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Visit-to-visit variability in systolic blood pressure: correlated with the changes of arterial stiffness and myocardial perfusion in on-treated hypertensive patients

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Abstract

Background: Visit-to-visit variability in blood pressure (BP) was demonstrated to correlate with cardiovascular events independent of mean BP. The goal of the present study was to investigate the correlation of visit-to-visit BP variability with artery stiffness and myocardial perfusion in on-treated hypertensive patients.

Methods: BP was measured in 271 hypertensive patients at every visit over the course of the antihypertensive treatment, and the standard deviation (SD), coefficient of variation (CV), maximum, and minimum in serial BP were calculated. Non-invasive pulse wave analysis was performed in all patients.

Results: Compared with baseline, carotid-femoral pulse wave velocity (cfPWV), aortic augmentation index (Aix) and Aix adjusted to a "standard heart rate" of 75 beats/min (Aix@HR75) were markedly declined, and sub-endocardial viability ratio (SEVR) was obviously increased in each group (p < 0.001). The changes of cfPWV, SEVR, Aix and Aix@HR75 in patients with lower SD of systolic blood pressure (SBP) were significantly greater than those in patients with higher SD of SBP. And the changes were statistically correlated with both SD and CV of serial SBP during follow-up, even after adjusted for mean SBP and mean diastolic blood pressure (DBP).

Conclusion: Visit-to-visit SBP variability is independently correlated with changes of artery stiffness and myocardial perfusion in on-treated hypertensive patients.

Keywords

Antihypertension, artery stiffness, blood pressure variability, myocardial perfusion, pulse wave velocity

Introduction

Recently, Rothwell and co-workers (1,2) suggested that the incidence of cardiovascular events in on-treated hypertensive patients increases progressively with the increase in visit-to-visit blood pressure (BP) variability obtained during the treatment period. Excessive visit-to-visit systolic blood pressure (SBP) fluctuation is a significant indicator for all-cause mortality, cardiovascular events, deterioration of renal function and proteinuria (3,4), carotid artery atherosclerosis (5), and cognitive impairment (6) independently of mean BP. Moreover, visit-to-visit variability in BP measurements in a real-world setting is well reproducible and consistent within individuals over time, independently of any correlation with average BP (7,8). But, visit-to-visit variability in SBP is usually dismissed as an obstacle to the reliable estimation of usual BP and a limitation of measuring BP in the office setting (8).

Pulse wave analysis measurement, a reliable non-invasive method using applanation tonometry, can provide important information about several arterial stiffness and hemodynamic parameters including pulse wave velocity (PWV), sub-endocardial viability ratio (SEVR) and aortic augmentation index (Aix). The advent of this reliable non-invasive diagnostic method has offered the possibility to make PWV, SEVR and Aix assessment easier and feasible in clinical practice, even in challenging conditions (9).

Increased PWV is strongly associated with atherosclerotic cardiovascular disease and cardiovascular disease-related mortality, independent of other conventional atherosclerotic risk factors in both low- and high-risk non-diabetic population (10–12). Carotid-femoral PWV (cfPWV) is considered a measure of central stiffness and has the most evidence to support its predictive value (11,13). 2013 ESH/ESC Guidelines recommend that cfPWV is the “gold standard” for non-invasive evaluation of regional arterial stiffness (14). Aix, which represents a percentage of the increment of the aortic pulse pressure caused by the reflected wave, provides a measure of systemic arterial stiffness (14). Epidemiological
studies showed that Aix is an independent predictor of all-cause and cardiovascular mortality in patients with end-stage renal disease (15). These findings were confirmed in several populations (16). As Aix in an individual patient is influenced by heart rate, it is adjusted to a “standard heart rate” of 75 beats/min (Aix@HR75) (17).

SEVR, measured by means of applanation tonometry and introduced by Buckberg at the beginning of the 1970s (18), is an index of myocardial workload and perfusion (O2 balance between cardiac blood flow supply and demand) (18,19) calculated through pulse wave analysis (15). Low SEVR has been reported to be associated with decreased coronary flow reserve in patients with healthy coronary arteries or diabetes (20–22).

The major aim of this study was, thus, to investigate the relationship of visit-to-visit variability in SBP with cfPWV, SEVR, aortic Aix and Aix@HR75 in patients with hypertension.

Methods

Study design and patients

This study was conducted as a part of the Chinese Hypertension Intervention Efficacy (CHIEF) study (23,24). Amlodipine was used as basic antihypertensive medication. Two hundred and seventy-nine hypertensive patients aged 50–79 years were initially enrolled from clinics in rural area of Shandong Province, China between May 2008 and October 2012. There were 142 males and 137 females. Hypertension was defined as the clinic SBP ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg on at least three occasions, or there was a previous diagnosis of hypertension with current antihypertensive medication use.

