Validity and Usefulness of Aortic Arch Calcification in Chest X-Ray

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Background: Arterial calcification is associated with cardiovascular (CV) disease, to be leading to vessel wall stiffness and causing the management of hemodynamics in the elderly more difficult. Here, we compared the extent of calcification in the aortic arch by reviewing chest X-rays to that in the abdominal aorta as assessed by more detailed examinations. In addition, the validity of the grading and the relationship of this useful grading to clinical risk factors were evaluated.

Methods and Results: The extent of aortic arch calcification (AAC) on a postero-anterior plain chest X-ray was divided into four grades (0 to 3). First, AAC grade was assessed in patients who underwent two quantitative examinations for abdominal aortic calcification; lateral radiograph of lumbar spine and/or computer tomography, and was positively correlated with the abdominal aortic calcification level. Subsequently, AAC grade in 239 out-patients (115 men; mean age, 61.9 years) was also evaluated, and was 0, 1, 2, and 3 in 46%, 22%, 29%, and 4% of the population, respectively, was significantly associated with pulse pressure and intima-media thickness. AAC grade in patients with diabetes or renal dysfunction was significantly higher than in those without each risk, but there was no association with other risk factors. In addition, AAC grade was positively correlated with risk factor clustering.

Conclusion: Assessment of AAC detectable on a chest X-ray is very useful and its grade reflects the magnitude of calcified change in the whole aorta. In addition, AAC evaluation may provide supportive information for atherosclerotic risk stratification.


Key words: Aortic arch calcification, Grading, Risk factor clustering, Atherosclerotic risk stratification

Introduction

Arterial calcification is a complication of advanced atherosclerosis. Arterial stiffness resulting from calcification is shown to be strongly associated with variable blood pressure (such as isolated systolic hypertension and orthostatic hypotension)¹, ² and an increase in myocardial afterload, leading to left ventricular hypertrophy³. In addition, loss of elastic recoil due to arterial calcification results in unstable hemodynamic consequences, leading to a decline in end-organ perfusion. In general, arterial calcification occurs at two anatomical sites in the arterial wall, the media and the intima⁴, ⁵. Medial calcification, which is frequently seen in the elderly⁶, diabetes⁷, ⁸ and chronic renal failure patients on dialysis⁹, ¹⁰, is observed as continuous linear deposits along the internal elastic lamina. On the other hand, intimal calcification, which is seen as patchy scattered deposits only occurring within atherosclerotic plaques, has been shown to be associated with plaque vulnerability¹¹, ¹². Several imaging examinations have been employed to detect and quantify macroscopic arterial calcification. Plain radiographs have traditionally been a valuable and inexpensive tool for detecting arterial calcification, especially aortic calcification, in routine clinical work. Arterial medial calcification is radiographically visible as a radio-opaque finding, like a linear...
tram-track\textsuperscript{13}. In contrast, intimal calcification is characteristically identified as a spotty and patchy radiopaque finding; however, it is difficult to distinguish these calcified changes in the arterial wall solely by radiographic techniques without a pathological approach. Recently, high-tech non-invasive examinations, such as electron beam-computer tomography (EB-CT) and multi-detector row CT (MD-CT), have been shown to be the gold standard for evaluating coronary artery calcification (CAC), with the power of quantifying its severity and progression\textsuperscript{14}. Several reports have demonstrated that the extent of CAC as assessed by these examinations is a good predictor of coronary events\textsuperscript{15, 16}; however, these examinations can not be easily or commonly performed.

In this study, we evaluated the extent of AAC by reviewing a chest X-ray, and compared it with abdominal aortic calcification. In addition, the AAC grade was evaluated in comparison with traditional atherosclerotic risk factors.

**Methods**

**Study Population**

First, the accuracy of two independent examinations to assess the extent of abdominal aortic calcification was confirmed in 27 patients who underwent both examinations described below. Second, AAC grade was determined by reviewing a simple chest X-ray in 239 consecutive asymptomatic outpatients (male/female = 115/124, mean age 61.9 ± 10.8 years) and was compared with the extent of abdominal aortic calcification. The Medical Ethics Committee of The University of Tokyo approved this study. Informed consent was obtained from all patients before the study.

