



Does vessel length impact transluminal attenuation gradient in 320-slice coronary CT angiography? Correlation with invasive angiography

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Abstract

Objectives This study aimed to investigate the influence of vessel length on transluminal attenuation gradient (TAG) and establish a new index, VLN-TAG (VLN-TAG (HU/100 mm²) = TAG (HU/10 mm)/vessel length (10 mm)), to estimate the diagnostic value using 320-slice computed tomography (CT).

Methods A total of 150 coronary arteries from 52 patients who underwent single-beat scanning using 320-slice CT and invasive coronary angiography (ICA) within 2 weeks were retrospectively enrolled. TAG was obtained from the major three epicardial vessels, and its interrelation with the measured length of the vessels was evaluated by Pearson correlation and regression analyses. The changes in TAG and VLN-TAG were compared with the corresponding stenosis severities ascertained by ICA using repeated measures ANOVA.

Results TAG had a significant interrelation with the measured length of the vessels ($r = 0.644$, $p < 0.001$). Neither TAG nor VLN-TAG with different stenosis degrees of < 50, 50–70, and 70–99% on ICA had significant difference among the three groups. Plaque composition had no influence on VLN-TAG in all groups. The combined TAG or VLN-TAG and coronary computed tomography angiography (CCTA) assessment did not significantly change the area under the curve compared with using CCTA only. In the calcified vessels group, adding VLN-TAG to CCTA improved the specificity (92.86 vs 85.71%).

Conclusions Vessel length is an important factor impacting TAG. TAG does not offer an incremental diagnostic value compared with CCTA only for detecting coronary stenosis.

Key Points

- Transluminal attenuation gradient (TAG) does not improve the diagnostic value of CCTA. Vessel length impacts TAG, but VLN-TAG does not improve the diagnostic value of CCTA.
- Plaque composition had no influence on VLN-TAG in all groups of stenosis degrees. There may be a minimal improvement in specificity when VLN-TAG is applied to the calcified vessels group.

Keywords Coronary stenosis · Multidetector computed tomography · Angiography

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Abbreviations

BMI	Body mass index
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
DS	Diameter stenosis
FFR	Fractional flow reserve
ICA	Invasive coronary angiography
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
NPV	Negative predictive value
PPV	Positive predictive value
RCA	Right coronary artery

TAG Transluminal attenuation gradient
TDG Transluminal diameter gradient

Introduction

Coronary computed tomography angiography (CCTA) has high accuracy in identifying coronary artery stenosis [1–5]. However, the overestimation of the severity of coronary lesions is common due to the influence of calcified plaques [6, 7].

Transluminal attenuation gradient (TAG) is defined as the gradient of intraluminal CT attenuation in the coronary artery and introduced as a quantitative parameter in detecting significant coronary stenosis [8]. It is the change in CT attenuation (Hounsfield unit, HU) per 10-mm length of the coronary artery (unit: HU/10 mm) and is decided by the linear regression coefficient between CT attenuation and distance from the ostium [8]. TAG seemed to assist CCTA in improving its diagnostic performance, but using TAG has many pros and cons in recent years [8–15]. Since the cutoff values of TAG have also been shown to vary widely [11–14], no unified cutoff value exists. Single-beat scanning was considered ideal for TAG application because it could avoid the variability in contrast enhancement in the coronary artery due to the lack of temporal uniformity in the scan [9, 16]. However, a new study found that the TAG of multi-beat and single-beat scans correlated with each other well in all coronary arteries and were not affected by temporal nonuniformity [10].

The use of TAG is controversial probably because a number of factors influence the accuracy of the TAG. It has been mentioned in some studies that the intraluminal coronary attenuation of smaller arteries might be different from bigger arteries [17–19]. Vessel length might be a way to explain these findings. The primary aim of this study was to investigate whether vessel length influenced the value of the TAG. In cases when vessel length was a factor influencing the TAG, a new index VLN-TAG (vessel length normalized transluminal attenuation gradient) was established to decrease the influence in this study. It was defined as follows: $\text{VLN-TAG (HU/100 mm}^2\text{)} = \text{TAG (HU/10 mm)}/\text{vessel length (10 mm)}$. Then, the diagnostic value of TAG or VLN-TAG combined with CCTA using the single-beat scan with 320-slice CT would be assessed in terms of plaque composition. Invasive coronary angiography (ICA) was used as the reference standard.

