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# The Effects of a Vasodilator on Transluminal Attenuation Gradient at Coronary Computed Tomography Angiography

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**Objective:** To evaluate the effects of vasodilators on contrast enhancement and transluminal attenuation gradient (TAG) of coronary arteries at coronary computed tomography angiography (CCTA).

**Materials and Methods:** We retrospectively reviewed CCTA scans of patients who underwent double-acquisition CCTA; CCTA without a vasodilator, and CCTA during a intravenous (IV) infusion of nitrate. Among them, we enrolled 19 patients who had no significant atherosclerotic lesions or coronary spasms. In the control group, 28 patients were enrolled who showed normal coronary arteries on CCTA, which was acquired by a conventional method (sublingual vasodilator). We measured the TAG and Hounsfield units for each of the three major epicardial coronary arteries (reported as 'ProxHU') and then compared the results between the nitrate administration methods (CT without vasodilator [$CT_{pre}$], CT with IV vasodilator [$CT_{iv}$], and CT with sublingual vasodilator [$CT_{sub}$]).

**Results:** The mean TAG showed a significant difference between the coronary arteries (right coronary artery [RCA] > left anterior descending artery [LAD] > left circumflex artery [LCX], $p < 0.05$), while there was no difference in ProxHU of each coronary artery in all three types of nitrate administration methods ($p > 0.05$). The TAG of $CT_{pre}$ group showed steeper slope than those of vasodilator groups ($CT_{iv}$ and $CT_{sub}$) on LAD and LCX ([LAD: $CT_{pre}$ = -22.1 ± 6.66, $CT_{iv}$ = -16.76 ± 5.78, and $CT_{sub}$ = -16.47 ± 5.78, $p = 0.005$], [LCX: $CT_{pre}$ = -31.26 ± 17.43, $CT_{iv}$ = -23.74 ± 14.06, and $CT_{sub}$ = -20.94 ± 12.15, $p = 0.051$]), while that of RCA showed no significant differences ($p = 0.600$). When comparing proxHU, $CT_{iv}$ showed higher proxHU than that of $CT_{pre}$ or $CT_{sub}$, especially on LCX ($CT_{pre}$ = 426.7 ± 68.3, $CT_{iv}$ = 467.9 ± 84.9, and $CT_{sub}$ = 404.9 ± 63.3, $p = 0.013$). ProxHU showed a negative correlation with TAG on all three of methods ($r = -0.280$, $p < 0.001$).

**Conclusion:** TAG in CCTA was significantly affected by vasodilator administration. Both TAG and ProxHU of coronary arteries tend to increase with vasodilator administration on CCTA.

**Keywords:** *Multi-detector computed tomography; Wide area detector; Coronary vessels; Vasodilator agents; Cardiac imaging techniques*

## INTRODUCTION

Coronary computed tomography angiography (CCTA) is useful for the diagnosis of coronary artery diseases (1, 2). CCTA has been employed in various studies to diagnose coronary artery stenosis (3-6). Transluminal attenuation gradient (TAG), defined as the gradient of intraluminal radiological attenuation, is a recent index that can be used to evaluate the severity of coronary artery stenosis (3). With wide-area (16 cm) coverage detector CT (320- or 256-detector row CT), TAG can be measured at near isophasic and single-beat imaging of the whole coronary tree (5).

In clinical practice, vasodilators such as nitroglycerin are used for coronary vasodilatation, which can increase

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the diagnostic accuracy of CCTA by increasing the number of evaluable coronary segments and improving the image quality by increasing the diameter of the coronary artery (7, 8). The American College of Cardiology/American Heart Association (ACC/AHA) recommends the administration of nitrates for conventional coronary angiography to improve reliability when assessing the degree of coronary stenosis (9). Sublingual nitroglycerin is routinely applied and is the preferred method of administration during the CCTA, since it is the most efficacious and associated with fewer side effects (2, 7, 10).

Because vasodilators can change the condition of the coronary artery, it can somehow affect TAG in CCTA. Park et al. (11) reported that the intraluminal attenuation decreased with diminution of the vessel diameter, and that TAG showed a significant correlation with the transluminal diameter gradient in CCTA. However, many factors may influence the delivery of contrast media to distal branches on CT in addition to the luminal diameter of vessels, although there have been no studies on the effects of vasodilators on TAG in CCTA. Therefore, in this study, we aimed to determine the relationship between TAG and vasodilators and the value of TAG at CCTA.

