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Influence of Coronary Artery Diameter on Intracoronary Transluminal Attenuation Gradient During CT Angiography

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ABSTRACT

OBJECTIVES The goal of this study was to assess the effect of coronary artery diameter on luminal attenuation and the correlation between the transluminal attenuation gradient (TAG) and transluminal diameter gradient (TDG) on computed tomography (CT) coronary angiography.

BACKGROUND Recent studies have reported promising results of TAG in detecting significant stenosis. However, because of the intrinsic nature of CT reconstruction algorithms, luminal attenuation may be affected by vessel diameter.

METHODS In this 3-part study, phantom simulating vessels of various diameters immersed in different contrast mixtures were scanned, and intraluminal attenuations were measured. In addition, dynamic volume CT scanning was performed in 3 mongrel dogs (untreated, a stenosis model, and an occlusion model) using 320-row area detector computed tomography and intraluminal attenuations, and TAGs were calculated at each temporal scan and compared. In a separate clinical study, TAGs and TDGs of 152 coronary arteries from 62 patients who underwent 320-row area detector computed tomography coronary angiography and invasive angiography were measured and compared.

RESULTS Intraluminal attenuation of phantom vessels gradually decreased along with a decrease in diameter. Animal studies revealed that the peak attenuation of distal smaller coronary arteries did not reach that of proximal larger coronary arteries: 55.2% to 78.1% peak attenuation of proximal coronary arteries. No differences in TAG were found between stenotic and normal left circumflex arteries at temporal scans (all, $p > 0.05$). The clinical study demonstrated significant correlation between TAG and TDG ($r = 0.580$; $p < 0.0001$).

CONCLUSIONS Intraluminal attenuation was shown to decrease with diminution of vessel diameters. In addition, TAG exhibited a significant correlation with TDG, implying that TAG may be a secondary result because of differences in diameters. (J Am Coll Cardiol Img 2016;9:1074–83) © 2016 by the American College of Cardiology Foundation.

According to a recent statistical update report from the American Heart Association, despite a significant reduction in the death rate from cardiovascular diseases, the leading cause of morbidity and mortality in 2020 will still be cardiovascular disease (1). At present, coronary computed tomography angiography (CTA) is widely used for the assessment of patients with suspected coronary artery disease (CAD); this test is a highly accurate noninvasive technique for the diagnosis of CAD, capable of providing detailed information of coronary artery anatomy, plaque characteristics, and the degree of stenosis (2). However, coronary CTA has an important limitation in that it cannot determine functionally significant stenosis (3). Thus, there have been several attempts to add functional information to anatomic CAD assessment so as to determine the hemodynamic significance of CAD lesions, including computed tomography (CT) perfusion (4), vulnerable plaque characterization (5,6),

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the intracoronary transluminal attenuation gradient (TAG) (7-9), corrected coronary opacification (10), and CT fractional flow reserve (FFR) (11).

TAG, initially introduced by Steigner et al. (7), has demonstrated the ability to differentiate hemodynamically significant CAD in several previous clinical studies (8,12). TAG is based on the concept that if all the factors which affect coronary artery attenuation were kept constant, including left ventricular function, contrast media volume and concentration, and contrast bolus rates, the gradual diminution gradient of intraluminal attenuation from the proximal to distal segment could then be used as a surrogate to resting coronary flow (13). However, intraluminal coronary attenuation has been shown to be affected by the diameter of the coronary artery lumen because attenuation of smaller arteries may decrease because of the intrinsic point-spread function of CT scanning using reconstruction algorithms (14). Thus, we hypothesized that intraluminal attenuation may decrease as the diameter decreases, even though it is filled with consistently concentrated contrast media, and that TAG may be related to the transluminal diameter gradient (TDG).

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The present study therefore evaluated the effect of coronary artery diameter on luminal attenuation by using a vessel phantom, an animal study with a canine coronary artery stenosis model, and a clinical study to investigate the correlation between TAG and TDG.

METHODS

PHANTOM STUDY. A vessel phantom was built with 25 tubular holes in a 5-cm thick polyethylene disc (Online Figure 1). The diameter of each hole was 5.0, 4.5, 4.0, 3.5, 3.0, and 2.9 mm to 1.0 mm with 0.1-mm intervals, simulating vessels of different diameters. The phantom was immersed in 2 different mixtures of an iodine contrast agent (Ultravist, Shering, Berlin, Germany) and saline, approximating attenuations of 800 and 600 HU at 100 kVp, with all tubular holes completely filled with the contrast mixture. CT scans were performed with the phantom immersed in the 600-HU contrast mixture using 80, 100, and 120 kVp. Thereafter, the phantom was washed and immersed in the 800-HU contrast mixture and scanned using 100 kVp. CT scans were performed 5 times in each protocol. All examinations were performed with a 320-row area detector computed tomography (320-ADCT) scanner (Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan) with a field of view of 120 × 120 mm and a matrix size of 512 × 512 mm, resulting in a pixel size of 0.23 mm. The intraluminal attenuation of each hole was measured using dedicated software for coronary CTA (Xelis Cardiac, INFINITT Healthcare, Seoul, Republic of Korea) by 1 board-certified radiologist with 3 years of experience in cardiovascular imaging (Y.K.K.).

The centerline of each tubular hole was semi-automatically selected, and the attenuation was measured at every pixel through the centerline. Intraluminal attenuation was calculated as the average attenuation of 9 pixels (3 × 3 pixels) around the centerline pixel indicating a square-shaped region of interest (ROI) of 0.70 mm in length and 0.49 mm^2 in area.

