Title
Assessment of Coronary Artery Aneurysms Cased By Kawasaki Diesease Using Transluminal Attenuation Gradient Analysis of CT Angiograms

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Assessment of Coronary Artery Aneurysms Caused By Kawasaki Disease Using Transluminal Attenuation Gradient Analysis of CT Angiograms

A Thesis submitted in partial satisfaction of the
requirements for the degree Master of Science

in

Engineering Sciences (Applied Mechanics)

by

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Professor Juan Carlos del Alamo
Professor Andrew Kahn

2015

The Thesis of Noelia Grande Gutierrez is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

2015

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ABSTRACT OF THE THESIS

Assessment of Coronary Artery Aneurysms Caused By Kawasaki Disease Using Transluminal Attenuation Gradient Analysis of CT Angiograms

by

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Master of Science in Engineering Sciences (Applied Mechanics)

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Professor Alison L. Marsden, Chair

Patients with coronary artery aneurysms (CAA) resulting from Kawasaki Disease (KD) are at risk for thrombosis and myocardial infarction. Current guidelines recommend using CAA diameter >8 mm as the criterion for initiating systemic anticoagulation, but there is little outcome data to support this choice. Transluminal Attenuation Gradient (TAG) has been proposed as a non-invasive method for evaluating the functional significance of coronary stenoses using CT Angiography (CTA). However TAG has not previously been used to assess CAA. We hypothesized that abnormal flow dynamics in CAA caused by KD could be quantified using TAG. We quantified TAG in the major coronary arteries by performing linear regression of the average lumen intensity

as a function of vessel length and compared TAG values for aneurysmal and normal arteries. Aneurysm geometry was characterized using maximum aneurysm diameter, aneurysm shape index and sphericity index. TAG of aneurysmal arteries was significantly lower than in normal arteries. Significant differences were also seen between aneurysmal vs. normal left anterior descending and right coronary. Geometrical parameters showed minimal to no correlation with TAG. This study 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 information on hemodynamic conditions not available from anatomy alone. The use of TAG in KD patients represents a possible extension to standard CTA that could aid in clinical decision-making and help to better evaluate the risk of thrombus formation.

1   Introduction

Kawasaki Disease (KD) is the leading cause of acquired childhood heart disease in developed countries. KD is an acute, self-limited vasculitis of unknown etiology that typically occurs in young children and infants less than 5 years of age, often affecting the coronary arteries. KD can result in coronary aneurysms in up to 25 % of patients if not treated with intravenous immunoglobulin therapy within 10 days of fever onset. Aneurysms may also occur in up to 5 % of treated patients [8].

Unlike cerebral or abdominal aneurysms, the main risk associated with coronary artery aneurysms (CAA) in KD patients is not rupture but thrombus formation, with associated risks of myocardial infarction and sudden death. The primary long-term clinical decision in KD patients with aneurysms is whether and how aggressively to treat with anticoagulation therapy. Recommendations on thrombosis prevention for these patients are primarily based on pathophysiologic arguments, data from retrospective case series in children with KD, and extrapolation from adults with coronary artery aneurysms due to atherosclerotic disease [11], but there are no robust outcome data to support them. Current clinical guidelines recommend CAA diameter $8 \geqslant$ mm as the criterion for initiating systemic anticoagulation therapy [17, 18].

Recent data suggest insights from hemodynamics may be useful in developing more quantitative risk guidelines for KD patients with aneurysms.. CAAs create abnormal flow conditions within vessels, which are distinct from those associated with obstructive atherosclerotic coronary artery disease. Studies have reported low blood flow velocities and areas of flow stasis in aneurysms via invasive methods, such us Doppler flow wire measurements [9, 12] and have

related these findings with the risk of thrombus formation [12]. In addition, recent patient specific modeling and computer blood flow simulations in KD patients [13, 14] showed that hemodynamic parameters may be a promising approach for identifying aneurysmal regions at higher risk of thrombus formation. Results suggest that thrombotic risk assessment by means of hemodynamic parameters such wall shear stress, oscillatory shear index or particle residence time may be superior to using diameter alone. However, while patient specific modeling can provide a wealth of hemodynamic information, there are numerous challenges associated with performing these simulations in routine clinical practice, as they are currently labor-intensive and require substantial computational resources.

