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Usefulness of Calcium Scoring as a Screening Examination in Patients With a History of Kawasaki Disease



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Subsets of patients with a remote history of Kawasaki disease (KD) have coronary artery aneurysms with associated risks of late morbidity. In a pilot study, we previously showed that computed tomography (CT) coronary artery calcium (CAC) scoring detects late CAC in patients with aneurysms and a remote history of KD. We performed CT calcium volume scoring in 166 subjects (median age 19.5 years) with a remote history of KD (median interval from KD to CT 15.1 years). Coronary arteries were classified as normal ($n = 100$), transiently dilated ($n = 23$), persistently dilated ($n = 10$), remodeled aneurysm ($n = 9$), or aneurysm ($n = 24$) based on echocardiography. All subjects with coronary arteries classified as normal, persistently dilated, or remodeled aneurysm had zero CAC. Of the 24 subjects with coronary aneurysms, all but 5 had CAC (median volume 542 mm³; range 17 to 8,218 mm³). For subjects imaged ≥ 9 years after their acute KD ($n = 144$), the presence of CAC had a sensitivity of 95% and a specificity of 100% for detecting coronary artery abnormalities (defined as coronary artery aneurysm and/or stenosis). In conclusion, coronary calcification was not observed in subjects with a history of KD who had normal coronary arteries by echocardiography during the acute phase. Coronary calcification, which may be severe, occurs late in patients with coronary aneurysms. Therefore, CAC scanning may be a useful tool to screen patients with a remote history of KD or suspected KD and unknown coronary artery status. © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;119:967–971)

Computed tomography (CT) coronary artery calcium (CAC) scoring requires no contrast and relatively little radiation. This test is widely used to detect plaque due to atherosclerotic coronary artery disease.¹ In a pilot study, we previously showed that CAC scoring also detects calcium in patients with coronary artery aneurysms (CAA) and a remote history of Kawasaki disease (KD).² Here, we present the results of a larger follow-up study evaluating the utility of CAC scoring by CT to detect coronary artery abnormalities in patients with a history of KD.

Methods

We recruited subjects of age ≥ 10 years from 2 cohorts. Cohort 1 ($n = 90$) consisted of patients with a history of KD

diagnosed, treated, and followed by the KD Research Center at UCSD Medical Center and Rady Children's Hospital San Diego. Cohort 2 ($n = 76$) were self-referred, had a remote history of KD, and were originally diagnosed at another center. In 3 subjects in cohort 2, the diagnosis of KD was based on a history of a KD-compatible illness and the presence of proximal CAAs diagnosed by CT or coronary angiography independently reviewed by 2 cardiologists. This study was approved by the Institutional Review Board of the University of California, and all subjects provided informed consent or assent with parental consent as appropriate.

Coronary artery status was determined based on initial echocardiograms performed during the acute and subacute phases of KD. Subjects with a coronary artery z score (standard deviation from the mean for the internal diameter of the coronary artery normalized for body surface area) for the right coronary artery (RCA) or left anterior descending coronary artery (LAD) < 2.0 on serial echocardiograms during the acute and subacute illness were designated as normal. Subjects with a CA z score of > 2.0 and < 3.0 that returned to normal within 6 weeks of fever onset were designated as transiently dilated. Subjects with a z score ≥ 3.0 but < 10.0 were designated as aneurysm, and subjects with $z \geq 10.0$ or CA internal diameter ≥ 8 mm were designated as giant aneurysm. For subjects with dilated or aneurysmal coronary artery abnormalities or unknown initial coronary artery status, the most recent CTA or invasive coronary angiogram was used when available. Subjects were classified into 5 categories by coronary status: (1) no history of coronary artery dilation (American Heart Association [AHA] risk level I), (2) transient (< 6 weeks)

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See page 971 for disclosure information.

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Table 1
Patient characteristics