ANIMAL STUDY. *Animal preparation.* The animal experiment, which established 1 stenosis model, 1 occlusion model, and an untreated mongrel as a control subject, was approved by our Institutional Animal Care and Use Committee. Two mongrel dogs who weighed 30 to 35 kg were anesthetized with a subcutaneous injection of a 15-mg/kg mixture of zolazepam (Zoletil, Yuhan Corp., Seoul, Republic of Korea), 5 to 10 mg/kg of xylazine hydrochloride (Rompun, Bayer Korea, Seoul, Republic of Korea), and 0.02 to 0.04 mg/kg of atropine sulfate (Atropine, DAHIHAN Pharm, Co., Ltd., Seoul, Republic of Korea); they were intubated and mechanically ventilated during preparation. After vascular cut-downs, 5-F sheaths were placed in the left carotid artery. Left thoracotomy was performed in the fifth intercostal space, and the pericardium was excised. The left circumflex coronary artery was carefully dissected and ligated completely for the occlusion model; it was ligated with a 5-F microintroducer with subsequent removal of the catheter for the stenosis model. Through the sheath in the carotid artery, catheter angiography of the left coronary artery was performed to confirm the stenosis and occlusion of the coronary artery (Online Figure 2). After confirmation of stenosis and occlusion, the thoracotomy incision was closed, and the carotid artery was repaired.

Dynamic volume CT imaging protocol. Dynamic volume CT examinations were performed 15 times in total in the 3 mongrel dogs using 320-ADCT (Toshiba Medical Systems) under anesthesia 7 days after modeling: 4 times in the dog with no treatment, 6 times in the stenosis model, and 5 times in the occlusion model. Intravenous esmolol (1 to 2 mg) was injected to achieve a heart rate of <80 beats/min. Mean heart rate was maintained from 70 to 80 beats/min during the

ABBREVIATIONS AND ACRONYMS

ADCT = area detector computed tomography

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

FFR = fractional flow reserve

LAD = left anterior descending coronary artery

LCx = left circumflex coronary artery

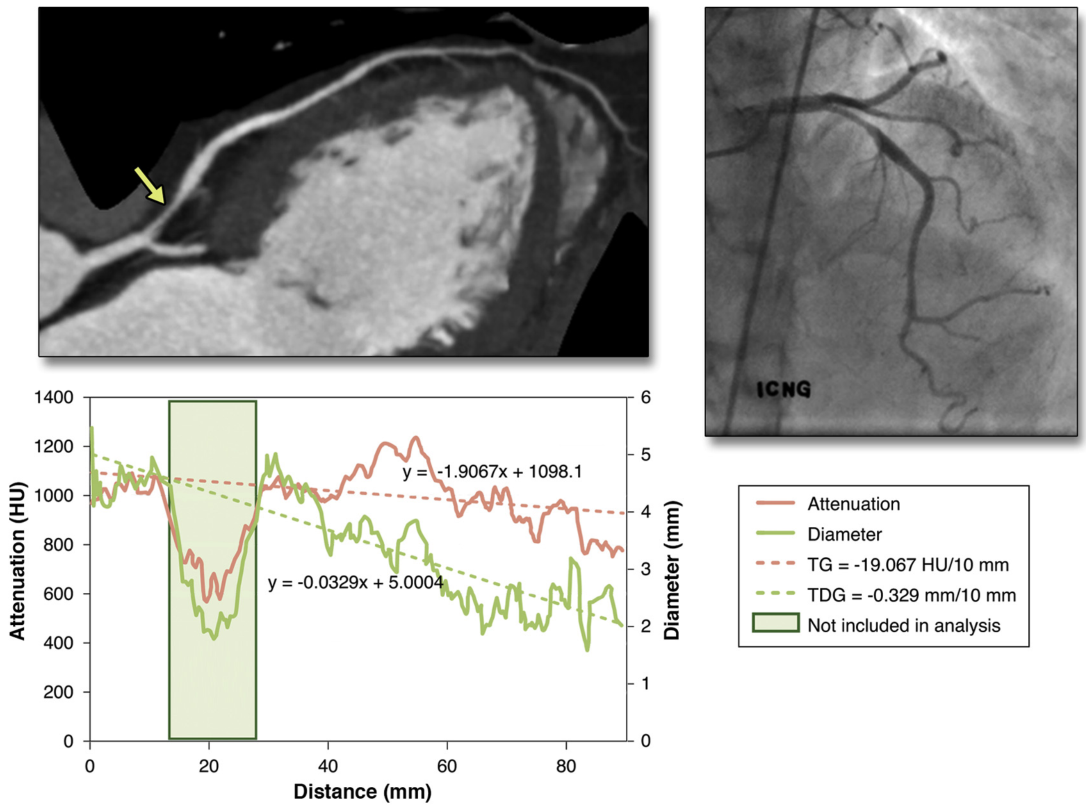
MDCT = multi-detector row computed tomography

ROI = region of interest

TAG = transluminal attenuation gradient

TDG = transluminal diameter gradient

FIGURE 1 Representative Example of the Analysis of TAG and TDG



Note there is a significant stenosis up to 70% **(arrow)** in the proximal segment of the left anterior descending coronary artery. TAG = transluminal attenuation gradient; TDG = transluminal diameter gradient.

scans; 20 ml of a nonionic contrast medium (Iomeron 400, Bracco Diagnostics, Milan, Italy) was injected into the right cephalic vein at 4 ml/s, followed by 20 ml of normal saline at the same flow rate. CT scanning was initiated 10 s after contrast administration and performed every heartbeat during the 40 s by using the prospective ECG triggering technique. CT parameters were as follows: tube voltage, 100 kVp; field of view, 122 × 122 mm; matrix size, 512 × 512 mm; and pixel size, 0.24 mm. ^{Sure}Exposure (Toshiba Medical Systems) with a target SD of 25 was used. Reconstructed phases were selected manually at each temporal scan to minimize motion artifacts.

