Relation of blood pressure variability to left ventricular function and arterial stiffness in hypertensive patients

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ABSTRACT

Introduction: Variability of blood pressure (BP) has been reported to be related to worse cardiovascular outcomes. We examined the impact of daytime systolic BP variability on left ventricular (LV) function and arterial stiffness in hypertensive patients.

Methods: Ambulatory BP monitoring (ABPM) and echocardiography were performed in 116 hypertensive patients. We assessed BP variability as standard deviations of daytime systolic BP on 24-hour ABPM. Conventional echocardiographic parameters, area strain and 3D diastolic index (3D-DI) using 3D speckle tracking were measured. Arterial stiffness was evaluated by acquiring pulse wave velocity (PWV) and augmentation index.

Results: Patients with higher BP variability showed significantly increased left ventricular mass index and late mitral inflow velocity, as well as decreased E/A (early mitral inflow velocity/late mitral inflow velocity) ratio, area strain and 3D-DI than those with lower BP variability (LVMI: $p = 0.02$; A velocity: $p < 0.001$; E/A ratio: $p < 0.001$; area strain: $p = 0.02$; 3D-DI: $p = 0.04$). In addition, increased BP variability was associated with higher PWV and augmentation index ($p < 0.001$). Even among patients whose BP was well controlled, BP variability was related to LV mass, diastolic dysfunction and arterial stiffness.

Conclusion: Increased BP variability was associated with LV mass, dysfunction and arterial stiffness, suggesting that BP variability may be an important determinant of target organ damage in hypertensive patients.

Keywords: arterial stiffness, blood pressure, echocardiography

INTRODUCTION

Hypertension has been established to be a risk factor for cardiovascular events due to its effects on target organs. Many studies have indicated that blood pressure (BP) is predicative of cardiovascular morbidity and mortality. 24-hour ambulatory BP monitoring (ABPM) has been shown to provide a more representative estimate of BP level than conventional clinic BP and to be more closely related to target organ damage than office BP.[1-5] In addition, for any given 24-hour average BP, target organ damage might be more pronounced in patients with greater BP variability.[6-10] Therefore, in addition to BP itself, fluctuations in BP may also affect prognosis to some extent, as prior studies have reported.[1,2]

Daytime BP has higher levels and more fluctuation compared with nighttime BP. Also, systolic BP variability in the daytime has been reported to be predictive of cardiovascular outcome.[11,12] Hence, we examined if daytime systolic BP variability impacts left ventricular (LV) structure and function as well as arterial stiffness in hypertensive patients.

METHODS

Consecutive hypertensive patients were enrolled from Inha University Hospital, South Korea. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We excluded patients who had atrial fibrillation or significant arrhythmia, LV ejection fraction $< 50\%$, regional wall motion abnormality or significant valvular disease. ABPM, echocardiography and measurements of arterial stiffness were performed, and the relationship among BP variability, echocardiographic parameters and arterial stiffness was assessed.

ABPM results were recorded over 24 hours during the patient's normal daily

activities with an autonomic device (ABD-Monitor 90207; Spacelabs, Snoqualmie, WA, USA) that was programmed to obtain the readings at a 30-minute interval during daytime (defined as between 6 am and 12 am) and at a one-hour interval during nighttime (defined as between 12 am and 6 am). The following readings were omitted due to the potential presence of technical artefacts: systolic BP > 250 mmHg or < 70 mmHg, diastolic BP > 200 mmHg or < 40 mmHg, or pulse pressure > 200 mmHg or < 20 mmHg. BP variability was assessed as standard deviations (SD) of daytime systolic BP (SBP) and diastolic BP (DBP) on the 24-hour ABPM. Nocturnal dipping was defined as a decline in average SBP or DBP at nighttime of more than 10% compared with average daytime BP.[13] Pulse pressure variability was calculated as SD of pulse pressure on the ABPM.

Imaging was performed with a commercially available echocardiographic system (Artida[TM]; Toshiba, Tokyo, Japan). Conventional parameters were measured, including peak early (E) and late (A) mitral inflow velocity, the E/A ratio, deceleration time of early mitral flow velocity (DT) and early mitral annular velocity (Em) at the septal annular site. LV internal dimension (LVID), septal wall thickness (SWT) and posterior wall thickness (PWT) were measured at end-diastole according to American Society of Echocardiography recommendations.[14] LV mass (in grams) was calculated with the following formula and corrected for body surface: LV mass = $0.8 \{1.04 \times [(LVID + PWT + SWT)^3 - (LVID)^3]\} + 0.6$.

