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Assessment of Coronary Artery Aneurysms Caused by Kawasaki Disease Using Transluminal Attenuation Gradient Analysis of Computerized Tomography Angiograms

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Abstract

Patients with coronary artery aneurysms (CAAs) resulting from Kawasaki disease (KD) are at risk for thrombosis and myocardial infarction. Current guidelines recommend CAA diameter ≥ 8 mm as the criterion for initiating systemic anticoagulation. Transluminal attenuation gradient (TAG) analysis has been proposed as a noninvasive method for evaluating functional significance of coronary stenoses using computerized tomography angiography (CTA), but has not previously been used in CAA. We hypothesized that abnormal hemodynamics in CAA caused by KD could be quantified using TAG analysis. We studied 23 patients with a history of KD who had undergone clinically indicated CTA. We quantified TAG in the major coronary arteries and aneurysm geometry was characterized using maximum diameter, aneurysm shape index, and sphericity index. A total of 55 coronary arteries were analyzed, 25 of which had at least 1 aneurysmal region. TAG in aneurysmal arteries was significantly lower than in normal arteries (-23.5 ± 10.7 vs -10.5 ± 9.0 , $p = 0.00002$). Aneurysm diameter, aneurysm shape index, and sphericity index were weakly correlated with TAG ($r^2 = 0.01$, $p = 0.6$; $r^2 = 0.15$, $p = 0.06$; $r^2 = 0.16$, $p = 0.04$). This is the first application of TAG analysis to CAA caused by KD, and demonstrates significantly different TAG values in aneurysmal versus normal arteries. Lack of correlation between TAG and CAA geometry suggests that TAG may provide hemodynamic information not available from anatomy alone. TAG represents a possible extension to standard CTA for KD patients who may improve thrombotic risk stratification and aid in clinical decision making.

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Disclosures

The authors have no conflicts of interest to disclose.

Transluminar attenuation gradient (TAG) is defined as the linear regression coefficient fit to the luminal attenuation as a function of axial distance from the coronary ostium. TAG has been proposed as a noninvasive method for extracting functional information from computerized tomography angiography (CTA) in patients with atherosclerotic coronary artery disease.¹⁻³ In particular, TAG analysis has been used to characterize the functional significance of coronary artery stenoses, and has shown moderate correlation with the gold standard of invasive fractional flow reserve, providing additional data beyond the anatomic information usually obtained from CTA.⁴⁻⁶ Recent work also proposed the use of TAG analysis in combination with computational blood flow simulations as a method of quantifying flow in the coronary arteries.⁷ TAG analysis has not been previously used for the assessment of coronary artery aneurysms (CAA). We hypothesized that abnormal flow conditions in CAA caused by Kawasaki disease (KD) could be characterized and quantified using TAG analysis, and that this technique could provide clinically useful data not available from anatomic characterizations of CAA. In this pilot study, we report the results of the first application of TAG analysis to CAA caused by KD, and compare results with those of coronary arteries without aneurysms, and with geometric measurements of CAA.

Methods

This study was approved by the Institutional Review Board at the University of California San Diego, First Moscow State Medical University, Nippon Medical School, and Stanford University, and written patient consent (or assent and parental consent as appropriate) was obtained. A total of 23 patients with a history of KD who underwent clinically indicated CTAs were retrospectively enrolled in the study. The cohort included patients with a range of coronary artery pathology, from normal coronary arteries to giant aneurysms. Patients with a history of percutaneous revascularization or coronary artery bypass graft surgery were excluded.

CTAs were obtained at 3 different centers: University of California San Diego (CT750 HD 64-slice CT scanner; GE Healthcare, Milwaukee, Wisconsin), Sechenov First Moscow State Medical University (Aquilion ONE 320-slice CT scanner; Toshiba, Tokyo, Japan), and Nippon Medical School (LightSpeed VCT 64-slice CT scanner; GE Healthcare). All scans were performed using prospective triggering. Scanner voltages and tube currents and contrast injection rates were selected based on patients' body mass indexes as per standard cardiac CTA protocols at each institution. Radiation doses were available for 16 of the 23 patients. The median radiation dose-length product for these patients was 121 mGy cm, which corresponds to a median effective radiation dose of 1.7 mSv.

For each patient, we selected arteries for analysis among the right, left anterior descending (LAD), and left circumflex coronary arteries. We excluded from analysis coronary arteries that were thrombosed (1 vessel), had significant imaging artifacts (3 vessels), or were too small to adequately define the lumen of the vessel to perform TAG analysis (10 vessels). Otherwise, all 3 major coronary arteries were analyzed for each patient.