## MATERIALS AND METHODS

### Subjects

A total of 57 consecutive patients with a high clinical probability of vasospastic angina between March 2017 and April 2019 were enrolled. All subjects were part of the Dual-acquisition of Noninvasive Cardiac Imaging in Vasospastic Angina Korean Registry (NAVIGATOR study) and were reviewed retrospectively (12, 13). These patients underwent baseline CCTA ($CT_{pre}$) without a vasodilator in the early morning followed by a catheterized coronary angiography with an ergonovine provocation test. Then, within the same day, the patients underwent repetitive CCTA during a continuous intravenous (IV) infusion of nitrate ($CT_{iv}$). Among them, we retrospectively enrolled the 21 patients who did not have significant atherosclerotic lesions or suspicious coronary spasm. As a control group, we also retrospectively enrolled 31 patients who showed normal coronary arteries as confirmed with CCTA with a conventional nitrate infusion method (sublingual nitrate spray [$CT_{sub}$]).

Among the 52 patients who were enrolled, 5 patients showed left-sided coronary dominance (short right coronary artery); thus, we excluded them from this study because TAG may be influenced by the vessel diameter and length (14). Finally, 47 patients were selected as the study population: 19 patients who received both $CT_{pre}$ and $CT_{iv}$ (dual acquisition group) and 28 patients who received $CT_{sub}$ (control group) (Table 1).

This is a retrospective single-center study. The institutional ethics committee approved this study, and written informed consent was waived.

### CCTA Data Acquisition and Analysis

All CCTAs were performed on a 320-detector-row CT system (Aquilion One; Canon Medical Systems) with 2 collimations at 320 x 0.5 mm, a 350-ms gantry rotation time, and 175-ms temporal resolution. The details of the scan protocol for dual acquisition CT were based on the image acquisition protocol of the NAVIGATOR study (12, 13). The premedication and scan method for intravenous (IV) nitrate CT was as follows: before the CT scan, a vasodilating agent (isosorbide dinitrate, Isoket® 0.1% injection; Schwarz Pharma) diluted in saline (500 mL) was administered to the patient as an IV infusion (infusion rate 2 mg/h). Twenty minutes after the start of the nitrate infusion, the blood pressure (BP) was measured every 2 minutes with a continuous IV injection of the vasodilator. When both systolic and diastolic BP decreased by 10 mm Hg from the initial value, CT was performed during the IV vasodilator infusion. After the CT scan was completed, the infusion of nitrate was terminated (12). The administration of nitrate spray for the control group CT was based on the routine imaging acquisition protocol in our hospital: immediately before the start of the CT scan, two puffs of nitrate spray (isosorbide dinitrate 375 mg/15 mL, Isoket spray; Avara Shannon Pharma) was administered sublingually.

The tube voltage and current were modulated with commercial software (Sure Exposure 3D®, Canon Medical Systems). The tube voltage was 120 kVp, and the tube current ranged from 130 to 250 mA. A bolus of 50–70 mL of nonionic contrast material (iobitridol, Xenetix® 350 mgI/mL; Guerbet) was administrated intravenously at 4 mL/s, followed by 30 mL of a contrast/saline mixture (2:8 dilution) infused at 4 mL/s. The CT scans were initiated using an automatic bolus trigger in the ascending aorta (the triggering threshold was 100 Hounsfield units [HU]) with a delay of 5 seconds. All CT scans were acquired using one heart beat volume scanning method. When the heart rate (HR) was sufficiently reduced (≤ 65 beat/min), CT scans were obtained by prospectively triggered data acquisition at 70–80% of the RR interval.


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**Table 1. General Characteristics of Enrolled Subjects**

| | Total | Control Group ($CT_{sub}$) | Dual Acquisition Group ($CT_{pre}$/$CT_{iv}$) | *P* |
|---|---|---|---|---|
| No. of patients | 47 | 28 | 19 | |
| Age (years) | 59.8 ± 10.5 | 58.7 ± 7.9 | 61.4 ± 13.6 | 0.391 |
| Male sex (%) | 25 (53.2) | 15 (53.6) | 10 (52.6) | 0.949 |
| Hypertension (%)* | 10 (21.3) | 8 (28.6) | 2 (10.5) | 0.138 |
| Diabetes mellitus (%)† | 5 (10.6) | 4 (14.3) | 1 (5.3) | 0.325 |
| Dyslipidemia (%)‡ | 9 (19.1) | 4 (14.3) | 5 (26.3) | 0.304 |
| Smoking (%) | | | | 0.286 |
| Never | 30 (63.8) | 16 (57.1) | 14 (73.7) | |
| Current | 9 (19.2) | 5 (17.9) | 4 (21.0) | |
| Past | 8 (17.0) | 7 (25.0) | 1 (5.3) | |
| Height (cm) | 163.8 ± 7.58 | 163.5 ± 7.8 | 164.2 ± 7.3 | 0.754 |
| Weight (kg) | 63.4 ± 10.1 | 62.8 ± 10.3 | 64.4 ± 10.0 | 0.603 |
| BMI ($kg/m^2$) | 23.6 ± 3.0 | 23.5 ± 3.3 | 23.8 ± 2.6 | 0.697 |
| Agatston score | 64.3 ± 200.8 | 0.0 ± 0.0 | 159.2 ± 295.1 | 0.006 |

