Late Wall Thickening and Calcification in Patients After Kawasaki Disease

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Objectives To evaluate the relationship between the initial diameters of the coronary arteries immediately after the onset of Kawasaki disease (KD) and late increased coronary wall thickening/coronary artery calcification (CAC).

Study Design Sixty-five patients (50 males and 15 females) who had undergone selective coronary angiography (CAG) <100 days after the onset of KD were studied late in disease by dual-source computed tomography (DSCT). The maximum diameters of each segment were measured in the initial CAGs, and the relationship between the maximum diameters and the appearance of increased wall thickening/CAC was analyzed. The study cohort was divided into 2 groups: the branches group (BG) and bifurcation at the left coronary artery (LCA) group. The cutoff point of acute coronary artery dilatation for increased wall thickening/CAC was calculated for each group. Risk factors for the appearance of CAC in each group were investigated, as was the sex difference related to the prevalence of CAC in coronary artery lesions (CALs) of the initial CAGs.

Results The cutoff points of acute coronary dilatation for increased wall thickening were 4.8 mm in the BG (n = 344; area under the curve [AUC], 0.89; $P < .001$) and 5.3 mm in the LCA group (n = 65; AUC, 0.87; $P < .001$). The interval from the onset of KD ($P < .0001$) and sex ($P = .0084$) were also related to the appearance of CAC in the BG.

Conclusion Acute coronary dilatation of exceeding ~5.0 mm can lead to late abnormalities of the coronary artery wall. The prevalence of CAC increases with age. There was a sex-based difference in the late incidence of CAC in the CALs. *(J Pediatr 2017;181:167-71).*

Kawasaki disease (KD) involves coronary arteries in the acute phase, and coronary aneurysms appear in approximately 10% of patients with KD.[1] Calcified coronary aneurysms located in the proximal segments of epicardial coronary arteries in the late period are characteristic of coronary artery lesions (CAL) caused by KD.[2] How the coronary artery wall changes after acute vasculitis in the long term, and whether such changes cause ischemic heart disease in adulthood, remain unknown, however. Stenotic lesions leading to myocardial involvement are caused mainly by coronary wall abnormalities after destruction of the vessel wall structure from acute severe vasculitis.[3,4] Wall thickening, including coronary artery calcification (CAC), indicates irreversible changes in the coronary artery wall.

Computed tomography angiography (CTA) has been used to successfully diagnose CALs. CTA using dual-source computed tomography (DSCT) has been established as an accurate and valuable tool for detecting CAL caused by KD.[5,6] Wall thickening, including CAC, also can be detected noninvasively by DSCT. There are no previous reports on wall thickening detected by DSCT in this population, however. In the present study, we retrospectively investigated the appearance of late wall thickening and CAC detectable by DSCT on a segment-by-segment basis of the major epicardial coronary arteries in patients who experienced at least a coronary aneurysm after KD.

Methods

Sixty-five patients (50 males and 15 females) who had undergone previous selective coronary angiography (CAG) <100 days after the onset of KD underwent late DSCT. All 65 patients had sustained a coronary artery aneurysm in the initial CAG. CTA was performed between July 2007 and March 2015. Written informed consent for each examination was obtained from a parent

AUC	Area under the curve
BG	Branches group
CAC	Coronary artery calcification
CAG	Coronary angiography
CAL	Coronary artery lesion
CTA	Computed tomography angiography
DSCT	Dual-source computed tomography
IVUS	Intravascular ultrasound
KD	Kawasaki disease
LCA	Left coronary artery

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of each child from each patient aged >20 years. All CTAs had been performed as part of clinical care. In patients who had undergone more than 2 CTAs, the latest CTA findings were used for this study. Our institution approved this retrospective study from an ethical perspective.

CTA by DSCT

Prospective electrocardiograph-triggered CTA DSCT was performed with a SOMATOM Definition scanner (Siemens Healthcare, Erlangen, Germany) between July 2007 and October 2009, and with a SOMATOM Definition Flash scanner (Siemens Healthcare) from October 2009 to March 2015. In patients aged >10 years, 10 mg of oral propranolol was administered 1 hour before DSCT scanning. Electrocardiography gated scans in mid- or end-systole phase or flash spiral scans were performed. The contrast medium was iopamidole 370 1.0-2.0 mL/kg, administered via a dual-chamber mechanical power injector.

Scanning was automatically triggered by the bolus tracking technique with breath holding in patients aged >10 years. The scan was performed at a tube voltage of 100 or 120 kV with slice widths of 0.6, 0.75, and 1.0 mm. All images were transferred to an external workstation (Zio Station; Ziosoft, Tokyo, Japan), at which the radiologist developed maximum intensity projection and curved multiplanar reconstruction images.

