Day-by-day variability in self-measured blood pressure at home: effects on carotid artery atherosclerosis, brachial flow-mediated dilation, and endothelin-1 in normotensive and mild–moderate hypertensive individuals

Zhendong Liu, Yingxin Zhao, Fanghong Lu, Hua Zhang and Yutao Diao

Objective **To investigate variability in self-measured home blood pressure (HBP) and its effects on carotid artery atherosclerosis and endothelial function in normotensive and mild–moderate hypertensive individuals.**

Materials and methods **This is a cross-sectional study. HBP monitoring over 7 consecutive days, carotid artery ultrasound, and brachial artery flow-mediated dilation (FMD) were performed in 314 normotensive, prehypertensive, and mild–moderate hypertensive volunteers. Variability in HBP was assessed by the SDs of the daily BP average of the last 6 consecutive days. The plasma endothelin-1 (ET-1) level was tested using an enzyme-linked immunosorbent assay.**

Results **The tendency of SD of systolic HBP increased significantly from the normotension to the moderate hypertension group. SD of systolic HBP was significantly correlated with carotid intima-media thickness (IMT) ($r=0.569$, $P<0.001$), stiffness parameter β ($r=0.447$, $P<0.001$), FMD ($r=-0.636$, $P<0.001$), and ET-1 ($r=0.649$, $P<0.001$). SD of diastolic HBP was also correlated with carotid IMT, stiffness parameter β, FMD, and ET-1, but the strength of the correlation was weaker than SD of systolic HBP (All $P<0.001$). After adjustment of all covariants, SD of systolic HBP was always significantly associated with carotid IMT, stiffness parameter β, FMD, and ET-1.**

Conclusion **Day-by-day variability in HBP increased with increasing BP level. This was significantly associated with carotid artery atherosclerosis and endothelial function in normotensive and mild–moderate hypertensive individuals. Day-by-day variability in HBP may serve as an important prognostic factor for atherosclerosis and endothelial dysfunction.** ***Blood Press Monit*** **00:000–000**
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Blood Pressure Monitoring 2013, **00**:000–000

Keywords: atherosclerosis, blood pressure variability, endothelial function, home blood pressure monitoring

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Received 25 April 2013 **Revised** 26 July 2013 **Accepted** 11 September 2013

Introduction

Recently, increasing attention has been paid to the clinical relevance of blood pressure variability (BPV) [1]. Evidences [2] have shown that higher BPV was closely associated with advanced arterial stiffness or target-organ damage (TOD), even after controlling for the mean BP level. Studies [3,4] reported that short-term BPV, assessed within 24 h, and long-term BPV, assessed within visit-to-visit BPV in a clinical setting, were associated significantly with TOD and independent determinants of cardiovascular events. However, there are some shortcomings of these approaches that limit their applicability in the daily management of hypertensive patients. 24-h ambulatory blood pressure monitoring (ABPM) is expensive, there is limited availability in most medical communities, and physicians may not be familiar with interpretation of ABPM data. For visit-to-visit BP monitoring, several office visits are required over a period of time and it is difficult to obtain BP data under a stable antihypertensive treatment regimen over a consistent number of visits. One possible way to resolve these problems is to evaluate day-by-day home blood pressure variability (HBPV). Self-monitoring of BP by patients at home [home blood pressure monitoring (HBPM)] avoids both observer and regression dilution biases. It also eliminates white-coat and masked hypertension phenomena [5,6], provides multiple measurements of BP over a much longer period [7], and more accurately reflects an individual's BP [8]. In addition, HBPM provides information on day-by-day BPV under relatively well-controlled conditions [9]. It was reported that increased day-by-day BPV, calculated as the SD of home blood pressure (HBP), was associated with the severity of TOD and cardiovascular outcomes [5,10]. However, to the best of our knowledge, beyond the mean HBP level, the associations between day-by-day HBPV and atherosclerosis and endothelial function have not been explored in much detail.

Carotid intima-media thickness (IMT) has been used for the detection of subclinical atherosclerosis and applied for the noninvasive assessment of future cardiovascular risks. A few previous studies [11,12] have reported that increased carotid IMT is markedly correlated with

1359-5237 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MBC.0000000000000001

numerous risk factors for atherosclerosis including hypertension. Stiffness parameter β, mainly used to examine the compliance and distensibility of the carotid artery, was found to be associated with coronary artery disease, insulin resistance, and decreased kidney function [3,13]. In addition, studies have shown that stiffness parameter β was minimally affected by acute changes in BP [3,14].

Flow-mediated dilation (FMD) of the brachial artery, assessed by high-sensitivity ultrasonography, is another noninvasive assessment and clinically useful tool for indicating subclinical atherosclerosis [15]. Brachial FMD reflects early and predominantly functional changes in the arterial wall [16] and is an independent predictor of future cardiovascular events and mortality [17,18]. Moreover, FMD is considered as a surrogate marker of endothelial function [19]. Impaired FMD response reflects endothelial dysfunction [20]. Endothelial dysfunction modulates vascular tone and structure through the release of endothelin-1 (ET-1) [21]. ET-1 belongs to a family of endothelium-derived peptides, is a potent vasoconstrictor, and plays a fundamental physiological role in the pathogenesis of atherosclerosis [22].

The aim of the present study was to investigate whether or not day-by-day HBPV is associated with carotid artery atherosclerosis, brachial FMD, and ET-1 independent of the mean HBP level.

Materials and methods

Study population

From August 2010 to June 2012, a total of 347 volunteers were screened by HBPM, carotid artery sonography, and brachial FMD from clinics in the Jinan area of Shandong Province (China). Of these, 314 individuals agreed to participate in and were eligible for this study. There were 143 men and 171 women. Their ages ranged from 44 to 83 years (mean: 62.6±8.5 years).