Data are expressed as mean ± standard deviation or numbers of patients (%) unless otherwise indicated. *Patients were considered hypertensive if their blood pressure was consistently > 140/90 mm Hg, or if they were currently taking anti-hypertensive medication, †Patients were considered to have diabetes mellitus if their fasting glucose level was ≥ 126 mg/dL, at least in one assessment, or if they were currently taking oral hypoglycemic agents or insulin, ‡Patients were considered to have dyslipidemia if they had range of lipid abnormalities in combination: increased total cholesterol (> 200 mg/dL), low-density lipoprotein cholesterol (> 140 mg/dL), and triglyceride levels (> 150 mg/dL) or decreased high-density lipoprotein cholesterol (< 40 mg/dL). BMI = body mass index, $CT_{iv}$ = CT with intravenous vasodilator, $CT_{pre}$ = CT without vasodilator, $CT_{sub}$ = CT with sublingual vasodilator

The patients with rapid HRs (> 65 beat/min) underwent retrospective data acquisition with electrocardiography (ECG)-based tube current modulation (full tube current 30–80%). All datasets were processed with iterative reconstruction (AIDR 3D, Canon Medical Systems). Axial images were reconstructed in a field of view adapted to each individual's heart size at a slice thickness of 0.5 mm and interval of 0.5 mm. An initial reconstruction was performed using axial images from the 75% cardiac phase or the automatically suggested best phase (ms). Additional systolic or diastolic phase images were reconstructed for patients with rapid HRs as needed.

### TAG and Proximal Enhancement (ProxHU) Measurements

All images were transferred to commercial software (Vitrea®, Vital images) for analysis. TAG values were measured with semi-automated methods on dedicated computer software (Canon Medical Systems) for the each of the three major epicardial coronary arteries (left anterior descending artery [LAD], left circumflex artery [LCX], and right coronary artery [RCA]) as previouly reported (3). Vessel centerline and contouring were automatically determined for each major coronary artery and manually corrected if necessary. Cross-sectional images perpendicular to the vessel centerline were reconstructed for the vessels. Mean luminal attenuation in HU was measured at 1-mm intervals, from the ostium to distal levels (cross-sectional area < 2 $mm^2$). The data points in the segments with motion or blooming artifacts from luminal calcium were manually excluded from the analysis. TAG values were determined from the change in CT attenuation (HU) per 10-mm length of the coronary artery and defined as the linear regression coefficient between intraluminal HU and length from the ostium. Representative examples are shown in Figure 1. We also measured attenuation in the contrast-enhanced lumens of the proximal segments of the three major coronary arteries ('ProxHU') by drawing the region of interests as large as possible with carefully avoided calcifications on the cross-sectional images of each vessel's curved multiplanar plane.

The TAG and ProxHU were measured in 10 randomly selected subjects by two experienced radiologists to assess interobserver variability. The measurements were performed independently of each other, and discrepant readings were reconciled by consensus.

### Statistical Analysis

The clinical characteristics were compared between patients in the double acquisition and control groups. The mean TAG and ProxHU for each three major coronary arteries (LAD, LCX, and RCA) were compared between three CT acquisition methods ($CT_{pre}$, $CT_{iv}$, and $CT_{sub}$). The continuous variables are expressed as mean ± standard deviation,