Measurements in the Initial CAGs and Diagnosis of Wall Thickening/CAC and CAL Detected by DSCT

In this study, a CAL including aneurysm was defined by diagnostic guidelines prepared by the Japanese Circulation Society.[7] The maximum diameters of segments 1, 2, 3, 5, 6, 7, and 11 were measured in the initial CAGs. If an aneurysm was present at the bifurcation of the left coronary artery (LCA), then the diameter of the aneurysm at the LCA was measured instead of segment 5. Measurement of coronary arteries has been described previously.[6,8]

The appearance of wall thickening/CAC and CAL in each segment by CTA was evaluated by a pediatric cardiologist and a radiologist. The pediatric cardiologist measured the maximal diameter of segments in the initial CAG (**Figure 1**). We previously reported excellent interobserver and intraobserver agreement for the measurements of coronary aneurysm diameter in CAGs and the diagnosis of CAL by DSCT.[6] In this study, wall thickening was considered increased when the coronary arterial wall was thicker than the aortic wall at the sinotubular junction. CAC is considered a progressive stage of increased wall thickening, because it usually occurs with severe wall thickening[3]; therefore, the segments with CAC were also included in the group with increased wall thickening. The CALs detected by DSCT were classified into the 3 groups: dilated lesions, stenotic lesions, and regression. Stenotic lesions included occlusion, localized areas of >25% stenosis, and segmental stenosis.[7]

Evaluated segments were divided into 2 groups because of the differences in vessel diameter and characteristics of the aneurysm at the bifurcation. One group comprised the branches of segments 1, 2, 3, 6, 7, and 11, and the second group consisted of the LCA, including aneurysms at the bifurcation of the LCA or segment 5. The effects of some large aneurysms at the LCA extended to segments 6, 7, and 11, often hindering measurements of the maximal diameter of segments 6, 7, and 11. Moreover, these segments also were excluded when coronary arteries were occluded in the initial CAGs or when the detection of coronary arteries by CTA with DSCT was insufficient to allow evaluation of the abnormalities.

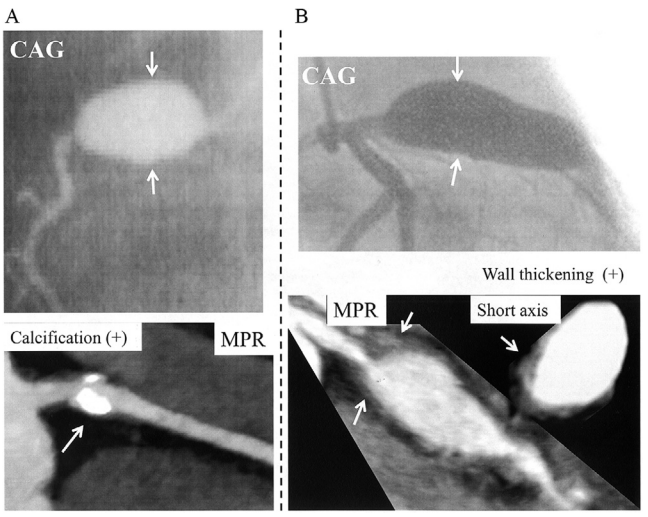

Figure 1. **A,** CAC after regression of the right coronary artery aneurysm. A 31-year-old patient had KD at age 5 months. In the initial CAG done 2 months after the onset of KD, the maximum diameter at the segment 1 of the right coronary artery was 10.0 mm. CAC was detected at the regressed site after the right coronary artery aneurysm. **B**, wall thickening in an aneurysm of the left coronary descending artery. A 11-year-old male had KD at age 9 years. In the initial CAG performed 2 months after the onset of KD, the maximum diameter at segment 6 of the left coronary artery was 10.9 mm. Wall thickening was detectable in the aneurysm by DSCT. MPR; multiplanar reconstruction.

Statistic Analyses

We compared the prevalence of wall thickening/CAC by detected DSCT between the CAL group and non-CAL group in the initial CAG using the χ^2 test in the BG and the LCA group. We then analyzed the relationship between the maximum diameters of coronary arteries in the initial CAGs and the appearance of wall thickening/CAC detected by DSCT. We calculated the cutoff points of acute coronary artery dilatation for wall thickening and CAC in each group using receiver operator characteristic analysis. We also investigated the risk factors for the appearance of CAC after KD in each group.

We analyzed the prevalence of CAC by sex in CALs of the BG using the Kaplan-Meier method, and assessed differences using the log-rank test. Statistical analyses were performed using JMP 10 (SAS Institute, Cary, North Carolina). Measurements are expressed as mean ± SD. A P value <.05 was considered statistically significant. The Turkey-Kramer test was used to test for differences between the groups.