The exclusion criteria in the present study were as follows: diabetes mellitus; second hypertension; severe/stage 3 hypertension; currently taking antihypertensive medicine; cardiovascular event, such as a stroke or myocardial infarction within the preceding 3 months; congestive heart failure; history of a major neurologic disorder, such as Alzheimer disease, Parkinson disease, or seizures; chronic renal failure and dialysis treatment; shift workers; and difficulty providing informed consent.

The Research Ethics committee of the Shandong Academy of Medical Sciences approved this study, and the participants provided written informed consent.

Self blood pressure monitoring at home

The methods of HBPM have been reported previously [23]. All participants and at least one of their relatives attended classes for systematic training on how to perform HBP measurements instructed by physicians and/or trained public health nurses. Participants and their relatives were asked to perform each step in the procedure of HBP measurements. After their ability to measure HBP was verified, participants were supplied with an automatic device [BP3MX1-1, Microlife WatchBP Home; CX Electronic (Shenzhen) Co. Ltd, Shenzhen, Guangdong, China], which was previously validated and fulfilled the criteria of the International Protocol of the European Society of Hypertension [24,25], such as a home sphygmomanometer. The device incorporates an integrated circuit memory and a clock to store BP and heart rate readings and measurement times. The participants were instructed to place the cuff directly on the nondominant arm, which was kept at the level of the heart during HBP measurements. HBP was measured in a sitting position two times each morning (06:00–09:00 h) and two times each evening (17:00–21:00 h) for 7 consecutive days after 5 min of sitting rest and with a gap of 2 min between measurements. Morning BP was measured within 1 h after rising, after micturition, and before breakfast. Evening BP was measured just before going to bed and at least 30 min after taking a bath. The HBP level was calculated as the average of within-subject readings. The day-by-day HBPV was calculated as SD of the daily BP average of the last 6 consecutive days. Similarly, the day-by-day morning and evening BPV were defined as SD of the daily BP average in the morning and evening of the last 6 consecutive days. Participants with fewer than six valid HBP measurements were excluded.

Office blood pressure measurement

Office BP was obtained before and after the above-mentioned period of HBP measurements by the nurses in the morning, using the same device as those used for HBP. The mean of the twice visit-measurements was used for further analysis. At each office visit, three consecutive readings were taken on the nondominant arm with a 1 min interval after 5 min in a sitting position and office BP was recorded as the average of triplicate measurements.

Measurement of carotid intima-media thickness and arterial stiffness parameter β

Testing was performed under quiet and warm conditions. The right and left carotid arteries were imaged using high-resolution ultrasound (Vivid *i*; GE Medical Systems Ultrasound Israel Ltd, Tirat-Hacarmel, Israel) with a handheld 7.5-MHz transducer (7.5-SPC mechanic sector transducer; GE Medical Systems Ultrasound Israel Ltd) as reported previously [26,27]. One experienced ultrasonographer performed all examinations and was blinded to the participants' clinical details. The participants were asked to maintain a supine position, the head tilted slightly to the contra lateral side during testing. A region 1.5 cm proximal to the origin of the bulb of the carotid artery was identified using B-mode ultrasound. Digital movies were recorded for 10 s while the participant was holding his/her breath. The images were digitized and

saved on a computer for subsequent analysis. IMT was measured in both carotid arteries between the lumen–initima interface and the collagen-containing upper layer of the adventitia. Lumen diameter (D) was measured from the luminal–intimal interface of the near wall to that of the far wall. End-diastolic (minimum) and peak systolic (maximum) lumen diameters were obtained from carotid ultrasonography performed. BP was simultaneously measured at the upper arm using a Dinamap automatic blood pressure recorder (Omron Health Care, Kyoto, Japan) during the measurement session. Arterial stiffness parameter β was evaluated according to the following equation: stiffness parameter $\beta = \ln(P_s/P_d)/([D_s - D_d]/D_d)$, where P_s and P_d are the aortic systolic and the diastolic pressure, respectively, and D_s and D_d are carotid systolic and diastolic diameters, respectively [28].

Brachial flow-mediated dilation measurement

To assess brachial FMD, the left brachial artery diameter was measured by high-resolution ultrasound images at rest and during reactive hyperemia. Increase in flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 min, followed by a release. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker at baseline and 40, 60, and 80 s after cuff release. The vessel diameter in scans after reactive hyperemia was expressed as the percentage relative to the baseline scan. The maximum diameter between 40 and 80 s was used to derive FMD. FMD was computed using the formula (maximum diameter – baseline diameter)/baseline diameter × 100%. All the FMD measurements were performed by one experienced reader.

Clinical laboratory measurements

Venous blood samples of each participant were collected in the morning after an overnight fasting. Blood samples were collected in Na + EDTA tubes, subjected to 3000 rpm centrifugation for 30 min, plasma frozen immediately, and stored at −80°C until analysis.

Plasma level of ET-1 was measured before and after the period of HBP measurements using enzyme-linked immunosorbent assay kits following the manufacturer's instructions (Bender MedSystems, Vienna, Austria). The mean of two measurements was used in the final data analysis. The minimum detectable concentration was less than 1.0 pg/ml. Intra-assay and interassay coefficients of variation for enzyme-linked immunosorbent assay were less than 5%. All samples were measured in duplicate.

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.