Transluminal attenuation gradient (TAG) is defined as the linear regression coefficient between luminal attenuation and axial distance from the coronary ostium. TAG has been proposed as a non-invasive method for extracting functional information from CT angiography (CTA) in patients with atherosclerotic coronary artery disease (CAD) [3, 15]. In particular, TAG analysis has been used to characterize the functional significance of coronary artery stenoses, and has been shown to correlate with the gold standard of invasive fractional flow reserve (FFR), providing additional data beyond the anatomic information usually obtained from CTA [2, 19, 20].

Despite this recent increasing interest, TAG has not been previously used for the assessment of CAA. We hypothesized that abnormal flow conditions in CAA caused by KD could be characterized and quantified using TAG analysis, and that this technique would 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 the results with those from coronary arteries without aneurysms, and with geometric measurements of CAA.

2 Methods

2.1 Patient Population

This study was approved by the Institutional Review Board at the University of California San Diego, First Moscow State Medical University, and Nippon Medical School, and written subject consent (or assent and parental consent as appropriate) was obtained. The study group consisted of patients with a history of KD who underwent clinically indicated CT Angiograms (CTAs). A total of 23 patients were enrolled in the study . This group included patients with a range of coronary artery pathology, from normal coronary arteries to giant aneurysms. Exclusion criteria were previous coronary artery bypass graft surgery, a previous myocardial infarction, or previous coronary artery thrombosis.

2.2 CT Angiography acquisition

CT Angiograms (CTA) were obtained at three different centers: University of California San Diego (CT750 HD 64-slice CT scanner, GE Medical, Milwaukee, WI), Sechenov First Moscow State Medical University (Aquilion ONE 320 slice CT scanner, Toshiba, Tokyo, Japan) and Nippon Medical School (Aquilion ONE 320 slice CT scanner, Toshiba, Tokyo, Japan). Scanner voltages and tube currents were selected based upon patients body mass indices (BMI) as per standard cardiac CT protocols at the institutions. Contrast volume and injection rates were also chosen as per BMI-based institutional cardiac CT protocols. Acquisition timing was determined

based upon ascending aortic opacification measured using a test bolus scan (University of California San Diego) or dynamic triggering based upon descending aortic opacification (Moscow State Medical University).

2.3 Coronary artery segmentation

Vessel lumen segmentation and 3D anatomical model construction of major coronary arteries (RCA, LAD and LCX) was performed using the open source SimVascular software package (simvascular.org). First, centerline paths were created for vessels of interest. Segmentation of the vessel lumen was performed through a combination of pixel intensity thresholding, level set methods and manual correction if needed (e.g. at branches). Some aneurysms presented calcification of the wall, in those cases the segmentation was corrected manually to leave out the calcified regions. 2DTwo-dimensional image slices perpendicular to the vessel path were obtained at sequential positions evenly spaced along the length of the vessel. The starting point for segmentation was set at the ostium. For the right coronary artery the end point was set at the origin of the posterior descending artery For the left cornary artery vessels (LAD and LCX) the end point was the most distal position where vessel lumen segmentation quality was judged to be adequate.

2.4 Transluminal Attenuation Gradient

Mean contrast intensity in Hounsfield Units (HU) 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 using the mean intensity as a function of the distance from the ostium. TAG was reported in HU as the slope of the linear regression per 10 mm. For the LAD and LCX coronaries the left main coronary artery was excluded from the linear regression calculation to allow for independent evaluation of the two vessels. Representative examples of the changes in luminal intensity average along the vessel are

