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FULL PAPER

The transluminal attenuation gradient in coronary CT angiography for the detection of hemodynamically significant disease: can all arteries be treated equally?

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Objective: Results of the use of the transluminal attenuation gradient (TAG) at coronary CT angiography (CCTA) to predict hemodynamically significant disease vary widely. This study tested whether diagnostic performance of TAG to predict fractional flow reserve (FFR) ≤ 0.8 is improved when applied separately to subsets of coronary arteries that carry similar physiological flow.
Methods: 28 patients with 64 × 0.5 mm CCTA and invasive FFR in ≥1 major coronary artery were retrospectively evaluated. Two readers assessed TAG in each artery. The receiver operating characteristic (ROC) area under the curve (AUC) was used to assess the diagnostic performance of TAG to detect hemodynamically significant disease following a clinical use rule [negative: FFR > 0.8 or ≤ 25% diameter stenosis (DS) at invasive catheter angiography; positive: FFR ≤ 0.8 or ≥ 90% DS at invasive catheter angiography]. ROC AUC was compared for all arteries pooled together, *vs* separately for arteries carrying similar physiological flow (Group 1: all left anterior descending plus right-dominant left circumflex; Group 2: right-dominant RCA plus left/co-dominant left circumflex).
Results: Of the 84 arteries, 30 had FFR measurements, 30 had ≤25% DS and 13 had ≥90% DS. 11 arteries with 26–89% DS and no FFR measurement were excluded. TAG interobserver reproducibility was excellent (Pearson r = 0.954, Bland–Altman bias: 0.224 Hounsfield unit cm^{-1}). ROC AUC to detect hemodynamically significant disease was higher when considering arteries separately (Group 1 AUC = 0.841, p = 0.039; Group 2 AUC = 0.840, p = 0.188), than when pooling all arteries together (AUC = 0.661).
Conclusion: Incorporating information on the physiology of coronary flow via the particular vessel interrogated and coronary dominance may improve the accuracy of TAG, a simple measurement that can be quickly performed at the time of CCTA interpretation to detect hemodynamically significant stenosis in individual coronary arteries.
Advances in knowledge: The interpretation of TAG may benefit by incorporating information regarding which coronary artery is being interrogated.

INTRODUCTION

Use of the transluminal attenuation gradient (TAG),[1] the average contrast opacification drop-off along the length of a coronary artery at coronary CT angiography (CCTA), towards improved detection of significant coronary artery disease (CAD) from CCTA[2–8] is desired as its measurement requires neither additional radiation or contrast as in CT perfusion,[9] nor complex computation as in fractional flow reserve (FFR) calculated from CCTA (FFR-CT).[10–12 13] Most studies have, nonetheless, reported a weak relationship of TAG and a significant FFR ≤0.8, the reference standard to establish CAD hemodynamic significance at invasive catheter angiography (ICA).[2,5–7]

In theory, TAG carries information regarding blood flow in a vessel. This was elegantly established by Chow et al who reported that contrast opacification drop-off across a stenosis at CCTA correlates with thrombolysis in myocardial infarction flow Grade <3.[4] Choi et al confirmed this result and also found that TAG differs substantially between left and right coronary arteries with <49% angiographic stenosis severity,[3] the majority of which do not cause ischemia.[14] This difference suggests that a single TAG cutoff is unlikely to yield a successful diagnostic test for all arteries.

A large study of coronary flow measured at ICA[15] reported that the left anterior descending (LAD) regardless of coronary dominance, and left circumflex (LCX) arteries of right-dominant patients carry approximately the same flow. The right coronary artery (RCA) in right-dominant patients, and LCX in left-dominant or balanced circulation patients carry similar, significantly higher flow, while the RCA in left-dominant patients carries significantly less flow. If TAG is associated to flow, its value would differ amongst these three groups of arteries, and we hypothesize that its interpretation to predict disease should differ for each group.