Methods

Study population

A total of 52 patients with suspected or known CAD, subsequently confirmed by ICA within 2 weeks between

March 2015 and November 2016, were retrospectively included in this study for evaluation. The exclusion criteria were (1) pregnancy, (2) a history of coronary artery bypass surgery, (3) arrhythmia, (4) congenital heart disease, (5) heart failure, (6) adrenal insufficiency, (7) allergy to iodine, and (8) thyrotoxicosis. This study was approved by the Institutional Review Board with the waiver of the informed consent.

CCTA protocol

All included patients underwent a prospective electrocardiography-gated scan by the volume mode on a 320-detector row CT scanner (Aquilion ONE, Toshiba Medical Systems). Oral metoprolol (25–50 mg) was administered when the resting heart rate was > 70 beats/min. Prior to image acquisition, 0.5 mg of sublingual nitroglycerin was administered to every patient. Images were then obtained from 1 cm below the bifurcation of the trachea to the diaphragm, in a craniocaudal direction under inspiratory breath hold. The scan was acquired while injecting 50–70 mL of iodixanol (Visipaque 270; GE Healthcare Ireland, Co.) at 4.5–6.5 mL/s (depending on the body mass index (BMI)), followed by 50 mL of saline. Scanning was triggered in the arterial phase using automated contrast bolus tracking with the region of interest (ROI) placed in the descending aorta and automatically triggered at 300 HU. The scanning parameters were as follows: detector collimation 320 × 0.5 mm, tube current 300–800 mA with automatic tube current modulation, tube voltage 100–120 kV (depending on BMI), and gantry rotation time 275 ms. Adaptive iterative dose reduction using three-dimensional processing was used for all patients, with the intensity at the standard setting (50%).

CCTA analysis

CCTA images were evaluated for each vessel with a dedicated workstation (Extended Brilliance Workspace v. 3.4; Philips Healthcare) by two expert radiologists who were blinded to clinical ICA results. Every coronary artery tree was divided into 18 segments [4]. The severity of diameter stenosis (DS) was quantified by least internal lumen dimension and grouped as none (DS 0%), mild (DS 1–49%), moderate (DS 50–69%), severe (DS 70–99%), and total occlusion (DS 100%). For the convenience of analysis, none to mild stenosis comprised one category. Plaque composition was classified as noncalcified (< 30% calcified plaque volume), partially calcified (30–70%), or calcified (> 70%) by the volume of calcific component (calcific component > 130 HU) in the plaque. Both partially calcified and calcified plaques were combined into one category (calcified plaques) to facilitate analysis. The vessels with noncalcified plaque at the narrowest sites of lesions were designated as the noncalcified group, whereas those with calcified plaque at the narrowest sites of lesion were considered

as the calcified group. Moreover, all vessels were divided into three types according to the percentage of total calcification length in the whole vessel: total calcification length/vessel length < 1/3 (type A), between 1/3 and 2/3 (type B), and ≥ 2/3 (type C).

Transluminal attenuation gradient

The central line was determined for each major coronary artery and manually adjusted if necessary. Then, cross-sectional images perpendicular to the central line were reconstructed. The ROI was positioned at the center of the cross-sectional images. The position and contour of the ROI were manually corrected if a plaque existed (Fig. 1). The mean luminal attenuation was obtained at 5-mm intervals from the ostium to the