LV hypertrophy (LVH) was defined as LV mass index > 95 g/m^2 for women and > 115 g/m^2 for men.[14] Relative wall thickness (RWT) was calculated with the formula (PWT + SWT)/LVID. In addition, three-dimensional (3D) full-volume images were acquired with a volume rate of 20–30 volumes/second, and recently developed 3D speckle tracking was applied to the 3D volume dataset to assess the global area strain (Artida, Toshiba, Tokyo, Japan).[15,16] 3D wall motion-tracking software automatically showed 3D data with apical

two-chamber, four-chamber and three short-axis views at different levels of the LV (base, middle and apex). After adjusting the orientation of two-dimensional planes and tracing LV endocardial and epicardial borders on long-axis images manually, the 3D endocardial contour was reconstructed and tracked in 3D data from frame to frame throughout the cardiac cycle, following which 3D strain data was displayed. Tracking quality was verified for each segment with manual adjustment if needed. 3D diastolic index of area strain (3D-DI) was calculated as percentage change of global area strain during the first one-third of the diastolic period.[17,18] Global area strain and 3D-DI were averaged from 16 LV segments.

Arterial stiffness was evaluated by acquiring pulse wave velocity (PWV) and augmentation index (AIx) with radial artery applanation tonometry (SphygmoCor®, AtCor Medical, New South Wales, Australia). The patients refrained from smoking, heavy meals, drinking alcohol or caffeinated beverages, and antihypertensive medication on the day of examination. A small pencil-sized tonometer was placed on the skin over the carotid and femoral arteries, and steady pulse waveforms were obtained on the sites. Carotid-femoral PWV was determined from measurements of pulse transit time and the distance travelled between two recording sites using cardiac gating to the R wave in electrocardiography. AIx, the difference between early and late pressure peaks divided by pulse pressure, was also calculated with a computer algorithm. AIx was adjusted to a standard heart rate of 75 beats/minute, based on previous studies showing that it was influenced by heart rate.[19]

Summarised data for continuous variables was expressed as mean ± SD, while categorical variables were expressed as number and percentage. We categorised the patients in tertiles according to the SD of the mean of daytime BP or pulse pressure variability and applied a trend test, an extension of the Wilcoxon rank-sum tests, for assessing a systemic increase or decrease across the ordered groups. Multiple regression analysis was used to control for the effects of SBP on the relationship between the measurements and daytime SBP

variability. A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 116 consecutive hypertensive patients were enrolled (age 57 ± 12 years, 56 male, 60 female) and categorised into three tertiles according to daytime SBP variability. Daytime SBP variability was associated with older age (p < 0.001) and female gender (p < 0.02; Table I). The prevalence of diabetes mellitus (p = 0.72) and dyslipidaemia (p = 0.06) was similar among the groups. For medication, the patients with greater BP variability were more likely to take beta blockers than those with less BP variability (p = 0.01).

Table I. Baseline demographic variables according to daytime SBP variability.

Parameter	No. (%)/mean ± standard deviation			p-value
	< 12 (n = 39)	12–15 (n = 39)	≥ 15 (n = 38)	
Age (yr)	51.0 ± 9.3	57.8 ± 12.0	61.1 ± 12.7	< 0.001
Female gender	13 (33)	24 (62)	23 (61)	0.02
Diabetes mellitus	4 (10)	3 (8)	2 (5)	0.72
Dyslipidaemia	8 (21)	17 (44)	16 (42)	0.06
Medication				
Aspirin	7 (18)	5 (13)	7 (18)	0.75
ACE inhibitor/ARB	26 (67)	18 (46)	19 (50)	0.11
Beta blocker	1 (3)	5 (13)	8 (21)	0.01
Calcium channel blocker	21 (54)	25 (64)	15 (39)	0.09
Diuretic	11 (28)	11 (28)	12 (32)	0.95
Statin	4 (10)	4 (10)	5 (13)	0.32

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker

Table II shows blood pressure results and its variability in patients in the three tertiles. SBP was significantly higher in patients who were in the uppermost tertile of daytime SBP variability (p < 0.001), whereas DBP was not significantly different among the groups (p = 0.89). Nocturnal decreases in SBP and DBP were not significant across the three groups.

Table II. Ambulatory blood pressure parameters according to daytime SBP variability.

Parameter	No. (%)/mean ± standard deviation			p-value
	< 12 (n = 39)	**12–15 (n = 39)**	**≥ 15 (n = 38)**	
SBP (mmHg)	129 ± 12	131 ± 10	140 ± 13	< 0.001
DBP (mmHg)	84 ± 7	84 ± 9	85 ± 12	0.89
SBP variability (mmHg)	10.6 ± 2.1	13.8 ± 1.5	19.2 ± 4.1	< 0.001
DBP variability (mmHg)	9.0 ± 1.8	10.1 ± 1.7	12.0 ± 2.7	< 0.001
Dippers				
SBP	17 (44)	15 (38)	23 (61)	0.09
DBP	23 (59)	16 (41)	16 (42)	0.12