The purpose of this study was to test whether incorporating knowledge of the different physiological flow carried by coronary arteries can enhance interpretation of TAG. Specifically, we tested whether diagnostic performance of TAG to predict FFR <0.8 is increased when applied separately to subsets of coronary arteries that carry relatively similar physiological flow.

METHODS AND MATERIALS

Study population

This retrospective study was human research committee-approved. The requirement for written informed consent was waived. All 28 consecutive patients who underwent clinically indicated CCTA between May 2012 and August 2014 and that had a subsequent ICA with FFR measurement in ≥1 vessel at a single institution in Japan were included in the study.

CCTA, ICA and FFR techniques

Retrospectively-gated CCTA (64 × 0.5 mm; Aquilion 64, Toshiba Medical Systems, Otawara, Japan) was performed at 120 kVp. Patients with heart rate >65 beats min^{-1} received beta-blockade. Contrast (300 mgI ml^{-1} for patients weighing <68 kg, 350 mgI ml^{-1} otherwise) was injected for 13 s followed by contrast plus saline (1.5:1 ratio) for 10 s at a flow rate of 0.06 × body weight ml s^{-1}. Acquisition was timed by bolus tracking. Gantry rotation time (0.35–0.45 s) and helical pitch (0.125–0.26) were automatically determined by the manufacturer's algorithm. Filtered back projection images were reconstructed (0.5/0.25 mm thickness/overlap) at the phase of least motion determined by the software.

ICA and FFR were performed according to standard clinical practice. Percent stenosis was calculated for the most significant lesion in each vessel in the angle showing the narrowest degree of stenosis and classified into six categories: 1–25, 26–50, 51–75, 75–90, 91–99, and 100% diameter stenosis (DS). FFR was performed at the discretion of the operator. The pressure wire was calibrated and equalized with aortic pressure and FFR was calculated at steady-state hyperemia after intracoronary isosorbide dinitrate (0.5–1 mg) and intracoronary papaverine hydrochloride (left coronary: 12 mg, right coronary: 8 mg) injection.

TAG measurements

Two blinded readers (1 and 6 years of experience in cardiovascular imaging) independently measured TAG in the LAD, LCX, and RCA using previously validated semi-automated software.[16] Measurements were performed from coronary ostia to a distal location where vessel lumen cross-sectional area tapered to approximately 2 mm^2.[6,16]

Statistical analysis

TAG interobserver agreement was measured using Pearson correlation and Bland–Altman analysis. A clinical use rule, previously used to assess diagnostic accuracy of FFR-CT[17] was adopted to define the CAD hemodynamic significance outcome variable. Specifically, vessels with FFR ≤0.8 or those without FFR measurement and ≥90% DS at ICA were considered positive for hemodynamically significant disease.[11,18] Vessels with FFR >0.8 or without FFR measurement and ≤25% DS at ICA were considered negative.[17] Vessels with intermediate stenosis (26–89% DS) and no FFR measurement were excluded from analysis, as hemodynamic significance is uncertain.[14]

Based on physiological flow characteristics of different coronary arteries,[15] and given the limitations of our study cohort (see "Results"), the receiver operating characteristic (ROC) area under the curve (AUC) to predict hemodynamically significant CAD using TAG as the diagnostic variable was calculated for (a) all arteries pooled together, (b) all LAD plus right-dominant LCX arteries and (c) right-dominant RCA plus left-dominant LCX arteries. To assess the effect of outcome variable imputation for vessels with ≤25 or ≥90% DS at ICA and no FFR measurement, the ROC AUC was additionally calculated for (d) the subset of arteries in (b) only if FFR was measured. All analyses were performed in STATA (StataCorp, College Station, TX); ROC AUCs were compared using the roccomp routine. A p-value < 0.05 was considered significant.