CT analysis. All measurements were performed by a board-certified cardiovascular radiologist with 10 years of experience (P.E.A.) using 3-dimensional dedicated software (Xelis Cardiac, INFINITT Healthcare). Mean vessel attenuation at 7 different anatomic regions at each temporal scan was measured using a 2 cm^2-circular ROI for the aorta and a 1 mm^2circular ROI for the coronary arteries: proximal ascending aorta, left anterior descending coronary artery (LAD) proximal (1.0 cm from the ostium), LAD mid (3.0 cm from the ostium), LAD distal (5.5 mm from the ostium), left circumflex coronary artery (LCx) proximal (1.5 cm from the ostium), LCx distal (7.0 cm from the ostium), and posterior descending artery proximal (9.0 cm from the ostium). Thereafter, the percentage of the peak attenuation of each region was calculated and compared with the peak attenuation of the ascending aorta. Vessel diameter at each coronary region analyzed was also calculated. In addition, TAG was manually measured by using a method described in a previous study (8). The method included 5 heartbeat scans previous to that at peak aortic enhancement and 8 images after peak aortic enhancement, to minimize the effect of different hemodynamic statuses. The total length of the coronary artery measured for TAG was 5.0 cm for LAD and 8.5 cm for LCx.

CLINICAL STUDY. Our institutional review board approved the clinical study protocol of this

TABLE 1 Diameter, Distance From the Ostium, and Relative Peak Attenuation to the Ascending Aorta of Analyzed Coronary Artery Segments in Each Coronary Arterial Model

	LCx			LAD		
	LCx Proximal	LCx Distal	PDA Proximal	LAD Proximal	LAD Mid	LAD Distal
Distance from ostium, mm	15	70	90	10	30	55
Normal model (n = 4)						
Diameter (median), mm	3.8	2.4	1.8	2.8	2.1	1.5
Relative peak attenuation, %	96.0 ± 3.6	87.9 ± 5.5	69.3 ± 2.9	85.6 ± 3.0	79.4 ± 2.4	55.2 ± 1.4
LCx stenosis model (n = 6)						
Diameter (median), mm	2.9	1.9	1.5	2.8	1.9	1.4
Relative peak attenuation, %	93.4 ± 2.7	77.9 ± 5.0	73.3 ± 5.5	92.0 ± 3.5	79.6 ± 3.2	64.5 ± 1.2
LCx occlusion model (n = 5)						
Diameter (median), mm	2.4	2.1	2.0	3.4	2.5	1.8
Relative peak attenuation, %	90.8 ± 6.2	81.7 ± 4.5	78.1 ± 6.6	95.6 ± 5.4	89.2 ± 5.0	75.6 ± 4.7

Values are mean ± SD unless otherwise indicated.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PDA = posterior descending artery.

retrospective study and waived the requirement for informed consent.

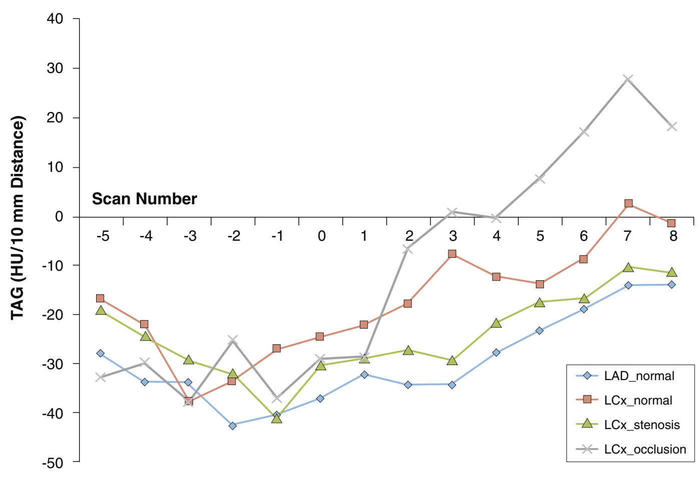
Study population. From January 2012 to July 2012, patients who underwent coronary CTA and invasive coronary angiography within 90 days were included. Exclusion criteria were as follows: 1) inadequate CT image quality due to motion artifacts or beam-hardening artifacts by a coronary stent; 2) adaptive multisegment reconstruction due to a fast heart rate; 3) diffuse severe coronary calcification, which made measurement of the exact intraluminal attenuation difficult; 4) hypoplastic coronary arteries with proximal coronary artery diameters <3 mm; 5) left main coronary artery stenosis >50%; and 6) patients with acute coronary syndrome within 90 days. Ultimately, 152 coronary arteries of 62 patients (32 men; mean age 65.9 years; age range 27 to 87 years) were included for analysis.

CT protocol. All CT examinations were acquired using a 320-ADCT system (Aquilion ONE, Toshiba Medical Systems) with mid-diastolic prospective scanning, as described in detail in a previous study (15). The pixel size was 0.33 mm.

