Clinical Significance of Coronary Calcification

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Coronary artery calcification (CAC) was assessed by cinefluoroscopy and its extent was scored (CAC score) in 2,163 consecutive patients undergoing coronary angiography, based on the angiographic and clinical data, the patients were categorized into 8 types of coronary artery disease (CAD). The CAC score was lowest in angiographically normal subjects (0.12±0.60) and highest in patients with silent myocardial ischemia (14.31±8.61). Risk factors for CAC were advanced age, male sex (at age <80 years), hypertension, diabetes mellitus, and a high grade of organic coronary stenosis. The CAC score in patients with acute coronary syndrome (unstable angina + acute myocardial infarction; 5.48±7.42) was significantly lower than that in those with chronic CAD (silent ischemia + stable angina; 9.72±8.73; p<0.0001), but was still higher than that in normal subjects or those with vasospastic angina (0.92±2.88; p<0.0001). The results indicate that CAC is a manifestation of coronary atherosclerosis and its appearance depends on the pathological type of ischemic heart disease. Fixed stenosis with a slow and chronic process tends to be associated with CAC. The clinical implication of extensive CAC in acute coronary syndrome compared with normal subjects should be further investigated. (Circ J 2002; 66: 473–478)

Key Words: Acute coronary syndrome; Cinefluoroscopy; Coronary artery calcification; Ischemic heart disease; Stenosis

Coronary artery calcification (CAC) is increasingly attracting the attention of clinical cardiologists because it may provide valuable information for the treatment and prevention of ischemic coronary diseases; for example, the presence of calcification around a target lesion for coronary intervention can predict coronary artery dissection in response to balloon angioplasty (PTCA). In diffusely and severely calcified lesions, PTCA or coronary stenting alone is likely to be inadequate and prior rotational atherectomy is highly recommended. As prophylaxis, electron-beam computed tomography (EBCT) has been used in the USA to identify individuals with CAC who are currently asymptomatic, but are at increased risk of developing acute coronary syndrome (ACS). However, the primary etiologic mechanism of ACS is either acute thrombus arising from the ruptured fibrous cap of a soft atherosclerotic plaque or thrombosis associated with plaque surface erosion during inflammation. A large-scale angiographic study in Japan has demonstrated that ACS is more likely to develop from insignificant than significant stenotic lesions. On the other hand, CAC develops in histologically matured, progressed atherosclerotic plaques, so it is questionable whether CAC can accurately predict the risk of acute coronary events.

In Japan, acute myocardial infarction accounts for 35–36% of sudden non-traumatic deaths of adults which affects families through the loss of their mainstay and thus contributes to some social problems. There is an urgent need for a practical method of reliably identifying individuals likely to develop this condition.

Although CAC may be a clue to the risk of ACS there has not been a study of the prevalence of CAC according to the type of CAD (ie, ACS, effort angina pectoris, silent myocardial ischemia etc). The present study aimed to clarify the clinical significance of CAC by comparing its prevalence, age- and sex-related differences, and risk factors among Japanese patients with different types of CAD.

Methods

During the period from June 1990 to September 1999, 2,163 patients (1,354 men, 809 women; age 62.5±10.5 years) underwent initial coronary angiography at International Goodwill Hospital (excluding those who had previously undergone PTCA or coronary artery bypass grafting (CABG) and those with chronic renal failure maintained on chronic dialysis). The 2,163 patients were divided into 8 groups by type of heart disease diagnosed from the combined assessment of medical history and data from electrocardiography (ECG), 2-dimensional echocardiography, coronary angiography, and left ventriculography (Table 1).

Patient Groups

Normal Patients (NORMAL; n=523; 269 men, 254 women; age 58.5±10.8 years) This group included those who underwent coronary angiography for the suspicion of angina, congenital cardiac anomaly, idiopathic cardiomyopathy, valvular disease or aortic aneurysm, but were found to have no radiographic abnormalities of the coronary arteries.

Patients With Vasospastic Angina Pectoris (VAP; n=334; 217 men, 117 women; age 58.9±9.8 years) These subjects...
either had angina symptoms at rest and coronary spasms observed on angiography or no apparent angina symptoms but coronary spasms were induced by exogenous acetylcholine.

Patients With Suspected Effort Angina (R/O AP; n=410; 213 men, 197 women; age 65.8±8.9 years) This group were suspected to have some CAD from their histories and ECG findings during exercise, but only had insignificant (<50%) coronary stenosis on angiography.