shown in Figure 2.1.
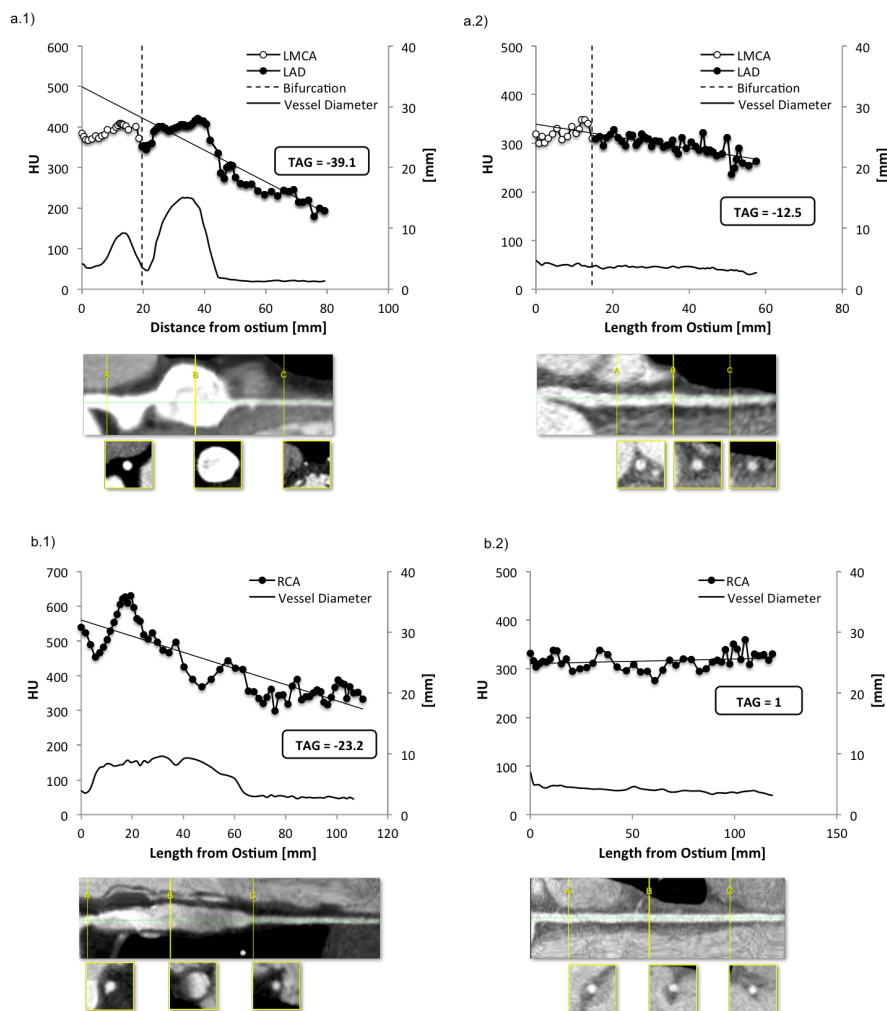
Figure 2.1: Representative examples of contrast intensity plots, transluminal attenuation gradient (TAG) measurements, and corresponding reconstructed CTAs in KD patients: Left anterior descending artery a.1) with giant aneurysm and a.2) normal. Right coronary artery b.1) with aneurysm and b.2) normal

2.5   Sensitivity to Region of Interest

To evaluate the effect of the ROI size on TAG and the luminal intensity axial distributions we used different ROI sizes in X vessels. In particular, we compared the following ROIs: Total

lumen, ROI80, ROI50, ROI20, and a 1mm2 circular ROI centered to the vessel centerline, where ROI80, ROI50, ROI20 were defined as the lumen area 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. With the exception of this sensitivity analysis, ROI80 was used for all reported TAG values.

2.6   Geometrical Parameters

Aneurysm geometry was characterized using the following geometrical parameters: Maximum aneurysm diameter (Dmax), Z-score [4, 10], Aneurysm Shape Index (ASI), Sphericity Index (Ψ) and relative aneurysm length (Lr). 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 non-dimensional 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 . Aneurysm volume and area measurements where determined from the patient specific 3D model of the vessels. Low aneurysm sphericity indicates a more fusiform shape while higher aneurysm sphericity indicates a more saccular shape, where $\Psi = 1$ is a perfect sphere. Relative aneurysm length (Lr) was defined as the ratio of the representative aneurysm length to the total vessel length used for TAG analysis.

2.7 Statistical Analysis

Continuous demographic data are reported as medians and interquartile tertiles. 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 statistically significant. We report p values only for statistically significant quantities. The fit of the liner regression line to the luminal intensity vs. distance from the ostium was evaluated using Pearsons linear correlation coefficient. Similarly, Pearson's correlation coefficient was also used to evaluate the correlation between TAG values and the geometrical parameters.