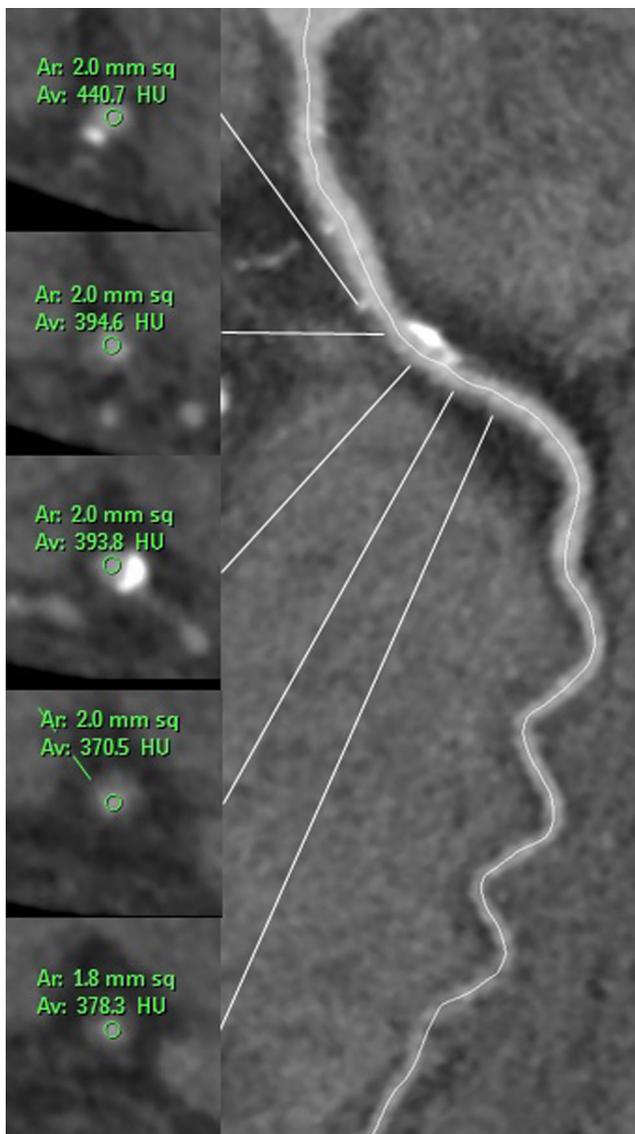


Fig. 1 The position and the contour of the ROI were manually corrected if plaque existed

distal level where the vessel cross-sectional area dropped to < 2 mm². Two cardiovascular radiologists measured CT values in the same vessels four times in total (each one measured twice), and then the mean CT values of the four measurements in each vessel were recorded as the final data for TAG calculation. TAG was determined from the change in attenuation per 10-mm length of the coronary artery (HU/10 mm), defined as the linear regression coefficient between intraluminal contrast opacification and length from the ostium [8]. The linear regression formula ($y = ax + b$, where y = intraluminal attenuation, x = the distance from the ostium, and $a = \text{TAG}/10$) was used to calculate TAG. The length of a measured vessel was calculated as: Vessel length (mm) = 5 mm × (the number of ROIs – 1), which was determined from the position of the first ROI to the position of the last one.

Invasive coronary angiography

ICA was performed using the standard techniques (Artis Zee Ceiling, Siemens Healthcare), and at least two different views were obtained for each main vessel. DS quantified by least internal lumen dimension was evaluated on each major epicardial coronary artery of ≥ 1.5 mm by two experienced cardiologists blinded to the CCTA results. Disagreements between the two readers were resolved by consensus. The stenosis extent was classified into five subgroups: none (0% stenosis), mild (1–49% stenosis), moderate (50–69% stenosis), severe (70–99% stenosis), and occluded. According to CCTA, none to mild stenosis comprised one category.

Statistical analysis

All analyses were performed on a per-vessel basis. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies or percentage. The Wilcoxon signed-rank test was used to compare

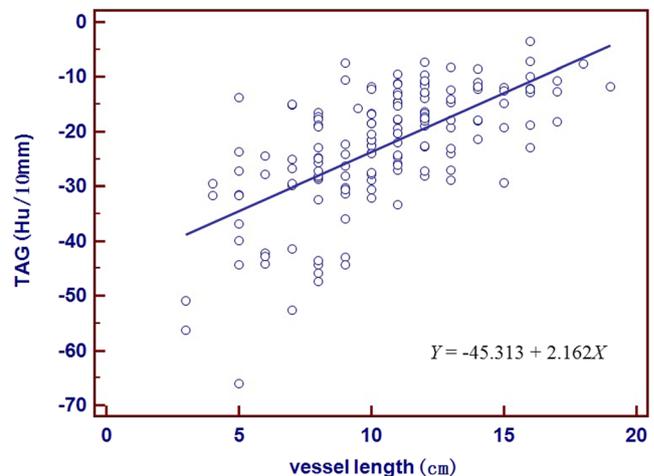


Fig. 2 TAG correlated highly with the vessel length ($r = 0.644$, $p < 0.001$)