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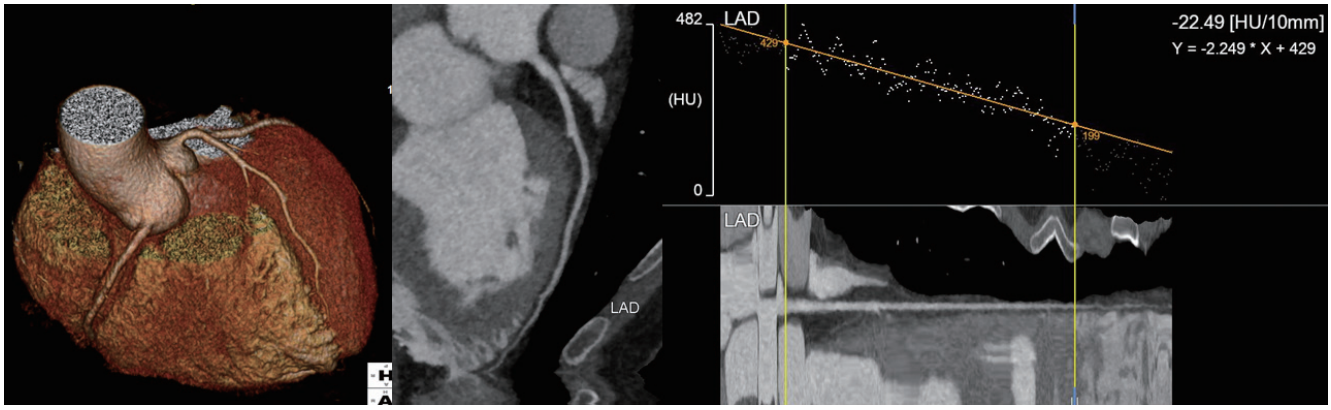
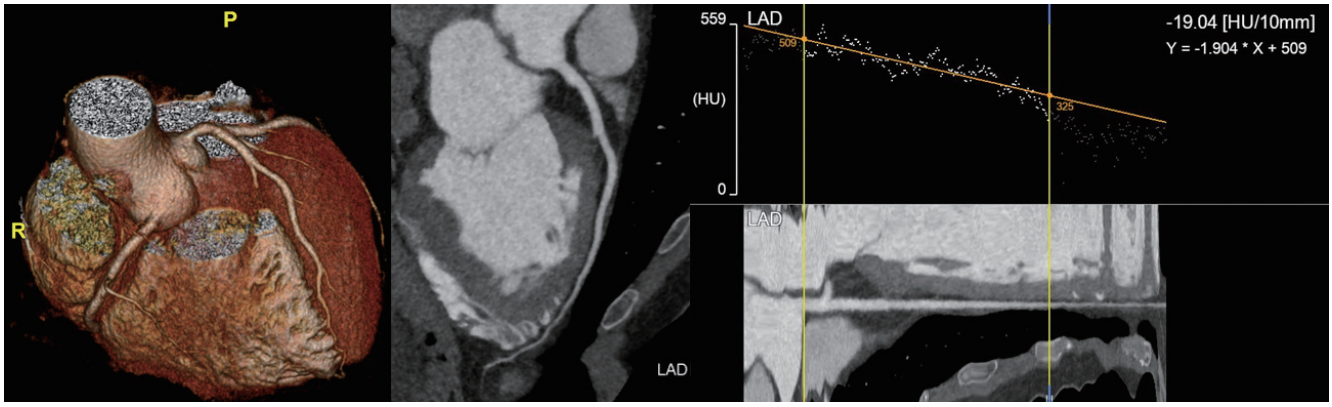



A




B

**Fig. 1. Representative images of TAG of LAD in 54-year-old male (A, CCTA without nitrate; B, CCTA with intravenous nitrate infusion).** TAG of LAD was measured with semiautomatic methods via dedicated computer software (Canon Medical Systems). Mean luminal radiologic attenuation (HU) was measured at 1-mm intervals, from ostium to distal level (cross-sectional minimal area < 2 $mm^2$). Then TAG was automatically calculated from changes in HU per 10-mm length of coronary artery. TAGs were -22.49 **(A)** and -19.04 **(B)**, respectively.
CCTA = coronary computed tomography angiography, HU = Hounsfield units, LAD = left anterior descending artery, TAG = transluminal attenuation gradient

and categorical variables are expressed as frequency (percentage). The independent *t* test or Mann-Whitney U test was performed for within-group differences, and one-way analysis of variance (ANOVA) or Kruskal–Wallis test was performed for between-group differences according to the results produced by the normality test. The correlations between the TAG and ProxHU were analyzed using Pearson's correlation coefficient: Correlation coefficients of < 0.20, 0.20–0.39, 0.40–0.59, 0.60–0.79, and ≥ 0.80 indicate a very weak, weak, moderate, strong, and very strong correlation. The inter-observer agreement for the measurement of TAG and ProxHU were assessed using the intraclass correlation coefficient (ICC). ICC values of 0.0–0.20 were indicative of poor agreement; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good agreement; and 0.81 or more, very good agreement. SPSS (version 20.0; IBM Corp.) was used for all data analyses. *P* values < 0.05 were considered significant.

## RESULTS

### Clinical Characteristics

The mean age of the subjects population was 59.8 ± 10.5 years, and 25 (53.2%) patients were male (Table 1). Ten patients had hypertension, 5 patients had diabetes, 9 patients had dyslipidemia, and 16 patients had smoking history. Between the control and dual acquisition groups, there were no significant differences in age, sex, and other comorbidities. The values of body habitus (height, weight, and body mass index) were similar in both groups, without significant differences. The mean coronary arterial calcium score (Agatston method) was 159.2 ± 295.1 in the dual acquisition group, while all patients in the control group had a calcium score of 0. However, we only enrolled patients in the dual acquisition group who had no significant luminal stenosis on the conventional coronary angiography.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### Comparison of TAG and ProxHU between the Three Major Coronary Arteries

The mean TAG of each coronary artery showed significant differences, regardless of the nitrate administration methods ($p < 0.001$, Table 2). In the $CT_{pre}$ group, RCA showed the highest TAG value (which means gentlest slope), followed by LAD and LCX (RCA, -11.74 ± 7.88; LAD, -22.10 ± 6.66; LCX, -31.26 ± 17.43). Both $CT_{iv}$ and $CT_{sub}$ groups also showed the same trends for TAG as the $CT_{pre}$ group (RCA > LAD > LCX, Table 2).

