and mortality.

**References**