Eligible patients were treated with at least one antihypertensive agent. Follow-up visit was performed at 3-month intervals. Clinic BP measurements were performed at each visit and pulse wave analysis measurement and clinical laboratory measurements were conducted at baseline and end of trial.

Exclusion criteria for patients were secondary hypertension, major cardiovascular event, advanced renal dysfunction, advanced hepatic or renal diseases, malignant tumor, gout, pregnancy, any changes of medication for hypertension during the follow-up period of data collection, difficulty providing informed consent, or any other clinical conditions unsuitable for this trial.

This study confirmed to good clinical practice guidelines and was conducted in compliance with the “Declaration of Helsinki”. The Research Ethics Committee of the Shandong Academy of Medical Sciences approved this study, and written informed consent was obtained from each participant.

Antihypertensive medication adherence

Antihypertensive medication adherence was evaluated using the medication possession ratio (MPR) (25). MPR was calculated as the sum of the days’ supply obtained between the first pharmacy fill and the last fill, with the supply obtained in the last fill excluded, divided by the total number of days in this time period.

Clinic BP measurements and definition of BP variability

Clinic BP was measured by trained research nurses using a validated electronic, oscillometric, fully automatic digital BP monitor (HEM-7071, OMRON, Dalian, China) at baseline and at 3-month intervals thereafter. At each clinic visit, BP measurements were performed at 0700 to 0900 in the same clinical setting. Three consecutive measurements with a 2-min interval were obtained with patient in sitting position, feet on the floor and arm supported at heart level after at least 5 min quiet rest. The mean of the three readings was used as the representative BP value for the visit. Standard deviation (SD), as well as coefficient of variation (CV), maximum and minimum BP were calculated as the visit-to-visit variability in serial BP over consecutive visits. CV = SD/mean BP value × 100%.

Pulse wave analysis

Carotid-femoral PWV (cfPWV) is considered as a measure of central stiffness and has the most evidence to support its predictive value (11,13). 2013 ESH/ESC Guidelines recommend that cfPWV is the “gold standard” for non-invasive evaluation of regional arterial stiffness (15). Measurement was performed using applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) with high-fidelity micromanometer in a quiet, temperature-controlled room (20–25 °C). Patients were required in fasting status, and to rest in a sitting position for at least 10 min before examination. Brachial BP was measured three times at the right brachial artery using an automatic digital BP monitor (HEM-7071, OMRON). The average of the three readings was used to calibrate femoral waveforms. The surface distance between carotid and femoral recording site was measured. Pulse wave analysis was performed at the right femoral artery. Patients were required to relax, in a supine position, and head turned to contra lateral of the being checked after BP value and the distance value were entered the program. Tonometer was placed on the prominent location of carotid artery and femoral artery in order. The clear waveforms were captured, and then computer calculated automatically. All measurements were performed by a single skilled investigator.

For measurements of Aix and SEVR, the radial pulse waveform was generated from at least 20 consecutive radial pressure waveforms, and central aortic pulse wave was derived from the radial pulse wave using applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) with an automated generalized transfer function. The integral system software was used to calculate an Aix, as well as Aix@HR75 and SEVR. All measurements were performed by a single skilled investigator.

Clinical laboratory measurements

Total cholesterol (TCHO), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and fasting plasma glucose (FPG) were measured by routine enzymatic laboratory methods using a Hitachi 7600 automated biochemical analyzer (Hitachi High-Technologies Co., Ltd., Tokyo, Japan).
Statistical analyses

Continuous data were expressed as means ± SDs or median with inter-quartile range (IQR, the range between the 25th and 75th percentile) depending on the normality of data. Categorical data were expressed as numbers (percentages). Patients were classified into three groups, namely, low SD of SBP group (low group), middle SD of SBP group (middle group) and high SD of SBP group (high group) by tertile of SD of SBP during follow-up. Comparisons among groups were assessed by a one-way analysis of variance. If a significant difference was found, Bonferroni procedure with type I error was used to adjust the p value for multiple comparisons. Chi-square test was used to compare categorical variables among groups. The relationship of each clinical variable and BP parameters with changes of cfPWV, SEVR, Aix and Aix@HR75 as continuous variables was determined using Pearson’s correlation coefficients. Subsequently, factors deemed significant in Pearson were inserted separately into a multivariate regression model. Variables known to impact vascular function, such as age, gender, body mass index (BMI), TCHO, TG, HDL-c, LDL-c, FPG and treatment agent were also inserted into the model. If BP variability parameters entered into the model, the model will be adjusted for mean BP. Change rate was calculated as follows: (value of measures at end of treatment period – value of measures at baseline)/ value of measures at baseline. Values of p < 0.05 were considered statistically significant. Statistical analysis was performed using the SPSS for Windows software package, version 17.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics

