

Composition of Coronary Arterial Calcifications Following Kawasaki Disease as Determined by Single-Source Dual-Energy Computed Tomography

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Background: Composition of materials can be determined by dual-energy computed tomography (CT), which we used to analyze coronary arterial calcifications following Kawasaki disease (KD) using effective atomic number (EAN).

Methods and Results: We studied coronary calcifications measuring more than 1 mm in 11 post-KD patients. Age of KD onset ranged from under 1 year to 6 years old (median, 3), while age at imaging ranged from 15 to 45 years (median, 36). We reframed the field of view as 6.0 cm images and randomly placed 3 regions of interest (ROI) 0.7 mm in diameter within each calcification. We calculated averages and displayed histograms of distributions of median, minimal, and maximal EANs, and correlated medians with clinical variables. Medians averaged 13.27 ± 0.83 ; minima, 12.80 ± 0.93 ; and maxima, 13.59 ± 0.72 . The median was similar to that for atherosclerotic coronary arterial calcifications. EANs in KD differed significantly, according to age at KD onset.

Conclusions: Compositions of coronary arterial calcifications following KD resembled those in atherosclerosis, irrespective of additional factors. Clinical coronary events in KD should be assessed carefully, including characteristics of related arterial calcifications.

Keywords: Kawasaki disease, dual-energy computed tomography, calcification, effective atomic number

Introduction

Since Kawasaki disease (KD) was reported in 1967, some patients have been known to develop coronary arterial lesions (CALs).^{1,2)} Various treatments for KD show some promise in decreasing likelihood of subsequent CALs.³⁻⁷⁾ For now, however, the number of patients with CALs emerging after KD has been increasing, which possesses a serious clinical problem. Calcified CALs following KD are of great concern, since a calcified stenotic lesion is known to increase risk of coronary artery events.⁸⁾ We hypothesized that the composition of coronary arterial calcifications following KD might differ from that of atherosclerotic calcifications because KD-associated lesions occur at an earlier age, and that

we might better prevent cardiac events following KD if we understood the differences.⁹⁾

Recently, dual-energy computed tomography (CT) has been used to determine the composition of materials. Dual-energy CT is an imaging method using X-rays with 2 different energy levels to obtain the difference in attenuation coefficients for the material examined. This approach allows us to determine effective atomic numbers (EANs) of materials. When X-rays penetrate a subject, X-ray amplitude and frequency change (Fig. 1). The ratio of changes in amplitude and frequency is characteristic with an element. EAN is an atomic number of this element which is defined with the ratio of changes.¹⁰⁾ Human studies concerning EANs of teeth, urinary stones, and atherosclerotic coronary arterial cal-

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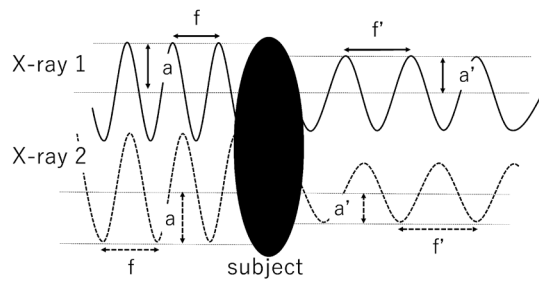


Fig. 1 The method to identify EAN simply

When X-rays with 2 different energy levels pass through a subject, amplitude and frequency of each X-ray change. We can identify EAN from the ratio of changes in amplitude and frequency. If the subject is a compound or mixture of materials, the EAN is an average atomic number of the material(s). a, amplitude; f, frequency.

cifications have been reported.^{11–13} The EAN of atherosclerotic coronary arterial calcifications was 13.8 ± 0.8 , close to that of calcium oxalate monohydrate (13.8).¹¹ However, we know of no similar reports dealing with the composition of coronary arterial calcifications that can follow KD.

In this study we used dual-energy CT to determine the compositions of such coronary arterial calcifications.