**Assessment of Aortic Arch Calcification**

The extent of AAC was assessed in a routine postero-anterior chest X-ray. As shown in Fig. 1, AAC extent was divided into four grades according to the categorization proposed in a previous report\textsuperscript{17}. Briefly, we scored the area of calcification as four grades: grade 0, no visible calcification; grade 1, small spots of calcification or a single thin area of calcification of the aortic knob; grade 2, one or more areas of thick calcification; grade 3, circular calcification of the aortic knob.

**Quantitative Assessment of Abdominal Aortic Calcification**

To quantify the extent of abdominal aortic calci-
Atherosclerotic Risk Factors

Hypertension was defined as a systolic blood pressure (BP) of more than 140 mmHg, diastolic BP of more than 90 mmHg, and/or use of anti-hypertensive drugs. To measure serum low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol and triglyceride, a blood sample was obtained after overnight fasting. Dyslipidemia was defined as an LDL-C level of more than 140 mg/dL, HDL-C level of less than 40 mg/dL, triglyceride level of more than 150 mg/dL and/or use of lipid-lowering drugs. Diabetes mellitus was defined as a fasting glucose level of more than 126 mg/dL, post-prandial glucose level of more than 200 g/dL, and/or use of anti-diabetic drugs. In addition, renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) level of less than 60 mL/min/1.73 m².

Measurement of Carotid Artery IMT

Ultrasound measurements of intima-media thickness (IMT) of the common carotid artery were performed by longitudinal scanning. IMT of the carotid artery was measured on high-resolution, 2-dimensional ultrasound images obtained with an SSA-270A ultrasound machine (Toshiba) with a 7.5-MHz linear-array transducer. This procedure was performed by an examiner who was unaware of the subjects’ clinical background, as previously described.

Statistical Analysis

Analysis of variance (ANOVA) and paired Student’s t-test were used for parametric procedures. The Mann-Whitney U test and Wilcoxon tests were alternatively used as nonparametric tests. When data were normally distributed, the two groups were compared by unpaired t-test; otherwise, the Mann-Whitney U test was used. Statistical comparisons among more than three groups were performed by the Kruskal-Wallis test. Data in the text, tables, and figures are expressed as the mean ± standard deviation (SD). A value of \( p < 0.05 \) was considered significant.

Results

Positive Correlation of Calcification Extent Between Aortic Arch and Abdominal Aorta

First, the extent of calcification in the aortic arch and abdominal aorta was assessed by three independent non-invasive examinations, postero-anterior chest X-ray (grading), lateral radiograph of the lumbar spine (sum length; mm) and plain abdominal CT scan (%ACI) (Fig. 1). The positive correlation between the sum length and %ACI showed consistent accuracy in the quantitative assessment of abdominal aortic calcification \((r = 0.671, p < 0.01)\) (data not shown); thereafter, we evaluated AAC grade by reviewing the chest X-rays of 239 patients. Baseline characteristics of the population are shown in Table 1. There was no difference between male and female groups in atherosclerotic risk factors (hypertension, diabetes, dyslipidemia and renal dysfunction), except for smoking. Regarding medication, there was no difference between male and female groups, except calcium channel blockers. AAC grade was 0, 1, 2, and 3 in 46%, 22%, 29% and 4% of the population, respectively (Fig. 2A). The accuracy and reproducibility of this technique for grading were 82%, 79%, 75% and 88% in grade 0, 1, 2 and 3, respectively. Regarding sex differences, the distribution of AAC grade was similar (Fig. 2B). Elderly patients (over 65 years) had a significantly higher AAC grade than those go anser than 65 years, and the tendency was more marked in patients over 75 years (Fig. 2C).

In 27 patients who underwent all examinations, the correlation between AAC grade and the extent of abdominal aortic calcification was investigated. Background characteristics of these patients showed hypertension (40.7%), dyslipidemia (29.6%), diabetes (7%), and renal dysfunction (25.9%). The sum length of abdominal aortic calcification was positively associated with AAC grade (30.3 ± 15.5, 58.9 ± 14.2, 75.3 ± 21.2, and 145.0 ± 14.2 in AAC grade 0, 1, 2, and 3, respectively) (Fig. 3A). Similarly, comparison of AAC grade with %ACI also showed a positive correlation \((2.5 ± 0.8\% \text{, } 7.4 ± 1.7\% \text{, } 15.6 ± 2.7\% \text{, and } 21.2 ± 4.3\% \text{ in AAC grade 0, 1, 2, and 3, respectively})\) (Fig. 3B).