Variable	Cohort		
	1 (N=90)	2 (N=76)	Total (N=166)
Males (%)	60 (67)	44 (58)	104 (63)
Age at onset of KD (years):	2.4 (1.4-5.2)	4.0 (2.1-7.1)	3.5 (1.5-5.9)
Age at time of calcium score, (years):	16.7 (13.6-19.6)	24.9 (20.1-31.1)	19.7 (15.8-25.4)
Interval from onset of KD to calcium score (years):	13.2 (10.6-15.8)	20.0 (13.6-27.1)	15.1 (11.1-20.6)
Body mass index (kg/m ²):	22 (19-24)	23 (20-27)	22 (20-25)
Coronary artery status			
Normal:	51 (57%)	49 (64%)	100 (60%)
Transiently dilated:	22 (24%)	1 (1%)	23 (14%)
Persistently dilated:	6 (7%)	4 (5%)	10 (6%)
Remodeled aneurysm:	9 (10%)	0 (0%)	9 (5%)
Aneurysm:	2 (2%)	22 (29%)	24 (14%)
Atherosclerosis risk factors			
Hypertension:	1 (1%)	13 (17%)	14 (8%)
Diabetes mellitus:	1 (1%)	3 (4%)	4 (2%)
Tobacco use, ever:	8 (9%)	14 (18%)	22 (13%)
Hyperlipidemia:	5 (5%)	18 (24%)	23 (14%)
Family history of early CAD (< 55 years):	18 (19%)	17 (22%)	35 (21%)
Medications			
Statin:	1 (1%)	9 (12%)	10 (6%)
ACE-I or ARB:	2 (2%)	5 (7%)	7 (4%)
Beta blocker:	0	10 (13%)	10 (6%)
Calcium channel blocker:	0	3 (4%)	3 (2%)
Warfarin or NOAC:	1 (1%)	11 (14%)	12 (7%)
Aspirin:	3 (3%)	26 (34%)	29 (17%)
Clopidogrel:	0	5 (7%)	5 (3%)
MACE	1 (1%)	12 (16%)	13 (8%)
Myocardial infarction	1 (1%)	6 (8%)	7 (4%)
Coronary artery bypass graft surgery	0	5 (7%)	5 (3%)

Cohort 1: Patients originally diagnosed, treated, and followed by the Kawasaki Disease Research Center at the University of California, San Diego Medical Center and Rady Children's Hospital.

Cohort 2: All other patients.

Remodeled aneurysm: Artery that is acutely aneurysmal but undergoes myointimal proliferation with filling in of the aneurysm such that the lumen is no longer dilated on follow-up imaging.

Hyperlipidemia: Subject report of having this diagnosis.

Values for continuous variables are listed as median (IQR).

Values for discrete variables are listed as n (%).

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; NOAC = novel oral anticoagulant (rivaroxaban, apixaban, edoxaban, dabigatran).

coronary artery dilation (AHA II), (3) persistent (≥ 6 weeks) coronary artery dilation, (4) remodeled aneurysm (AHA III/IV), and (5) aneurysm (AHA III/IV). Subjects completed a standardized questionnaire documenting medications, cardiac history, and risk factors for atherosclerotic coronary artery disease (physician-diagnosed hypertension, diabetes mellitus, hyperlipidemia, family history of early atherosclerotic coronary artery disease defined as disease diagnosed at age <55 years in a first-degree relative, and current smoking). Coronary artery abnormality was defined as the presence of CAA and/or stenosis on the most recent available imaging. Major adverse cardiac events (MACE) were defined as myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention.

The CT scanning protocol has been previously described.² In brief, subjects were scanned during a single breath-hold on a 64-slice Discovery CT750 HD scanner (GE Healthcare, Milwaukee, Wisconsin) in gated axial mode with 2.5-mm

slice thickness. For 3 of the subjects, the tube energy was set to 120 kVp, and for the remainder, the tube energy was set to 100 kVp (instead of the tube energy of 120 kVp traditionally used for calcium scoring) to minimize the radiation dose, and the tube current was chosen based on subjects' body mass index. The median radiation dose-length product was 43 mGy-cm, corresponding to a median effective radiation dose of 0.61 mSv. If clinically indicated, CT angiography was performed in selected patients using the scanner described previously with prospective gating.

Images for CAC scoring were reconstructed using a 512 × 512 matrix and analyzed offline using a Ziostation workstation (QI Imaging, Redwood City, California). Coronary calcium volume was measured using a minimum threshold of 130 Hounsfield units for the 3 patients imaged using 120 kVp and 147 Hounsfield units for the remainder imaged using 100 kVp, following the work of Nakazatu et al³ to adjust for the lower tube energy and a minimum

Table 2
Calcium score results

Coronary Artery Status	Calcium Volume (mm ³)			
	0	1-100	101-1000	>1000
Normal	100	0	0	0
Transiently Dilated	22	0	1	0
Persistently Dilated	10	0	0	0
Remodeled Aneurysm	9	0	0	0
Aneurysm	5	5	8	6

volume of 2.5 mm³. Regions of calcification of the coronary arteries were manually identified on the workstation, and for each subject, the total volume of coronary calcification was measured.