Vessel lumen segmentation and 3-dimensional anatomical model construction of the major coronary arteries were performed using the open source SimVascular software package

(www.simvascular.org). First, centerline paths were created for vessels of interest. Starting from the ostium, 2-dimensional image slices perpendicular to the centerline path were obtained at sequential positions along the length of the vessel. Segmentation of the vessel lumen was performed through a combination of pixel intensity thresholding, level set methods, and manual correction as needed (e.g., at branches).

Mean contrast intensity in Hounsfield units was computed over sequential regions of interest (ROIs) at cross-sections perpendicular to the vessel centerline for each coronary artery segment analyzed. Subsequently, linear regression was performed on the mean intensity data as a function of the distance from the ostium. TAG was reported in Hounsfield units as the slope of the linear regression per 10 mm. The left main coronary artery was excluded from the linear regression calculation to allow for independent evaluation of the LAD and left circumflex coronary arteries.

To evaluate the effect of the ROI size on TAG and the luminal intensity axial distributions, we used different ROI sizes in 6 vessels (3 right, 3 LAD arteries). In particular, we compared the following ROIs: total lumen, ROI80, ROI50, ROI20, and ROI01, where ROI80, ROI50, and ROI20 were defined as the lumen delimited by a circumference of radius 80%, 50%, and 20%, respectively, of the local average segmentation radius positioned in the center of the vessel lumen and ROI01 was a 1-mm² circular centered ROI. Note that except ROI01, ROIs vary with axial location and are proportional to the lumen area. Following this sensitivity analysis, ROI80 was then used for all reported TAG values.

Aneurysm geometry was characterized using the following geometrical parameters: maximum aneurysm diameter ($D_{\max}$), Z-score,^{8,9} aneurysm shape index, sphericity index (Ψ), and relative aneurysm length. Aneurysms were classified into 4 groups based on the maximum diameter: $3 \text{ mm} < D_{\max} \leq 5 \text{ mm}$, $5 \text{ mm} < D_{\max} \leq 8 \text{ mm}$, $8 \text{ mm} < D_{\max} \leq 10 \text{ mm}$, and $10 \text{ mm} < D_{\max}$. Aneurysm shape index and sphericity were defined to classify aneurysm geometries on a continuous scale from saccular to fusiform. The aneurysm lengths were defined as the segments of the coronary artery for which the diameter was greater than a Z-score value of 1.5. The aneurysm shape index was then defined as the nondimensional ratio of the representative aneurysm length to the maximum aneurysmal diameter. A high shape index value indicates a more fusiform shape, while low value indicates a more saccular shape. Aneurysm sphericity (Ψ) was defined using the following equation:

$$\psi = \frac{\pi^{1/3} (6V)^{2/3}}{A},$$

where V is the aneurysm volume and A is the surface area. Low aneurysm sphericity indicates a more fusiform shape while higher aneurysm sphericity indicates a more saccular shape, with $\Psi = 1$ corresponding to a perfect sphere. Relative aneurysm length was defined as the ratio of the representative aneurysm length to the total vessel length used for TAG analysis.

The Mann-Whitney U test was used to determine statistical significance of the TAG values between the aneurysmal and normal coronary arteries, with p values <0.05 considered to be

significant. Correlation between TAG values and the geometrical parameters was evaluated using Pearson's linear correlation coefficient.

Results

Patient characteristics at the time of the CTA are summarized in Table 1. A total of 55 coronary arteries were analyzed, of which 25 had at least one aneurysmal region. Representative examples of contrast intensity plots and TAG analyses are shown in Figure 1. The TAG of aneurysmal arteries was significantly lower than normal arteries (-23.5 ± 10.7 vs -10.5 ± 9.0 , $p = 0.00002$). This difference remained statistically significant for a subset of patients who were all imaged using the same scanner ($n = 16$ at University of California San Diego, -21.5 ± 10.3 vs -10.7 ± 9.6 , $p = 0.002$). Differences were also significant in aneurysmal versus normal for the LAD, left circumflex, and right subgroups (-26.7 ± 9.7 vs -17.2 ± 9.0 , $p = 0.03$; -27.5 ± 10.9 vs -12.1 ± 7.0 , $p = 0.005$; -16.1 ± 8.9 vs -2.9 ± 5.3 , $p = 0.001$; Figure 2). Among the nonaneurysmal arteries, we found significant differences in TAG values among the left and right coronaries (right vs LAD $p = 0.0001$, right vs left circumflex $p = 0.006$).

