Scientific Contributions

Pulse Pressure Is an Independent Predictor for the Progression of Aortic Wall Calcification in Patients With Controlled Hyperlipidemia

Yoshikazu Miwa, Motoo Tsushima, Hisatomi Arima, Yuhei Kawano, Toshiyuki Sasaguri

Abstract—Recent epidemiological studies suggested that calcifications of the aorta and the coronary arteries are important predictors for cardiovascular morbidity and mortality. However, the relation between blood pressure components and the progression of vascular wall calcification has remained unclear. We quantified calcium deposits in the abdominal aorta as the percentage of aortic calcification volume (%ACV) using computed tomography in patients with hyperlipidemia. Those who had aortic calcification were treated with lipid-lowering agents and followed-up for >2 years (6.3±3.2 years). The relationship between the components of blood pressure and the increase in %ACV per year (Δ%ACV/year) was assessed in subjects in whom serum lipid levels were well controlled during the follow-up periods. An age- and sex-adjusted correlation analysis showed that Δ%ACV/year was significantly correlated to body mass index (r=0.229, P=0.015), systolic blood pressure (r=0.244, P=0.009), and pulse pressure (r=0.359, P<0.001). A multivariate regression analysis revealed that pulse pressure is an independent and the most sensitive predictor for Δ%ACV/year (β=0.389, P<0.001) among the blood pressure components. These results suggested that increase in pulse pressure promotes the progression of vascular calcification. (Hypertension. 2004;43:536-540.)

Key Words: hypertension ■ calcium ■ aorta ■ pulse ■ imaging ■ risk factors

Calcification in the aorta and coronary arteries is a strong predictor for cardiovascular morbidity and mortality.1,2 Previous studies have shown the close relationships between arterial wall calcification and abnormal serum lipid levels. Arterial wall calcification is common in patients with familial hypercholesterolemia, a genetic disorder of cholesterol metabolism.3-5 Several studies have identified the relationship between the serum level of low-density lipoprotein cholesterol (LDL-C) and arterial wall calcification; moreover, lipid-lowering therapy using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has been reported to inhibit the progression of arterial wall calcification.6-7 In patients receiving long-term hemodialysis, elevated serum triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels are risk factors for coronary artery calcification.8 These studies suggested that abnormal serum lipid levels promote calcium deposition in the arterial wall.

Several studies have examined the influence of hypertension on the progression of arterial wall calcification. In these studies, antihypertensive therapy has been shown to inhibit the formation of calcified lesions, suggesting that hypertension promotes calcium deposition in the arterial wall.9-11 However, it remains undetermined which blood pressure (BP) component, ie, systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), or pulse pressure (PP) is responsible for the accelerated formation of calcification, probably because the abnormal serum lipid levels may have made it difficult to assess the effect of BP alone on the formation of calcified lesions.

Computed tomography (CT) is a useful tool to evaluate the level of arterial wall calcification. Most of the previous studies used the “calcium score” determined by CT as a semi-quantitative index of calcification of the aorta or coronary arteries.3-7 However, the calcium score may not accurately reflect subtle changes in calcium deposit levels. To accurately quantify the degree of calcium deposition, we developed an image color analysis software program that can automatically determine the percentages of calcified volume against whole vascular volume (%ACV) using plain CT.9 We previously reported a strong correlation between %ACV and aortic calcification dimension in aortas of autopsy specimens, the latter of which was determined using soft X-ray photographs.12

In the present study, using our method, we studied the relationship between the BP components and the progression of aortic wall calcification. To exclude interference by serum lipid levels, only subjects whose lipid levels were well controlled during the follow-up periods were analyzed.
Methods

Subjects
This prospective cohort study was started in April 1988 at the National Cardiovascular Center (Suita, Japan). Recruitment of the subjects was closed in March 1999 and the follow-up ended in April 2001. We obtained informed consent to join this study from asymptomatic patients with untreated hyperlipidemia (serum total cholesterol (TC) levels $>5.72$ mmol/L or serum triglyceride (TG) levels $>1.70$ mmol/L). Patients with severe hyperlipidemia (TC $>9.10$ mmol/L or TG $>5.65$ mmol/L), genetic disorders in lipid metabolism such as familial hypercholesterolemia, severe diabetes mellitus (HbA1c $>7.0$%), secondary hypertension, renal insufficiency, and abdominal aortic aneurysm were excluded from the analysis. Those using warfarin were also excluded. They were subjected to lipid-lowering therapy and followed until 2001. Simultaneously, we started antihypertensive therapy in all subjects with untreated hypertension. To subjects already using antihypertensive agents, we re-administered the drugs after a washout period of at least 1 month.