3 Results

3.1 Patient Demographics

Patient characteristics at the time of the CTA are summarized in Table 3.1. One patient was noted to have aneurysm enlargement diagnosed by CTA. Otherwise, no cardiovascular complications were reported for these patients at the time of the study. A total of 41 coronary arteries were analyzed. Among those 41 arteries, 22 of them had at least one aneurysmal region.

3.2 Transluminal Attenuation Gradient

TAG of aneurysmal arteries was significantly lower compared to normal arteries (-22.410.5 vs. -9.310, p=0.0003; Table 3.2). Differences were also significant in aneurysmal vs. normal LAD and RCA sub-groups (-26.79.7 vs. -16.59.0, p=0.02; -14.78.2 vs. -0.14.4, p=0.001; Figure 3.1). Among the non-aneurysmal arteries we found significant differences in TAG values among the three coronary artery subgroups (RCA vs. LAD p= 0.0007, RCA vs. LCX p= 0.048, LAD vs. LCX p= 0.04). On average, Pearson coefficient indicated a moderate correlation between luminal intensity and axial distance (r2= 0.44).

Table 3.1: Patient Demographics (N=23)

|	KD Patients (N=23)
Males	17 (74%)
Age at onset of KD (years)	6.9 (0.8 - 18.7)
Age at CTA study (years)	10 (0.8 - 35)
Body Surface Area (m2)	1.57 (0.6 -2.15)
Coronary artery status:	
Normal	7 (30%)
At least one aneurysmal coronary artery	16 (70%)
Atherosclerosis risk factors:	
Hypertension	1 (4%)
Diabetes mellitus	0 (0%)
Tobacco use, ever	2 (9%)
Hyperlipidemia	3 (13%)
Family history of early CAD (< 55 yrs)	0 (0%)
Medications:	
Statin	2 (9%)
ACE-I or ARB	2 (9%)
Beta blocker	1 (4%)
Calcium channel blocker	1 (4%)
Warfarin or NOAC	9 (39%)
Aspirin	13 (57%)
Clopidogrel (or other P2Y12 inhibitor)	0 (0%)

3.3   Sensitivity to Region of Interest

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 3.2). The overall structure of the curves described by the luminal intensity axial distribution remained qualitatively similar, though with smaller ROIs the variations in contrast intensity were smaller (Figure 3.2).

Table 3.2: Transluminal Attenuation Gradient analysis per vessel according to presence of aneurysmal region.

		No. Vessels	TAG (mean sdev)	p Value
ALL (N=41)	CAA	22	-22.4 10.5	0.0003
	Normal	19	-9.3 10.0	
LAD (N=19)	CAA	11	-26.7 9.7	0.02
	Normal	8	-16.5 9.0	
LCX (N=8)	CAA	3	-27.6 7.6	0.07
	Normal	5	-8.7 7.3	
RCA (N=14)	CAA	8	-14.7 8.2	0.001
	Normal	6	-0.1 4.4	

