ORIGINAL ARTICLE

Visit-to-visit variability in systolic blood pressure is a novel risk factor for the progression of coronary artery calcification

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Recent studies have suggested that variability in the systolic blood pressure (SBP) is a risk factor for cardiovascular disease (CVD). The aim of this study was to investigate the relationship between variability in the SBP and the progression of coronary artery calcification (CAC), which is a useful marker for CVD. We measured SBP in 164 consecutive patients at every visit over the course of a year and calculated the coefficient of variation and s.d. of the SBP. We performed a follow-up study using multislice computed tomography to assess the progression of the CAC score, the mean interval of which was 3.93 ± 1.36 years. We then evaluated the relationship between variability in the SBP and progression of the CAC score. The coefficient of variation for the SBP correlated positively with the progression of the CAC score ($r=0.4382$, $P<0.0001$). Multiple regression analysis demonstrated that the coefficient of variation of the SBP ($\beta=0.3826$, $P<0.0001$) was independently associated with the progression of the CAC score. The visit-to-visit variability in SBP could be a novel risk factor for the progression of CAC. *Hypertension Research* (2013) 36, 996–999; doi:10.1038/hr.2013.66; published online 4 July 2013

Keywords: atherosclerosis; coronary artery calcification; variability of blood pressure

INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in the general population, and several risk factors, including diabetes, smoking, hypertension and dyslipidemia, have been shown to accelerate the progression of CVD.^{1,2} Visit-to-visit variability in the systolic blood pressure (SBP) has been reported to be a strong predictor of CVD.³ We reported previously that visit-to-visit variability in the SBP was correlated with atherosclerosis in a cross-sectional study.⁴ The coronary artery calcification (CAC) score has recently been developed as a marker of coronary atherosclerosis that can be assessed noninvasively using multislice computed tomography (MSCT). The CAC score is an established quantitative and objective measure of coronary artery atherosclerosis, and several studies have demonstrated a correlation between the CAC score and CVD.^{5,6} The relationship between variability in the SBP and the progression of CAC has not been investigated. The aim of this study was to investigate the association between visit-to-visit variability in the SBP and the progression of CAC.

METHODS

Patients and study design

We performed a retrospective cohort study with 164 participants at the Department of Cardiology Yamashiro Public Hospital (Kyoto, Japan) from

April 2006 to March 2012. The inclusion criterion was a clinical suspicion of coronary artery disease. All the participants were in stable clinical condition and agreed to participate in the investigation.

Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.⁷ The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. The patients were classified as nonsmokers, past smokers or current smokers according to a self-administered questionnaire. The patients with advanced renal dysfunction (serum Cr over 2.0 mg dl^{-1}) or malignancy, those with major cardiovascular event during the follow-up and those with any changes in medication for hypertension during the year of data collection were excluded from this study. A cardiovascular event was defined as the presence of a myocardial infarction, cerebral infarction or angina that required a revascularization.

We then evaluated the relationship between variability in the SBP and the progression of CAC. This study was approved by the local Research Ethics Committee and conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all of the participants.

Measurement of the blood pressure and data collection

We measured the blood pressure at every visit for a year and calculated the visit-to-visit variability in blood pressure, as described below. After collecting the blood pressure data, we performed MSCT, and blood samples were

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collected as baseline data. In a follow-up study, we performed MSCT again and calculated the progression of the CAC score.

The sitting blood pressure was measured after a 5-min rest in a quiet space at every visit over the course of a year using a device (HEM-906; OMRON, Kyoto, Japan) that is able to automatically measure blood pressure. The visit-to-visit variability in SBP was calculated as follows: coefficient of variation (CV) = s.d. of SBP $\times$ 100/average SBP. We calculated the CV and s.d. of the SBP, as well as the diastolic blood pressure (DBP) or pulse pressure, as parameters of the blood pressure variability.