CT analysis. Two board-certified cardiovascular radiologists (W.L. [with 11 years of experience] and Y.K.K. [with 3 years of experience]) reviewed and analyzed the coronary CTA images in consensus. Intraluminal attenuation was measured using dedicated software for coronary CTAs (Xelis Cardiac, INFINITT Healthcare). The centerline of the coronary artery was semi-automatically selected, and if needed, the centerline was edited by manual drawing on a perpendicular plane to the coronary artery at each level (Figure 1). Intraluminal attenuation at the centerline (Hounsfield units), luminal diameter (millimeters), and luminal area (square millimeters) were automatically measured at each pixel through the centerlines of the coronary arteries. Measurements were performed until the luminal diameter of the distal coronary artery reached 1.5 mm. Intraluminal attenuation was calculated in the same manner as described in the phantom study.

The definition of TAG was applied from a previous study (8). TAG was determined from the change of attenuation (Hounsfield units) per 10 mm of length of

FIGURE 2 Changes in TAG Over Time in Each Coronary Artery Model



Scan number was coded as zero when attenuation of the ascending aorta reached to peak. There were no significant differences in transluminal attenuation gradient (TAG) values between stenotic and normal left circumflex coronary artery (LCx) or between stenotic LCx and normal left anterior descending coronary artery (LAD) at each time point (all, p > 0.05). Significant difference in TAG values was only found between normal LAD and occluded LCx in the fifth to eighth repeated scans, and between stenotic LCx and occluded LCx in the third to eighth repeated scans (all, p < 0.05).

the coronary artery and defined as the linear regression coefficient between the attenuation (Hounsfield units) and length from the ostium (millimeters). A TAG ≥20 was considered to indicate a TAG-positive artery.

Similarly, TDG was determined from the change of diameter per 10 mm of length of the coronary artery and defined as the linear regression coefficient between the diameter and length from the ostium. Attenuation and diameter data at the level of stenosis and calcifications were excluded when calculating TAG and TDG (**Figure 1**).

Coronary angiography analysis. Quantitative analysis of invasive coronary angiography was performed with quantitative coronary angiography (CAAS 5.7 QCA system, Pie Medical Imaging, Maastricht, the Netherlands) by a single experienced observer who was blinded to coronary CTA findings. Diameter stenosis was used as the reference of standard. A diameter stenosis ≥50% was defined as significant stenosis.

STATISTICAL ANALYSIS. All data processing and analyses were performed using SPSS version 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York). Two-tailed p values <0.05 were considered to indicate a significant difference. All statistical analyses were performed nonparametrically because neither clinical nor animal data showed a normal distribution. Data are presented as medians and interquartile ranges. In the animal study, differences in TAG values at each temporal scan were evaluated by using the Kruskal-Wallis test and Dunn's multiple comparison post hoc test. In the clinical study, the correlation between TAG and TDG was performed by using Spearman correlation analysis. In addition, the Mann-Whitney *U* test was performed for the comparison of TDG between TAG-positive and TAG-negative arteries.

RESULTS

PHANTOM STUDY: INTRALUMINAL ATTENUATION ACCORDING TO THE DIAMETER OF HOLES. Even though all holes were filled with the same contrast mixture, intraluminal attenuation was observed to gradually decline along with the decreased diameter of the holes (Online Figure 1); the reduction of intraluminal attenuation was much greater as the diameters became smaller. The same findings were observed regardless of the tube voltage used or the concentration of contrast mixture filled in the phantom. Detailed attenuation values are provided in Online Table 1.

ANIMAL STUDY: CHANGE IN ATTENUATION AND TAG OF EACH CORONARY MODEL OVER TIME. Peak attenuation of distal small coronary arteries was slightly delayed in cases in which LCx was longer

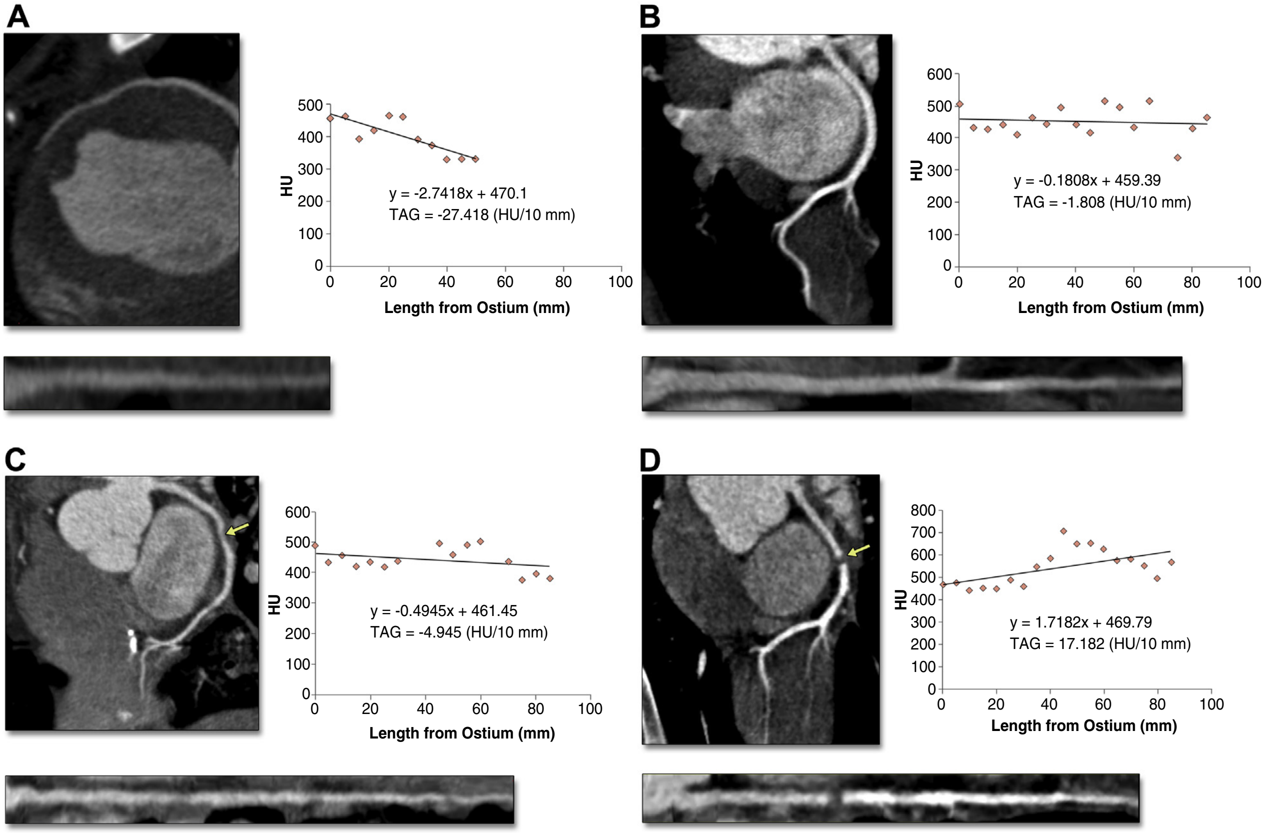
TABLE 2 Changes in TAG of Each Coronary Artery Model Over Time