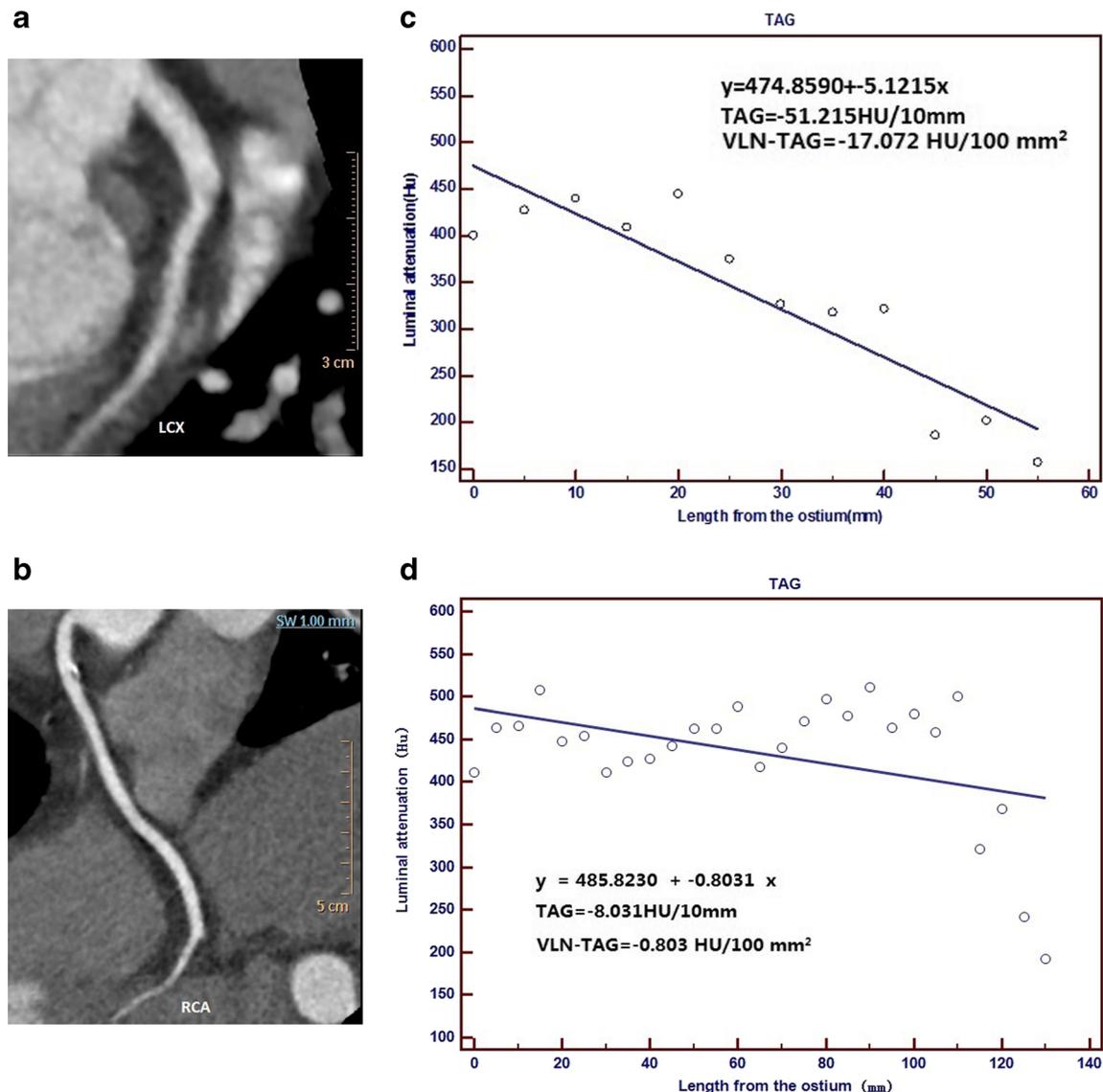


Fig. 3 The short LCX exhibited higher TAG absolute value compared with that of the long RCA (right coronary artery) even if both vessels have no stenosis determined by ICA in this patient. **a** Curved planar

reformation of LCX. **b** Curved planar reformation of RCA. **c** TAG and VLN-TAG of LCX. **d** TAG and VLN-TAG of RCA

ICA and CCTA. As three branches of the coronary artery were measured in the same patient, TAG or VLN-TAG with different degrees of stenosis severity was compared using repeated measures ANOVA test. The Mann–Whitney *U* test was used to compare plaque composition. The Pearson correlation and regression analyses were used to test the relationship between TAG and vessel length. The diagnostic performance of TAG, VLN-TAG, CCTA, and their combinations was then assessed using the receiver operating characteristic (ROC) curve analysis. The optimal cutoff values were determined using values with the highest Youden index. Given the optimal cutoff value, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with corresponding 95% confidence intervals. A two-tailed *p* value <0.05 was considered statistically significant. The ROC

analysis and Youden *J* statistics were performed with MedCalc version 11.4 (MedCalc software). Other statistical analyses were accomplished using the SPSS version 20.0 (SPSS).