Of the 279 eligible patients recruited, eight patients were excluded from this study due to death, withdrew or failed to complete the study. Finally, 271 patients met the criteria and were used for further analysis. There were 139 males and 132 females, and mean age was 54.04 ± 7.10 years. Figure 1 shows the process for the recruitment of study patients. The mean number of visits was 16 during the follow-up. Table 1 summarizes the detail of demographic, baseline clinical characteristics and treatment variables in three groups classified by tertile of SD of SBP. There were no differences in these variables among three groups (all p > 0.05).

![Figure 1. The process for the recruitment of study patients.](image)

Changes of cfPWV, SEVR, Aix and Aix@HR75 in three groups classified by tertile of SD of SBP

Figure 2 summarizes the change rate of cfPWV (Figure 2A), SEVR (Figure 2B), Aix (Figure 2C) and Aix@HR75 (Figure 2D) in three groups. Compared with baseline, cfPWV, Aix and Aix@HR75 were markedly declined, and SEVR was obviously increased in each group (p < 0.05). The declined rates of cfPWV, Aix, Aix@HR75 and increased rate of SEVR in lower SD of SBP groups were statistically greater than in higher SD of SBP groups and there were significant differences between any two groups (p < 0.05).

Correlations of visit-to-visit BP variability parameters with change rate of cfPWV, SEVR, Aix and Aix@HR75 in overall

We assessed possible correlations between visit-to-visit BP variability parameters with cfPWV, SEVR, Aix and Aix@HR75. The correlation coefficients are shown in Table 2. Change rate of cfPWV positively related to SD of SBP, CV of SBP, maximum SBP and mean SBP (p < 0.001). Change rate of SEVR was negatively correlated with SD of SBP, CV of SBP, maximum SBP, mean SBP, SD of DBP, CV of DBP, maximum DBP and mean DBP (p < 0.05). Both change rate of Aix and Aix@HR75 positively related to SD of SBP, CV of SBP, maximum SBP, mean SBP, SD of DBP, CV of DBP and mean DBP (p < 0.05), meanwhile, negatively correlated with minimum DBP (p < 0.05).

Multiple regression analysis

Multiple linear regression analysis was used to determine the potentially independent factors correlated with changes of cfPWV, SEVR, Aix and Aix@HR75 in this study (shows in Table 3). Baseline characteristics, such as age, gender, BMI, baseline SBP and DBP, TCHO, TG, HDL-c, LDL-c, FPG, treatment agent, MPR, mean SBP and mean DBP were adjusted in each model. For change rate of cfPWV, there were statistically significant results for SD and CV of SBP, baseline SBP, smoking and maximum SBP. For change rate of SEVR, there were significant results for SD and CV of SBP, smoking and HDL-c. For change rate of Aix, there were significant results for SD and CV of SBP and baseline SBP. For change rate of Aix@HR75, there were significant results for SD and CV of SBP and maximum SBP. However, most importantly, SD and CV of SBP were always statistically correlated with changes of cfPWV, SEVR, Aix and Aix@HR75.

Discussion

This is the first study to assess the relationship of visit-to-visit variability in SBP with parameters of pulse wave analysis, especially myocardial workload and perfusion in patients with on-treated hypertension. Our study demonstrated that cfPWV, Aix and Aix@HR75 were significantly declined, and SEVR was significantly increased during the antihypertensive treatment in three groups by tertile of SD of serial visit-to-visit SBP. Changes of cfPWV, SEVR, Aix and Aix@HR75 patients with lower SD of SBP were significantly greater than those in patients with higher SD of SBP. And the changes were statistically correlated with both SD and CV of serial SBP.
during follow-up, even after adjusted for mean SBP and mean DBP.