	Repeated Scan													
	–5th	–4th	–3rd	–2nd	–1st	0	1st	2nd	3rd	4th	5th	6th	7th	8th
Normal LAD (n = 15)	−27.9 (18.0)	−33.8 (20.4)	−33.8 (18.5)	−42.6 (19.5)	−40.4 (26.4)	−37.1 (22.4)	−32.3 (27.7)	−34.2 (36.1)	−34.2 (36.0)	−27.7 (26.7)	−23.3* (32.0)	−18.9* (31.5)	−14.0* (20.3)	−13.9* (16.3)
Normal LCx (n = 4)	−16.9 (1.4)	−22.1 (14.1)	−37.5 (20.2)	−33.6 (2.4)	−27.1 (13.3)	−24.6 (18.6)	−22.3 (16.9)	−17.8 (13.3)	−7.7 (19.5)	−12.3 (21.4)	−13.9 (3.96)	−8.9 (10.5)	2.6 (10.2)	−1.4 (13.7)
Stenotic LCx (n = 6)	−19.0 (7.4)	−24.3 (12.5)	−29.1 (15.1)	−31.9 (5.0)	−41.1 (10.5)	−30.3 (14.3)	−28.9 (15.0)	−27.3 (13.0)	−29.4* (6.8)	−21.7* (11.2)	−17.5* (17.8)	−16.6* (9.8)	−10.2* (8.6)	−11.3* (13.6)
Occluded LCx (n = 5)	−32.8 (0.0)	−29.9 (11.3)	−37.7 (8.6)	−25.2 (21.1)	−37.2 (17.1)	−29.0 (15.8)	−28.7 (21.5)	−6.6 (19.2)	0.7* (20.6)	−0.5* (27.8)	7.7* (25.4)	17.1* (12.1)	27.9* (28.0)	18.3* (18.4)
p Value	0.148	0.245	0.364	0.154	0.270	0.160	0.203	0.089	0.014	0.017	0.013	0.005	0.004	0.004

Values are median (interquartile range). Kruskal-Wallis test with post hoc Dunn multiple comparisons. Repeated scan number 0 indicates the scan in which attenuation of the ascending aorta reached to peak. *Adjusted $p < 0.05$, corrected by post hoc Dunn multiple comparisons after the Mann-Whitney *U* test.

TAG = transluminal attenuation gradient; other abbreviations as in Table 1.

FIGURE 3 **Representative Examples of TAG Measurements in Each Animal Model**



TAG values were calculated in **(A)** normal LAD, **(B)** normal LCx, **(C)** LCx with stenosis **(arrow)**, and **(D)** LCx with occlusion **(arrow)** at a specific time point (the fifth repeated scan after the peak attenuation of the ascending aorta). At this particular time point, the short normal LAD showed a larger value of TAG, compared with the longer LCx, because the diameter decreased more rapidly. However, there seems to be no significant difference in TAG values between normal and stenotic LCx. In an occlusion model, TAG is reversed to positive value. Abbreviations as in Figure 2.

than LAD but did not reach that of proximal large coronary arteries. They exhibited only 55.2% to 78.1% of the maximum enhancement of proximal segments, regardless of type of coronary arteries (Table 1, Online Figure 3).

Figure 2 displays TAG values of each coronary model over time. There were significant differences in TAG values starting from the third repeated scan after the attenuation of the ascending aorta reached a peak to the eighth repeated scan (Table 2): between TAG values of normal LAD and occluded LCx in the fifth to eighth repeated scans, and between TAG values of stenotic LCx and occluded LCx in the third to eighth repeated scans (all, $p < 0.05$) (Figure 3). However, there were no significant differences in TAG values between stenotic and normal LCx or between stenotic LCx and normal LAD (all, $p > 0.05$).