Serum high-sensitivity C-reactive protein (hsCRP) was measured by ELISA (GenWay Biotech, Inc) in a subset of subjects (n = 106) on whom blood samples were collected as part of their participation in the San Diego Adult KD Collaborative Study. Concentration of hsCRP was also determined for 80 age-matched control subjects with a median value of 1.58 mg/l, interquartile ranges (IQR) 0.39 to 1.11 mg/l.

We calculated medians and IQR for all continuous parameters studied. The 2-tailed Mann–Whitney U test was used to assess differences between continuous variables, and the chi-square test was used to compare proportions for discrete variables. Correlation between continuous variables was assessed using the Pearson correlation coefficient. For all tests, a 2-sided p < 0.05 was considered statistically significant.

Results

Demographic data are summarized in Table 1. The median subject age was 19.5 years (IQR 15.6 to 25.5 years, range 10.0 to 59.8 years), and the median interval from KD to CT was 15.1 years (IQR 11.1 to 20.6 years, range 1.5 to 53.3 years).

CAC volume scores are summarized in Table 2 and shown graphically in Figure 1 for those subjects in cohort 2. All but 1 subject in cohort 1 had zero CAC. All subjects (n = 100) with normal coronary arteries during the acute and subacute illness had zero CAC. Similarly, all subjects with transient coronary artery dilation (n = 23) and remodeled aneurysms (n = 9) had zero CAC. For subjects with persistently dilated coronary artery arteries dilation (n = 10), 1 subject, a 33-year-old man described previously,² had a CAC of 666 and all others had zero CAC. The 1 subject with the elevated CAC presented with unstable angina and required emergent bypass surgery for a critical stenosis that was heavily calcified in the left main coronary artery.

For subjects with aneurysms, 19 of 24 (79%) patients had calcification (median volume score 542 mm³; range 17 to 8,218 mm). Of the 5 subjects with aneurysms and zero calcification, 4 were imaged within 6 years of KD onset.

For the subjects (n = 20) with nonzero CAC scores, there was no significant correlation between the CAC scores and times since KD onset ($r^2 = 0.05$, p = NS). Of the 20

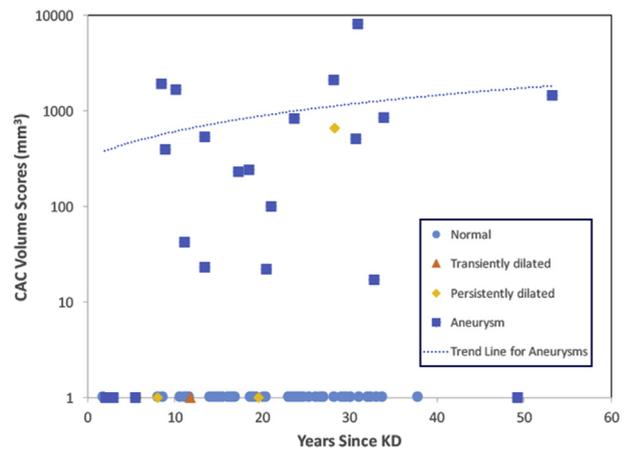


Figure 1. CT calcium volume scores (on a logarithmic scale) for cohort 2 subjects as a function of time since KD onset, coded by coronary artery status (n = 74 subjects; 2 subjects are not included because the interval since KD onset is unknown). A linear fit to the CT calcium scores is shown for subjects with aneurysms. Assessment of coronary artery status by echocardiography during the acute and subacute phase. Normal = no coronary artery dilation; Transiently dilated = dilated internal dimension of at least 1 coronary artery with subsequent normalization.

subjects with nonzero calcium scores, 9 had zero CAD risk factors, 5 had 1 risk factor, and 6 had ≥ 2 risk factors. The patients in this group with zero CAD risk factors were younger than those with ≥ 1 CAD risk factors (median age 20.8 vs 33.2 years, p = 0.01). The most common risk factor for patients in this group was hyperlipidemia (n = 8).

Figure 2 shows an example of calcification of the RCA artery from a subject with giant aneurysms. Figure 3 shows images from a 34-year-old man with a history of KD at age 1 but unknown coronary artery status. CT calcium scoring detected calcification of the subject's LAD and ramus intermedius arteries. Therefore, a CT angiogram was obtained that demonstrated a 7-mm aneurysm of the proximal ramus intermedius artery for which the patient was initiated on aspirin and warfarin with a target international normalized ratio of 2.0 to 3.0.