Several recent studies have demonstrated that visit-to-visit variability in BP, commonly defined as SD or CV of SBP, correlated strongly with target organ damage (TOD), and other cardiovascular events independent of mean BP in patients with hypertension and with on-treated hypertension (1–6,26,27). Okada et al. (28) demonstrated that visit-to-visit CV of SBP independently correlated with PWV ($\beta = 0.337$, $p < 0.0001$) in patients with type 2 diabetes. Nagai et al. (5) reported that CV and delta of SBP, based on 12 visits once a month, were associated with carotid artery stiffness index $\beta$ independently of mean SBP in the elderly at high risk of cardiovascular disease. In our study, in agreement with

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Table 1. Demographic and clinical characteristics in three groups classified by standard deviation of serially systolic blood pressure during follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low group ($n = 90$)</th>
<th>Middle group ($n = 94$)</th>
<th>High group ($n = 87$)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, (Female, %)$^a$</td>
<td>43 (47.78)</td>
<td>47 (50.00)</td>
<td>42 (48.28)</td>
<td>0.951</td>
</tr>
<tr>
<td>Age (year)$^a$</td>
<td>54.41 ± 7.59</td>
<td>53.78 ± 6.64</td>
<td>55.08 ± 6.99</td>
<td>0.468</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)$^b$</td>
<td>25.90 (23.81, 27.72)</td>
<td>25.59 (24.05, 28.19)</td>
<td>25.45 (23.93, 28.04)</td>
<td>0.978</td>
</tr>
<tr>
<td>Smoker, n (%)$^a$</td>
<td>11 (12.22)</td>
<td>13 (13.83)</td>
<td>11 (12.64)</td>
<td>0.945</td>
</tr>
<tr>
<td>SBP (mm Hg)$^c$</td>
<td>153.46 ± 11.66</td>
<td>154.24 ± 13.03</td>
<td>154.34 ± 13.78</td>
<td>0.881</td>
</tr>
<tr>
<td>DBP (mm Hg)$^c$</td>
<td>87.58 ± 10.45</td>
<td>88.93 ± 9.73</td>
<td>87.76 ± 7.19</td>
<td>0.562</td>
</tr>
<tr>
<td>Heart rate (beats/min)$^c$</td>
<td>76.31 ± 9.86</td>
<td>74.17 ± 8.53</td>
<td>75.37 ± 10.04</td>
<td>0.309</td>
</tr>
<tr>
<td>TCHO (mmol/L)$^c$</td>
<td>5.42 ± 0.89</td>
<td>5.68 ± 1.10</td>
<td>5.49 ± 1.04</td>
<td>0.199</td>
</tr>
<tr>
<td>TG (mmol/L)$^b$</td>
<td>1.60 (1.20, 2.28)</td>
<td>1.50 (1.20, 2.05)</td>
<td>1.60 (0.93, 2.10)</td>
<td>0.589</td>
</tr>
<tr>
<td>HDL-c (mmol/L)$^b$</td>
<td>1.30 (1.03, 1.50)</td>
<td>1.30 (1.20, 1.55)</td>
<td>1.20 (1.10, 1.40)</td>
<td>0.165</td>
</tr>
<tr>
<td>LDL-c (mmol/L)$^c$</td>
<td>3.11 ± 0.80</td>
<td>3.17 ± 0.93</td>
<td>3.06 ± 0.67</td>
<td>0.659</td>
</tr>
<tr>
<td>FPG (mmol/L)$^b$</td>
<td>5.75 (5.40, 6.48)</td>
<td>5.80 (5.40, 6.15)</td>
<td>6.10 (5.53, 7.25)</td>
<td>0.150</td>
</tr>
<tr>
<td>Hydrochlorothiazide n (%)$^a$</td>
<td>41 (45.56)</td>
<td>48 (51.06)</td>
<td>41 (47.13)</td>
<td>0.826</td>
</tr>
<tr>
<td>BB, n (%)$^c$</td>
<td>12 (13.33)</td>
<td>13 (13.83)</td>
<td>12 (13.79)</td>
<td>0.994</td>
</tr>
<tr>
<td>ARB, n (%)$^a$</td>
<td>49 (54.44)</td>
<td>46 (48.94)</td>
<td>46 (52.87)</td>
<td>0.826</td>
</tr>
<tr>
<td>Statin, n (%)$^a$</td>
<td>20 (22.22)</td>
<td>20 (21.28)</td>
<td>19 (21.84)</td>
<td>0.988</td>
</tr>
<tr>
<td>MPR (%)$^b$</td>
<td>96.00 (95.00, 97.65)</td>
<td>96.72 (94.50, 98.00)</td>
<td>96.33 (94.70, 97.58)</td>
<td>0.859</td>
</tr>
<tr>
<td>cfPWV (m/s)$^c$</td>
<td>12.41 ± 1.97</td>
<td>12.36 ± 1.69</td>
<td>12.59 ± 1.95</td>
<td>0.689</td>
</tr>
<tr>
<td>SEVR (%)$^c$</td>
<td>140.36 ± 22.36</td>
<td>139.98 ± 21.61</td>
<td>138.43 ± 23.76</td>
<td>0.834</td>
</tr>
<tr>
<td>Aix (%)$^c$</td>
<td>27.28 ± 17.28</td>
<td>29.30 ± 11.22</td>
<td>28.75 ± 13.29</td>
<td>0.608</td>
</tr>
<tr>
<td>Aix@HR75 (%)$^c$</td>
<td>25.19 ± 15.81</td>
<td>27.63 ± 10.32</td>
<td>25.80 ± 11.94</td>
<td>0.409</td>
</tr>
</tbody>
</table>