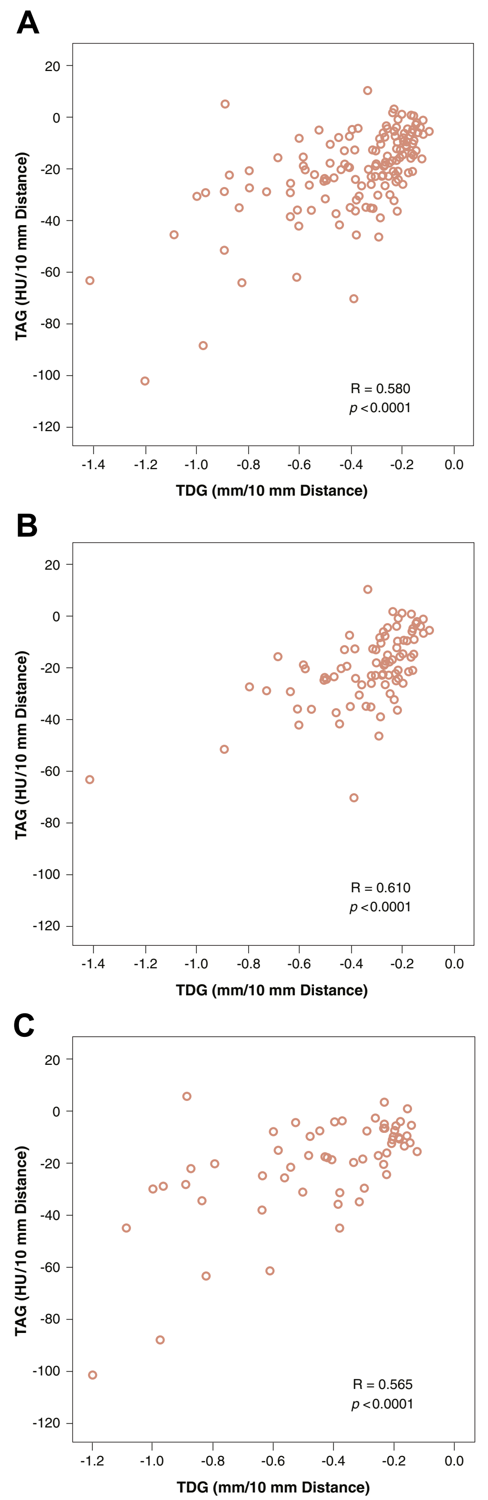
CLINICAL STUDY: ASSOCIATION BETWEEN TAG AND TDG. Although the correlation coefficient was modest, a significant correlation was found between TAG and TDG in total arteries ($r = 0.580$; $p < 0.0001$) (Figure 4). Separate analysis of significant and nonsignificant stenosis groups also showed a significant correlation between TAG and TDG ($r = 0.610$ [$p < 0.0001$] for nonsignificant stenosis; $r = 0.565$ [$p = 0.0001$] for significant stenosis). In addition, TAG-positive arteries exhibited significantly greater TDG values in both groups with significant stenosis ($p < 0.0001$) and without significant stenosis ($p < 0.0001$) (Table 3). There were no significant differences in TAG values between groups with significant stenosis and without significant stenosis ($p = 0.884$), whereas a significant difference was found in TDG values ($p = 0.021$) (Table 4).

DISCUSSION

The principal findings of the present study can be summarized as follows: 1) the vessel phantom study found that intraluminal attenuation declined as vessel diameter decreased even though all vessels were filled with the same concentration of contrast media without any active flow; 2) according to the animal study, even in vivo, the peak attenuation of distal small coronary arteries did not reach that of larger arteries; and 3) in the clinical study, TAG showed significant correlation with the diameter gradient, implying that TAG may be a secondary result of decreased intraluminal attenuation because of decreased diameter.

Our study showed that the diameter of the vessel affected intraluminal attenuation. Particularly when the diameter was small, intracoronary luminal attenuation was more greatly affected. For example, in the 2-mm coronary artery model of our phantom study, we observed approximately one-half of the CT number compared with that of the 5-mm coronary artery even though both vessels were filled with the same concentration of contrast media. Although these findings have not previously been reported in the published data, we found 2 examples of supporting evidence from previous studies. First, even in normal coronary arteries, it has been shown that TAG values were different depending on the kind of coronary artery measured. An elaborate, preliminary study by Steigner et al. (7), who analyzed 36 patients with normal coronary arteries using 320-ADCT, explored 3 methods of measuring iodinated contrast opacification gradients (i.e., using the distance from the coronary ostium, lumen cross-sectional area, and lumen short-axis diameter). They found that the contrast gradient over distance was significantly smaller in the right coronary artery compared with the left coronary system despite having normal coronary arteries: -6.5 ± 4.1 for right coronary artery, -13.7 ± 8.0 for LAD, and -12.5 ± 7.8 for LCx. This outcome can be interpreted as that the right coronary artery would be longer and bigger, resulting in a smaller diameter change over distance, compared with the left coronary artery system. Thus, the investigators suggested the superiority of coronary lumen cross-sectional areas and short-axis diameter gradients over distance gradients as these were not significantly influenced by the coronary artery. However, even though the coronary lumen cross-sectional area and short-axis diameter gradients are not influenced by the type of the coronary artery, a smaller diameter or lumen cross-sectional area would

FIGURE 4 Correlation Between TAG and TDG



Significant correlations were found in **(A)** all subjects, **(B)** those with nonsignificant stenosis, and **(C)** those with significant stenosis. Abbreviations as in Figure 1.