For all subjects, MACE occurred in a total of 13 subjects, all but 1 of whom had aneurysms. The 1 subject with a MACE who did not have an aneurysm was the subject with persistent dilation and CAC of 666. For subjects with aneurysms, MACE occurred in 2 of 5 (40%) subjects with CAC = 0. One subject, a 57-year-old Filipino male, had a history consistent with missed KD in childhood and presented with an ST-elevation myocardial infarction associated with a thrombus in a distal RCA aneurysm.⁴ The other subject, a 19-year-old man, was treated with intravenous immunoglobulin for acute KD at age 13 years. Despite treatment, he developed giant aneurysms of the RCA and LAD and was placed on warfarin and aspirin. Warfarin therapy was discontinued at age 17 years, and he presented 2 years later with a myocardial infarction associated with occlusion of the aneurysmal RCA. His CAC score was obtained within 6 years of the onset of his KD. MACE occurred in 11 of 20 (55%) patients with CAC > 0 (range, 17 to 8,218) and included 5 myocardial infarctions and 5 coronary artery bypass graft surgeries. For subjects imaged

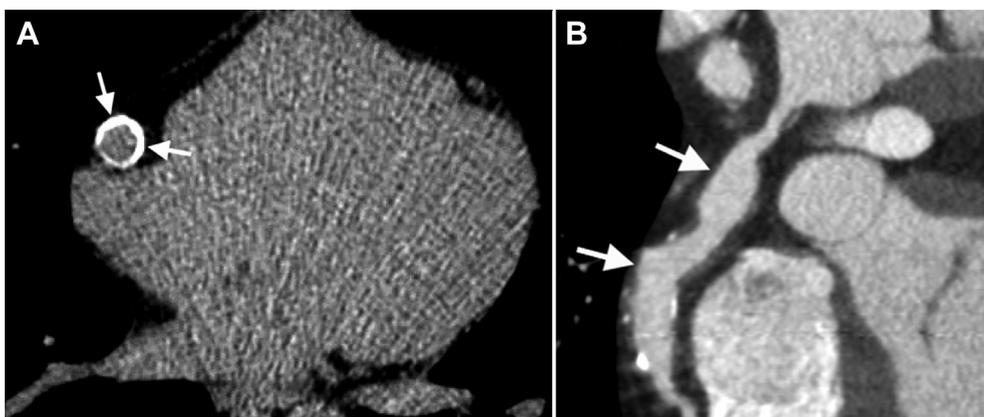


Figure 2. CT images from a 28-year-old man with a history of KD at age 14 years and coronary aneurysms. (A) Image from CT calcium scan demonstrating coronary calcification of the right coronary artery (arrows). (B) Curved oblique images from CT angiogram demonstrating a large fusiform aneurysm (arrows) of the right coronary artery.

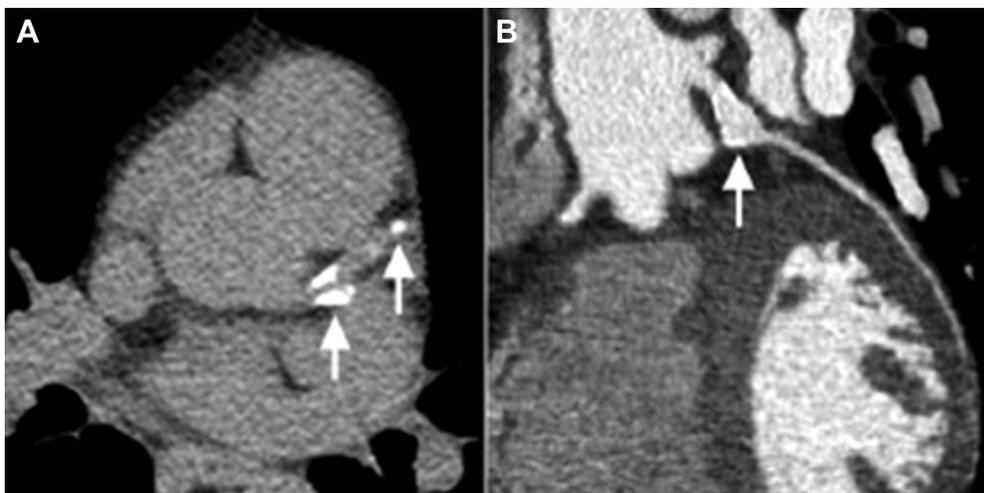


Figure 3. CT images from a 34-year-old man with a history KD at age 1 years and unknown coronary artery status. (A) Image from CT calcium scan demonstrating coronary calcification of the left anterior descending and ramus intermedius arteries (arrows). (B) Curved oblique images from CT angiogram demonstrating a large focal proximal aneurysm (arrow) of the ramus intermedius artery.