DBP: diastolic blood pressure; SBP: systolic blood pressure

Patients with higher daytime SBP variability showed significantly increased LV mass (p = 0.02) and A velocity (p < 0.001), and decreased E/A ratio (p < 0.001), Em (p = 0.02), area strain (p = 0.02) and 3D-DI (p = 0.04) than those with lower BP variability (Table III). In addition, increased BP variability was associated with higher PWV (p < 0.001) and AIx (p < 0.001). Such relationships between BP variability and echocardiographic or arterial stiffness parameters were not apparent for nighttime SBP variability as well as daytime or nighttime DBP variability. Even among 68 patients whose BP was well controlled (< 140/90 mmHg), BP variability was related to LV mass, diastolic dysfunction and arterial stiffness (LV mass: p = 0.03; A velocity: p < 0.001, E/A ratio: p = 0.02; PWV: p = 0.04; AIx: p < 0.001). When adjusted for SBP in the whole cohort, the relationships between variables remained similar (RWT: p = 0.005; A velocity: p < 0.001; E/A ratio: p = 0.01; area strain: p = 0.04; PWV: p = 0.009; AIx: p < 0.001).

Table III. Echocardiographic characteristics and arterial stiffness according to daytime SBP variability.

Parameter	Mean ± standard deviation			p-value
	< 12 (n = 39)	**12–15 (n = 39)**	**≥ 15 (n = 38)**	
Conventional parameter				
LVEDD (mm)	46.4 ± 3.4	46.0 ± 3.5	46.3 ± 4.2	0.40
LVESD (mm)	31.0 ± 2.6	30.2 ± 3.4	30.0 ± 3.5	0.08
LVEF (%)	62.5 ± 4.2	63.1 ± 3.9	62.2 ± 5.2	0.74
LVMI (g/m^2)	93.7 ± 19.6	94.6 ± 16.2	103.6 ± 21.2	0.02
Relative wall thickness	0.41 ± 0.05	0.44 ± 0.05	0.46 ± 0.07	0.05

LA dimension (mm)	37.4 ± 4.0	37.8 ± 4.5	38.4 ± 5.1	0.32
E (cm/s)	66.5 ± 16.5	67.3 ± 12.7	65.1 ± 15.1	0.68
A (cm/s)	66.6 ± 13.7	80.2 ± 17.4	81.4 ± 19.6	< 0.001
E/A	1.03 ± 0.32	0.88 ± 0.27	0.83 ± 0.22	< 0.001
Deceleration time (ms)	248.9 ± 49.8	247.0 ± 53.5	263.5 ± 45.0	0.10
Em (cm/s)	8.3 ± 1.3	7.4 ± 1.9	7.2 ± 1.9	0.02
E/Em	8.6 ± 2.3	9.6 ± 2.6	9.6 ± 2.7	0.24
3D STE				
Area strain (%)	41.8 ± 4.2	40.3 ± 3.8	38.4 ± 4.1	0.02
3D diastolic index (%)	35.1 ± 12.3	27.2 ± 10.8	26.8 ± 12.6	0.04
Arterial stiffness				
Pulse wave velocity (m/s)	8.7 ± 1.1	9.6 ± 2.1	10.3 ± 2.4	< 0.001
Augmentation index (%)	21.1 ± 9.8	28.9 ± 9.7	31.0 ± 5.9	< 0.001

A: late mitral inflow velocity; E: peak early mitral inflow velocity; Em: early mitral annular velocity; LA: left atrium; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; SBP: systolic blood pressure; STE: speckle tracking echocardiography

41 (35%) patients showed the presence of LVH. In patients without LVH, SBP variability was associated with LV diastolic function and arterial stiffness (A velocity: $p = 0.03$; PWV: $p = 0.008$; AIx: $p < 0.001$). On the other hand, SBP variability in patients with LVH had a significant relationship with LV diastolic function but not with arterial stiffness (E velocity: $p = 0.001$; A velocity: $p = 0.02$; E/A ratio: $p < 0.001$; DT: $p < 0.001$; Em: $p = 0.002$). Patients with LVH had higher values of arterial stiffness than those without LVH (PWV: $p = 0.03$; AIx: $p = 0.003$). In addition, patients with higher pulse pressure variability showed increased LV mass, poorer diastolic function and higher arterial stiffness (LV mass: $p = 0.018$; RWT: $p = 0.001$; A velocity: $p < 0.001$; E/A ratio: $p = 0.001$; Em: $p = 0.006$; E/Em: $p = 0.04$; PWV: $p = 0.001$; AIx: $p = 0.01$).

DISCUSSION

Our study showed that older age, female gender and beta-blocker use were associated with higher daytime SBP variability in the hypertensive patients. In addition, daytime SBP variability was related to LV mass, LV diastolic function and arterial stiffness even in the

patients whose BP was well controlled, which might suggest BP variability can be attributable to vascular and myocardial damage. These findings are compatible with prior studies demonstrating that SBP variability was related to subclinical target organ damage.[8,20-23] Additionally, when we assessed pulse pressure variability, it was also associated with LV diastolic function and arterial stiffness.