Patients With Stable Effort Angina Pectoris (SAP; n=243; 156 men, 87 women; age 66.1±8.7 years) This patient group were suspected to have some CAD from their histories and ECG on exercise findings and were found to have a significant (≥50%) stenosis of at least one main coronary branch on angiography.

Patients With Unstable Angina Pectoris (UAP; n=145; 111 men, 34 women; age 64.8±10.2 years) These patients had Braunwald type B-1, II or III UAP and had a significant (≥50%) stenosis of at least 1 main coronary branch on angiography.

Patients With a Myocardial Infarction (MI) This group comprised 3 types of MI: (i) acute myocardial infarction (AMI; n=268; 215 men, 53 women; age 61.7±11.6 years), (ii) old MI (OMI; n=195; 143 men, 52 women; age 66.1±9.3 years), and (iii) silent myocardial ischemia (SILENT; n=44; 29 men, 15 women; age 69.3±6.9 years) for which there were no angina symptoms (eg, apparent chest pain) but there were ischemic changes on ECG at rest or during exercise and a significant (≥50%) stenosis of at least 1 main coronary branch on angiography.

CAC was defined as positive if there is a mobile white spot or linear tract in the cinefilm at the position of each epicardial coronary artery. The CAC extent (CAC score) was semiquantitatively scored by Yamanaka’s method (Fig 1A). Briefly, CAC was graded from 0 to 4 in each of the 3 main branches (right coronary artery [RCA], left anterior descending artery [LAD], and left circumflex artery [LCX]). The CAC score was calculated as (grade in the RCA + grade in the LAD + grade in the LCX) × number of calcified main branches.

The degree of each fixed coronary stenosis was determined according to the American Heart Association criteria. Overall severity of CAD was scored as a sum of the grades of all coronary stenoses in a similar fashion to the allocation of the Friesinger score (F score) (Fig 1B).

For each of the 8 pathological groups, the relationship of the CAC score with the following parameters was investigated: age, sex, coronary risk factors (hyperlipidemia, hypertension, diabetes mellitus [DM], smoking, obesity, and family history), and F score.

Statistics Statistical analyses were performed using ANOVA and multivariate analysis.
Results

Coronary Atherosclerosis and CAC
There was a positive correlation between the CAC score and F score (r=0.537, p<0.0001). The CAC extent increased with an increase of in the number and severity of coronary atherosclerotic stenoses (Fig 2).

Sex-Related Differences in the Incidence of CAC
CAC occurred significantly more frequent in men (p<0.01) at ages less than 80 years and insignificantly more frequent in women at age 80 years or more.

Age- and Sex-Related Differences in CAC and F Scores
In both men and women, the CAC score increased exponentially with increased age over 50 years. As age increased, the F score increased linearly in men, even when less than 50 years of age, and exponentially in women aged 50 years or more (Fig 3).

CAC Score Analyzed by Age and CAD (Fig 4)
Regardless of age, CAC was absent in all patients with normal coronary arteries, and the patients in the VAP group had only minimal to mild CAC. In contrast, the CAC score increased with age in patients with at least one angiographically proven coronary stenosis (R/O AP, SAP, UAP, AMI, OMI, and SILENT groups). In particular, the CAC score was very high in patients in the SILENT group even at young ages; the mean CAC score in this group was significantly higher (p<0.0001) than that in the SAP group, which had the next highest CAC score of the 8 groups studied.

CAC in Patients With Acute or Chronic Ischemic Heart Disease (Fig 5)
Acute ischemic heart diseases (AMI + UAP groups) were associated with a significantly lower CAC score than that

Table 2 Relationship of F and CAC Scores With Established Coronary Risk Factors (p values)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>F score</th>
<th>CAC score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLP</td>
<td>&lt;0.0001</td>
<td>0.5426</td>
</tr>
<tr>
<td>HT</td>
<td>&lt;0.0001</td>
<td>0.0142</td>
</tr>
<tr>
<td>DM</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>&lt;0.0001</td>
<td>0.1145</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.3855</td>
<td>(0.0180)</td>
</tr>
<tr>
<td>FH</td>
<td>0.0043</td>
<td>0.4700</td>
</tr>
<tr>
<td>TCHO</td>
<td>0.0835</td>
<td>0.4999</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.1059</td>
<td>0.5238</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.0761</td>
<td>0.4953</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>0.1559</td>
<td>0.5437</td>
</tr>
<tr>
<td>TG</td>
<td>0.0812</td>
<td>0.4984</td>
</tr>
<tr>
<td>UA</td>
<td>0.8642</td>
<td>0.7542</td>
</tr>
<tr>
<td>HbA1C</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

TCHO, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides; UA, uric acid; F score, modified Freisinger score; CAC, coronary artery calcification. ( ), CAC score was less with obesity.
associated with chronic ischemic heart diseases (SILENT + SAP groups) \( (p<0.0001) \). Nevertheless, the CAC scores in the AMI+UAP groups (consisting of patients with ACS) were significantly higher than in the NORMAL group.

