Heart Rate Variability, Blood Pressure Variability: What Is Their Significance in Hypertension

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Uday M. Jadhav and Shilpa A. Kadam

10.1 Introduction

Heart rate variability (HRV) represents changes in the RR interval and instantaneous heart rate (HR). The interval between successive beats is analysed. HRV is recognised as an important marker of autonomic activity imbalance, and indicates reduced vagal activity and increased sympathetic activity [1, 2]. Reduced HRV has been shown to be a marker of increased risk after acute myocardial infarction (AMI), and can provide an early indication of diabetic neuropathy [3].

Blood pressure variability (BPV) is also being increasingly recognised as an independent risk factor for target organ damage and cardiovascular events. Variations in BP can occur over the very short term (beat-to-beat), short term (over 24 h) or long term (between visits or seasons). There is increasing evidence showing that both short-term and long-term BPV correlate with target organ damage (TOD) and CV events in patients with hypertension [4]. Increase BPV is also associated with increased microvascular complications in diabetes mellitus (DM) and progression of renal failure in patients with chronic kidney disease (CKD) [5].

10.2 Heart Rate Variability

HRV is a non-invasive clinical tool that can help to detect cardiac autonomic dysregulation in hypertension. HRV is generally assessed by 2-min and 6-min beat-to-beat heart rate recordings [1, 6, 7]. Common HRV measures are summarised in Table 10.1.

U. M. Jadhav (✉) · S. A. Kadam
Cardiology Department, MGM New Bombay Hospital, New Mumbai, India

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Table 10.1 Commonly used measures of heart rate variability

Variable, units	Description
Statistical measures	
SDNN, ms	SD of all NN intervals
SDANN, ms	SD of the averages of NN intervals in all 5-min segments of the entire recording
RMSSD, ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
SDNN index, ms	Mean of the SD of all NN intervals for all 5-min segments of the entire recording
SDSD, ms	SD of differences between adjacent NN intervals
Geometric measures	
HRV triangularindex, ms	Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale
Differential index, ms	Difference between the widths of the histogram of differences between adjacent NN intervals measured at selected heights

NN normal to normal, *SD* standard deviation

Some of these measures are described below:

1. Mean normal-to-normal (NN) RR interval length: the RR interval reflects the sum of parasympathetic and sympathetic influences.
2. Standard deviation of NN RR intervals (SDNN): SDNN reflects total variability.
3. Root mean square of successive differences in NN RR intervals (RMSSD): RMSSD reflects high-frequency variations in heart rate and is a marker for the actions of the parasympathetic nervous system.

10.2.1 Reduced HRV: A Risk Factor

The autonomic background of HRV is well recognised. It reflects decreased vagal and increased sympathetic influences on the heart which cause electrical instability. Reduced HRV is a strong predictor of mortality after AMI [8]. Reduced HRV can also predict the development of diabetic neuropathy, especially the autonomic involvement [9]. Reduced HRV has been observed in heart failure, hypertension, mitral valve prolapse and hypertrophic cardiomyopathy [2]. Reduced parasympathetic and increased sympathetic activity has been shown in hypertension [10].

The autonomic nervous system and alteration of its regulation can potentially contribute to the development of hypertension [10]. The temporal sequence of HRV and blood pressure (BP) rise of interest to determine whether decreased HRV can predict incident hypertension or whether hypertension can alter HRV.

In a hypothesis proposed by Julius et al., mild hypertension is characterised by high heart rate and cardiac output, and normal vascular resistance [11, 12]. Over time, HRV of normotensive individuals and patients with persistent hypertension tends to converge. The heart rate will then decrease, cardiac output normalises, and vascular resistance increases. This is due to the combined effect of increased sympathetic activity and decreased parasympathetic activity, and can be labeled as the

"BP-seeking property" of the central nervous system [11–13]. Resistance to antihypertensive therapy may be associated with activation of the neurohormonal system as indicated by reduced SDANN and RMSSD [14, 15].

HRV may precede clinical hypertension, and low values of HRV indices such as SDNN and RMSSD at very low frequency (VLF), low frequency (LF) and high frequency (HF), have been shown to be related to the incidence of hypertension in normotensive subjects (BP <120/80 mmHg) and those with pre-hypertension (BP 120/80–139/89 mmHg) over 4 years of follow-up [16].

Sympathetic overactivity and parasympathetic withdrawal have been proposed in the development of clinical hypertension. Reduced HRV on 24-h Holter monitoring was significantly associated with hypertension, and was more common in patients with uncontrolled versus controlled BP [17].