There was no statistically significant difference in ProxHU between the three major coronary arteries in all three kinds of nitrate administration methods (e.g., ProxHU of $CT_{pre}$ group: 446.0 ± 72.4 in LAD; 426.7 ± 68.3 in LCX; and 439.7 ± 71.1 in RCA; $p = 0.651$, Table 2).

**Table 2. Comparison of TAG and ProxHU among Groups of $CT_{pre}$, $CT_{iv}$, and $CT_{sub}$**

| | $CT_{pre}$ | $CT_{iv}$ | $CT_{sub}$ | *P* |
|---|---|---|---|---|
| TAG | | | | |
| LAD | -22.10 ± 6.66 | -16.76 ± 5.78 | -16.47 ± 5.78 | 0.005* |
| LCX | -31.26 ± 17.43 | -23.74 ± 14.06 | -20.94 ± 12.15 | 0.051 |
| RCA | -11.74 ± 7.88 | -10.15 ± 5.25 | -9.86 ± 6.36 | 0.600 |
| *p* | < 0.001 | < 0.001 | < 0.001 | |
| ProxHU | | | | |
| LAD | 446.0 ± 72.4 | 463.0 ± 97.4 | 433.0 ± 66.3 | 0.418 |
| LCX | 426.7 ± 68.3 | 467.9 ± 84.9 | 404.9 ± 63.3 | 0.013† |
| RCA | 439.7 ± 71.1 | 472.0 ± 101.1 | 420.5 ± 72.6 | 0.101 |
| *p* | 0.651 | 0.817 | 0.795 | |

Data are expressed as mean ± standard deviation unless otherwise indicated. *† = Scheffe test (*$CT_{pre}$ > $CT_{sub}$, $CT_{iv}$; †$CT_{iv}$ > $CT_{sub}$). LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery, ProxHU = CT numbers of proximal coronary artery, TAG = transluminal attenuation gradient

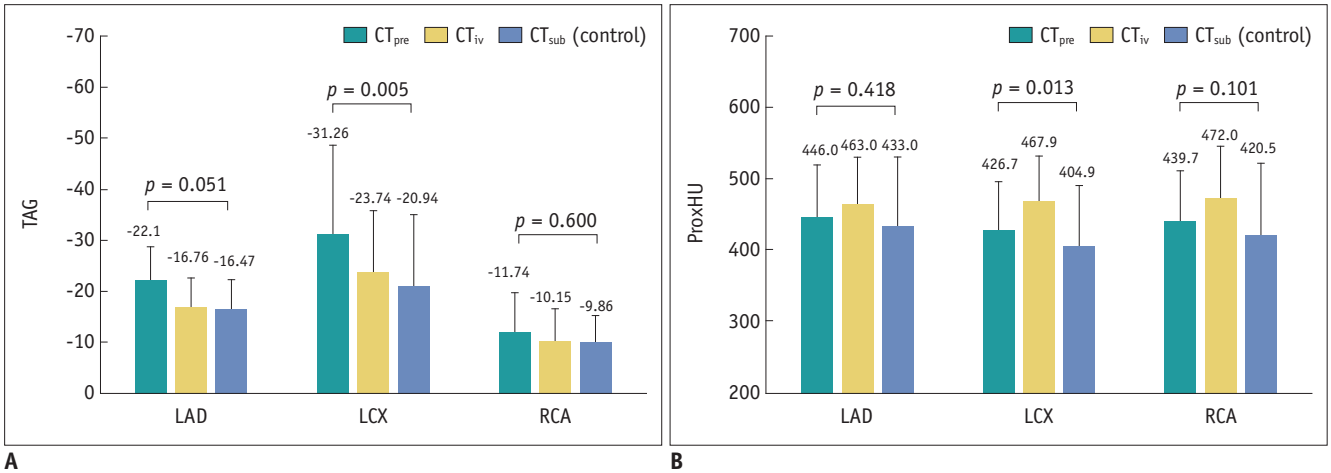
### Comparison of TAG and ProxHU according to Nitrate Administration Methods ($CT_{pre}$, $CT_{iv}$ and $CT_{sub}$)