Association of Aortic Calcification with Pulse Pressure and Carotid IMT

AAC grade was not associated with systolic or diastolic BP (systolic BP; 130 ± 18, 135 ± 24, 134 ± 17,
**Table 1.** Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>239</td>
<td>115</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.9±10.8</td>
<td>60.6±11.6</td>
<td>63.2±10.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hypertension</td>
<td>135 (56.5%)</td>
<td>72 (62.6%)</td>
<td>63 (50.8%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>70 (29.3%)</td>
<td>38 (33.0%)</td>
<td>32 (25.8%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>162 (67.8%)</td>
<td>82 (71.3%)</td>
<td>80 (64.5%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>62 (25.9%)</td>
<td>31 (27.0%)</td>
<td>31 (25.0%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smoking</td>
<td>83 (34.7%)</td>
<td>72 (62.6%)</td>
<td>11 (8.9%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2±4.3</td>
<td>24.9±4.4</td>
<td>23.7±4.2</td>
<td>n.s.</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic BP</td>
<td>132.5±18.9</td>
<td>133.2±18.0</td>
<td>131.9±19.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>76.2±12.2</td>
<td>77.9±12.8</td>
<td>74.7±11.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pulse Pressure</td>
<td>56.3±14.7</td>
<td>55.3±14.0</td>
<td>57.2±15.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anti-hypertensive drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>27 (11.3%)</td>
<td>16 (13.9%)</td>
<td>11 (8.9%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CCB</td>
<td>95 (39.7%)</td>
<td>53 (46.1%)</td>
<td>42 (33.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>a/β blockers</td>
<td>25 (10.5%)</td>
<td>14 (12.2%)</td>
<td>11 (8.9%)</td>
<td>n.s.</td>
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<tr>
<td>Anti-diabetic drugs</td>
<td></td>
<td></td>
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<tr>
<td>Sulfonyl urea</td>
<td>23 (9.6%)</td>
<td>12 (10.4%)</td>
<td>11 (8.9%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Biguanide</td>
<td>1 (0.4%)</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>aGI s</td>
<td>5 (2.1%)</td>
<td>1 (0.9%)</td>
<td>4 (3.2%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Insulin</td>
<td>7 (2.9%)</td>
<td>2 (1.7%)</td>
<td>5 (4.0%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>43 (18.0%)</td>
<td>16 (13.9%)</td>
<td>27 (21.8%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Others</td>
<td>10 (4.2%)</td>
<td>5 (4.3%)</td>
<td>5 (4.0%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; BP, blood pressure; ACEI/ARB, angiotension-converting enzyme inhibitors and/or angiotension II receptor blockers; CCB, calcium channel blockers; αGI s, αglucosidase inhibitors; statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors; p value, probability value; n.s., not significant

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**Fig. 2.** Distribution of AAC grade in chest X-ray.
(A) Distribution of AAC grade determined by reviewing chest X-rays in all subjects. (B) There was no significant sex difference in the distribution of AAC grade. (C) Elderly patients (over 65 years) had a significantly higher AAC grade than those less than 65 years, and the tendency was more marked in patients over 75 years (p<0.01).
and 136 ± 14 mmHg, diastolic BP; 77 ± 13, 78 ± 13, 74 ± 10, and 172 ± 10 mmHg in AAC grade 0, 1, 2, and 3, respectively). AAC grade was positively correlated with pulse pressure (53 ± 12, 58 ± 19, 60 ± 14, and 65 ± 14 mmHg, in AAC grade 0, 1, 2, and 3, respectively) (Fig. 4A). Significantly greater IMT, a marker of atherosclerosis, was found in patients with higher AAC grade (Fig. 4B).