≥ 9 years after their acute KD ($n = 144$), the presence of CAC on CT had a sensitivity of 95%, specificity of 100%, negative predictive value of 99%, and positive predictive value of 100% for detecting coronary artery abnormalities.

HsCRP was measured in 85 subjects. For 51 of these subjects, hsCRP was drawn the same day as the CT calcium score, and for the remaining 32 subjects, the median time between phlebotomy and CT calcium score was 15 days (IQR 1 to 224 days). For subjects with CAC = 0, the median hsCRP was 0.51 mg/l ($n = 69$, IQR 0.31 to 1.27 mg/l), and for subjects with CAC >0, the median hsCRP was 0.47 mg/l ($n = 14$, IQR 0.25 to 2.21 mg/l). There was no significant difference in hsCRP between these 2 groups. For subjects with CAC >0, the CAC volume scores did not correlate with hsCRP values ($R^2 = 0.05$, $p = \text{NS}$).

Discussion

All 100 subjects with normal coronary arteries by echocardiography during the acute and subacute illness had CAC scores of zero. These data provide strong evidence that

patients with normal coronary arteries acutely do not develop late CAC within 3 decades of the onset of KD and support the concept that these patients have no evidence of coronary artery abnormalities. In the 1 individual who was told he had normal coronary arteries by echocardiogram, the elevated CAC score prompted discovery of a heavily calcified aneurysm followed by initiation of systemic anticoagulation to prevent thrombosis of the aneurysm and surveillance by a cardiologist for potential ischemic complications.

In the present study, of the patients with transient dilation, persistent dilation, and remodeled aneurysms, all but 1 had CAC scores of zero. The 1 subject was classified as persistently dilated and had coronary artery calcification with associated severe stenosis. The echocardiogram in this subject was performed in 1978 at an outside institution and was not available for review. Clearly, the resolution and precision of echocardiography for detecting coronary artery dilation has improved over the ensuing 4 decades. Many young adults presenting today with a history of KD had their initial echocardiography during an era when the imaging

was limited because of technical issues. Hence, the possibility of clinically important coronary abnormalities cannot be excluded in patients with echocardiograms performed in past decades, and a CT calcium scan may be reasonable to evaluate for the presence of coronary artery abnormalities that might have been missed in these patients.

Of the 9 subjects with remodeled aneurysms documented by echocardiogram or CT angiography, all were from cohort 1, and the original echocardiograms were not available for review. Five of these subjects were less than 1 year of age when they developed acute KD and 3 of the 5 had giant aneurysms that remodeled over the first 2 years after disease onset. This is consistent with published literature suggesting that young age at KD onset is associated with a greater likelihood of aneurysm remodeling.⁵ However, the long-term outcome for such patients has not yet been determined.

This study provides further evidence that patients with a history of KD and CAAs virtually always develop late coronary artery calcification. The degree of calcification did not correlate with the interval since acute KD; however, our study suggests that calcification is a process that is often not detected in the first decade after disease onset. It is not known why some patients develop more severe calcification and whether the degree of calcification has prognostic significance, as is the case for atherosclerotic CAD.⁶

The findings of coronary calcification on chest x-rays in patients with a history of KD has been well reported.^{7–11} We did not have chest x-rays on the subjects in this study and hence were unable to compare data between chest x-rays and CT. Some of the subjects in this study had dense calcification that would be expected to be apparent on chest x-rays. Compared to chest x-rays, we expect that CT calcium scoring provides a more sensitive and quantitative measure of coronary calcification.

As increasing numbers of patients with a history of KD reach adulthood and transfer their care to physicians who care for adults, clinicians will encounter patients with a history of KD for whom original records may be difficult to obtain and for whom the coronary artery status during the acute illness is uncertain. For these patients, CT calcium scoring to assess for coronary calcification seems ideally suited. When performed approximately one decade or more after acute KD, this test appears to be very sensitive and specific for the presence of coronary artery abnormalities.

In this study, we used a modified CT protocol with relatively low radiation dose (median dose equivalent to 2.4 months of background radiation). The exact risk of this low amount of radiation is unknown but is likely to be small, and hence, the risk to benefit ratio for this inexpensive

test seems favorable for patients with a history of KD. A limitation of the study is that the original echocardiograms could not be directly evaluated.

Disclosures

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