TABLE 3 Comparison of TDG Values Between TAG-Positive and TAG-Negative Groups (n = 152 Coronary Arteries)

	Stenosis <50% (n = 93)			Stenosis ≥50% (n = 59)		
	TAG Positive	TAG Negative	p Value	TAG Positive	TAG Negative	p Value
No. of arteries	43	50		24	35	
TDG	−0.342 (0.249)	−0.229 (0.128)	<0.0001	−0.622 (0.507)	−0.231 (0.234)	<0.0001

Values are median (interquartile range).
TAG = transluminal attenuation gradient; TDG = transluminal diameter gradient.

still produce a much greater attenuation gradient. Second, similar to our phantom results showing that the slope of the intraluminal attenuation reduction was greater as the diameter became smaller, previous studies (7,8) demonstrated that the diameter range of TAG-positive arteries was much smaller than TAG-negative arteries: from 3 to 1 mm versus from 4.5 to 1.7 mm (7), and from 2.9 to 1.7 mm versus from 4.5 to 2.9 mm (8). Choi et al. (8) also showed that arteries with more severe stenosis had smaller distal caliber. This finding suggests that the downstream coronary arteries with high-grade stenosis or occlusion may become smaller.

The diminution of the attenuation of small objects such as small lung nodules has previously been described as occurring due to the partial volume average effect (16); that is, lung nodules are smaller than the slice thickness. However, the partial volume average effect is not likely to happen in the luminal attenuation of small vessels in our study for 2 reasons. First, in both in vivo and in vitro images, slice thicknesses were smaller than the diameters of vessels, and the size of the ROIs was small enough to avoid containing the vessel wall. Second, in our phantom study, the imaging plane was perpendicular to the vessel orientation, and the vessel was oriented straight; therefore, the partial volume averaging would not have affected the attenuation drop. Rather, we believe that the diminution of intraluminal attenuation in small vessels can be caused by the point-spread function, which is an essential parameter in CT reconstruction algorithms (14). The point-spread function is regarded as a resolution-limiting factor that can lead to images which are not exact replicas of real objects (14,17). Theoretically, CT scanners can produce isotropic image voxels, allowing a uniform sampling of the point-spread function (18), but any deviation from this ideal function causes the point-spread function to widen, resulting in image blurring (14). This effect increases much more in the case of smaller voxels in CT images; thus, in the small vessels of our study, it caused a decrease in CT number.

TABLE 4 Comparison of TAG and TDG Values Between Stenotic and Nonstenotic Groups (N = 152 Coronary Arteries)

	Stenosis <50% (n = 93)	Stenosis ≥50% (n = 59)	p Value
TAG	−18.783 (16.630)	−17.659 (21.269)	0.884
TDG	−0.273 (0.191)	−0.379 (0.377)	0.021

Values are median (interquartile range).
Abbreviations as in Table 3.

The animal study revealed that the length of the coronary artery was shown to be an important factor in calculating TAG. For instance, because LAD was shorter than LCx in the dogs studied, the diameter of LAD rapidly decreased from proximal to distal, indicating a higher value of TDG. Thus, a normal LAD exhibited higher TAG than that of a normal LCx even though it did not show a statistical significance. In addition, even normal vessels that are short and show rapid changes in diameter exhibited higher TAG values. The significant correlation between TAG and TDG both in normal vessels and the stenosis models also support our observation.

In the occlusion model, the distal segment to the occlusion exhibited higher attenuation than the proximal segment in the delayed phase 4 heartbeats after the attenuation of the ascending aorta reached its peak. This phenomenon is referred to as the "reversed attenuation sign" representing the retrograde collateral flow distal to the occlusive lesion. In the study by Li et al. (19), they found that the reverse attenuation sign was highly specific for chronic total occlusion and helped to differentiate chronic total occlusion from subtotal occlusion and in diagnosing stent occlusion (20). Choi et al. (21) also used the reverse attenuation sign to identify the presence of well-developed collateral in coronary arteries with chronic total occlusion.

As for our clinical study, we failed to find significant TAG differences between stenotic and nonstenotic coronary arteries and recorded consistent correlations between TAG and TDG in both stenotic and nonstenotic coronary arteries. Debate remains as to the significance of TAG. Several researchers have previously reported a significant difference in TAG between functional significant and nonsignificant stenosis (12), whereas others were not able to find a meaningful difference in TAG in stenoses (22,23). A distinguishing characteristic of our experimental and clinical observations was that it was evident that the attenuation of the coronary artery was highly affected by artery diameter; however, this factor was not considered in the previous research on TAG. Because the diameter of the coronary artery can be one of the biggest confounding factors in evaluating TAG, we emphasize the need to take this diameter into account when assessing TAG as a clinical parameter in CAD. We also want to point out that the TAG of coronary CTA can only represent the rest flow of the coronary artery, as most functional parameters showed positive results only in the stress condition, not in the rest condition. Therefore, it is also hard to expect that the TAG derived from rest phase coronary CTA can be a meaningful functional parameter of coronary artery flow.

STUDY LIMITATIONS. First, in the animal study, intracoronary attenuation may have been influenced by motion artifacts, although the canines' heart rates were controlled with use of beta-blockers. Second, we did not confirm the hemodynamic significance of the coronary stenosis by using hemodynamic data (e.g., flow measurements or FFR in the animal study as well as in the clinical study). Third, in the clinical study, calcium at small coronary artery walls could not have been excluded from the analysis with certainty when the attenuation was below the visual threshold for detection. Lastly, this clinical study is a retrospective, single-center study. Therefore, selection bias may have been present.