Four hundred eight patients agreed to join the study. They were subjected to a plain CT examination, and aortic wall calcification was found in 204 subjects. During the study, 2 subjects died of cerebral infarction, 16 subjects chose to discontinue their participation in the study, and serum lipid levels could not be well controlled in 70 subjects. Finally, 116 subjects (74 men and 42 women) who achieved optimal serum lipid levels (whose average TC and TG concentrations through the follow-up periods were $5.72$ and $1.70$ mmol/L, respectively) entered into the present study.

Calculation of %ACV and Δ%ACV/Year
We conducted plain CT at the first examination and every 6 months thereafter during follow-up periods for $>2$ years. The lower abdominal aortas of subjects in the supine position were scanned for 9.6 seconds at 120 kV and 200 to 250 mA at 10-mm intervals using a CT/T 2-8800 (GE Company, Milwaukee, Wisc). The percentages of calcified areas against the whole vascular area were calculated from images of 4 consecutive slices just above the bifurcation of common iliac arteries using the TES-100 image color analysis software program as described.

As shown in Figure 1A, when an observer traced the edge of the aorta after placing CT images into the computer system, this software transformed the monochrome CT image into a color image indicating the levels of density with 10 different colors. We considered the areas with 2 yellow colors (Figure 1B, No.1 and No. 2) to be calcified. The percentage of the sum of these areas against the whole area was automatically calculated by the software program; %ACV was determined by averaging the values of the 4 slices (Figure 1C).

To assess the reproducibility of %ACV measurements, paired examinations were performed by a single observer on 2 different occasions (intraobserver reproducibility) and by two observers on the same occasion (interobserver reproducibility) in a group of 50 subjects. The intraobserver and interobserver coefficients of variation were 4.4% and 5.1%, respectively.

Two independent masked observers determined the level of %ACV. The rate of progression of %ACV was represented by Δ%ACV/year calculated with the following formula: (%ACV at the end of follow-up − %ACV at the baseline)/follow-up period (year).

Clinical Parameters
We evaluated several clinical parameters at the first examination and every 6 months thereafter during follow-up periods for more than 2 years. In each examination, we measured BP, fasting serum lipid levels (TC, LDL-C, HDL-C, and TG), fasting plasma glucose (FPG), and %ACV. The measurements were performed in the morning after an overnight fast. BP was measured after 15 minutes of quiet rest in the supported right arm of the seated subjects with a mercury sphygmomanometer cuff-size adjusted for arm circumferences. Phases I and V of the Korotkoff sounds were considered SBP and DBP, respectively, PP and MBP were calculated with the following formula: PP = SBP − DBP and MBP = DBP + PP/3. Three measure-
ments performed with intervals for more than 2 minutes were averaged. Hypertension was defined as: (1) current use of antihypertensive agents and/or a history of hypertension; (2) SBP≥140 mm Hg; or (3) DBP≥90 mm Hg. During follow-up periods for more than 2 years, we examined BP, lipid levels, and FPG every 6 months. TC, HDL-C, and TG levels were enzymatically determined using an autoanalyzer. The levels of LDL-C were calculated using Friedewald equation. The concentration of FPG was measured by the glucose oxidase method.

### Statistical Analyses
In the present study, we used the values of clinical parameters obtained at the first examination after starting treatment as baseline values. To compare the mean values of %ACV, analysis of covariance was used. When a significant difference was obtained by analysis of variance, the differences among groups were assessed by Scheffe test. In a simple regression analysis, Pearson correlation coefficients were used for continuous variables and Spearman correlation coefficients were used for categorical variables. Age- and, sex-adjusted, and multivariate-adjusted correlations were analyzed by multiple regression models. In a multivariate-adjusted analysis, age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking (yes=1, no=0), antihypertensive treatment (yes=1, no=0), and follow-up period were entered into the model. Values were represented as means±SD. P<0.05 was considered statistically significant. Statistical analyses were performed with Stat View Version 5.0 (SAS Institute Inc, Cary, NC).

### Results
First, to confirm that our method is able to evaluate the progression of aortic calcification, we analyzed the change of %ACV during follow-up for 5 years in 50 randomly selected subjects. As shown in Figure 2, %ACV significantly increased at 1.5 or more years after the baseline examination. The increase in %ACV was almost linear. Therefore, we considered Δ%ACV/year as a marker of the progression of calcification in subjects whom we could follow-up for >2 years in the present study.

Table 1 shows the characteristics of the subjects at the baseline (first examination after the beginning of the treatment). Their ages ranged from 43 to 75 years. The mean value of basal %ACV was 5.0%. The mean follow-up period was 6.3 years. %ACV decreased in 12 subjects and increased in 103 subjects when the study was completed.