Results

Clinical characteristics

CCTA images from 52 consecutive patients (33 males, 63.5%) who underwent ICA were included for the analysis. The mean patient age was 65.4 ± 9.9 years. One hypoplastic vessel with diameter < 1.5 mm and five vessels with stents were excluded. A total of 150 coronary arteries were analyzed for the final

Table 1 Comparison of the two types of plaque composition in terms of VLN-TAG. Values are n and mean \pm SD. The p values were determined using the Mann–Whitney U test. HU/100 mm² is the unit of VLN-TAG

	ICA stenosis (%)	Noncalcified plaque		Calcified plaque		p value
		n^*	Mean \pm SD	n^*	Mean \pm SD	
VLN-TAG (HU/100 mm ²)	0–49	29	–2.18 \pm 1.52	14	–3.51 \pm 3.58	0.061
	50–69	13	–2.59 \pm 1.47	11	–3.03 \pm 2.85	0.104
	70–99	30	–2.21 \pm 1.45	17	–2.55 \pm 1.73	0.637
	100	2	–10.19 \pm 9.61			

ICA, invasive coronary angiography; SD, standard deviation; TAG, transmural attenuation gradient

* Forty-two (29.8%) vessels comprised the calcified group and 74 (52.5%) vessels comprised the noncalcified group due to the plaque composition of the narrowest segment after excluding 9 vessels of type B/C and 25 normal vessels

evaluation. Significant stenosis (DS \geq 50%) was detected in 85 of 150 (56.7%) vessels using ICA and in 95 of 150 (63.3%) vessels using CCTA.

Correlation between vessel length and TAG

The Pearson correlation analysis indicated that TAG correlated significantly with vessel length ($r = 0.644$, $p < 0.001$; Fig. 2). Moreover, regression analysis was used to evaluate the relationship between vessel length and TAG ($F = 104.658$, $p < 0.001$, $R^2 = 0.414$). Therefore, 41.4% variation of TAG could be explained by the vessel length. The regression formula could be established as: $Y(\text{TAG}) = -45.313 + 2.162X$ (vessel length).

Due to the influence of the vessel length, VLN-TAG was established to decrease the influence for TAG. Figure 3 is an example in this study.

Correlation of TAG and VLN-TAG with stenosis severity detected using ICA

As three branches of the coronary artery were measured in the same patient, TAG or VLN-TAG with different degrees of stenosis severity was compared using repeated measures ANOVA test. So, only patients with the same degrees of stenosis severity in the three branches were enrolled into this analysis. No patient with occluded vessel matched this condition.

In the total vessel evaluation, 42 vessels of 14 patients with the same degrees of stenosis severity in the three branches were enrolled. TAG did not show any significant difference among the different degrees of stenosis severity (none or mild, moderate, severe stenosis) determined using ICA ($p = 0.578$).

A total of 141 type A vessels, 8 type B vessels, and 1 type C vessel were found according to the percentage of total calcification length in the whole vessel. Considering the measurement bias based on long calcification, nine vessels of types B and C (total calcification length/vessel length \geq 1/3) were excluded. In the remaining 141 vessels, the same analyses were performed. Thirty vessels of ten patients with the same

degrees of stenosis severity in the three branches were enrolled, and no significant difference was noted among the different degrees of stenosis severity determined using ICA ($p = 0.644$).

Comparison of VLN-TAG also showed no significant difference among the different degrees of stenosis severity determined using ICA in the 30 type A vessels ($p = 0.663$).