Patients and Methods

A retrospective search of clinical records at our hospital for patients who had undergone dual-energy CT to evaluate CALs following KD between February 2014 and December 2015 identified 25 individuals. Dual-energy CT is performed with a prospective ECG-gated step and shoot technique, so patients who cannot hold their breath

or still have a heart rate exceeding 70 beats per minute after beta-blocker administration undergo ECG-gated helical CT rather than dual-energy CT. We excluded 14 patients, 9 patients did not have a calcification exceeding 1 mm and 5 patients' raw data had been erased.

Among the 11 patients studied, 9 were male and 2 were female. The age of KD onset ranged from 3 months to 6 years (median, 3 years). The age when dual-energy CT was performed ranged from 15 to 45 years (median, 36 years). A total of 23 CALs were studied, including 14 in the right coronary artery and 9 in the left coronary artery (4 in the left main coronary trunk and 5 in the left anterior descending artery). Six patients experienced coronary arterial events (the past-history of acute myocardial infarction or coronary artery bypass grafting). Three of them underwent coronary artery bypass grafting, while 2 experienced acute myocardial infarction; 1 of these patients had infarction and bypass grafting. In the acute phase of KD, 4 patients were given intravenous immunoglobulin, while 1 patient received a corticosteroid. For 6 patients, details about treatment in the acute phase are not known because treatment was carried out at other hospitals. No patient had a history of hypertension, diabetes, administration of warfarin (which can promote coronary arterial calcification), or smoking.¹⁴ Only one patient had hyperlipidemia. Patient profiles are described in Table 1.

The imaging device used was Discovery CT750HD FREEdom Edition (GE Healthcare Japan, Tokyo, Japan).

Before scanning, the patient was initiated in an intravenous drip forearm. A scout scan and a simple radiographic image, (a single-energy CT) were obtained to determine the imaging range. An intravenous contrast

Table 1 Patient profiles

Patient	Gender	Age at KD onset	Age at imaging	Number of CALs (number in RCA)	CAE [†]	Treatments during acute period	Other risk factors
1	M	11 months	15 years	1 (0)	CABG	Aspirin + IVIG + UTI	None
2	M	4 years	17 years	1 (1)	None	Aspirin + IVIG	None
3	M	6 years	18 years	1 (1)	CABG	Aspirin + IVIG + UTI	None
4	M	4 years	25 years	2 (1)	None	Aspirin + IVIG	None
5	M	3 months	34 years	3 (2)	CABG	Unknown	None
6	M	3 years	36 years	3 (2)	AMI, CABG	Unknown	None
7	M	5 years	36 years	4 (3)	None	Unknown	None
8	M	5 years	37 years	2 (1)	AMI	Unknown	None
9	F	1 year	38 years	1 (0)	None	Unknown	None
10	F	2 years	39 years	2 (1)	None	Unknown	Hyperlipidemia
11	M	1 year	45 years	3 (2)	AMI	Corticosteroid	None
Median		3 years	36 years	2			

M, male; F, female; KD, Kawasaki disease; CAL, coronary arterial lesion; RCA, right coronary artery; CAE, coronary arterial event; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; IVIG, intravenous immunoglobulin; UTI, ulinastatin.

[†]The past-history of acute myocardial infarction or coronary artery bypass grafting.

agent was injected (0.8 to 1.0 mL/kg) over 13 seconds, regardless of patient weight; then cardiac dual-energy CT was performed. Before the dual-energy scan, nitroglycerin (isosorbide spray, 1.25 mg to the oral cavity) was administered as a pre-treatment. When the heart rate was elevated, a beta-blocker (landiolol, 0.125 mg/kg) was given intravenously before the scanning.