3.4   Geometrical Parameters

TAG was not correlated with the maximum aneurysm diameter (r2=0.04). CAA classification according to diameter size showed a large spread in TAG values that does not correspond to the CAA diameter > 8 mm cutoff (Figure 3.3). Other geometrical parameters analyzed: Z-score, ASI, Sphericity and Lr also showed little to no correlation with TAG (r2=0.13, r2=0.18, r2=0.17, r2=0.05; (Figure 3.4).
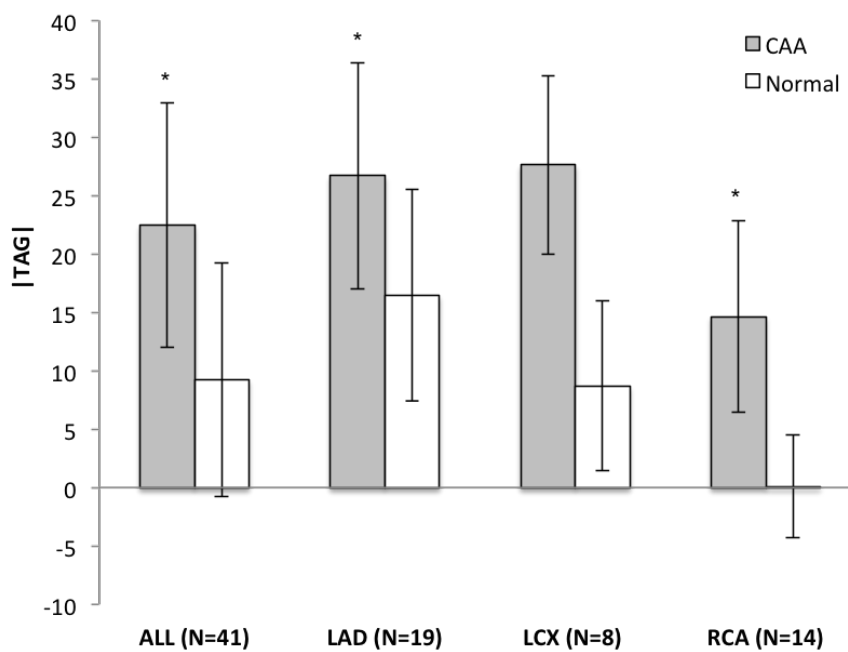
Figure 3.1: Transluminal attenuation gradient (TAG) analyses for different subgroups of coronary arteries (* indicates p ¡ 0.05; LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery).
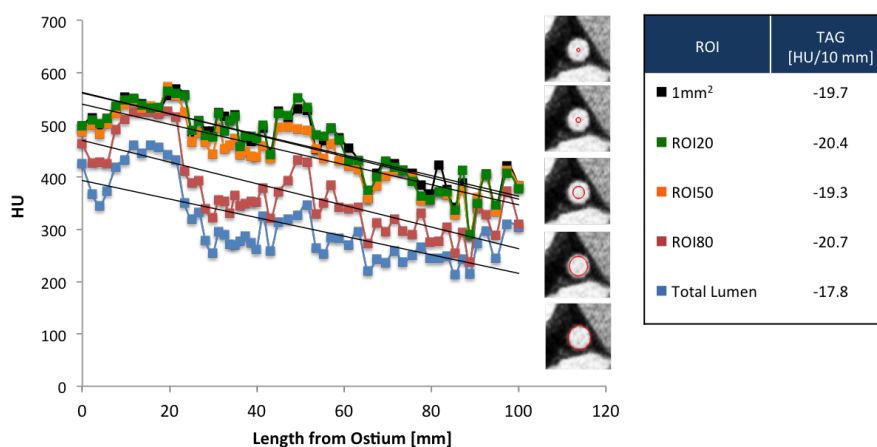
Figure 3.2: Example sensitivity to region of interest (ROI). Luminal intensity distribution longitudinal to coronary artery according to the different ROI considered: Total lumen, ROI80 (80%), ROI50 (50%), ROI20 (20%), and a 1mm^2 circular ROI.
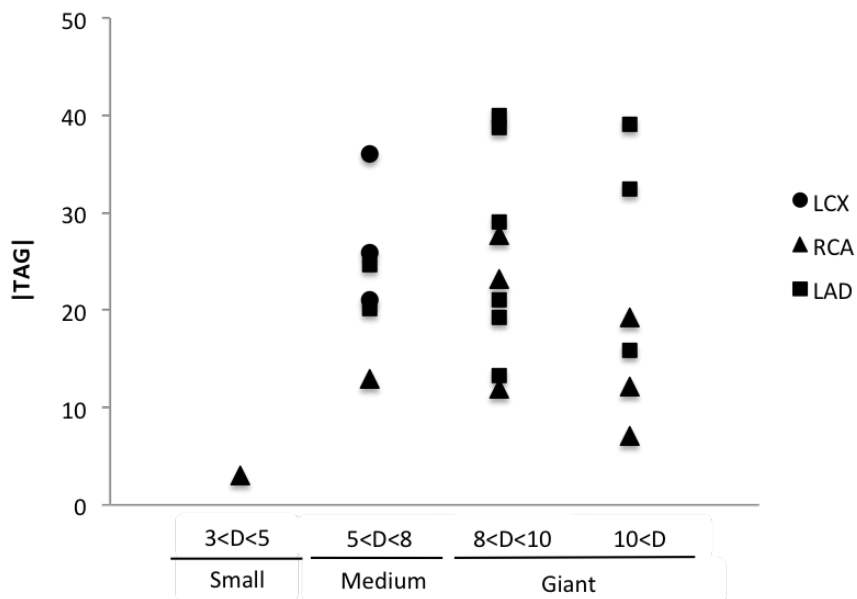
Figure 3.3: Transluminal attenuation gradient (TAG) in aneurysmal coronary arteries according to maximum aneurysm diameter.
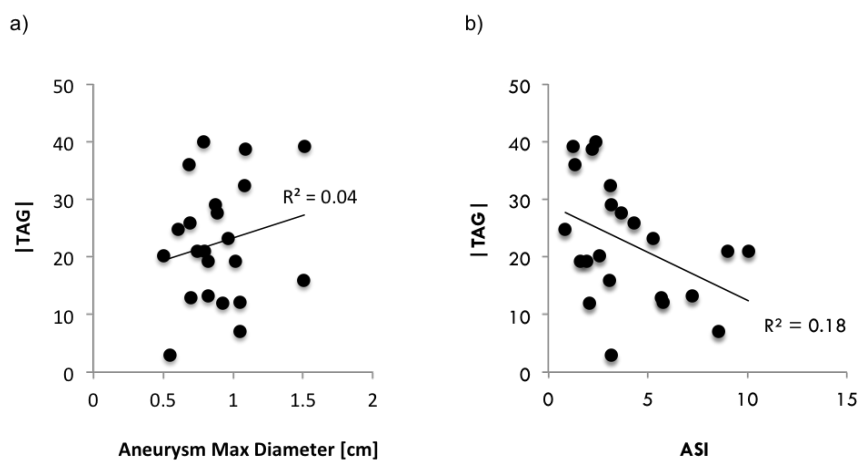
Figure 3.4: Correlation analysis between Transluminal Attenuation Gradient (TAG) and geometrical parameters: a) Aneurysm maximum diameter b) Aneurysm Shape Index (ASI).