Statistical analyses

All statistical analyses for the present study were carried out using the SPSS for Windows software package, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as means ± SDs or median with interquartile range (the range between the 25th and 75th percentile) depending on the normality of data. Categorical variables were expressed as numbers (%). Continuous variables were compared among groups by one-way analysis of variance or Kruskal–Wallis tests. If a significant difference was found, multiple comparisons were performed using the Bonferroni procedure with type I error adjustment or the Wilcoxon rank-sum test to test the difference between any two groups. Categorical variables were compared among groups by χ^2-tests. Results of HBP comparisons between the first and the second monitoring, and morning and evening monitoring were obtained using paired-samples t-test. Pearson correlation coefficients were determined to assess possible relationships between common carotid artery IMT, stiffness parameter β, FMD, and ET-1 with HBP and HBPV, respectively. Subsequently, stepwise multiple regression analysis was carried out to select factors associated independently with carotid IMT, stiffness index β, brachial FMD, and ET-1. The following factors were considered simultaneously as independent variables: age, sex, BMI, smoking, alcohol consume, official SBP, official DBP, systolic HBP, diastolic HBP, TCHO, TG, HDL-c, LDL-c, FPG, SD of systolic HBP, and SD of diastolic HBP. The significance level was set at P less than 0.05.

Results

Study participants

A total of 347 volunteers were recruited from August 2010 to June 2012. Three hundred and fourteen individuals were eligible for this study. Thirty-three individuals were excluded: seven because of incomplete data; 15 because office systolic BP exceeded 179 mmHg and/or office diastolic BP exceeded 109 mmHg; two because of diabetes mellitus; four because of incomplete/unqualified data for HBPM; and five because of inability to provide informed consent. Table 1 presents the baseline demographic and clinical characteristics of the participants.

Baseline demographic and clinical characteristic of participants

Participants were classified into four groups on the basis of casual BP according to the JNC-7 criteria, namely, normotension group, prehypertension group, mild hypertension group, and moderate hypertension group. Table 1 presents the demographic and clinical characteristics on the basis of these classifications. Only BP readings showed significant differences among the four groups ($P < 0.05$), but there were no significant differences in terms of age, sex, smoking, alcohol consumption, BMI, TCHO, TG, HDL-c, LDL-c, and FPG.

Table 1 Baseline demographic and clinical characteristics of participants in the four groups

	Normotension ($n=73$)	Prehypertension ($n=79$)	Mild hypertension ($n=82$)	Moderate hypertension ($n=80$)	P-value
Age (years)[d]	60.0 (56.5, 66.0)	62.0 (56.0, 72.0)	62.0 (56.0, 71.0)	60.5 (55.0, 67.8)	0.448
Sex (male) (%)[e]	27 (37.0)	25 (31.7)	25 (30.5)	28 (35.0)	0.796
BMI (kg/m^2)	24.8 (22.5, 27.4)	24.6 (22.4, 27.3)	25.4 (23.4, 27.7)	24.4 (21.8, 27.6)	0.382
Smoker (%)[e]	11 (15.1)	14 (17.7)	9 (11.0)	11 (13.8)	0.536
Alcohol consume (%)[e]	23 (31.5)	18 (22.8)	25 (30.5)	21 (26.3)	0.757
Official systolic BP (mmHg)[d]	112.0 (108.0, 115.0)	132.0 (125.0, 135.0)[a]	149.0 (143.0, 152.0)[a, b]	167.5 (163.0, 174.0)[a, b, c]	<0.001*
Official diastolic BP (mmHg)[d]	73.0 (108.0, 115.0)	77.0 (72.0, 83.0)[a]	87.0 (78.8, 93.0)[a, b]	91.0 (83.0, 96.0)[a, b, c]	<0.001*
Systolic HBP (mmHg)[d]	109.0 (105.0, 111.0)	128.0 (121.0, 132.0)[a]	144.5 (140.0, 149.0)[a, b]	164.0 (159.0, 170.8)[a, b, c]	<0.001*
Diastolic HBP (mmHg)[d]	70.0 (66.0, 74.0)	74.0 (69.0, 80.0)[a]	83.0 (75.0, 89.3)[a, b]	87.0 (80.0, 92.0)[a, b, c]	<0.001*
TCHO (mmol/l)[d]	4.4 (3.8, 4.9)	4.2 (3.9, 4.9)	4.4 (3.8, 4.8)	4.3 (4.0, 4.9)	0.751
TG (mmol/l)[d]	1.2 (1.0, 1.7)	1.3 (1.0, 1.7)	1.3 (1.0, 1.7)	1.4 (1.1, 1.8)	0.581
HDL-c (mmol/l)[d]	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)	0.970
LDL-c (mmol/l)[d]	2.7 (2.2, 3.0)	2.5 (2.2, 2.9)	2.5 (2.1, 2.9)	2.6 (2.1, 2.8)	0.934
FPG (mmol/l)[d]	4.2 (3.9, 4.5)	4.3 (4.0, 4.8)	4.4 (3.9, 4.9)	4.2 (4.0, 4.8)	0.229

Results are medians (25th, 75th percentiles) for continuous variables and n (%) for categorical variables.
BP, blood pressure; FPG, fasting plasma glucose; HBP, home blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TCHO, total cholesterol; TG, triglycerides.
*$P<0.05$, significantly different among the four groups.
[a]$P<0.05$, as compared with the normotension group.
[b]$P<0.05$, as compared with the prehypertension group.
[c]$P<0.05$, as compared with the mild hypertension group.
[d]One-way analysis of variance and Bonferroni test.
[e]Kruskal–Wallis H test.

Day-by-day variability in self-measured blood pressure at home in four groups

SDs of systolic and diastolic HBP are shown in Fig. 1. For SD of systolic HBP (Fig. 1a), the median values for the normotension, prehypertension, mild hypertension, and moderate hypertension groups were 5.2, 6.1, 6.9, and 8.3 mmHg, respectively. There was a significant increasing trend from the normotension to the moderate hypertension group and the differences between any two groups were highly significant (all adjusted $P < 0.05$).