Effect of plaque composition on VLN-TAG

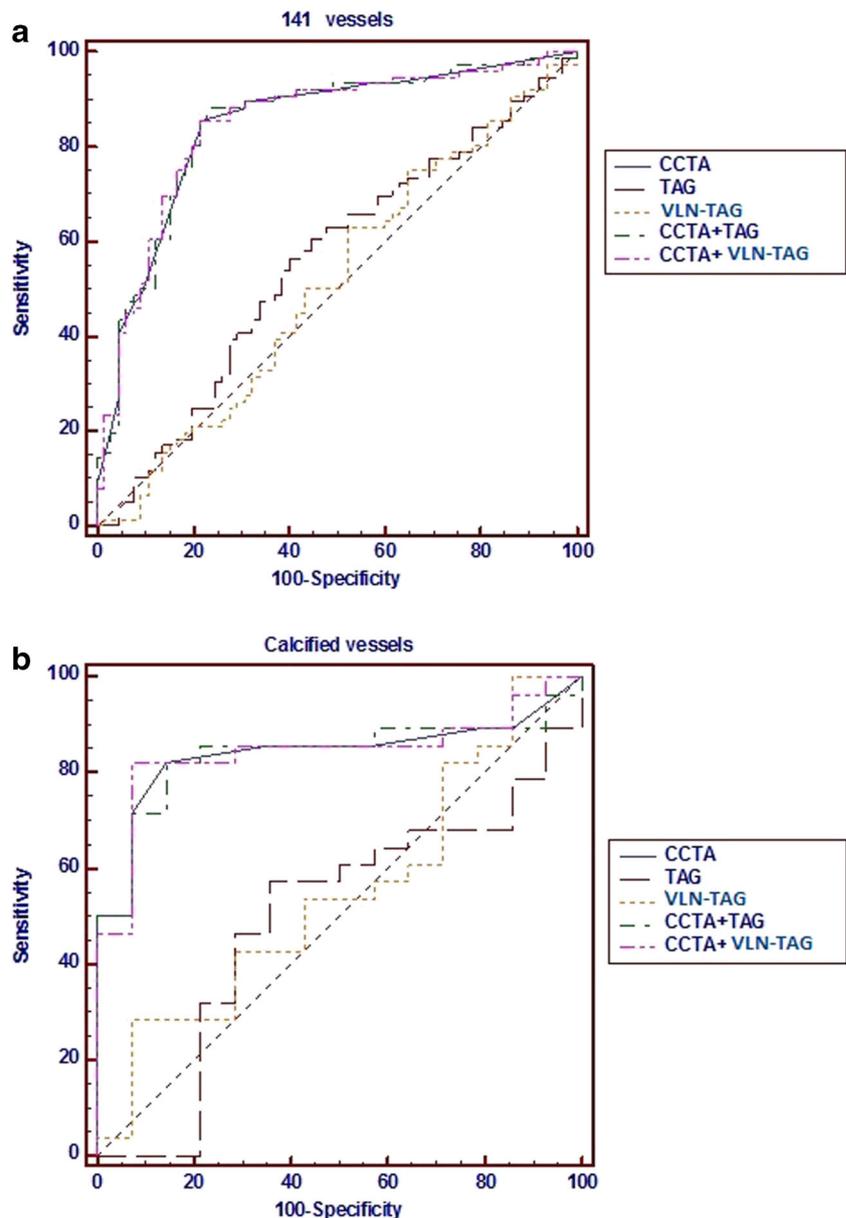
Overall, 42 (29.8%) vessels comprised the calcified group and 74 (52.5%) vessels comprised the noncalcified group due to the plaque composition of the narrowest segment after excluding 9 vessels of type B/C and 25 normal vessels. No statistically significant difference in VLN-TAG was demonstrated between the noncalcified and calcified groups in the different degrees of stenosis severity determined using ICA (Table 1). No calcified group of total occlusion (DS 100%) existed. Therefore, the noncalcified group of total occlusion could not be compared.

Diagnostic values of TAG, VLN-TAG, CCTA + TAG, and CCTA + VLN-TAG

Figure 4a and Table 2 illustrate the difference in diagnostic performance for detecting stenosis severity in 141 vessels on a per-vessel basis after adding TAG and VLN-TAG to CCTA. The area under the curve (AUC) did not increase significantly when TAG or VLN-TAG was combined with CCTA (0.845 vs 0.845, $p = 0.9070$; 0.846 vs 0.845, $p = 0.9066$, respectively). Adding TAG or VLN-TAG to CCTA did not significantly increase the diagnostic performance in terms of specificity and sensitivity.

The differences in AUCs in the calcified vessels were similar (Fig. 4b and Table 2). However, when VLN-TAG was added to CCTA, the diagnostic specificity increased (92.86 vs 85.71%) and the sensitivity was the same as for CCTA only (82.14 vs 82.14%). VLN-TAG only performed slightly better but insignificantly compared with TAG only in the calcified vessels (0.548 vs 0.492, $p = 0.7706$).