On the CT without a vasodilator group ($CT_{pre}$), the TAGs of LAD and LCX showed steeper slope (lower values) compared to those of CT with a vasodilator groups ($CT_{iv}$ and $CT_{sub}$). TAGs of LAD on $CT_{pre}$, $CT_{iv}$ and $CT_{sub}$ were -22.10 ± 6.66, -16.76 ± 5.78, and -16.47 ± 5.78, respectively ($p = 0.005$). Those of LCX were -31.26 ± 17.43, -23.74 ± 14.06, and -20.94 ± 12.15, respectively ($p = 0.051$). Whereas, those of RCA showed no significant difference (-11.74 ± 7.88, -10.15 ± 5.25, and -9.86 ± 6.36, $p = 0.600$) (Fig. 2, Table 2).

When comparing the mean proxHU according to the nitrate administration methods, $CT_{iv}$ showed higher proxHU than that of $CT_{pre}$ or $CT_{sub}$, especially in LCX ($CT_{pre}$ = 426.7 ± 68.3, $CT_{iv}$ = 467.9 ± 84.9 and $CT_{sub}$ = 404.9 ± 63.3, $p = 0.013$). The LAD and RCA showed the same trends for proxHU values, but no statistically significant difference was observed. Mean proxHUs of LAD on $CT_{pre}$, $CT_{iv}$, and $CT_{sub}$ were 446.0 ± 72.4, 463.0 ± 97.4, and 433.0 ± 66.3, respectively ($p = 0.418$) and those of RCA were 439.7 ± 71.1, 472.0 ± 101.1, and 420.5 ± 72.6 ($p = 0.101$).

### Correlation between TAG and ProxHU in Groups of $CT_{pre}$, $CT_{iv}$, and $CT_{sub}$

The ProxHU showed a weak negative correlation with




A B

**Fig. 2. Comparison of TAG (A) and contrast enhancement (proxHU, B) of three major coronary arteries.**
**A.** TAGs of CT without vasodilator group ($CT_{pre}$) was lower (steeper downslope) than those of vasodilator groups ($CT_{iv}$ and $CT_{sub}$) on LAD and LCX ($p = 0.051$ for LAD, 0.005 for LCX). Whereas, those of RCA showed no significant difference ($p = 0.600$). **B.** CT with intravenous vasodilator ($CT_{iv}$) showed higher proxHU than that of $CT_{pre}$ or $CT_{sub}$, especially in LCX ($p = 0.013$). LAD and RCA showed same trends, but no statistically significant difference was observed ($p = 0.418$ for LAD, 0.101 for RCA). $CT_{iv}$ = CT with intravenous vasodilator, $CT_{pre}$ = CT without vasodilator, $CT_{sub}$ = CT with sublingual vasodilator, LCX = left circumflex artery, RCA = right coronary artery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TAG ($r$ = -0.280, $p$ < 0.001) (Fig. 3A). Therefore, the higher contrast-enhancing vessel tends to have lower values of TAG (steeper slope). This trend was present regardless of the CT acquisition method ($CT_{pre}$, $r$ = -0.299; $CT_{iv}$, $r$ = -0.275; $CT_{sub}$, $r$ = -0.305; $p$ < 0.05) (Fig. 3B-D).

### Interobserver Variabilities for Both TAG and ProxHU Analyses

The interobserver variabilities for both TAG and ProxHU analyses of the three major coronary arteries were highly reproducible (very good agreement) between observers in 10 randomly selected subjects. The ICCs were 0.992 (95% confidence interval: 0.984–0.996) in the TAG analysis and 0.995 (95% confidence interval: 0.988–0.999) in the ProxHU analysis.

## DISCUSSION

Various CT methods for the diagnosis and evaluation of major coronary artery disease have been studied, and more efficient or less-invasive methods have been pursued if possible (15, 16). As a result, several additional techniques have been developed, one of which is TAG. Although many researchers have agreed on the advantages of TAG with CCTA in patients with coronary artery disease (3, 4, 17), there have been several discrepancies for the diagnostic value or clinical significance of TAG. Stuijfzand et al. (6) demonstrated that TAG did not improve the diagnostic