AW VolumeShare5 Plus XT for FREEdom (GE Healthcare Japan, Tokyo, Japan) was used to manipulate images. We adjusted the field of view to 6.0 cm to include mainly calcified lesions. Using the work station, randomly we selected 3 regions of interest (ROI); each 0.7 mm in diameter within the calcification (Fig. 2). An EAN value was obtained for each pixel. With constriction of the field of view, image resolution increased while numbers of pixels and numbers of EAN values for the ROI also increased. We obtained 36 EAN values per 1

ROI, then calculating average values constructing histograms of the distributions of the median, minimal, and maximal EANs of each ROI. In addition, we compared the median EANs of groups defined by features; fenders, coronary arterial events, age at KD onset, years from onset of KD to imaging, and number of CALs.

Statistical analysis was performed using IBM SPSS Statistics 22. The *t*-test was used to examine the comparison between 2 groups. A *p* value less than 0.05 was considered to indicate statistical significance. Continuous variables were expressed as mean \pm SD or median (interquartile range), as appropriate.

This study was approved by the Institutional Review Board of Kindai University, Faculty of Medicine (28-139).

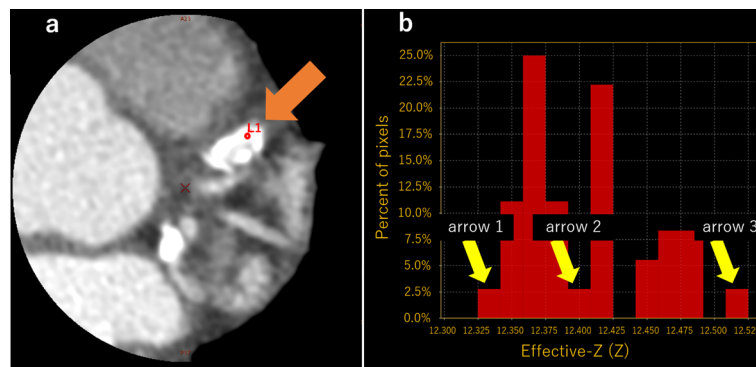


Fig. 2 Placement of an ROI and histogram of EAN in the ROI

(a) We reframed the field of view of images (6.0 cm) to include mainly calcified lesions. We placed 3 ROIs, each of 0.7 mm in diameter, within the calcification. We then obtained EANs these ROIs. One of the ROIs, designated L1, is indicated by the arrow. (b) Histogram showing percentage of EANs in L1. The horizontal axis shows EAN values, while the vertical axis displays percentage of EANs having these values. In L1, 12.358–12.375 accounted for 25% of EANs, with followed by 12.408–12.425 being the next most frequent. The minimal EAN was 12.33 (arrow 1), the median EAN was 12.39 (arrow 2), and the maximal EAN was 12.52 (arrow 3) were shown in this figure. EAN, effective atomic number; ROI, region of interest.

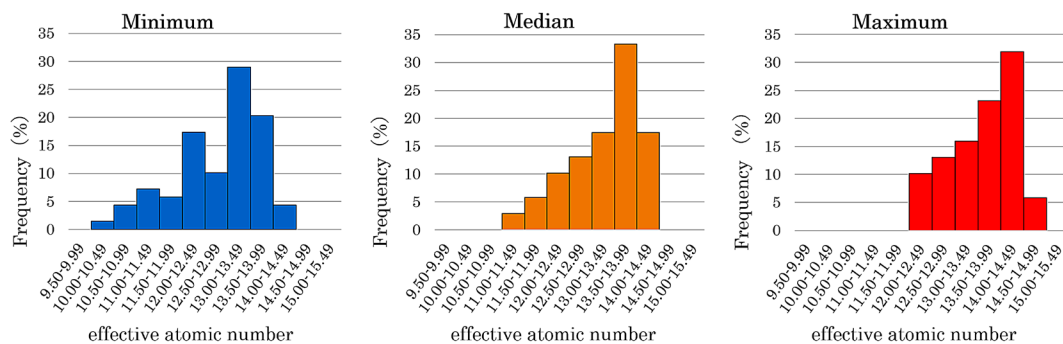


Fig. 3 Minimum, Median, and Maximum EANs obtained for 69 ROIs from 23 coronary arterial calcifications following KD

For these, frequencies are shown in parantheses, similar to Fig. 1b. EAN, effective atomic number; ROI, region of interest.