For SD of diastolic HBP (Fig. 1b), the median values for the normotension, prehypertension, mild hypertension, and moderate hypertension groups were 3.7, 4.1, 4.2, and 4.6 mmHg, respectively. There was an increasing trend from the normotension to the moderate hypertension group ($P < 0.05$). SD of diastolic HBP in the moderate hypertension group was markedly higher than that in the other three groups (all adjusted $P < 0.05$), and SD in the mild hypertension group was higher than that in the normotension group (adjusted $P < 0.05$).

Results of self-measured blood pressure at home in the morning and the afternoon measurements in four groups

We compared the results of HBP morning measurements with the evening measurements (Table 2). There were significant differences in diastolic HBP and SD of systolic HBP in the normotension group (all $P < 0.05$). Except in SD of diastolic HBP, there were significant differences in systolic HBP, diastolic HBP, and SD of systolic HBP in the other three groups (all $P < 0.05$).

We also compared the difference in systolic HBP between morning and evening measurements among the four groups (Table 2). There was a significant difference among the four groups ($P < 0.05$). Compared with the normotension group, the differences in systolic HBP between morning and evening measurements were higher in the mild hypertension group and the moderate hypertension group (all adjusted $P < 0.05$).

We also compared the difference in SD of systolic HBP between morning and evening measurements among the four groups (Table 2). There was a significant difference among the four groups ($P < 0.001$). Multiple comparisons using Bonferroni analysis showed statistical difference only in the normotension group and the moderate hypertension group (adjusted $P < 0.05$).

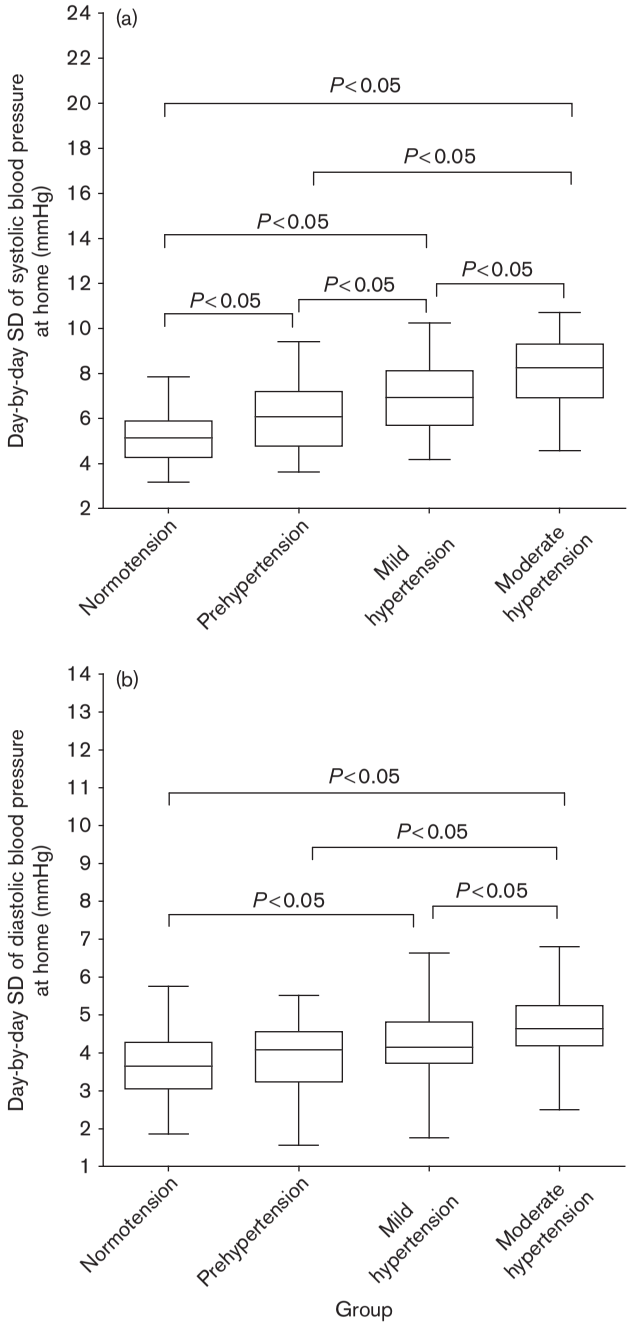
We also compared the difference in diastolic HBP and the difference in SD of diastolic HBP between morning and evening measurements among the four groups (Table 2). There were no statistical differences among the four groups.

Results of carotid artery intima-media thickness, stiffness parameter β, brachial flow-mediated dilation, and endothelin-1 in the four groups

Figure 2 summarizes carotid artery IMT (Fig. 2a), stiffness parameter β (Fig. 2b), brachial FMD (Fig. 2c), and ET-1 (Fig. 2d) in the four groups. For IMT (Fig. 2a), the median values for the normotension, prehypertension, mild hypertension, and moderate hypertension groups were 1.2, 1.3, 1.4, and 1.6 mm, respectively. There was an increasing trend from the normotension to the moderate hypertension group ($P < 0.05$). IMT in the mild hypertension group was significantly higher than that in the normotension group (adjusted $P < 0.05$). IMT in the moderate hypertension group was markedly higher than that in the other three groups (all adjusted $P < 0.05$).

For stiffness parameter β (Fig. 2b), the median values for the normotension, prehypertension, mild hypertension, and

Fig. 1



Day-by-day SD of self-measured systolic blood pressure (a) and diastolic blood pressure (b) at home in the four groups. Results are medians (horizontal bars in boxes) and 25th and 75th percentiles (lower and upper error bars, respectively).