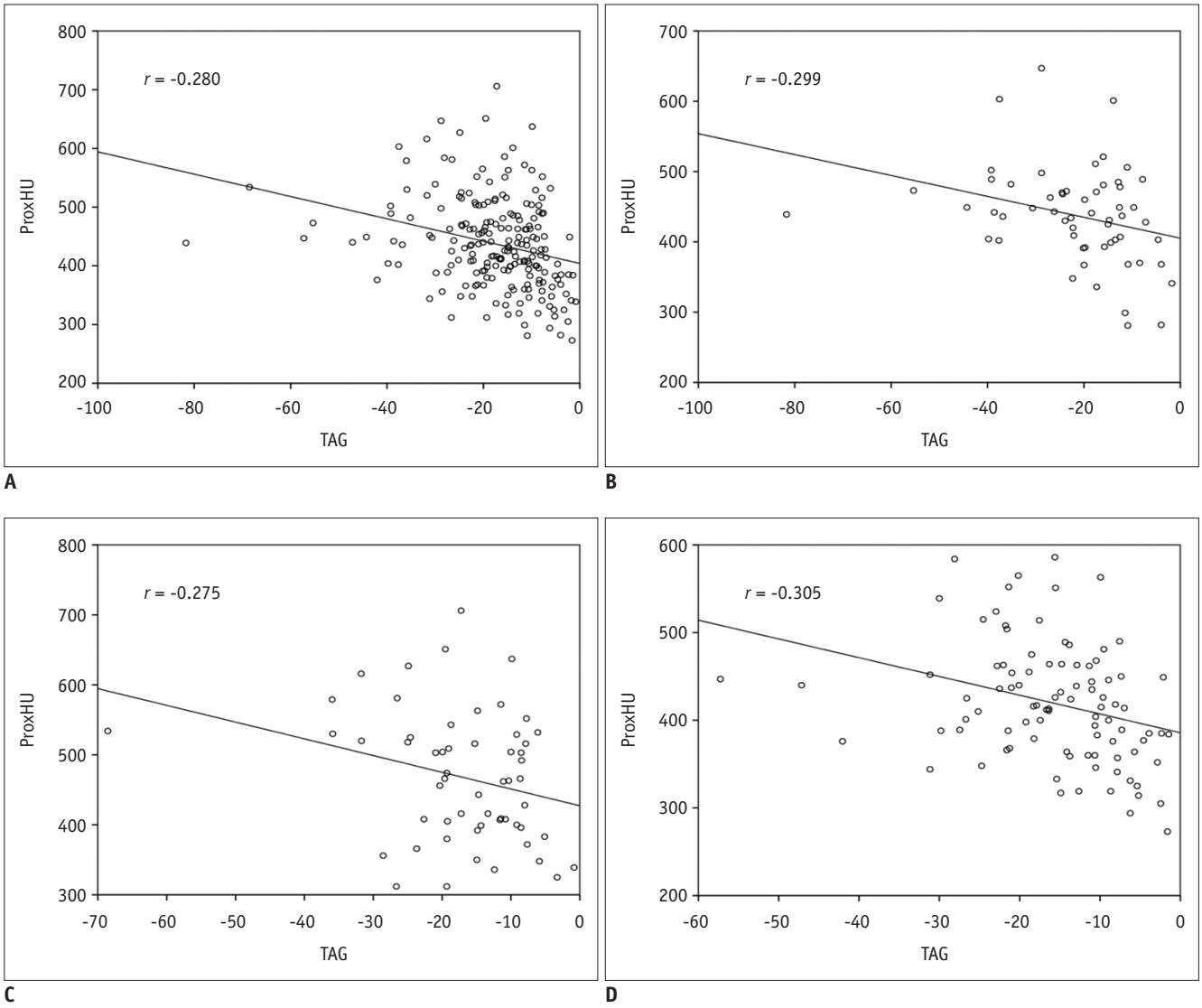


**Fig. 3. Correlation between TAG and contrast enhancement (proxHU) of coronary arteries (A, overall; B, $CT_{pre}$; C, $CT_{iv}$; D, $CT_{sub}$).**
ProxHU showed weak negative correlation with TAG ($r$ = -0.280, $p$ < 0.001). This trend was observed regardless of CT acquisition method **(B-D)**.


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value using a 256-slice CCTA by itself when assessing the hemodynamic condition of a coronary stenosis. Kato et al. (18) also argued that TAG has limited availability because it reflects the coronary blood flow in the resting state. On the other hand, according to the study by Fujimoto et al. (14), the interpretation of TAG may benefit from the incorporation of information to detect hemodynamically significant coronary artery disease.

The aims of most published studies were to investigate the incremental diagnostic value of TAG- over CCTA-derived diameter stenosis alone for the identification of ischemia in different patients (4-6, 14, 18). Park et al. (11) investigated the effect of coronary artery diameter on TAG, and correlation between TAG and the diameter gradient in phantoms, dogs, and patients with clinical study. However, many factors may influence the delivery of contrast media to distal branches on CT in addition to the luminal diameter of vessels. In the present study, we investigated the effects of vasodilators (may include both the diameter and flow) on TAG in the same individuals with isotemporal acquisition. To the best of our knowledge, the effects of vasodilators have not been previously reported.