The TAG value was not significantly affected by a different choice of ROI. However, increasing ROI was associated with lower contrast intensity on average, resulting in a downward shift in the curves (Figure 3). The overall structure of the curves described by the luminal intensity axial distribution remained qualitatively similar.

CAA classification according to diameter size showed a large spread in TAG values that did not correspond to the CAA diameter >8 mm cutoff (Figure 4). TAG was not correlated with the maximum aneurysm diameter ($r^2 = 0.01$, $p = \text{NS}$; Figure 5). Differences in TAG between maximum diameter groups were also not significant. Other geometrical parameters analyzed, including Z-score, aneurysm shape index, sphericity, and relative aneurysm length, also showed little to no significant correlation with TAG ($r^2 = 0.07$, $p = 0.19$; $r^2 = 0.15$, $p = 0.06$; $r^2 = 0.16$, $p = 0.04$; $r^2 = 0.07$, $p = 0.19$; Figure 5).

Discussion

Invasive methods such as Doppler flow wire measurements^{10–12} and patient-specific blood flow simulations in KD patients^{13,14} reported abnormal hemodynamics in CAA and showed that hemodynamic parameters may be a promising approach for CAA assessment, in particular for identifying aneurysmal regions at higher risk of thrombosis.^{11,14} The present study is the first to evaluate CAA caused by KD using TAG analysis. We found significantly lower TAG values for aneurysmal compared with nonaneurysmal arteries. Differences in TAG values suggest that the abnormal flow pattern induced by an aneurysm has an impact on the contrast gradient along the vessel. Hence, TAG analysis may provide a means to quantify the effect of an aneurysm on coronary flow dynamics.

Aneurysmal arteries analyzed showed a relatively consistent pattern of intensity variation along the vessel length. A moderate increase in the average intensity in Hounsfield was observed in the regions coincident with the aneurysm, while the overall trend of the distribution was toward a negative gradient. This may be because of contrast-enhanced blood

accumulating and recirculating within the aneurysmal region because of flow stagnation, development of flow recirculation regions, and low velocities. This is consistent with the results obtained from invasive studies evaluating coronary flow velocity dynamics and flow reserve in CAA,¹² and from computer blood flow simulations showing that particle residence times are increased within coronary aneurysms.¹⁴

Of note, the distribution of the intraluminal intensity average along the aneurysmal vessels showed a complex structure that may not be fully captured with a linear regression analysis. For the purpose of this study, we used the same linear TAG analysis as has been used previously.^{1,2} A different approach using a more complex analysis of luminal intensity variations may provide additional information and insights into flow patterns in aneurysmal vessels.

The observed differences in attenuation gradients between the right and the left coronary arteries for the nonaneurysmal arteries are consistent with previous studies¹ showing a more negative gradient for the left coronary arteries. The increased branching of the left coronary circulation may affect hemodynamics and be responsible for this difference. Computer simulations quantifying transport of contrast along the vessel may lead to better understanding of the effect of branching and aneurysmal regions on hemodynamics and intraluminal contrast gradients.

Simulation data have shown that flow inside aneurysms is complex and nonuniform across the cross-sectional lumen area, with spatially varying regions of relative stasis and recirculation in many cases.^{13,14} Using a small ROI compared with the lumen of the aneurysm may provide a less representative measurement of the average luminal intensity, while an ROI closer to the lumen size may better represent the overall average intensity at a particular axial position. In this study, we chose to use ROI80, because this ROI size appeared to capture the variation in intensity along the vessel length, while minimizing artifacts from the edges of the vessel lumen segmentation seen with a larger ROI.

Lack of correlation between TAG and CAA geometry suggests that TAG may encode hemodynamic information not available from anatomy alone. Aneurysm shape varies greatly among KD patients, from saccular to fusiform, and exhibits varying degrees of tortuosity. In addition, many aneurysms occur at or near bifurcation sites, which are known to affect flow dynamics. Therefore, the clinical utility of a single anatomic measure to assess thrombosis risk in a coronary aneurysm seems uncertain. Previous patient-specific simulations have suggested that diameter characterization of coronary aneurysms is not predictive of relative stasis and the risk of thrombosis.¹⁴ Future work comparing the results of TAG analyses with results from patient-specific computational fluid dynamic simulations will be necessary to determine the extent to which TAG analyses capture essential hemodynamic data not described by anatomic parameters.