Fig. 4 Predicted probability of TAG in addition to CCTA stenosis severity in 141 vessels (a) or calcified vessels (b) with reference to the results from ICA. ICA, invasive coronary angiography; CCTA, coronary computed tomography angiography; TAG, transluminal attenuation gradient



Discussion

The most important result of this study was that TAG correlated significantly with vessel length. Most previous studies did not pay any attention to this, but some related discussions could be found in a few studies. The diameter of the coronary artery lumen was shown to affect the intraluminal coronary attenuation because the attenuation of smaller arteries might decrease due to the intrinsic point-spread function of CT scan using reconstruction algorithms [17]. Steigner et al [18] found that the contrast gradient over distance was significantly smaller in the right coronary artery compared with the left coronary system in normal coronary arteries: -6.5 ± 4.1 for the right coronary artery, -13.7 ± 8.0 for the left anterior descending coronary artery (LAD), and -12.5 ± 7.8 for the left

circumflex coronary artery (LCX). Park et al [19] considered that this outcome was attributed to a smaller diameter change over the distance in the right coronary artery because the right coronary artery was longer and bigger compared to the left coronary artery system. Their study showed that TAG significantly correlated with transluminal diameter gradient (TDG) in both normal vessels and stenosis models. For instance, the diameter of LAD decreased from proximal end to distal end rapidly because LAD was shorter than LCX in the animal studies, indicating a higher value of TDG. Then, a normal LAD exhibited higher TAG absolute value compared with a normal LCX. It was also a good interpretation for the results of the present study. Some previous studies [8, 18] also showed that the diameter range of TAG-positive arteries was smaller than that of TAG-negative arteries. As with the correlation

Table 2 Diagnostic accuracy of CCTA, TAG, CCTA + TAG, VLN-TAG, and CCTA + VLN-TAG in 141 type A or calcified vessels. Values are mean (95% confidence interval)

Optimal cutoff	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
141 type A vessels					
CCTA	0.845 (0.775–0.901)	85.5 (75.6–92.5)	78.5 (66.5–87.7)	82.3 (72.1–90.0)	82.3 (70.4–90.9)
TAG $\leq -22.059^*$	0.555 (0.469–0.639)	56.58 (44.7–67.9)	60.00 (47.1–72.0)	62.3 (49.8–73.7)	54.2 (42.0–66.0)
CCTA + TAG	0.845 (0.774–0.900)	88.16 (78.7–94.4)	76.92 (64.8–86.5)	81.7 (71.6–89.4)	84.7 (73.0–92.8)
VLN-TAG $\leq -1.7787^*$	0.512 (0.426–0.597)	63.16 (51.3–73.9)	47.69 (35.1–60.5)	58.5 (47.1–69.3)	52.5 (39.1–65.7)
CCTA + VLN-TAG	0.846 (0.776–0.901)	85.53 (75.6–92.5)	78.46 (66.5–87.7)	82.3 (72.1–90.0)	82.3 (70.4–90.9)
Calcified vessels					
CCTA	0.841 (0.695–0.935)	82.14 (63.1–93.9)	85.71 (57.2–98.2)	92.0 (73.5–99.1)	70.6 (44.0–89.7)
TAG $\leq -22.059^*$	0.492 (0.335–0.651)	57.14 (37.2–75.5)	64.29 (35.1–87.2)	76.2 (52.8–91.8)	42.9 (21.8–66.0)
CCTA + TAG	0.839 (0.693–0.934)	82.14 (63.1–93.9)	85.71 (57.2–98.2)	92.0 (73.5–99.1)	70.6 (44.0–89.7)
VLN-TAG $> -1.0265^*$	0.548 (0.388–0.702)	28.57 (13.2–48.7)	92.86 (66.1–99.8)	88.9 (48.9–99.8)	39.4 (22.9–57.9)
CCTA + VLN-TAG	0.844 (0.699–0.938)	82.14 (63.1–93.9)	92.86 (66.1–99.8)	95.8 (78.3–99.9)	72.2 (46.5–90.3)

AUC, the area under the curve; PPV, positive predictive value; NPV, negative predictive value; CCTA, coronary computed tomography angiography; TAG, transluminal attenuation gradient

* Cutoff value was determined using the Youden index

between TAG and change in diameter, it is important because a low TAG due to a short vessel should not lead to an overestimation of the hemodynamic significance of a lesion.