To determine clinical parameters that influence the progression of aortic wall calcification, we analyzed the relationships between the conventional risk factors for atherosclerosis and Δ%ACV/year. In a simple correlation analysis, Δ%ACV/year was significantly correlated with age, BMI, SBP, and PP (Table 2). The lipid levels, FPG, habitual smoking, and the use of HMG-CoA reductase inhibitors showed no significant relationships with Δ%ACV/year. In an age- and sex-adjusted correlation analysis, BMI, SBP, and PP showed significant correlations with Δ%ACV/year. When the subjects were divided into 3 groups according to the levels of PP, age-adjusted and sex-adjusted Δ%ACV/year was significantly elevated in the high PP (≥60 mm Hg) group compared with the moderate PP (50≤PP<60 mm Hg) and low PP (<50 mm Hg) groups (Figure 3). Furthermore, by a multivariate regression analysis including age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking, antihypertensive treatment, and follow-up period, PP was revealed to be the strongest risk factor for the progression of aortic wall calcification, whereas DBP and MBP were not detected as a predictive factor (Table 3).

### Discussion
To our knowledge, this is the first prospective study revealing that PP is an independent risk factor for the progression of arterial wall calcification in patients with controlled hyperlipidemia to exclude the influence of abnormal lipid levels.

In general, SBP progressively increases while DBP decreases in humans older than 50 years, resulting in the
increase in PP. This change is thought to be caused by the remodeling of arterial walls resulting from the decrease in wall elasticity, for which vascular calcification is one of the major factors. In the present follow-up study, the multivariate regression analysis showed that PP was the strongest risk factor for the increase in %ACV/year. To take into account the interim measures every 6 months during the follow-up periods, we also assessed predictors for the increase in %ACV by the pooling of repeated observation method.13,14 By using this method, PP was again detected as the strongest predictor for %ACV increase (data not shown). These results suggest that the increase in PP on its own promotes arterial calcification.

Previous studies reported a difference between genders in the frequency of vascular calcification. In a cohort study in a large population of >100,000, the prevalence of aortic calcification detected with a chest x-ray examination did not differ between men and women before middle age. However, in subjects older than 65 years, the frequency was significantly larger in women than in men.15 One of the reasons for this difference was considered to be the change in hormone levels after menopause in women. The decrease in estrogen concentrations is associated with the increase in LDL-C levels and induces vascular calcification; furthermore, hormone replacement therapy suppresses the progression of aortic calcification in women after menopause.16–18 However, in our population, there was no significant gender difference in %ACV/year (Table 2), probably because most of our subjects were middle-aged and the lipid profiles were controlled.

The calcified lesions we analyzed in the present study were only atherosclerosis-related. There are 2 distinct forms of arterial wall calcification.19 One is an intimal calcification that develops as part of an atherosclerotic plaque, and the other is a medial calcification formed with aging and in patients with diabetes, end-stage renal disease, and microaneurysm, and a number of rare genetic disorders. Most previous studies did not discriminate between them, although the volume of vascular calcification has been reported to be proportional to that of whole atheromatous plaques including calcification.20,21 However, we excluded patients who had diseases that would promote the medial calcification, and almost all of the calcium deposits found with CT were located in the intima in our subjects. Therefore, our results may be applicable to the medial calcification.

Our study has several limitations. First, although ~80% of the subjects were administered HMG-CoA reductase inhibitors, the other classes of lipid-lowering drugs such as probucol and fibrates were also used. HMG-CoA reductase inhibitors22 and probucol23,24 have been reported to have pleiotropic effects besides cholesterol-lowering effects in recent studies. In our subjects, however, this lack of uniformity may not have affected the analysis because there was no significant difference in %ACV/year among lipid-lowering agents in a simple correlation analysis (Table 2). Second, BP was measured only in the office. Therefore, other factors such as the white-coat effect may have influenced the BP.

In conclusion, we demonstrated that PP is an independent predictor for the progression of atherosclerotic calcification in lipid-controlled subjects. Our results suggested that an increase in PP is not only a result of vascular wall stiffening but also an accelerator of vascular calcification. These results support, in part, the strong correlation between PP and cardiovascular morbidity and mortality.

### Table 2. Correlation Coefficients Relating to Δ%ACV/year

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Simple Correlation</th>
<th>Age- and Sex-Adjusted Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>0.206</td>
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<tr>
<td>Sex</td>
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<td>BMI</td>
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<td>SBP</td>
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<td>DBP</td>
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<td>MPP</td>
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<td>PP</td>
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<td>TC</td>
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<td>HDL-C</td>
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<td>LDL-C</td>
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<td>TG</td>
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<td>FPG</td>
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<td>Smoking habit (yes/no)</td>
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<td>HMG-CoA reductase inhibitor (yes/no)</td>
<td>−0.045</td>
<td>0.633</td>
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### Table 3. Multivariate Regression Coefficients Relating to Δ%ACV/year

<table>
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<th></th>
<th>r</th>
<th>β</th>
<th>P Value</th>
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<tr>
<td>SBP</td>
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<tr>
<td>DBP</td>
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<td>MBP</td>
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<tr>
<td>PP</td>
<td>0.436</td>
<td>0.389</td>
<td>&lt;0.001</td>
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</table>

Multivariate regression analysis including age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking, antihypertensive treatment, and follow-up period.
References


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