**CAC and Coronary Risk Factors (Table 2)**

Although there was a significant correlation between the F score and all coronary risk factors other than obesity, CAC only correlated independently with age, DM and hypertension. Above all, the CAC score significantly increased with an increase in hemoglobin A1c (HbA1c) \( (p<0.0001) \). CAC score was less in obese patients (see study limitations).

**Discussion**

CAC, a phenotypic presentation of coronary atherosclerosis, begins to appear immediately after formation of fatty streaks and is microscopically detected even in teenagers.\(^{11}\) With refined microscopic methods, the lesions in younger adults have been revealed to comprise small aggregates of crystalline calcium among the lipid particles of lipid cores.\(^{2,12}\) Such aggregates become more frequent and increase in number with advancing age and the progression of coronary atherosclerosis.\(^{12,13}\) From the pathophysiologic viewpoint, some have suggested that atherosclerotic calcification may represent active calcium mobilization mediated by Gla-containing proteins and osteopontin (ie, a process similar to ossification) and not merely calcification (passive calcium uptake) of the atherosclerotic lesions.\(^{12-14}\) Therefore, CAC appears in the more advanced or mature stage of coronary atherosclerosis.

On the other hand, ACS is the result of instability or disruption of relatively young and immature atherosclerotic plaques.\(^{5,12}\) Culprit lesions are found to be less calcified when assessed by angiography\(^ {15}\) and histology.\(^ {16}\) Therefore, there is a theoretical contradiction emerges in using CAC, which usually appears in the mature stage of coronary atherosclerosis, for predicting the risk of ACS in the same individual. Currently, fluoroscopy, helical computed tomography (CT) and EBCT are available for detecting CAC, and of these, EBCT is the more sensitive for identifying CAC and has the advantage of quantitative evaluation of coronary calcium deposits, though with low reproducibility of assay results. For these reasons, EBCT is widely used in the USA,\(^ {3,5,14}\) but in Japan, the size and cost of EBCT have prevented its extensive use for screening. Cinefluoroscopy can be simply performed with the instruments used for cineangiography and can be applied to screening in Japan. According to a survey by the Japanese Circulation Society, more than 1,200 cineangiography units have been installed in Japanese medical institutions and in the present study, the extent of CAC was investigated in the groups of patients with ischemic heart diseases using cinefluoroscopy.

Although the assessment of CAC extent was only semiquantitative, this study is the first to compare the extent of CAC among patients with different ischemic heart diseases in Japan and should provide valuable information about the relationship between CAC and ischemic coronary diseases, as well as the ability of the CAC score to non-invasively differentiate dilated cardiomyopathy from severe ischemic cardiomyopathy\(^ {10}\) and thus predict the risk of ACS.

Aside from methodological differences, the results of the present and previous studies\(^ {14,17}\) of the relationship between CAC and ACS seem to indicate that the absence of CAC reflects the absence of angiographically significant coronary lesions. Conversely, coronary angiography often fails to detect any significant coronary stenoses in patients with apparent CAC. At present, the most acceptable conclusion is that calcification detected in at least 1 coronary vessel does not necessarily mean the presence of an unstable atherosclerotic plaque at the site of calcification, but rather indicates the latent progression of young plaques that may cause acute coronary events in the future in other coronary branches or other sites of the same branch. This as yet undiscovered process leads to the increased risk of developing coronary events in patients with calcified lesions (risk ratio 1.9–2.7).\(^ {18,19}\) The applicability of the CAC score to the prediction of ACS is only based on this idea.