The studies on TAG were of major interest these years. Some [9, 20] showed that TAG decreased gradually with increasing stenosis severity, while others did not report a significant difference between the different degrees of stenosis severities [12, 13, 19, 21]. In this study, data were treated as nonindependent data because there were several vessels for each patient. The interaction effect of different vessels in the same patient was taken into account. Repeated measures ANOVA was used for nonindependent data. So, only patients with the same degree of stenosis severity in the three branches could be analyzed. TAG did not show any significant difference among the different degrees of stenosis severity in the total vessel evaluation or in vessels excluding long calcification evaluation. As the correlation of vessel length with TAG was confirmed, a new index named VLN-TAG was established to decrease the influence of vessel length. However, comparison of VLN-TAG showed no significant difference among the different degrees of stenosis severities in vessels excluding long calcification evaluation. This might be due to the complicated relationship between TAG and vessel length, or other complex factors influencing TAG.

In this cohort, no significant differences in VLN-TAG were found in stenosis severity between noncalcified and calcified plaques, consistent with the findings of previous studies [21, 22]. This was because TAG was a slope from a series of spots representing intraluminal CT attenuation, and one or two deflected spots would not affect the slope. Therefore, TAG was considered better than CCTA which often overestimated calcified lesions. However, TAG was affected by a number of deflected spots. Consequently, type B and C vessels with long

calcified lesions (total calcification length/vessel length $\geq 1/3$) were excluded from this analysis.

Adding TAG or VLN-TAG could not significantly improve the diagnostic performance of CCTA alone through AUC in the evaluation of total vessels or calcified vessels in this study. Although the diagnostic value of coronary stenosis severity assessed using TAG over anatomic stenosis evaluation using CCTA was demonstrated in previous studies [8, 22], some new studies showed that TAG measurement did not increase the diagnostic value of stenosis evaluation using conventional coronary CT and invasive fractional flow reserve (FFR) as reference [14, 21]. The diagnostic specificity increased (92.86 vs 85.71%) and the sensitivity was the same as for CCTA only (82.14 vs 82.14%) in the calcified vessels when VLN-TAG was added to CCTA, which was consistent with the findings of a previous study [22]. The high sensitivity and NPV of CCTA have been confirmed in previous studies [23], but calcified lesions influence the specificity and PPV of CCTA [24]. Therefore, the diagnostic value of VLN-TAG was shown to be better in the calcified vessels because it was not affected by minimal calcification. VLN-TAG also performed slightly but insignificantly better than TAG only in the calcified vessels through AUC (0.548 vs 0.492, $p = 0.7706$).

Although this study controlled some factors that could interrupt the measurement of TAG, for example, the one-beat scan, the exclusion of long calcification, and the effect of vessel length, the average TAG value and the cutoff value for TAG were different from those in other studies. This variability may be explained by the difference in study populations, image reconstruction algorithms, CT scanners, contrast injection protocols, scan mode, scan direction, and optimal scan timing [25]. The reproducibility

of TAG may be limited because of the difference. Moreover, one study indicated that the cardiac output and blood pressure in individual patients influenced the time of filling the coronary artery with contrast medium. It also considered acquisition timing as an important factor for TAG analysis and could not always be identified in actual clinical practice considering TAG analysis practically [21]. A new study tried the stress CCTA for TAG because TAG was thought to reflect the coronary blood flow at rest and might not be useful to diagnose moderate stenosis in which the coronary blood flow might be maintained constantly [21]. However, the incidence of uninterpretable segments and poor image quality was significantly higher in the stress CCTA because of the high heart rate [26].

The present study had some limitations. First, it was a single-center study with limited patient numbers using one-beat scan. Second, the low-concentration contrast medium was used in the study hospital as usual because of its good performance on CCTA [27]. Therefore, the TAG cutoff value in this study may not be generalizable to studies using different CT scanners, different scanning protocols, or high-concentration contrast medium. Third, ICA was chosen as the reference standard because few patients underwent invasive FFR in this study. The lack of correlation with FFR might also be a limitation. Fourth, the potential biases might exist by the selection of statistical analyses.

This study showed that TAG correlated significantly with vessel length. It is an important finding because the variation of TAG might be a secondary result due to the difference in the vessel length rather than a lesion. Neither TAG nor VLN-TAG combined with CCTA offered an incremental diagnostic value, and numerous limitations for reproducibility prevent it from being a uniform diagnostic standard.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Guangyu Tang.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology

- retrospective
- diagnostic or prognostic study
- performed at one institution

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