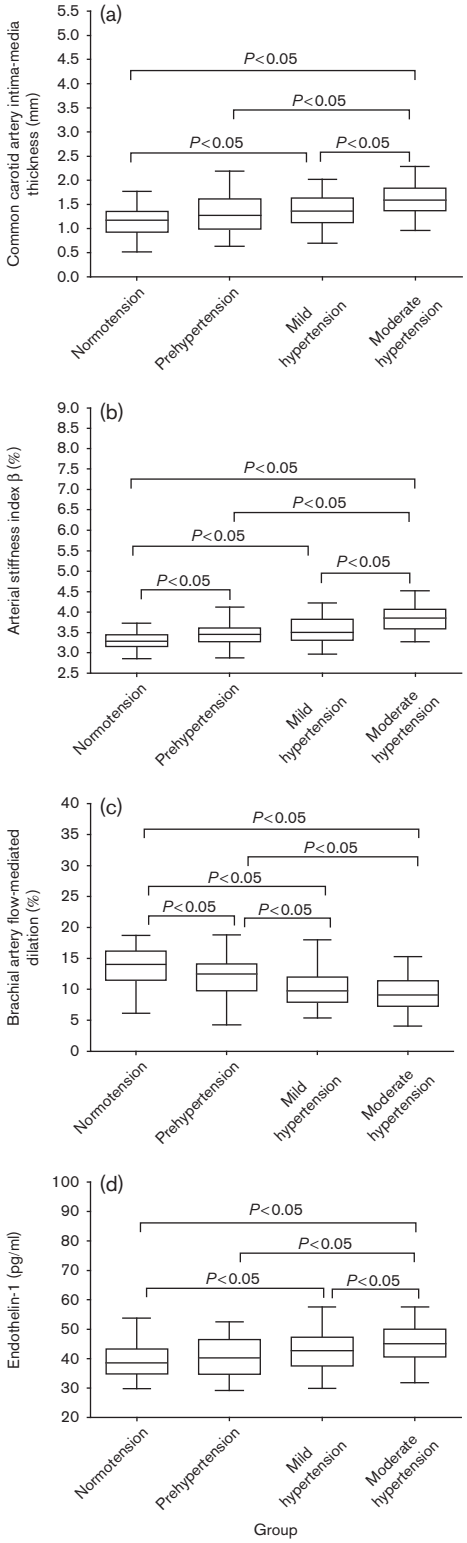
moderate hypertension groups were 3.3, 3.5, 3.5, and 3.9, respectively. There was an increasing trend from the normotension to the moderate hypertension group ($P < 0.05$). Compared with the normotension group, stiffness parameter β in the other three groups was significantly higher (all adjusted $P < 0.05$) and was markedly higher in the moderate hypertension group than that in the

Table 2 Results of self-measured blood pressure at home in morning and evening measurements in the four groups

	Normotension ($n=73$)	Prehypertension ($n=79$)	Mild hypertension ($n=82$)	Moderate hypertension ($n=80$)	*P*-value
Difference in systolic HBP between morning and evening measurements (mmHg)	0.2±3.4	1.2±3.2†	1.6±3.0†, ‡	1.9±2.8†, ‡	0.007*
Difference in diastolic HBP between morning and evening measurements (mmHg)	1.1±1.6†	1.2±1.7†	1.1±1.5†	1.4±1.5†	0.619
Difference in SD of systolic HBP between morning and evening measurements (mmHg)	1.1±0.4†	1.2±0.3†	1.2±0.4†	1.4±0.4†, ‡	<0.001*
Difference in SD of diastolic HBP between morning and evening measurements (mmHg)	0.0±0.2	0.0±0.2	0.0±0.2	0.0±0.3	0.363

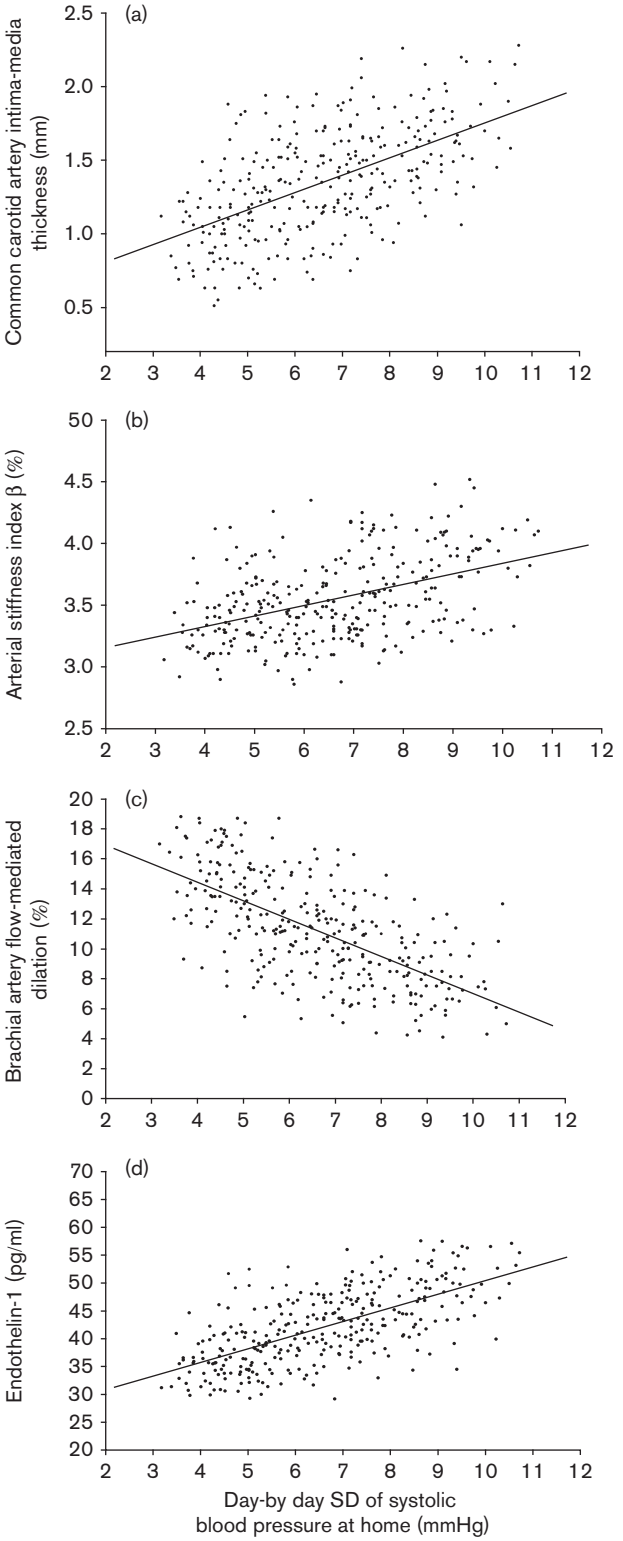
Results are means±SDs.
HBP, home blood pressure.
*$P<0.05$, as compared among the four groups.
†$P<0.05$, morning HBP measurement vs. evening HBP measurement.
‡$P<0.05$, as compared with the normotension group.