Because the study was retrospective, injection protocols were not controlled, and therefore the effect of these on the reported data could not be systematically assessed. The use of CTA data from 64-slice scanners may add contrast banding to the image data, because imaging during several cardiac cycles is required to cover the entire coronary tree. However, the

studied segments of the major coronary arteries typically lie within 1 or 2 consecutive bands, so that this effect is typically relatively small or nonexistent. Scanner effects such as kernel choice and partial volume effects may have some effect on the results.⁷

Hemodynamics and advection/diffusion within the aneurysms are complex and incompletely captured by the 1dimensional TAG analysis presented in this manuscript. In the present study, we focused on flow variations along the length of the vessel, and did not perform detailed analyses of variations in contrast intensity in the cross-sectional plane. The study was also not longitudinal and therefore did not include outcome data. However, outcome data are relatively challenging to obtain given that many KD patients with aneurysms are treated with anticoagulation and thrombosis events are relatively uncommon. Although CTA with TAG assessment does involve radiation, because of advances in scanner technology this is feasible in patients with a history of KD with relatively low radiation doses.¹⁵

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Figure 1
 . Representative examples of contrast intensity plots, TAG measurements, and corresponding reconstructed CTAs along centerlines in KD patients: left anterior descending artery with (A1) giant aneurysm and (A2) normal; right coronary artery with (B1) aneurysm and (B2) normal.

Figure 2
TAG analyses for different subgroups of coronary arteries. *p < 0.05. RCA = right coronary artery.

Figure 3
. Example of sensitivity to ROI. Luminal intensity distribution longitudinal to coronary artery (LAD) according to the different ROI considered: total lumen, ROI80 (80%), ROI50 (50%), ROI20 (20%), and ROI01 (1 mm²).

Figure 4. TAG in aneurysmal coronary arteries according to maximum aneurysm diameter (D_{max}). There was no significant difference between groups. RCA = right coronary artery.

Figure 5
Correlation analysis between TAG and geometrical parameters: (A) aneurysm maximum diameter and (B) aneurysm shape index. P = NS for each of these.

Table 1

Patient demographics and results (n = 23)

Patient ID	Age at KD	Age at CTA	SEX	BSA	LAD Z-score	Right Z-score	LAD D _{max} [mm]	RCA D _{max} [mm]	LAD TAG [HU]	RCA TAG [HU]	Aspirin	Anticoagulation Therapy
1	0	24	F	1.9	10.2	10.82	8.9	10.8	-40.0	-11.9	+	+
2	1	24	M	1.7	NML	NML	NML	NML	-35.7	3.5	-	-
3	1	35	M	2.2	4.7	3.73	7.4	6.0	-24.7	-3.0	+	-
4	1	9	M	1.2	-	16.28	-	11.7	EX	-19.2	+	-
5	2	10	M	1.3	-	NML	-	NML	EX	-6.6	+	+
6	3	8	M	1.2	20.3	13.51	11.8	9.4	-32.4	-27.7	+	+
7	3	7	M	0.8	24.41		12.7		-38.7	EX	+	+
8	3	3	F	0.6	9.8	-	5.9	-	-20.2	EX	+	+
9	4	16	M	1.9	NML	NML	NML	NML	-10.5	-2.5	-	-
10	4	26	M	1.7	NML	NML	NML	NML	-10.9	-10.6	-	-
11	5	20	F	1.4	NML	NML	NML	NML	-13.4	-5.6	-	-
12	5	16	M	1.8	NML	NML	NML	NML	-12.5	1.0	-	-
13	6	10	M	0.9	27.9	-	16.6	-	-39.1	EX	+	+
14	6	27	M	2.1	10.0	-	9.3	-	-13.3	EX	+	+
15	6	15	F	1.4	-	13.71	-	11.4	EX	-23.2	+	+
16	7	20	M	2.0	10.3	NML	8.7	NML	-19.3	-2.7	+	-
17	8	18	M	1.9	NML	NML	NML	NML	-13.6	-9.3	-	-
18	15	28	M	2.1	11.2	12.22	9.6	12.4	-29.1	-12.2	+	+
19	15	29	M	1.8	NML	NML	NML	NML	-10.5	5.6	-	-
20	16	16	M	1.8	10.6	13.27	8.8	11.2	-21.0	-7.1	+	+
21	18	20	M	1.9	NML	NML	NML	NML	-24.7	-1.3	-	-
22	19	25	F	1.3	NML	10.01	NML	7.5	-22.6	-24.4	+	+
23	ND	28	M	2.0	24.4	-	15.0	-	-15.9	EX	+	+

BSA = body surface area; CTA = computerized tomography angiography; EX = excluded from analysis; KD = Kawasaki disease; LAD = left anterior descending; NML = normal vessel with no aneurysm; RCA = right coronary artery.