Results

We obtained 2484 EAN values from 69 ROIs. The mean of the median EANs of ROIs was 13.27 ± 0.83 , while that of the minimum EANs was 12.80 ± 0.93 and that of the maximum EANs was 13.59 ± 0.72 . The median was similar to the EAN of atherosclerotic coronary arterial calcifications (13.8 ± 0.8). The histograms are presented in Fig. 3. According to the results, it suggested that these values did not have large differences.

Analysis of each ROI (Table 2) showed significant differences between groups defined by age at KD onset (<1 year, 13.77 ± 0.55 vs ≥ 1 year, 13.16 ± 0.80 , $p < 0.01$). This suggested that when KD occurred at an age of less than 1 year, EANs more closely resembled those seen in

Table 2 Comparison of median EANs according to patient characteristics

		n	EAN	<i>p</i>
Gender	M	60	13.27 ± 0.83	0.504
	F	9	13.23 ± 0.52	
Age at KD onset	<1	12	13.77 ± 0.55	<0.01
	≥ 1	57	13.16 ± 0.80	
Interval (years) between KD onset and imaging	<32	27	13.47 ± 0.62	0.142
	≥ 32	42	13.13 ± 0.87	
Number of CAL	<2	12	13.45 ± 0.55	0.618
	≥ 2	57	13.23 ± 0.84	

M, male; F, female; KD, Kawasaki disease; CAL, coronary arterial lesion; EAN, effective atomic number.

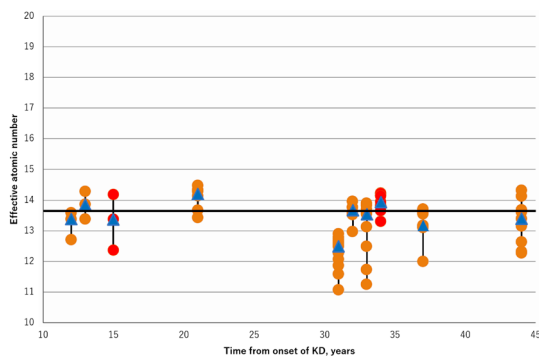


Fig. 4 Relationship between time from onset of KD and EANs

The black horizontal line at 13.8 shows the EAN representing the composition of the calcification of atherosclerosis. Orange circles show median EANs of ROIs for patients diagnosed with KD when 1 or more years old, while red circles show median EANs of the patients with initial diagnosis of KD when less than 1 year old. Blue triangles and black vertical lines respectively show median EANs for ROIs of every year and their associated ranges.

atherosclerosis. EANs showed no differences related to gender, coronary arterial events, years since onset of KD, or number of CALs.

Fig. 4 shows the relationship between years since onset of KD and median EANs. Median EANs were similar to EANs of atherosclerotic coronary arterial calcifications (13.8), irrespective of the time since KD onset.

Discussion

Calcification in CALs following KD is clinically significant, considering that calcification is a risk factor for coronary arterial events.¹⁵⁾ The composition of this calcification has not been reported previously, even in pathological studies. We hypothesized that the calcifications of CALs following KD might differ from those in atherosclerosis, but EANs of KD-related coronary arterial calcifications showed compositions resembling those in atherosclerosis.