Fig. 2



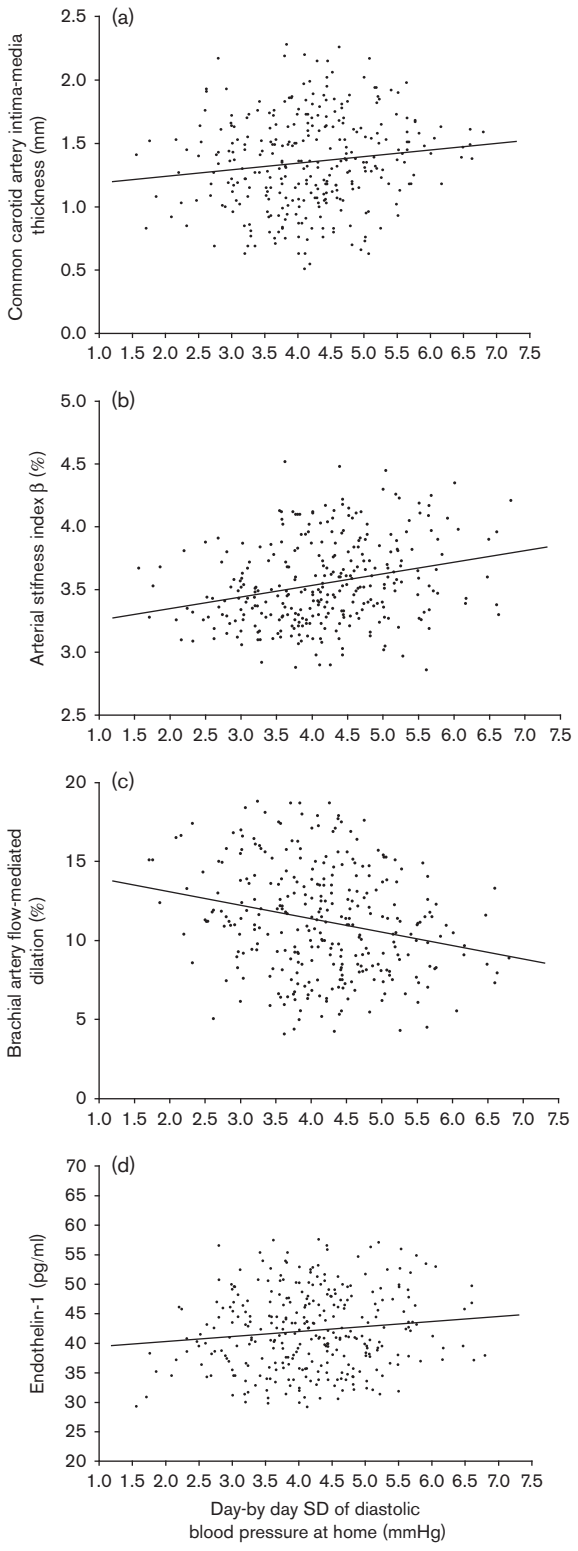
Carotid artery intima-media thickness (a), stiffness parameter β (b), brachial artery flow-mediated dilation (c), and endothelin-1 (d) in the four groups. Results are medians (horizontal bars in boxes) and 25th and 75th percentiles (lower and upper error bars, respectively).

Fig. 3



Correlations between SD of systolic home blood pressure and (a) carotid artery intima-media thickness ($r=0.569$, $P<0.001$), (b) artery stiffness parameter β ($r=0.447$, $P<0.001$), (c) brachial artery flow-mediated dilation ($r=-0.636$, $P<0.001$), and (d) endothelin-1 ($r=0.649$, $P<0.001$).

Fig. 4



Correlations between SD of diastolic home blood pressure and (a) carotid artery intima-media thickness (r=0.136, P=0.016), (b) artery stiffness parameter β (r=0.261, P<0.001), (c) brachial artery flow-mediated dilation (r= −0.236, P<0.001), and (d) endothelin-1(r=0.121, P=0.032).

prehypertension and mild hypertension groups (all adjusted $P < 0.05$).

For FMD (Fig. 2c), the median values for the normotension, prehypertension, mild hypertension, and moderate hypertension groups were 14.0, 12.5, 9.8, and 9.1, respectively. There was a decreasing trend from the normotension to the moderate hypertension group ($P < 0.05$). Compared with the normotension group, FMD in the other three groups was significantly lower (all adjusted $P < 0.05$). FMD in the mild hypertension and moderate hypertension groups was significantly lower compared with the prehypertension group (all adjusted $P < 0.05$).