Blood samples were taken in the morning at baseline. The serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride concentrations were assessed using standard enzymatic methods. The serum low-density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula (LDL cholesterol = total cholesterol – HDL cholesterol – triglycerides/5).⁸

The progression of the CAC score was calculated as follows: progression of CAC score = increase of CAC score/follow-up duration (year).

Measurement of the CAC score

We performed MSCT (Aquilion 64, Toshiba Medical, Tokyo, Japan) twice at baseline and at the end of a follow-up interval. The calcification scoring parameters included the 2-mm collimation width, a gantry rotation speed of 0.4 s per rotation, tube energy of 120 kV, and an effective tube current of 400 mA, using prospective ECG-gated axial scanning. The total CAC scores were determined on a workstation (ZIO Station, ZIO Soft, Tokyo, Japan) with software to determine the CAC using the Agatston method, as previously described.⁹ Two experienced observers who were blinded to the identity and clinical presentation of the participant analyzed the CAC scores.

Statistical analysis

The mean values and frequencies of the potential confounding variables were calculated. Because triglycerides and the progression of the CAC score showed skewed distributions, log transformations were carried out before performing the correlation and regression analysis. The progression of the CAC score was log-transformed after adding 1. The relationship between the visit-to-visit variability in SBP and the progression of the CAC score, as well as the relationship between the visit-to-visit variability in SBP and age or other variables, were examined using Pearson's correlation analysis. To examine the effects of various factors on the logarithm of the progression of the CAC score + 1, the following factors were considered simultaneously as independent variables for the multiple regression analyses: age, sex, follow-up duration, BMI, average SBP, heart rate, hemoglobin A1c, total cholesterol, logarithm of triglycerides, uric acid, smoking status, antihypertensive drug, statin and visit-to-visit variability, as well as the CV and s.d. of the SBP, DBP or pulse pressure. All of the continuous variables are presented as the mean $\pm$ s.d. or as the absolute number. A *P*-value < 0.05 was considered as significant.

RESULTS

The characteristics of the 164 patients enrolled in this study are shown in Table 1. The mean CV of the SBP was $6.12 \pm 4.16\%$. The average number of blood pressure measurements per subject during the year-long data collection period was 7.02 ± 2.40 . The average follow-up duration was 3.93 ± 1.36 years. The relationship between the CV of the SBP and the other variables are shown in Table 2. No significant correlations were found between the CV of the SBP and the average SBP, heart rate, hemoglobin A1c, total cholesterol, LDL cholesterol and uric acid. The CV of the SBP correlated positively with the logarithm of the progression of the CAC score + 1 ($r = 0.4382$, $P < 0.0001$). A simple correlation and multiple regression analysis on the logarithm of the progression of the CAC score + 1 is shown in Table 3. Multiple regression analysis demonstrated that the CV of the SBP ($\beta = 0.3826$, $P < 0.0001$) was independently associated with the logarithm of the progression of the CAC score + 1. Moreover, the s.d. of the SBP ($\beta = 0.3894$, $P < 0.0001$), the CV of the DBP ($\beta = 0.2218$,

Table 1 Characteristics of patients at baseline

n	164
Age (year)	68.7 (9.3)
Sex (male/female)	81/83
Duration of follow up (year)	3.93 (1.36)
Body mass index (kg m ⁻²)	23.6 (4.3)
Average arms SBP (mm Hg)	132.2 (16.2)
Average arms DBP (mm Hg)	74.2 (9.4)
Average pulse pressure (mm Hg)	58.2 (12.2)
Coefficient of variation of SBP (%)	6.12 (4.16)
Coefficient of variation of DBP (%)	8.10 (4.67)
Coefficient of variation of pulse pressure (%)	12.1 (7.82)
Heart rate	75.6 (11.1)
Hemoglobin A1c (%)	5.92 (1.51)
Total cholesterol (mmol l ⁻¹)	5.03 (0.96)
Low-density lipoprotein cholesterol (mmol l ⁻¹)	2.96 (0.83)
High-density lipoprotein cholesterol (mmol l ⁻¹)	1.37 (0.36)
Triglycerides (mmol l ⁻¹)	1.62 (0.92)
Uric acid (μmol l ⁻¹)	331.1 (86.8)
Creatinine (μmol l ⁻¹)	72.5 (41.5)
Type 2 diabetes (±)	139/25
Smoking (none/past/current)	112/32/20
Antihypertensive drug (calcium channel blocker/diuretics/ACE inhibitor/ARB/alpha blocker/beta blocker)	62/20/13/50/5/9
Statin (±)	107/57
Progression of CAC score/year	39.8 (99.3)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAC, coronary artery calcification; DBP, diastolic blood pressure; SBP, systolic blood pressure. Data are expressed as mean (s.d.) or absolute number.