The present study has shown that CAC is rarely present in individuals of any ages who have normal coronary arteries on angiograms. Patients with VAP had a low CAC score. In patients with other ischemic heart diseases, the CAC score increased with age and the degree of coronary atherosclerotic stenosis. Patients with chronic ischemic heart diseases (SILENT + SAP groups) had much more severe CAC than those with acute ischemic heart diseases (AMI + UAP groups), indicating that CAC extent may have greater predictive value for coronary events in patients with chronic coronary diseases (ie, requiring elective PTCA or CABG) than in those with acute coronary conditions. Analysis of CAC by sex revealed that the sex-related difference in the prevalence of CAC noted at ages less than 80 years disappeared for those older than 80 years, with a rather higher prevalence of CAC in females in this advanced age group. These aged individuals have generally escaped death from the 3 major causes (malignancies, cerebrovascular disorders and cardiovascular disease) and it is interesting that at this advanced age, CAC increases in frequency in women and becomes as prevalent as in men. CAC is part of the coronary atherosclerosis process, but can be regarded as the final product of unruptured atherosclerotic plaques. In the present study, the CAC scores in men and women, as well as the F score in women, increased exponentially with age after 50 years, whereas the F score in men increased linearly with age even at ages less than 50 years. This suggests that individuals aged around 50 years who are susceptible to atherosclerosis may have rapid progression of coronary stenoses caused by soft plaques that are not protected by the chronic mechanism associated with calcification. A recent report of Huang et al states that a large lipid pool in the plaque is primarily responsible for increased stresses upon the fibrous cap and that calcification does not necessarily increase fibrous cap stress;\(^ {20}\) that is, differing speeds of progression and healing of the coronary atheroma may decrease the mechanical stability of the plaque, eventually causing ACS. Clinically, this may explain the pathophysiology of ACS caused by rupture of an uncalcified plaque, which frequently occurs in middle-aged male smokers.\(^ {17}\)

Many previous studies have addressed the risk factors for CAC\(^ {14}\) CAC is the result of ectopic calcification in patients with renal failure who are maintained on hemodialysis,\(^ {21}\) and other risk factors include hypercholesterolemia,\(^ {22,23}\) decreased high density lipoprotein (HDL)-cholesterol concentration,\(^ {23}\) smoking,\(^ {23}\) hypertension,\(^ {24}\) obesity,\(^ {25}\) and the number of existing coronary risk factors.\(^ {24,25}\) DM\(^ {25}\) and hypertriglyceridemia.\(^ {25}\)

Recently, inflammatory change in the vascular wall caused by bacterial infection has been implicated in the pathogenesis of atherosclerosis, and it has long been known
that arterial diseases presenting primarily with severe inflammation (eg, Kawasaki disease and aortitis syndrome) are likely to be associated with vascular calcification. Diabetes mellitus increases the susceptibility to infection and thus to inflammation, which may eventually lead to chronic progression of the vascular calcification.

Although coronary arteries identified as uncalcified by fluoroscopy cannot be concluded to be normal, the present study has shown that angiographically normal coronary arteries have a very low CAC score, and patients with AMI or UAP have mild to moderate CAC, which suggests that the CAC score may be used in practice to identify individuals likely to develop ACS. Such individuals may have latent atherosclerotic plaques liable to rupture and are therefore strongly recommended to have a very-low-cholesterol diet, receive aggressive medication and change their lifestyle to modify existing coronary risk factors.

Study Limitations

The results of the present study indicate that obesity is a negative risk factor for CAC (Table 2). One limitation of this study is that obesity, which may be related to thickness of the chest wall, will compromise the cinefluoroscopic identification of CAC, especially in the left circumflex coronary artery, which is more distant from the cinefluoroscopic film than the other coronary branches. Moreover, if CAC in any main coronary branch escapes detection, the false-negativity is amplified in the CAC score. Thus, the CAC score used in this study tends to underestimate the actual extent of CAC in the presence of obesity.

Another limitation is that it only involved those who had access to International Goodwill Hospital; that is, those who reside in the western dormitory suburbs of Yokohama City. They have a typical urban lifestyle and thus may be more likely to have coronary risk factors such as hyperlipidemia, hypertension, DM and obesity compared with subjects from other regions of Japan. Despite its large scale (n=2,163), the present study may not necessarily provide data reflecting overall tendencies in Japanese individuals.

Conclusions

To the best of our knowledge, this is the first comparison of CAC extent among groups of patients with different CAD and the first investigation of the clinical significance of CAC in Japanese individuals. The results indicate that CAC should not be considered as merely a change associated with aging and that it does progress with increasing age in the presence of coronary atherosclerosis. CAC tended to be severer in patients with chronically progressive atherosclerotic coronary diseases. Diabetes mellitus, hypertension and male sex (at ages <80 years) were identified as the risk factors for CAC. With regard to the ability of the CAC score to predict ACS (eg, UAP, AMI), mild to moderate CAC may suggest the risk of ACS, but the absence of CAC does not completely eliminate the risk of ACS. Cineangiography is widely used in Japan and detecting the presence of CAC with cinefluoroscopy is a practical and worthwhile screening method for predicting the risk of ACS among Japanese people with high coronary risk factors. However, this has not begun and requires the predictive value, cost-performance, or/and balance of the risk–benefit ratio to be prospectively investigated.

References