Results are mean ± standard deviation or medians (25th, 75th percentiles). Abbreviation: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation; max, maximum; min, minimum. TCHO, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BB, β-adrenoceptor blockers; ARB, angiotensin receptor blocker; MPR, medication possession ratio; cfPWV, carotid-femoral pulse wave velocity; SEVR, sub-endocardial viability ratio; Aix, augmentation index; Aix@HR75, augmentation index adjusted for heart rate of 75 beats/min.

$^a$Chi-square test; $^b$Kruskal–Wallis tests; $^c$one way analysis of variance.

Figure 2. Change rate of cfPWV, SEVR, Aix and Aix@HR75 during the on-treatment period in three groups by tertile of SD of systolic blood pressure. Results are medians (horizontal bars in boxes) and 25th and 75th percentiles (lower and upper error bars, respectively). cfPWV, carotid-femoral pulse wave velocity; SEVR, sub-endocardial viability ratio; Aix, augmentation index; Aix@HR75, augmentation index adjusted for heart rate of 75 beats/min. *$p < 0.05$ compared to baseline, $\ddagger p < 0.05$ compared to low group, $\ddagger \ddagger p < 0.05$ compared to middle group.
previous studies, multiple regression analysis revealed that both SD and CV of SBP independently related to changes of cfPWV, Aix and Aix@HR75, even after adjustment for mean SBP, mean DBP and other clinical variables. However, results of European Lacidipine Study on Atherosclerosis (ELSA) (29) showed that CV or SD of SBP was not associated with carotid atherosclerosis. Some investigators deemed that the results may be due to the short duration of trial, predominantly disease-free participants and less cardiovascular outcomes (30,31). In our opinion, there exists a vicious circle between excessive variability of BP and arterial stiffness. Arterial stiffness will increase BPV, on the contrary, excessive BPV will enhance the progression of arterial stiffness.

SEVR is a validated method to determine myocardial workload, oxygen consumption of the sub-endocardial myocardium (19,20). Studies (20,32) reported that a lower SEVR is associated with a reduction in coronary flow reserve independently from other clinical and echocardiographic variables assessed during cardiac catheterization. Indeed, the marked reduction in SEVR has been shown to accelerate coronary artery disease progression, render atherosclerotic plaque more vulnerable, and be related to the occurrence of myocardial ischemia in coronary patients (33,34) and asymptomatic ventricular arrhythmias in subjects without subclinical coronary artery disease (9). However, there were no studies related to associations of visit-to-visit variability in BP with SEVR. In our study, we found that SD and CV of SBP were independently associated with the change of SEVR, even after adjustment for mean BP value and other traditional cardiovascular risk factors.

Okada et al. (28) suggested that the adverse effects of increased BP variability possibly relate to a greater traumatic effect of wider BP swings on vessel wall, promoting early target organ damage. Excessive visit-to-visit BP variability,
independently of mean BP level, diminishes baroreflex function, enhances neointimal formation, increases stiffness and decreases compliance of the large elastic arteries, and may thereby contribute to atherogenesis and myocardial ischemia (5,35).

There were several limitations to our study. First, our sample size was small. Second, this study was based on a cross-sectional design. Third, results in this study may not be applicable to general population, other ethnic groups or patients without antihypertensive treatment because patients were only selected from on-treated hypertensive patients in Chinese population. In addition, lifestyle was not included in the study. It may be one of confounders in influencing vascular function. Finally, eight patients exclusion from the analyses might have introduced a bias in this study.

In conclusion, our study demonstrated that visit-to-visit SBP variability is independently correlated with changes of artery stiffness and myocardial perfusion in patients with on-treated hypertension. However, further and large prospective trials are necessarily needed.

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Declaration of interest

The authors have no financial conflicts of interest.

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