Table 2 Correlation between coefficient of variation of systolic blood pressure and other variables

	<i>r</i> -value	<i>P</i> -value
Age	0.2499	0.0012
Duration of follow-up	0.2212	0.0042
Body mass index	-0.1815	0.0193
Average systolic blood pressure	0.0329	0.6740
Heart rate	0.0412	0.5981
Hemoglobin A1c	0.0686	0.3799
Total cholesterol	0.1160	0.2623
Low-density lipoprotein cholesterol	-0.1353	0.0821
High-density lipoprotein cholesterol	-0.2018	0.0091
Logarithm of triglycerides	0.2139	0.0056
Uric acid	0.1440	0.0641
Logarithm of progression of CAC score	0.4382	<0.0001

Abbreviation: CAC, coronary artery calcification.

$P = 0.0042$) and the s.d. of the DBP ($\beta = 0.2028$, $P = 0.0090$) were also independently associated with the logarithm of the progression of the CAC score + 1.

The CV ($\beta = 0.0657$, $P = 0.3978$) and s.d. ($\beta = 0.0889$, $P = 0.2631$) of the pulse pressure were not independently associated with the logarithm of the progression of the CAC score + 1.

DISCUSSION

The major finding of our study is that the visit-to-visit variability in the SBP is a risk factor for the progression of CAC, which is a good surrogate marker of the presence and severity of coronary

Table 3 Simple correlation and multiple regression analyses on logarithm of progression of coronary artery calcification score

	r-value	P-value	β	P-value
Age	0.1552	0.0386	0.1261	0.1375
Sex	—	—	0.1573	0.0579
Duration of follow-up	0.2016	0.0058	0.0572	0.4169
Body mass index	0.0196	0.7934	0.1033	0.2287
Average systolic blood pressure	0.2710	0.0004	0.2387	0.0014
CV of systolic blood pressure	0.4382	<0.0001	0.3826	<0.0001
Heart rate	0.1434	0.0065	0.0877	0.2341
Hemoglobin A1c	0.2450	0.0010	0.2000	0.0054
Total cholesterol	−0.0481	0.5211	0.1041	0.1756
Logarithm of triglycerides	0.0067	0.9297	−0.1534	0.0661
Uric acid	0.1686	0.0240	0.1002	0.1890
Smoking status	—	—	−0.0154	0.8352
Calcium-channel blocker	—	—	−0.0070	0.9213
Diuretic drug	—	—	0.0080	0.2685
ACE inhibitor	—	—	−0.1364	0.0639
ARB	—	—	−0.0624	0.4160
alpha blocker	—	—	0.0363	0.6394
beta blocker	—	—	−0.0437	0.5294
Statin	—	—	0.1472	0.0559

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CV, coefficient of variation. Sex was defined as female (=0) or male (=1), smoking status was defined as nonsmoker (=0), past smoker (=1), or current smoker (=2), and medication for hypertension or dyslipidemia was defined as without (=0) or with (=1).

atherosclerosis. Although previous studies have reported that the average SBP is an independent risk factor for atherosclerosis, recent studies have suggested that both the average SBP and the variability in SBP are independent risk factors for atherosclerosis and organ damage in patients with hypertension and with treated hypertension.^{3,4,10,11} Moreover, Rothwell *et al.*³ suggested that the average SBP was a weak predictor of stroke and coronary events, whereas the visit-to-visit variability in SBP was a strong predictor of both.