For ET-1 (Fig. 2d), the median values for the normotension, prehypertension, mild hypertension, and moderate hypertension groups were 38.6, 40.3, 42.7, and 45.0, respectively. There was an increasing trend from the normotension to the moderate hypertension group ($P < 0.05$). ET-1 in the moderate hypertension group was markedly higher than that in the other three groups (all adjusted $P < 0.05$), and was significantly higher in the mild hypertension group than that in the normotension group (adjusted $P < 0.05$).

Correlations of variability in home blood pressure with carotid artery intima-media thickness, stiffness parameter β, brachial artery flow-mediated dilation, and endothelin-1 in all participants

First, as shown in Fig. 3, we assessed possible correlations of SD of systolic HBP with IMT, stiffness parameter β, FMD, and ET-1 in all participants. SD of systolic HBP was significant positively correlated with IMT (Fig. 3a: $r = 0.569$, $P < 0.001$), stiffness parameter β (Fig. 3b: $r = 0.447$, $P < 0.001$), and ET-1 (Fig. 3c: $r = 0.649$, $P < 0.001$), and negatively correlated with FMD (Fig. 3d: $r = -0.636$, $P < 0.001$).

Then, as shown in Fig. 4, we assessed possible correlations of SD of diastolic HBP with carotid artery IMT, stiffness parameter β, FMD, and ET-1 in all participants. Similar to SD of systolic HBP, there were positive correlations between SD of diastolic HBP and IMT (Fig. 4a: $r = 0.136$, $P = 0.016$), stiffness parameter β (Fig. 4b: $r = 0.261$, $P < 0.001$), and ET-1 (Fig. 4d: $r = 0.121$, $P = 0.032$), and there was negative correlations between SD of diastolic HBP and FMD (Fig. 4c: $r = -0.236$, $P < 0.001$).

The strength of correlations of SD of systolic HBP with IMT, stiffness parameter β, FMD, and ET-1 was also compared with the strength of correlations of SD of diastolic HBP with IMT, stiffness parameter β, FMD, and ET-1, respectively. We found that the strength of correlation of SD of systolic HBP with IMT was stronger than that of diastolic HBP with IMT ($P < 0.001$). Similarly, the strength of correlations of SD of systolic HBP with stiffness parameter β, FMD, and ET-1 was stronger than those of SD of diastolic HBP with stiffness parameter β, FMD, and ET-1 (all $P < 0.001$).

Table 3 Factors possibly related to variables of carotid artery stiffness and elasticity using stepwise multivariate regression analysis

	IMT		Stiffness parameter β	
	Weighted coefficient (95% CI)	*P*-value	Weighted coefficient (95% CI)	*P*-value
Age (years)	0.000 (−0.005, 0.003)	0.759	0.002 (−0.002, 0.005)	0.372
BMI (kg/m^2)	−0.004 (−0.015, 0.007)	0.452	0.001 (−0.009, 0.011)	0.879
Systolic HBP (mmHg)	0.004 (0.002, 0.007)	<0.001*	0.009 (0.007, 0.011)	<0.001*
Diastolic HBP (mmHg)	−0.001 (−0.006, 0.003)	0.573	0.006 (−0.002, 0.008)	0.063
SD of systolic HBP (mmHg)	0.089 (0.065, 0.113)	<0.001*	0.029 (0.008, 0.050)	<0.001*
SD of diastolic HBP (mmHg)	0.012 (0.028, 0.053)	0.015*	0.037 (0.001, 0.073)	0.042*
TCHO (mmol/l)	0.055 (−0.041, 0.159)	0.248	0.061 (−0.028, 0.149)	0.177
TG (mmol/l)	0.018 (−0.075, 0.110)	0.561	−0.024 (−0.099, 0.051)	0.396
HDL-c (mmol/l)	−0.353 (−0.656, −0.049)	0.023*	−0.055 (−0.322, 0.212)	0.687
LDL-c (mmol/l)	0.029 (−0.074, 0.132)	0.579	−0.065 (−0.146, 0.017)	0.119
FPG (mmol/l)	0.029 (−0.027, 0.085)	0.108	0.003 (−0.047, 0.054)	0.892
	FMD		ET-1	
	Weighted coefficient (95% CI)	*P*-value	Weighted coefficient (95% CI)	*P*-value
Age (years)	−0.007 (−0.043, 0.002)	0.022*	0.007 (0.001, 0.013)	0.046*
BMI (kg/m^2)	−0.012 (−0.006, −0.019)	0.009*	0.046 (−0.147, 0.239)	0.474
Systolic HBP (mmHg)	−0.023 (−0.044, −0.002)	0.028*	0.014 (−0.027, 0.054)	0.056
Diastolic HBP (mmHg)	0.001 (−0.039, 0.042)	0.951	0.015 (−0.064, 0.094)	0.160
SD of systolic HBP (mmHg)	−1.041 (−1.252, −0.829)	<0.001*	2.519 (2.106, 2.932)	0.002*
SD of diastolic HBP (mmHg)	−0.295 (−0.524, −0.065)	<0.001*	0.153 (−0.148, 0.453)	0.083
TCHO (mmol/l)	−0.199 (−1.091, 0.693)	0.661	0.115 (−1.623, 1.853)	0.496
TG (mmol/l)	−0.052 (−0.900, 0.796)	0.536	1.290 (0.032, 2.548)	0.004*
HDL-c (mmol/l)	0.549 (−2.148, 3.247)	0.218	−1.748 (−4.496, −1.001)	<0.001*
LDL-c (mmol/l)	−0.041 (−0.952, 0.871)	0.930	0.026 (−1.750, 1.802)	0.561
FPG (mmol/l)	−0.152 (−0.658, 0.354)	0.555	0.357 (−0.628, 1.343)	0.476

CI, confidence interval; ET-1, endothelin-1; FMD, flow-mediated dilation; FPG, fasting plasma glucose; HBP, home blood pressure; HDL-c, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-c, low-density lipoprotein cholesterol; TCHO, total cholesterol; TG, triglycerides.
*$P<0.05$ indicates that the independent variable is a significant factor for the dependent variable.