4 Discussion

The current study is the first to evaluate coronary artery aneurysms caused by KD using TAG analysis. We found significantly larger TAG values for aneurysmal compared to non-aneurysmal arteries. Significant differences from normal were also present in the LAD and the RCA subgroups. For the LCX, the differences were not significant, but we note the sample size in this subgroup was relatively small. 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.

4.1 Pattern of contrast variation

Aneurysmal arteries analyzed showed a relatively consistent pattern of intensity variation along the vessel length. A moderate increase on the intensity average in HU was observed in the regions coincident with the aneurysm, while the overall trend of the distribution was towards a negative gradient. This may be due to contrast-enhanced blood accumulating and recirculating within the aneurysmal region due to flow stagnation and low velocities. This is consistent with the results obtained from computer blood flow simulations showing that particle residence times [14] are increased within coronary aneurysms.

Of note, the distribution of the intraluminal intensity average along the aneurysmal vessels showed a complex structure that is not 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 [3, 15].

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 right and left non-aneurysmal coronary arteries are consistent with previous studies [15] showing a more negative gradient for the left coronary arteries (Table 2). The increased branching of the left coronary circulation may affect hemodynamics and be responsible for this difference. Computer simulations of contrast advection along the vessel may provide additional information to help better understand the effect of branching and aneurysmal regions on hemodynamics and the intraluminal contrast gradients.

4.2   TAG sensitivity to Region of Interest

The sensitivity analysis shows that smaller ROIs result in overall higher contrast intensities and somewhat smoother intensity plots. Simulation data have shown that flow inside aneurysms is complex and non-uniform across the cross-sectional lumen area, with regions of relative stasis and recirculation in many cases citesengupta2012image , sengupta2014thrombotic . The variations in the intensity plots observed with ROI sizes are consistent with observations of complex flow patterns associated with aneurysms in other vascular beds. Biasetti et al. [1] related coherent vortices from hemodynamics to platelet activation, suggesting that vortical structures provided insight into locations of thrombus formation in abdominal aortic aneurysm. Using a small region of interest compared to the lumen of the aneurysm may provide a less representative measurement of the average luminal intensity, while a 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.

Previous work using TAG for stenosis characterization suggested that calcified vessel segments should be omitted in order to improve TAG analysis [3]. More recent work on the value

of TAG for the determination of hemodynamically significant stenoses reported non-significant differences when considering calcified segments for TAG analysis, though this was done using relatively small ROIs [16]. Patients with aneurysms secondary to KD typically have significant coronary artery calcification [7]. However, due to increased vessel diameter, the relative artifact from calcium blooming is smaller, permitting the use of relatively larger ROIs.