Some studies have reported that the CAC score is a better predictor of subsequent CVD events. The CAC score by MSCT can be related to the extent and severity of coronary atherosclerotic disease and can improve the prediction of the risk of CHD (coronary heart disease).^{12,13} In our study, multiple regression analysis revealed that the CV of the SBP was more predictive than was the average SBP for the progression of CAC.

Because variability in the SBP might be influenced by other risk factors associated with the calcium score, we have assessed the relationship between the CV of the SBP and other risk factors. Age, follow-up duration, BMI, HDL cholesterol and the logarithm of triglycerides were correlated with the CV of the SBP. Moreover, variability in the SBP may be affected by antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta blockers.¹⁴ However, variability in the SBP was independently associated with the progression of the CAC score, even after making adjustments for age, follow-up duration, BMI, the logarithm of triglycerides and antihypertensive drugs in this study.

Variability in the SBP is a dynamic and complex phenomenon that arises from intricate interactions among behavioral, environmental, humoral, and neural central or reflex pathways.¹⁵ For example, postural changes, prandial effects and psychological stress, as well as the effects of humoral factors, such as angiotensin II, bradykinin or nitric oxide, increased the central sympathetic drive and reduced the arterial compliance.¹⁵ On the other hand, it was reported that the

visit-to-visit variability was the result of improper titration of the antihypertensive therapy and improper downward titration of the antihypertensive drug regimen over the summer.¹⁶ Consequently, the patients in our study who underwent any changes in their medication for hypertension during the data collection period were excluded.

The structural vessel abnormalities resulted mainly from a biochemical derangement, and one possible mechanism connecting the blood pressure variability with structural vessel abnormalities is that an increased blood pressure variability might be related to a greater traumatic effect of wider blood pressure swings on the vessel wall, promoting target-organ damage.¹⁷ Eto *et al.*¹⁸ suggested that increased blood pressure variability, independent of the average blood pressure level, impairs endothelial function by inhibiting nitric oxide production and enhances neointimal formation, and may thereby contribute to atherogenesis in animal models. A greater blood pressure variability has also been attributed to increased arterial stiffness. Kikuya *et al.*¹⁹ suggested that increased arterial stiffness might cause an increase in the blood pressure variability.

There were several parameters of the variability in blood pressure other than the CV of the SBP. To assess whether these other parameters of the variability in blood pressure could be linked with the progression of the CAC score, we have incorporated the s.d. of the SBP, the CV or s.d. of the DBP and the CV or s.d. of the pulse pressure into multiple regression analyses. The multiple regression analysis demonstrated that the s.d. of the SBP, the CV of the DBP and the s.d. of the DBP were also independently associated with the progression of the CAC score. However, the CV and s.d. of the pulse pressure were not independently associated with the progression of the CAC score.

There are some limitations in our study. First, the study population consisted of Japanese men and women; therefore, it is uncertain whether these findings can be generalized to other ethnic groups. Second, medication non-adherence might have been one of the causes of visit-to-visit blood pressure variation; however, we have no data on medication adherence. Finally, we have no data on the reproducibility of the MSCT data. Moreover, a previous study has reported that the reproducibility of MSCT remains insufficient.²⁰

Previous studies have emphasized hypertension, diabetes, smoking and dyslipidemia as risk factors for the progression of atherosclerosis. We suggest that it is important to consider the variability in blood pressure and clarify its role in preventing the progression of coronary atherosclerosis. To the best of our knowledge, this is the first study to investigate the relationship between visit-to-visit variability in the SBP and the progression of CAC. Large prospective trials are needed to better assess this relationship.

CONCLUSIONS

In conclusion, visit-to-visit variability in the SBP could be a novel risk factor for the progression of CAC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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