In atherosclerotic lesion, chronic mild endothelial injury results from hypercholesterolemia, inflammation, and sometimes exposure to tobacco smoke constituents. As a result, endothelial cell function decreases.^{16, 17)} Ensuing events include inflammation with monocyte recruitment, smooth muscle cell proliferation, accumulation of lipid-laden macrophages, and formation of cholesterol crystals; constitutes an atheroma.¹⁷⁾ Gradually, calcification then ensues. Some details of this process remain incompletely understood.¹⁸⁾

In the acute phase of KD, on the other hand, cells such as monocytes, macrophages, and neutrophils infiltrate into coronary arteries from the lumen and adventitia, until inflammation extends through all layers of the coronary artery.^{19, 20)} As a result, vascular smooth muscle, the internal elastic lamina, and extracellular matrix, —all important in maintaining arterial structure—, are injured and CALs develop.²¹⁾ Coronary arterial calcifications seen 40 or more days after onset of KD have been thought to follow cicatrization of disordered and necrotic tissue in the walls of coronary arteries—i.e., dystrophic calcification— or alternatively, organization of a thrombus. As with atherosclerosis, however, mechanisms of coronary arterial calcification after KD are not fully evident.⁹⁾

Pathological studies late in the course of KD have described hyalinized fibrous tissue, lamellar calcification, intimal thickening and lesions like progression of CALs resembling that in atherosclerosis.^{22, 23)} Further

even late in the evolution of CALs following KD, sustained chronic inflammation was considered to increase risk of atherosclerosis.^{24, 25)} Therefore, atherosclerosis is expected to occur readily in CALs following KD, even though pathogenetic triggers and speeds of progression of calcification seem likely to differ. Mechanisms of progression are likely to overlap, and we found compositions of calcifications to be essentially the same.

Even for calcifications occurring in the patients whose age at KD onset was less than 1 year, EANs resembled those in atherosclerosis. When the acute stage of KD runs its course in less than 1 year, inflammation tends to be more severe, requires more aggressive treatments.^{4, 26)} Further, even in CALs examined long after KD, slight inflammation persists.²⁴⁾ We suspect that inflammatory cytokines persist longer and at higher levels when inflammation was more intense in the acute phase. Chronic sustained inflammation has been identified as a risk factor for atherosclerosis and arterial calcification, particularly when serum interleukin-6, 8, and 13 were high.^{24, 27)} When the age at KD onset was less than 1 year, patients who develop CALs after the acute stage might be suspected to develop atherosclerosis and calcification more rapidly. We suggest that in the year following onset of KD, stronger anti-inflammatory agents may be needed, and if CALs then still occur, a period of continuing-treatment will be needed, such as aspirin at 30 mg/kg. We believe that when possible, warfarin should be avoided for late-treatment because of a report associating such treatment with increased calcification in a population with atherosclerosis.²⁸⁾

As depicted in Fig. 3, the EANs in calcifications following KD resembled those in coronary arterial calcifications caused by atherosclerosis (13.8), regardless of duration. We believe that the KD-related lesions progressed like purely atherosclerotic ones and that calcification often progressed over as many as 10 years following onset of KD, while progression rarely remained steady regardless of duration. We therefore maintain that patients found to have CALs after the acute phase of KD require treatments aiming to prevent progression of atherosclerosis.

Unfortunately, more risk factors for occurrence of progression of coronary arterial calcification following KD remain to be determined. We intend to study these patients and additional ones over a longer time in the future.

Study Limitations

ROIs were placed by the first author alone. The number of patients was relatively small and ages of patients varied. We were concerned that EANs might have been skewed had numbers of investigators placing ROIs been large. In addition, treatments in the acute phase varied between patients as did the interval from KD onset to performance of imaging. Moreover, we did not have the data of inflammation markers in acute phase. These factors might have influenced the apparent speed of progression. However, EANs in calcifications varied little. Sequential examinations may be desirable.

Conclusion

We examined the composition of coronary arterial calcifications following KD based upon EAN. Composition of these calcifications resembled those in atherosclerosis irrespective of other risk factors, so vigilance against early coronary arterial events is required following KD.

Conflict of Interests

Nobuyoshi Kusano, Noboru Inamura, Satoshi Marutani, Tohru Shinohara, and Tsukasa Takemura received a research grant from GE healthcare Japan.

Abbreviations

KD, Kawasaki disease; CT, computed tomography; EAN, effective atomic number; ROI, region of interest; CAL, coronary arterial lesion

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