4.3 Effect of CTA Coverage

The use of CTA data from 64-slice scanners may add some contrast banding to the image data, since imaging during several cardiac cycles are required to cover the entire coronary tree. However, the studied segments of the major coronary arteries typically lie within one or two consecutive bands, so that this effect is often relatively small or non-existent. Contrast correction to TAG by computing TAG independently for the segments on different contrast bands showed some change in independent measurements, but little change in the trends observed. Differences between TAG and corrected TAG were far below those reported between aneurysmal and normal arteries. In addition, corrected TAG correlated with the results obtained without correction. Nevertheless, when feasible it makes sense to use a scanner that provides whole heart coverage in a single beat to avoid this issue.

4.4 TAG vs. Geometrical Parameters

Lack of correlation between TAG and CAA geometry suggests that TAG may provide information on hemodynamic conditions 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 likely affect flow dynamics. Therefore, the clinical utility of a single anatomic measure of an aneurysm seems uncertain. Previous patient-specific simulations have suggested that anatomic characterization of coronary aneurysms is not predictive of relative stasis and the risk of thrombosis (reference

Dibs work). 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.

Thrombosis is known to be a complex process with a number of factors contributing to increased thrombosis risk. Virchows triad identifies flow stasis, vessel wall injury, and hypercoagulability as the three primary contributory factors. The hemodynamic and flow abnormalities associated with aneurysms studied here may indirectly inform our assessment of relative blood stasis, but the other two factors cannot be inferred from CTA data. Histology studies of aneurysmal arteries reveal that the wall of KD aneurysms is abnormal, with an accumulation of macrophages, infiltration of smooth muscle cells into the intima, calcifications, and in general a reduction or disappearance of the tunica media together with intimal hyperplasia. In addition, a recent study using Optical Coherence Tomography (OCT) [5] showed significant structural abnormalities of the arterial wall layers of aneurysmal arteries of KD patients, that agrees with previous histological findings.

4.5   Clinical Implications

Due to advances in scanner technology, permitting high resolution non-invasive coronary imaging with relatively low radiation doses, CTA is emerging as a valuable technique in assessing and following aneurysms in patients with a history of KD [6]. Currently, there are a lack of data and tools to identify patients for whom the benefit of anticoagulation outweighs the risks. The current study provides pilot data, suggesting that TAG analysis of CTA images may provide hemodynamic information beyond anatomic measures. In the case of obstructive atherosclerotic coronary artery disease, the potential utility of TAG is determined by comparison with results from invasive fractional flow reserve (FFR), the gold standard for functional significance of coronary stenoses. However, there is no analogous gold standard in the case of coronary aneurysms. Therefore, the clinical utility of TAG analyses for assessing the risk of thrombosis will require

future studies comparing TAG results with patient outcomes.

4.6   Strengths and limitations of the study

The current study included CTA data from KD patients with a range of coronary artery aneurysm sizes. This is the first study to apply TAG analysis to patients with KD. In the current study we focused on variations of flow along the length of the vessel, and did not perform detailed analyses of variations in contrast intensity in the cross-sectional plane. Because the study was retrospective, injection protocols were not controlled, and therefore the effect of these upon the reported data could not be assessed. The study was not longitudinal and therefore did not include outcome data. However outcome data are relatively difficult to obtain given that many KD patients with aneurysms are treated with anticoagulation and thrombosis events are not common.

5 Conclusion

TAG analysis of CTA data in patients with a history of KD revealed significantly lower values in aneurysmal than normal coronary arteries. TAG values from aneurysmal vessels did not correlate with the maximal vessel diameter or other anatomic assessments of aneurysms, indicating that it may be adding additional information not provided by geometry alone. TAG analysis may provide a patient-specific non-invasive hemodynamic assessment that can be obtained from CTA data in patients with coronary artery aneurysms secondary to KD. This may be useful in risk-stratifying patients to better determine which patients would benefit from treatment with anticoagulation to prevent coronary artery thrombosis. Prospective outcome studies and correlation with results from flow simulations will be necessary to further evaluate the utility of this technique in this high-risk patient population.

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