RESULTS

Patient characteristics are provided in Table 1. FFR was measured in 30 arteries on average 33 days after CCTA (range: 4–83 days). Of the remaining 54 vessels with no FFR measurement, 30 had ≤25% DS at ICA and were considered negative for hemodynamically significant disease, and 13 had ≥90% DS at ICA and were considered positive for hemodynamically significant disease. The final 11 vessels were excluded from analyses. There was a single left-dominant coronary circulation patient with FFR measured in the LCX, and thus, this group of arteries was not separately assessed. Interobserver agreement of TAG

Table 1. Study population characteristics

Demographics	
Gender (male)	18 (64%)
Age (years)	69.3 ± 9.3
Height (cm)	162.3 ± 9.6
Weight (kg)	62.4 ± 8.8
BMI (kg cm^{-2})	23.6 ± 1.8
Risk factors for CAD	
Diabetes mellitusmerge	10 (36%)
Hypertension	17 (61%)
Hyperlipidemia	20 (71%)
Smoking	5 (18%)
History	
Prior myocardial infarction	4 (14%)
Prior percutaneous coronary intervention	5 (18%)
Angiographic stenosis severity (ICA)	
LAD	
≤25% DS	2 (7.1%)
25–50% DS	6 (21.4%)
50–75% DS	18 (64.3%)
75–90% DS	1 (3.6%)
≥90% DS	1 (3.6%)
LCX	
≤25% DS	9 (32.1%)
25–50% DS	11 (39.3%)
50–75% DS	5 (17.9%)
75–90% DS	2 (7.1%)
≥90% DS	1 (3.6%)
RCA	
≤25% DS	8 (28.6%)
25–50% DS	15 (53.6%)
50–75% DS	3 (10.7%)
75–90% DS	1 (3.6%)
≥90% DS	1 (3.6%)
Invasive FFR measurements	
LAD	22 (73%)
LCX	8 (27%)
RCA	0 (0%)
Coronary dominance	
Right	27 (96%)
CT indication	
Angina	13 (46%)
Abnormal/equivocal test	10 (36%)

(Continued)

Table 1. (Continued)

Pre-op evaluation	1 (4%)
Post-PCI evaluation	4 (14%)

CAD, coronaryartery disease; DS, diameter stenosis; FFR, fractional flow reserve; ICA, invasive catheter angiography; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; PCI, percutaneous coronary intervention.

measurements was excellent (Pearson r = 0.954, Bland–Altman bias: 0.224 Hounsfield unit cm^{-1}) with good limits of agreement (Figure 1). TAG for each artery independently, categorized by positive *vs* negative hemodynamically significant disease is shown in Figure 2.

TAG *vs* invasive FFR

There was no statistically significant difference between different readers' TAG measurements to detect hemodynamically significant CAD for any subset of arteries (Table 2) and thus the average TAG was used for subsequent analyses. The ROC AUC of TAG to detect hemodynamically significant CAD (Figure 3) was 0.661 [95% confidence interval (CI) (0.536–0.787)] when pooling all n = 73 vessels together. When separated into groups based on physiological flow characteristics, AUC was higher for each group: 0.841 [95% CI (0.725–0.957)] for LAD and right-dominant LCX (n = 50) arteries, 0.879 [95% CI (0.743–1.000)] for only those arteries in this subset that had an invasive FFR measurement (n = 29), and 0.840 [95% CI (0.605–1.000)] for the subset of right-dominant RCA and a single left-dominant LCX arteries (n = 22). Compared to pooling all vessels together, the increase in AUC was statistically significant for the second and third subsets (p = 0.039 and 0.021, respectively), but not for the fourth subset (p = 0.188).

DISCUSSION

This study suggests that the use of TAG to detect hemodynamically significant CAD may benefit by accounting for physiological differences in flow amongst coronary arteries. Given that TAG arises due to contrast propagation, a component of it must reflect flow velocity in a vessel; the higher the flow, the lower the magnitude of TAG, and vice versa. Prior data, including the correlation of both TAG and opacification differences across lesions with thrombolysis in myocardial infarction grade[3,4] support this hypothesis.