Multiple regression analysis

From the above results, it would appear that SDs of systolic and diastolic HBP are associated with carotid artery IMT, stiffness parameter β, brachial FMD, and ET-1. However, as shown in Table 1, there were numerous other factors, such as age, sex, smoking, alcohol consumption, BMI, BP, plasma lipids, and FPG, which might be associated with IMT, stiffness parameter β, FMD, and ET-1. To remove these possibilities, we used stepwise multivariate regression analysis to identify factors possibly associated with the dependent variables of IMT, stiffness parameter β, FMD, and ET-1 (Table 3). For IMT, there were significant results for systolic HBP, SD of systolic HBP, SD of diastolic HBP, and HDL-c. For stiffness parameter β, there were statistically significant results for systolic HBP, SD of systolic HBP, and SD of diastolic HBP. For FMD, there were statistically significant results for age, BMI, systolic HBP, SD of systolic HBP, and SD of diastolic HBP. For ET-1, there were statistically significant results for age, SD of systolic HBP, TG, and HDL-c. However, most importantly, SD of systolic HBP was always significantly associated with IMT, stiffness parameter β, FMD, and ET-1.

Discussion

Our major findings were as follows: (a) systolic HBPV, assessed by the calculation of SD, in groups with higher BP level was greater than that in groups with lower BP level; (b) day-by-day systolic HBPV was associated with carotid atherosclerosis and endothelial function independent of other covariates; (c) systolic HBPV in morning measurements was higher than that in evening measurements; and (d) there were statistical differences in the difference in systolic HBP and difference in SD of systolic HBP between morning and evening measurements among the four groups.

As is well known, BP fluctuates continuously over a 24-h period, and the variability is influenced by many pathological conditions such as neural, mechanical, and humoral factors [29,30]. However, higher BP level is one of the most important factors. Mancia *et al.* [31] analyzed BPV in 89 normotensive or essential hypertensive individuals using an invasive method. They found that not only short-term but also long-term variabilites in systolic and diastolic BP were lowest in normotensive individuals and greatest in severe hypertensive patients, whether in the wakefulness period or in the sleep period. Our study showed that the tendency of variability in systolic HBP increased significantly from the normotension to the moderate hypertension group. This tendency was also found in the variability of diastolic HBP. However, it was not as significant as in the variability of systolic HBP. This may be because systolic BP was more affected by BP level.

Studies [3,10] have shown that exaggerative BPV was closely related to advanced arterial stiffness or TOD. Kikuya *et al.* [5] reported that day-by-day HBPV was associated with cardiovascular events in a Japanese general population. Hoshide *et al.* [32] reported that day-to-day HBPV, assessed by SD of HBP during 14 days, was associated with urinary albumin excretion, left

ventricular mass index, and carotid IMT independent of the mean HBP level among untreated hypertensive patients. Similar results were obtained in the present study. After adjustment of all covariants, day-by-day HBPV was still statistically positively correlated with IMT and stiffness parameter β.

In our study, we also analyzed the relationship of HBPV with endothelial function. Endothelial dysfunction is an early and important event in the pathogenesis of atherosclerosis [22]. Diaz *et al*. [4] reported that 24-h BPV and visit-to-visit BPV were significantly associated with endothelial dysfunction. However, they did not assess the association between HBPV and endothelial dysfunction. In our study, brachial FMD and ET-1 were used to indicate endothelial function. Brachial FMD, a physiologic measure of subclinical atherosclerosis [16], is considered as endothelium-dependent vasodilation and impairment of FMD is considered a marker of endothelial dysfunction [19]. ET-1 was released when vascular tone and structure changed [21]. Results of multiple regression analysis showed that, after removal of all covariants, SD of systolic HBP still correlated with FMD and ET-1 in the present study.

We also found that systolic HBPV in morning measurements was higher than that in evening measurements in each group. Other previous studies are in agreement with our results. The Ohasama study had found that morning BP was consistently higher than evening BP (by about 2 mmHg systolic and diastolic) in normotensives and hypertensives, treated and untreated [33]. However, higher HBP in the morning compared with the evening was not found in Europe [34,35]. The difference may be because of different life styles in western and eastern countries. In our study, in terms of the difference in systolic HBPV between morning and evening measurements, there were no significant differences among the normotension, prehypertension, and mild hypertension group; only in moderate hypertension group systolic HBPV was higher than that in normotension group. In terms of differences in diastolic HBPV between morning and evening measurements, there were no significant differences among the four groups. This may be because of good training of participants, using a unified sphygmomanometer, measured in a quiet and safe family environment.

Study limitations

There are some limitations to our study. First, our study was a cross-sectional study. We do not know what effects HBPV may have in terms of long-term changes in atherosclerosis and endothelial dysfunction progression. Second, HBPM cannot yield night-time BP values. Third, patients with severe (stage 3) hypertension and currently taking antihypertensive medicines were excluded from the present study.

Conclusion

In summary, our investigation showed that day-by-day systolic HBPV was increasing with elevated BP level and was significantly associated with carotid artery atherosclerosis and impaired endothelial function in normotensive and mild–moderate hypertensive individuals. Thus, the day-by-day systolic HBPV may serve as an important prognostic factor for atherosclerosis and endothelial dysfunction.

Acknowledgements

This work was supported by the Natural Science Foundation of Shandong Province, China (NOs. ZR2009CL09, ZR2011HQ053, ZR2011HL053, and ZR2012HL46), and by the Shandong Science and Technology Development Program, China (NO. 2011GSF11822).

Conflicts of interest

There are no conflicts of interest.

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