**Correlation of Aortic Calcification with Risk Factor Clustering**

AAC grade was compared between the presence and absence of traditional risk factors (Fig. 5A). AAC grade in patients with diabetes was significantly higher than in those without diabetes. In addition, a similar significance was found in patients with renal dysfunction (eGFR level of less than 60 mL/min/1.73 m²). There was no significant difference in grade according to the presence or absence of hypertension and dyslipidemia. The clustering of these risk factors (up to 4 factors) was significantly associated with increasing AAC grade (Fig. 5B).

**Discussion**

The present study demonstrated the value of assessing AAC grade using a simple chest X-ray examination to allow semi-quantitative evaluation for atherosclerotic risk stratification. Because the progression of arterial calcification is very slow, it is easier to detect slight and time-related alterations of calcium deposition in the arterial wall using high-tech non-invasive imaging, such as EB-CT and MD-CT. In contrast, the detection of macroscopic arterial calcification by plain radiographs is relative crude. In addition, the extent of arterial calcification and its significance are generally easily disregarded in routine clinical work; however, this simple detection of arterial calcification is reproducible, inexpensive, and readily available for large populations, as compared to such high-tech imaging. In the present study, AAC grade was positively correlated with the extent of abdominal aortic calcification.
cation in independent examinations, suggesting that AAC grade as assessed by a simple chest X-ray may reflect the degree of calcification in the whole aorta. Thus far, few reports have fully evaluated the correlation of macroscopic calcification between the aortic arch and the abdominal aorta using independent examinations; therefore, our observations support the view that this simple examination, which is easy to follow up routinely, is indispensable for atherosclerotic risk evaluation, and may consequently help provide more information to predict the risk of CV events.

The atherosclerotic vasculature has many features, such as ‘atheroma’ and ‘sclerosis’ [4]. The condition leads to functional changes (such as arterial stiffening) and localized morphological changes (such as arterial wall thickening) [1, 4]. Arterial calcification can be seen at two different anatomical sites in the vessel wall; medial calcification (known as Mönckeberg’s sclerosis) and atherosclerotic intimal calcification [22]; however, it is difficult to distinguish these two calcified lesions clearly using only a plain radiographic approach, including simple chest X-ray, without a pathological approach. This difficulty is marked in the elderly, because there are likely to be mixed calcified lesions in their arteries. In fact, if spotty intimal calcification exists with massive medial calcification visible as linear tram-tracks radiographically, it will probably not be possible to distinguish them.

Several reports have shown a positive correlation of abdominal aortic calcification with CV events, using lateral lumbar X-ray [23]. Several huge clinical studies, including the Framingham Heart Study, have demonstrated that the extent of abdominal aortic calcification was a good predictor of CV events and congestive heart failure over a 20-year follow-up period (relative risk 1.9 and 2.2, respectively) [23-25]; however, this examination is not very common in clinical routine work, because it is basically used to assess bone mineralization in patients with suspected osteoporosis. In the present study, we confirmed the good correlation between AAC grade and the extent of abdominal aortic calcification. This result suggests that grading AAC detectable on a chest X-ray can be strongly recommended to evaluate the stratification of risk factors.

On the other hand, there are relatively few reports regarding the predictive value of AAC for CV events using a simple chest X-ray, although many studies have previously shown a positive correlation of abdominal aortic calcification with CV events. One report demonstrated that more CV events occurred in patients
with AAC than in those without AAC. However, the evaluation method in the report was dependent upon the presence or absence of AAC only using chest X-rays, without considering the extent of AAC; therefore, our evaluation method may be favorable to assess the predictive value of AAC grade for the new onset of CV events. It is necessary to further evaluate whether this assessment of AAC grade has incremental predictive value, beyond traditional coronary risk factors, for the new onset of CV events.

IMT, a prognostic indicator, is commonly used to assess the progression of atherosclerosis. Although few reports have compared IMT with aortic calcification, a good correlation between both factors was found in the present study. Indeed, carotid arterial wall thickening associated with plaques is frequently seen in patients with advanced atherosclerosis, and its magnitude is positively correlated with CV events; therefore, similar to IMT, the risk of CV events is probably higher in patients with a higher AAC grade on chest X-rays.