Figure 1. Correlation (left-hand panel) and Bland–Altman analysis (right-hand panel) of TAG measurements performed by two independent readers in n = 73 vessels included in this study. TAG, transluminal attenuation gradient.

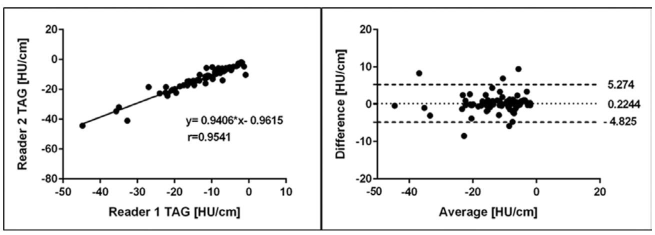
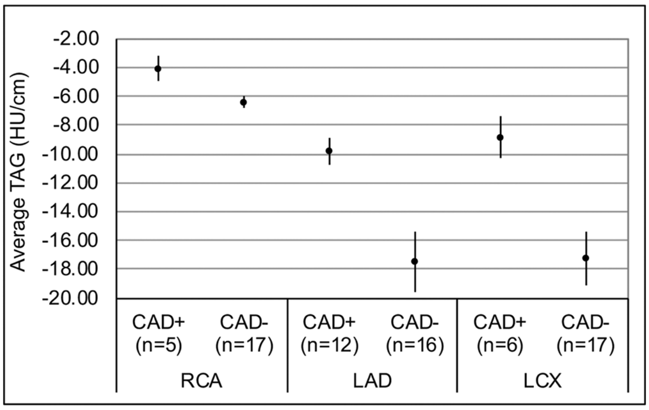


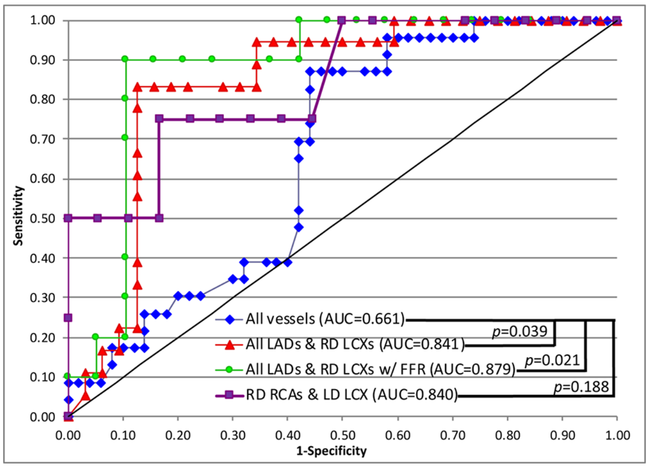
Figure 2. Average TAG in each major coronary artery categorized by positive *vs* negative for hemodynamically significant CAD. Vertical lines indicate measurement standard errors. CAD, coronary artery disease; HU, Hounsfield unit; TAG, transluminal attenuation gradient.



A single TAG cutoff value regardless of which artery is being interrogated may thus impair any ability to detect significant disease. Indeed, the AUC to detect significant disease was 0.661 when pooling all vessels, in agreement with prior results.[2,5,7] However, based on the fact that the LAD carries roughly the same flow regardless of coronary dominance and similar to that in the LCX in right-dominant coronary circulation patients, but different than that in other coronary arteries, a separate test characteristic for this subset of vessels yielded a higher AUC of 0.841. Similarly, adopting a separate test characteristic for right-dominant RCA and left-dominant LCX arteries, which also carry similar flow and different than that in other coronary arteries, had a higher AUC of 0.840. However, the AUC increase for this latter group was not statistically significant, potentially due to the smaller number of vessels in that subset.