BP variability increases along with sympathetic activity and can be enhanced in the hypertensive population. It is influenced by central, humoral, reflex and behavioural factors as well as the sympathetic nervous system.[24,25] The central autonomic drive, mediated by the baroreflex mechanism, may contribute to BP variability. In previous studies, BP variability was reported to be inversely correlated with the sensitivity of the baroreceptor-heart rate reflex or BP reflex, as assessed using vasoactive drug technique in hypertensive subjects, suggesting that baroreflex regulation may be a potential determinant of BP variability.[26,27] In animal studies, sinoaortic denervation resulted in markedly increased BP variability.[28] Considering these findings, impaired arterial baroreflex, which is related to increased arterial stiffness, could be partly responsible for BP variability. In our study, PWV and AIx were associated with greater BP variability, while patients with older age and female sex relating to increased arterial stiffness had higher BP variability. Interestingly, in our study, SBP variability was significantly related to LV diastolic function and arterial stiffness in patients without LVH, whereas in those with LVH, the only significant relationship was with LV diastolic function. This might be a result of less statistical power due to the small number of the study population. However, it might also suggest that SBP variability affects arterial stiffness more in patients without LVH. In hypertensive patients who have already developed LVH, SBP variability can still be related to worsened LV diastolic function, but it might affect arterial stiffness less significantly, since their arteries have already stiffened.

We herein utilised newly developed 3D speckle tracking to assess the impact of SBP

variability on subclinical systolic function. Strain has been reported to enable early detection of subtle changes in cardiac function, while 3D speckle tracking was recently developed to overcome the inherent drawbacks of 2D speckle tracking, such as the use of foreshortened images and motion of the speckles in and out of the imaging plane. Area strain, a new parameter based on the 3D speckle tracking method, refers to a percentile change of area in the endocardial layer and represents a combined parameter for longitudinal and circumferential strain.[14,15,18,29,30] Several studies suggested that area strain was more sensitive to the changes of regional deformation and produces more reproducible results than other unidimensional deformation parameters, including longitudinal or circumferential strains.[31-33] It may reduce tracking error through combining two types of directional deformation data and increasing the signal-to-noise ratio. In our data, the patients with higher SBP variability had lower area strain than those with lower SBP variability, suggesting that SBP variability might be related to LV subtle systolic dysfunction. In the group with increased SBP variability, LV was also more hypertrophied and diastolic function, assessed using conventional Doppler echocardiography and 3D speckle tracking, was more impaired. BP variation may cause a traumatic stress on the vessel wall, thus promoting early target organ damage.[34]

In the present study, the patients with higher BP variability more frequently received beta blockers. Even though the number was small, making a causal relationship uncertain, some beta blockers might have a worsening impact on BP variability. Decreasing BP variability may provide additive benefits to BP control in protecting against target organ damage to some extent. Similarly, antihypertensive drugs that reduce SBP variation in addition to average SBP may be more beneficial for hypertensive patients rather than simply lowering average SBP. Further studies are necessary to address the effect of antihypertensive drugs on BP variability and their possible differential impact on prognosis.

In our study, we used daytime SBP variability and not 24-hour BP variability to assess BP variability. 24-hour BP variability can be affected by BP decline between day and night, or dipping, which is reported to have a protective effect on target organ damage.[35,36] To exclude this possible confounding factor, we used daytime SBP variability and not overall 24-hour BP variability in assessing BP variation. In addition, prior studies have reported that daytime SBP variability was predictive of cardiovascular mortality and morbidity even after adjusting risk factors attributable to BP elevation.[11,12]

Our study was limited by the relatively small population size. Also, our BP devices were set to record with a measurement frequency set at 30-minute intervals at daytime and 60 minutes at nighttime. More frequent measurements might be better for more accurate and reliable assessment of BP variability. In addition, since our study is cross-sectional, its findings cannot show a causal relationship between BP variability and LV mass or arterial stiffness. However, prior animal studies revealing cardiac damage and aortic hypertrophy in sinoaortic-denervated rats, an experimental model of high BP variability without hypertension, suggest that BP fluctuations might alter cardiac morphology and arterial stiffness.[37] Wide swings in BP may play a role in the development of endothelial dysfunction and atherosclerosis, thus eventually leading to worse cardiovascular outcomes.[12,38,39]

In conclusion, increased BP variability was associated with LV mass and dysfunction as well as arterial stiffness. This suggests that BP variability was one of the important determinants of cardiac and vascular target organ damage in the hypertensive patients, although we could not determine the causality between BP variability and organ damage because of the study's cross-sectional design.

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