In our results, the mean TAG of each three major coronary arteries showed significant differences regardless of acquisition method (with or without vasodilator) on CCTA ($p < 0.05$). Park et al. (11) demonstrated that the TAG value is largely influenced by the diameter of coronary artery, and TAG decreased with decreasing vessel diameter. In our study, the TAG value was larger in the order of RCA, LAD, and LCX in patients who showed right-sided coronary dominance. We speculated that these results may be influenced by the diameter and length of coronary arteries, and thus our results were consistent with those published by Park et al. (11).

In our study, we confirmed the increased of TAG value in all three major coronary arteries with the administration of a vasodilator, regardless of type (both sublingual or IV infusion). Interestingly, there was a more significant increase in TAG in the LAD and LCX than in the RCA after administration of a vasodilator. The diameter changes in the proximal and distal portions of major coronary branches are usually more severe in the left side than in the right side (19). Steigner et al. (20) found that in normal coronary vessels, the contrast gradient over distance was significantly bigger in the left coronary system compared with the RCA. Because the RCA would be larger and longer, the change in vessel diameter over distance was thought to be smaller than that of the left coronary artery. Okada et al. (21) studied the influence of nitroglycerin on the coronary diameter, coronary luminal attenuation, and evaluable number of coronary segments on CCTA. They found that the use of sublingual nitroglycerin results in an increase in both the dimeter and luminal attenuation of coronary artery and reported that the vasodilating ratios of the small branches were larger than those of large vessels. However, the increased attenuation ratio was larger in the RCA than in the left coronary artery (21). Therefore, we speculate that vasodilators increase the diameter of coronary arteries, but other coexisting factors may influence contrast luminal attenuation, which may result in different effects on the TAG value in the three major coronary arteries. We also found higher values of ProxHU with IV nitrate-enhanced CT than non-nitrate-enhanced CT in the same patients. However, a significant difference was present in ProxHU with and without vasodilators only in LCX but not in others in our study. It was a relatively fragmented measurement of contrast enhancement compared to the TAG value.

There was no significant difference according to the method of nitrate administration. All forms of nitro vasodilators release nitric oxide in vascular smooth muscle cells, and they predominantly dilate large- and medium-sized coronary arteries and arterioles > 100 μm in diameter and decreases coronary vascular resistance in coronary circulation (22). The nitrate also has beneficial effects on coronary endothelial dysfunction and regional coronary blood flows via collateral and distal vessel vasodilation (22, 23). Although the effects and mechanisms are known to be nearly identical, intravenous-type nitrates tend to be used for patients hospitalized for hypertensive urgency and emergency, and they have faster onset and shorter duration of action compared with sublingual-type nitrates (24). We did not observe differences between $CT_{iv}$ and $CT_{sub}$ groups, which may be due to the lack of subjects in our study or little difference in the actual effects on the coronary vessels between them.

Regarding the relationship of TAG and proxHU, we found a weak negative correlation between TAG and ProxHU in all major coronary arteries before and after vasodilator administration. However, when comparing the $CT_{pre}$ and $CT_{iv}$ in the dual acquisition group, both TAG and ProxHU tended to increase with the use of a vasodilator CCTA, which showed discordant results in the correlational statistical analysis. We speculated that various factors are reflected in the TAG value, and we considered that ProxHU plays a role in only a small portion of them. This indicated that the TAG

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value was a relatively more comprehensive and consistent index than other simple numerical values, such as vessel density or diameter, and thus further research is needed.

Some limitations of this study deserve some consideration. First, this was single-center study, and the number of subjects was small. Second, IV-type vasodilators were compared in the same patient, whereas it was compared between different subjects in the control group. Therefore, many possible factors may affect the contrast bolus geometry, as seen in results of the statistical analysis. Due to ethical considerations, a patient cannot undergo two CCTA examinations after being administered with two types of vasodilators. However, there were no significant differences between the control and case groups in terms of age, sex, or body habitus. Moreover, all enrolled subjects showed a normal range of cardiac functions on echocardiography (ejection fraction, chamber size, wall motion, etc.), which were performed in a relatively short interval of time (within 3 months) from CCTA. Third, there was no consideration of severe stenosis of the coronary artery (> 50%) or other coronary disease in this study, and the vasodilator may have had different effects on these lesions. Some previous studies have shown that nitrates increase the coronary flow, particularly in the non-stenotic segment, and have a lesser effect on stenotic segments that an impaired vasodilator response (25, 26). We speculated that nitrates could enhance the detection of obstructive lesions by not only increasing the luminal diameter but also exaggerating the difference in TAG.

In conclusion, TAG in CCTA is significantly affected by vasodilators. Both TAG and ProxHU of coronary arteries tend to increase with vasodilators in coronary CT. The clinical utility of these results will rely on potential differences in TAG depending on the scanning protocol (with/without vasodilator) or patients' compliance with the vasodilator during the acquisition of CCTA.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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