In the present study, we compared AAC grade with traditional risk factors; diabetes, hypertension and dyslipidemia. First, among these factors, we found a significant association of diabetes with AAC grade among coronary risk factors. In general, diabetes is thought to be a strong risk factor for the progression of not only atherosclerosis, but also arteriosclerosis. It has been reported that high glucose-induced expression of the osteopontin gene and advanced glycation end products accelerated mineralization in microvascular pericytes in a culture model. In addition, our observations showed that patients with insulin treatment had a higher AAC grade than those without insulin in simple correlation analysis (data not shown), suggesting that the status of diabetic patients who need insulin treatment is probably more serious.

Systolic hypertension, in conjunction with a decline in diastolic blood pressure, results in a decrease in end-organ perfusion, including coronary flow. In addition, arterial stiffness augments an increase in myocardial afterload, finally leading to left ventricular hypertrophy. In this study, patients with a higher AAC grade had significantly higher pulse pressure, consistent with previous reports. The Framingham Heart Study demonstrated that the risk of coronary artery diseases was negatively correlated with diastolic BP at any level of systolic BP, suggesting that pulse pressure is a good predictor of coronary events; therefore, in our population, the new onset of CV events may frequently occur in patients with high AAC grade. Further investigation of the new incidence of CV events during long-term follow up in this population is necessary.

Many reports have shown the relationship of abnormal serum lipid levels (such as elevated cholesterol and TG and reduced HDL-C) to aortic calcification, suggesting that dyslipidemia promotes calcium deposition in the arterial wall; however, most these studies evaluated abdominal aortic calcification, but not AAC. In addition, the relationship between lipids and aortic calcification is likely to remain controversial, because several studies have indicated that no correlation is present between abdominal aortic calcification and serum lipid components. In this study, there was no association between AAC grade and the presence of dyslipidemia, although our cohort included 67.8% patients with dyslipidemia, including statin users (18%). One possible reason may be the small size of this cohort, suggesting that higher-powered studies are required to clearly define the relationship between lipids and AAC. Several retrospective studies have demonstrated that statins inhibit the progression of coronary artery calcification as a pleiotropic effect beyond their cholesterol-lowering effects. In addition, statins have also been shown to possess inhibitory effects on vascular smooth muscle cell calcification in vitro. Further analysis to evaluate the longitudinal change of AAC grade during a long-term follow-up period is necessary.

Renal dysfunction (so-called chronic kidney disease, CKD) has been shown to be associated with atherosclerotic diseases. Many reports have shown that CKD patients have arterial calcification due to mineral disorders, including hyperphosphatemia. Similar to diabetes in this study, the evidence that patients with a decline in eGFR had an increased AAC grade was consistent with previous reports.

Recently, the accumulation of atherosclerotic risk factors has been shown to act in a pro-atherogenic fashion, like metabolic syndrome. In the present study, the accumulation of these three factors was significantly associated with the AAC grade. This result suggests that the clustering of multiple risk factors, which provoke metabolic disorder, such as oxidative stress and aggressive adipocytokines, may augment calcium deposition in the aortic wall. Thus far, there is no established therapy to prevent arterial calcification, and therefore, at present, the most appropriate therapeutic strategy may be to manage modifiable risk factors strictly.

The principal limitation of the present study is that our assessment using AAC grades was relatively crude. This approach is not a quantitative method, and it is possible that the true calcium deposition in the aortic wall was underestimated. Clinically, CT
scan is frequently used to quantify abdominal aortic calcification as a percentage of the cross-sectional area of the aorta. In AAC, it has been thought to be difficult quantify the calcified level using plain chest CT scan. In the present study, the present population did not all undergo a chest CT scan. To make this evaluation of AAC grade more valid, further investigation to compare AAC grade by assessing chest X-ray and chest CT scan is necessary. In addition, the population in the present study was small; therefore, a further large-scale prospective study is necessary.

In conclusion, our cross-sectional study demonstrated that AAC grade was associated with the extent of abdominal aortic calcification, and the accumulation of traditional atherosclerotic risk factors was positively correlated with the AAC grade. Our results emphasize that the magnitude of aortic calcification is worthy of greater attention in routine clinical work. Our data strongly suggest that risk stratification by a simplified approach to assess aortic calcification may provide supportive information for the primary preventive management of atherosclerotic disease.

Acknowledgements

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