10.2.2 Some Evidence

10.2.2.1 International Studies

The Framingham study reported an association between logarithmically transformed low-frequency power among men and no association for SDNN and high-frequency power in either sex [14]. The Atherosclerosis Risk in Communities (ARIC) substudy found that the incidence of hypertension was significantly increased in patients with NN RR intervals in the lowest versus highest quartile (hazard ratio 1.24, 95% confidence interval 1.10–1.40) [18]. For these individuals with normal BP at baseline (n = 7099), low heart rate variability predicted greater risk of incident hypertension over 9 years of follow-up. However, the rate of change in HRV over time did not differ between those with versus without hypertension [18]. A study conducted in India that enrolled 30 patients with hypertension and 30 individuals with normal BP showed that SDNN, RMSSD and pNN50 were significantly lower, and the LF-HF ratio was significantly higher those with versus without hypertension [19].

HRV is related to vagal tone in atrial fibrillation (AF), irrespective of hypertension. Individuals with permanent AF have higher HRV than those with paroxysmal AF, probably due to autonomic dysregulation [20]. Interestingly, medications designed to control AF or BP did not improve HRV [20].

Twenty-four-hour recording of SDNN is proposed as the "gold standard" for medical stratification of cardiac risk. SDNN values of <50 ms, 50–100 ms and > 100 ms are classified as unhealthy, compromised health and healthy, respectively [2].

10.2.2.2 Asian Studies

Studies in Asian populations have shown that impaired autonomic nervous function in patients with hypertension is strongly associated with uncontrolled BP [2, 19, 21–24]. The Toon Health Study enrolled 1888 men and women aged 30–79 years, and participants self-monitored BP at home twice in the morning and evening for 1 week [23]. The results showed that the parasympathetic nervous system activity

parameters, low HF and RMSSD, were associated with increased home mean arterial pressure (MAP) in the morning rather than in the evening. These associations were independent of sex, age, body mass index, smoking, alcohol consumption, use of antihypertensive agents, diabetes and physical activity. The study also emphasised that physical inactivity, insomnia and socioeconomic stress factors induce sympathovagal imbalance and higher home BP in the morning.

With respect to antihypertensive drug classes, users of beta-blockers have been shown to have equivalent or higher HRV than non-users, while those using diuretics or angiotensin-converting enzyme inhibitors (ACEIs) had a lower HRV compared with non-users [18], and users of captopril had increased HRV [25].

10.3 Blood Pressure Variability

In patients with hypertension, increased BPV contributes to future cardiovascular events [4, 5]. The white coat effect is one indicator of BPV in clinical practice. Day-to-day BPV, visit-to-visit SBP variability and long-term BPV have been shown to be associated with an increased risk of stroke [4], cardiovascular events and mortality [1]. Short-term BPV can be measured by 24-h ambulatory BP monitoring [5] and long-term BPV can be determined based on visit-to-visit assessments [26]. Unlike morning BPV, evening BPV significantly predicted cardiovascular events independent of the corresponding home BP readings [27]. Lower nocturnal SBP, and non-dipper and reverse dipper patterns of nocturnal hypertension were associated with a higher risk of cerebral small vessel disease [28]. A summary of different BPV measures, how they are assessed and relevant influencing factors are summarised in Table 10.2.

Data from the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE) involving 14,000 hypertensive middle-aged and older subjects reported that there was a 10% increase in the risk of death and a 15% increase in risk of CV events for each 5 mmHg increase in the standard deviation (SD) of visit-to-visit and within-visit systolic BPV, respectively [29].

Rates of fatal and non-fatal cardiovascular events over a >15-year follow-up were significantly higher in the presence of high short-term (24-h) systolic BPV in

Table 10.2 Types of blood pressure variability

Type of BPV	Assessment	Measurement	Influencing factors
Very short term	Beat to beat	Intra-arterial recording with spectral analysis	Baroreceptor and chemoreceptor activity
Short term	Within 24 h	ABPM	↑ sympathetic activity, sleep, activity behavioral factors
Medium term	Day to day	HBPM	Age, increased arterial stiffness, emotional factor
Long term	Visit to visit	Repeat visit to the office	Behavioral change, drug choice and compliance, environmental factor

ABPM ambulatory blood pressure monitoring, *BPV* blood pressure variability, *HBPM* home blood pressure monitoring

1206 young patients with stage 1 hypertension (mean age 33 ± 8 years) [30]. In addition, BPV has been associated with arterial stiffness, left ventricular hypertrophy, decline in renal function, subclinical brain small vessel disease and the risk of developing foot ulcers in diabetes [31–36].