We believe our results suggest a physiological relationship of TAG and significant CAD. Specifically, a stenosis is more likely to be hemodynamically significant if it is located in an artery that supplies blood to a large myocardial territory and thus carries a large amount of flow at rest[19] (and consequently has a lower TAG magnitude), compared to an artery that supplies a smaller myocardial territory and carries a lesser amount of flow at rest (and consequently has a higher TAG magnitude). This would be in agreement with Bernoulli's principle, which relates the pressure drop across

Figure 3. ROC curves for the detection of significant coronary artery disease by TAG for subset of arteries defined in the text. AUC, area under the curve; FFR, fractional flow reserve; LAD, left anterior descending; LCX, left circumflex; LD, left dominant; RCA, right coronary artery; RD, right dominant; ROC, receiver operating characteristic; TAG, transluminal attenuation gradient.



a stenosis to not only the inverse of a stenotic vessel's cross-sectional area and length of the narrowing, but also the square of flow velocity.

Limitations

Beyond generating a potential hypothesis, limited conclusions can be drawn from this brief report given the small number of patients and inherent bias of a retrospective study, wherein only patients with greater disease burden presumably proceeded to ICA. Nonetheless, despite the small number of patients, a significant AUC increase was detected for one of three subsets of arteries suggested by physiology though we could not test one subset (left-dominant RCA) for which there was only a single patient. Bias was partly overcome by following a clinical use rule[17] reflecting a CCTA-based measurement, wherein all vessels must be interpreted regardless of downstream testing results. Misclassification of disease significance is nonetheless possible in this rule; *e.g.* 4% of ≥90% DS lesions are not hemodynamically significant.[14] However, misclassifications would have affected each subset, and thus any between-group differences we observed are likely to persist. To this end, we note that classifying vessels with 26–50% DS (commonly considered

Table 2. Per-reader and combined area under the curve of TAG for the detection of hemodynamically significant coronary artery disease.

	Reader 1	Reader 2	Reader 1 *vs* Reader 2 *p*-value
All vessels (*n*=73)	0.661 (0.538–0.784)	0.677 (0.553–0.800)	0.624
LAD & RD LCX (*n*=50)	0.834 (0.717–0.951)	0.840 (0.725–0.955)	0.885
LAD & RD LCX with FFR measured (*n*=29)	0.855 (0.706–1.000)	0.905 (0.784–1.000)	0.524
RD RCA & LD LCX (*n*=22)	0.764 (0.510–1.000)	0.847 (0.623–1.000)	0.251

Numbers in parentheses indicate the 95% confidence interval. RD, right-dominant circulation; LD, left-dominant circulation; FFR, fractional flow reserve.

non-obstructive) also as negative for CAD would not have altered our findings (ROC AUC = 0.655 for ensemble group, 0.851 for LAD plus right-dominant LCX subgroup with $p = 0.02$, and 0.847 for the right-dominant RCA plus left-/co-dominant LCX subgroup with $p = 0.153$).

Given that TAG measures changes in contrast enhancement, its magnitude is affected by the imaging protocol, including helical pitch, tube voltage, and contrast material dose and injection protocol.[20] Diagnostic tests based on TAG will likely require tuning the particular cut-offs used to detect significant CAD based on the scan protocol used in a particular practice. In this study, all patients were imaged at 120 kVp with an injection protocol that led to similar enhancement across patients [mean 368.3 ± 59.3 Hounsfield units in the ascending aorta at the level of the coronary arteries], which likely contributed to the success of our analyses. Nonetheless, our conclusions only apply to helical acquisitions as to our knowledge, no information is available at present regarding the possibility of applying the method to "step-and-shoot" acquisitions.

Despite its limitations, this research was intended as a proof of concept study and only provides a basis for future larger studies to test whether an increase in the diagnostic value of TAG can be achieved, when information on the physiology of coronary flow is incorporated in its interpretation.

CONCLUSION

Using information regarding the physiology of coronary flow may enhance the interpretation of TAG, a simple measurement that can be quickly performed at the time of CCTA interpretation. Different TAG diagnostic tests may be necessary to detect functionally significant CAD in each myocardial territory.

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