CONCLUSIONS

We showed that intraluminal attenuation decreased along with diminution of the vessel diameter and that TAG showed a significant correlation with TDG. These findings imply that TAG may be a secondary result because of differences in coronary artery diameters.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: TAG, which is known as a functional CT marker for determining a hemodynamic significance of coronary arterial disease, may be a secondary result because of differences in coronary artery diameters. Our 3-part study (phantom, animal, and clinical) revealed that intraluminal attenuation decreased along with diminution of the vessel diameter, and TAG showed a significant correlation with TDG.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine a significant relationship between TAG and TDG using hemodynamic data (e.g., flow measurements or FFR). Further research can be conducted to explore if TDG could be used as a potential functional CT marker for determining a significant functional stenosis in the coronary arteries.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127:e6–245.

2. Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. J Am Coll Cardiol 2008;52:357–65.

3. Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 2008;52:636–43.

4. Bamberg F, Becker A, Schwarz F, et al. Detection of hemodynamically significant coronary artery stenosis: incremental diagnostic value of dynamic CT-based myocardial perfusion imaging. Radiology 2011;260:689–98.

5. Maurovich-Horvat P, Schlett CL, Alkadhi H, et al. The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. J Am Coll Cardiol Img 2012;5:1243–52.

6. Seifarth H, Schlett CL, Nakano M, et al. Histopathological correlates of the napkin-ring sign plaque in coronary CT angiography. Atherosclerosis 2012;224:90–6.

7. Steigner ML, Mitsouras D, Whitmore AG, et al. Iodinated contrast opacification gradients in normal coronary arteries imaged with prospectively ECG-gated single heart beat 320-detector row computed tomography. Circ Cardiovasc Imaging 2010;3:179–86.

8. Choi JH, Min JK, Labounty TM, et al. Intracoronary transluminal attenuation gradient in coronary CT angiography for determining coronary artery stenosis. J Am Coll Cardiol Img 2011;4:1149–57.

9. Lackner K, Bovenschulte H, Stutzer H, Just T, Al-Hassani H, Krug B. In vitro measurements of flow using multislice computed tomography (MSCT). Int J Cardiovasc Imaging 2011;27:795–804.

10. Chow BJ, Kass M, Gagne O, et al. Can differences in corrected coronary opacification measured with computed tomography predict resting coronary artery flow? J Am Coll Cardiol 2011;57:1280–8.

11. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional

Flow Reserve) study. J Am Coll Cardiol 2011;58: 1989–97.

12. Wong DT, Ko BS, Cameron JD, et al. Transluminal attenuation gradient in coronary computed tomography angiography is a novel noninvasive approach to the identification of functionally significant coronary artery stenosis: a comparison with fractional flow reserve. J Am Coll Cardiol 2013;61:1271–9.

13. Min JK, Castellanos J, Siegel R. New frontiers in CT angiography: physiologic assessment of coronary artery disease by multidetector CT. Heart 2013;99:661–8.

14. Saba OI, Hoffman EA, Reinhardt JM. Maximizing quantitative accuracy of lung airway lumen and wall measures obtained from X-ray CT imaging. J Appl Physiol (1985) 2003;95:1063–75.

15. Lim J, Park EA, Lee W, Shim H, Chung JW. Image quality and radiation reduction of 320-row area detector CT coronary angiography with optimal tube voltage selection and an automatic exposure control system: comparison with body mass index-adapted protocol. Int J Cardiovasc Imaging 2015;31 Suppl 1:23–30.

16. Goo JM, Tongdee T, Tongdee R, Yeo K, Hildebolt CF, Bae KT. Volumetric measurement of synthetic lung nodules with multi-detector row CT: effect of various image reconstruction parameters and segmentation thresholds on measurement accuracy. Radiology 2005;235:850–6.

17. King GG, Muller NL, Whittall KP, Xiang QS, Pare PD. An analysis algorithm for measuring airway lumen and wall areas from high-resolution computed tomographic data. Am J Respir Crit Care Med 2000;161:574–80.

18. Wang G, Vannier MW, Skinner MW, Cavalcanti MG, Harding GW. Spiral CT image deblurring for cochlear implantation. IEEE Trans Med Imaging 1998;17:251–62.

19. Li M, Zhang J, Pan J, Lu Z. Obstructive coronary artery disease: reverse attenuation gradient sign at CT indicates distal retrograde flow—a useful sign for differentiating chronic total occlusion from subtotal occlusion. Radiology 2013;266: 766–72.

20. Li M, Zhang J, Zhang Q, Pan J, Lu Z, Wei M. Coronary stent occlusion: reverse attenuation gradient sign observed at computed tomography angiography improves diagnostic performance. Eur Radiology 2015;25:568–74.

21. Choi JH, Kim EK, Kim SM, et al. Noninvasive evaluation of coronary collateral arterial flow by coronary computed tomographic angiography. Circ Cardiovasc Imaging 2014;7:482–90.

22. Choi JH, Koo BK, Yoon YE, et al. Diagnostic performance of intracoronary gradient-based methods by coronary computed tomography angiography for the evaluation of physiologically significant coronary artery stenoses: a validation study with fractional flow reserve. Eur Heart J Cardiovasc Imaging 2012;13:1001–7.

23. Yoon YE, Choi JH, Kim JH, et al. Noninvasive diagnosis of ischemia-causing coronary stenosis using CT angiography: diagnostic value of transluminal attenuation gradient and fractional flow reserve computed from coronary CT angiography compared to invasively measured fractional flow reserve. J Am Coll Cardiol Img 2012; 5:1088–96.

KEY WORDS coronary artery disease, coronary artery stenosis, 320-row area detector CT

APPENDIX For a supplemental table and figures, please see the online version of this article.