10.3.1 BPV and Antihypertensive Treatment

Short-term BPV is calculated as the standard deviation of 24-h, daytime or nighttime systolic BP and diastolic BP. Different antihypertensive drugs classes may have a differential impact on BPV and this is probably more apparent on visit-to-visit BPV [37]. Short-term BPV is decreased by calcium channel blockers (CCBs), diuretics, and their combination [38]. Angiotensin receptor blockers (ARBs), beta-blockers and ACEIs may increase short-term BPV, as shown in a recent meta-analysis [38]. White coat effect was smaller in patients with hypertension treated mainly with the CCB amlodipine compared to those treated mainly with the beta-blocker atenolol. The addition of a CCB or diuretic to any antihypertensive treatment regimen may reduce BPV to the same extent as seen with monotherapy of these drugs. The addition of an ACEI or ARB agent did not have a similar impact [39, 40]. Amlodipine, which has a long elimination half-life of 34 h, has a positive effect on morning BPV [41].

The mechanism(s) underlying changes in BPV with different antihypertensive drug classes is not completely understood. Changes in peripheral vascular distensibility and differential effects on pulse wave velocity may explain some of the differences, such as the reduction in arterial compliance during treatment with beta-blockers and increased vascular compliance during CCB therapy [42, 43].

10.3.1.1 Circadian BPV

Recently, there has been renewed interest in bedtime chronotherapy after the results of Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC) [44]. In this study, ≥1 antihypertensive drug was given at bedtime to provide better control of nighttime BP. After a median follow-up of 5.6 years, participants who had bedtime antihypertensive dosing had a significantly lower relative risk of cardiovascular event than those who took all their antihypertensive therapy in the morning [44]. However, current guidelines do not recommend evening dosing of antihypertensive and additional studies are needed to determine the validity of this approach [45].

10.3.1.2 Non-circadian BPV

Three months of treatment with amlodipine and indapamide sustained release was associated with greater reductions in daytime, nighttime and 24-h systolic BPV in the X-CELLENT (Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients) study of 577 middle-aged patients with hypertension [46]. Two large analyses involving more than 4000 patients reported lower daytime BPV in those treated with telmisartan/amlodipine

versus telmisartan/hydrochlorothiazide [46–48]. The triple therapy combination of olmesartan plus a dihydropyridine CCB and a thiazide diuretic, and dual combinations of olmesartan plus a dihydropyridine CCB or a dihydropyridine CCB plus a thiazide diuretic were associated with greater decreases in BPV compared with placebo and monotherapies [49].

10.3.1.3 Mid-Term BPV

Greater decreases in day-to-day BPV were seen during treatment with a CCB/ARB combination compared with a diuretic/ARB combination in the Japan Combined Treatment with Olmesartan and a Calcium Channel Blocker Versus Olmesartan and Diuretics Randomized Efficacy Study, despite similar reductions in systolic BP [49].

10.3.1.4 Long-Term BPV

The superiority of CCBs for reducing BPV compared with ARBs, beta-blockers or diuretics was reported in the COLM (Combination of OLMesartan) [50], COPE (Combination Therapy of Hypertension to Prevent Cardiovascular Events) [51] and ASCOT-BPLA studies [52], but not in the ELSA (European Lacidipine Study on Atherosclerosis) trial [53]. Thiazide-like diuretics were shown to be more effective than beta-blockers in reducing long-term BPV in the MRC trial [54].

10.4 Conclusion

Autonomic nervous system dysregulation with reduced vagal effects and increased sympathetic activity plays a potential role in the development of hypertension. Reduced HRV is a marker of this autonomic imbalance and has been shown to be significantly associated with hypertension. Reduced HRV is now recognised as marker of increased mortality in AMI and is a useful marker of development of diabetic neuropathy. As a marker of autonomic imbalance suggesting increased sympathetic activity, it also is increasingly being recognised as an important marker in hypertension, heart failure and mitral valve prolapse.

Increased short- and long-term BPV has been shown to be a marker of increased TOD and cardiovascular risk in patients with hypertension, in addition to mean BP. The white coat effect and early morning rise in BP are markers of this BPV. Increased visit-to-visit BPV is also a marker of complications and TOD in hypertension. Some antihypertensive drugs, especially long-acting CCBs, can reduce BPV.

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