

Clinical Significance of Transluminal Attenuation Gradient in 320-row Area Detector Coronary CT Angiography

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Short title: No increment clinical value of TAG in 320-ADCT

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Abstract

Background: The clinical significance of the transluminal attenuation gradient (TAG) has not been established. We evaluated the incremental diagnostic value of TAG by 320-detector row computed tomography (320-ADCT).

Methods and Results: Subjects were 65 patients who underwent one-rotation scanning by 320-ADCT and invasive coronary angiography (ICA) within 3 months. TAG values were obtained for the major epicardial vessels 2 mm or more each in RCA, LAD and LCX using automatic analysis software. Moreover, TAG values that excluded calcified lesions in calculation of the regression line were also evaluated (excluded-TAG). In LAD, 21 intermediate lesions underwent functional flow reserve (FFR), and the incremental diagnostic value for functional stenosis was evaluated. The TAG values in the normal vessels were -8.3 ± 5.0 (HU/cm) for the RCA (n=32), -23.3 ± 4.3 for the LAD (n=9) and -20.6 ± 10.0 for the LCX (n=32). The RCA value was significantly higher ($p < 0.001$). The TAG values with stenosis degrees of $\leq 25\%$, 26–75%, $\geq 76\%$ on ICA were -8.3 ± 5.0 (n=32) vs -10.3 ± 7.2 (n=25) vs -10.0 ± 5.4 (n=4) in the RCA, -23.3 ± 4.3 (n=9) vs -21.0 ± 11.5 (n=35) vs -23.5 ± 15.3 (n=10) in the LAD and -21.1 ± 15.1 (n=32) vs -21.1 ± 15.1 (n=16) vs -17.7 ± 15.7 (n=6) in the LCX, with no significant difference among the three groups. The excluded-TAG values also showed no significant

difference. The area under the curve in the diagnosis of $FFR < 0.8$ in 21 LAD cases was 0.542 for CT only, 0.694 for CT+TAG, and 0.694 for CT+excluded-TAG.

Conclusions: In single time phase scanning by 320-ADCT, TAG does not offer an incremental diagnostic value.

Key words: 320-detector row coronary computed tomography angiography;
transluminal attenuation gradient; fractional flow reserve

Introduction

The usefulness of measuring the transluminal attenuation gradient (TAG) in conventional coronary CT angiography (CCTA) was previously reported [1], and diagnosis of significant coronary artery disease has since improved in some studies [2] [3]. However, negative results were obtained in other studies [4], and no consistent viewpoint has been reached with regard to its usefulness. In TAG, the reduction of contrast opacification by cross-sectional images along the coronary artery is measured, and it is defined as a linear regression of luminal opacification with distance from the vessel ostium. However, conventional CCTA images are constructed over several heartbeats, and the influence of this on TAG measurement has been of concern.

With 320-row area detector computed tomography (320-ADCT), a maximum of 16 cm coverage in the body axis direction became possible, allowing imaging of the entire heart by conventional scanning with a single rotation. Subsequently, TAG measurement at a single point became possible, and the variation in patient parameters was small in a preliminary study [1]. However, there are only limited reports on its usefulness in actual clinical practice [5] [6].

Automatic analysis software for TAG has recently been developed. Its accuracy and reproducibility are high, and a reduction of the analysis time by 68% compared to

conventional manual measurement has been reported [7].

In this study, using automatic analysis software, the diagnostic performance of TAG using 320-ADCT for degree of stenosis and functional stenosis evaluation with fractional flow reserve (FFR) was compared.

Methods

Study Population

This was a retrospective single-center study. The institutional human research committees of our institution approved the corresponding study components. Anonymous use of the test data for the study was orally explained to all subjects, and written consent was obtained. The subjects were 65 consecutive patients suspected of having coronary artery disease during a period from 1 October 2014 through 30 April 2016, and who underwent one-rotation scanning by 320-ADCT and invasive coronary angiography (ICA) within three months. Patients who had previously undergone revascularization (PCI and/or CABG) and patients with poor image quality were excluded.

CCTA protocol

Patients with a pre-scan heart rate ≥ 60 beats per minute were given 20 to 40 mg of metoprolol orally and, if the heart rate remained ≥ 61 beats per minute after 1 hour, they were given an intravenous injection of landiolol (0.125 mg/kg). Patients in whom beta-blockers were contraindicated (due to severe aortic stenosis, systolic blood pressure < 90 mm Hg, bronchial asthma, symptomatic heart failure, or advanced atrioventricular block) did not receive these treatments. The following devices were used: Aquilion ONE ViSION Edition™ (320-ADCT, Toshiba Medical Systems Corporation, Otawara, Japan), Dual Shot GX 7 (contrast injector, Nemoto Kyorindo Co., Ltd., Tokyo, Japan), Model 7800 ECG monitor (Chronos Medical Devices Inc., Tokyo, Japan), and Ziostation image analyzer (Zio M900, Ziosoft Inc., Tokyo, Japan). Scanning was performed at a tube voltage of 100 kV except in patients whose body mass index exceeded 30 kg/m^2 , who were scanned at 120 kV. The mean tube current was calculated with automatic exposure control for a standard deviation (SD) of 20. With a slice width of 0.5 mm and reconstruction interval of 0.25 mm, the minimum number of rows necessary to include all coronary arteries was selected from 200 rows (100 mm), 240 rows (120 mm), 256 rows (128 mm), 280 rows (140 mm), and 320 rows (160 mm) in reference to unenhanced CT performed when determining the calcium score. Prospective CTA mode was used for all patients, with a range of X-ray exposure of 75%

of the RR interval. The contrast agent iohexol (Omnipaque 350 mg I/ml; Daiichi Sankyo Company, Tokyo, Japan) was injected for 12 sec at 18 mg I/kg/s, followed by injection of 30 mL of saline at the same rate as contrast agent injection. Intermittent prep scanning with bolus tracking at the four-chamber-view level was performed once every 0.5 sec beginning 10 sec after the start of contrast agent injection. Scanning was started when the contrast agent reached to 300 HU at the ascending aorta. Adaptive iterative dose reduction using three-dimensional processing (AIDR3D) was used for all patients, with intensity at the standard setting.

CCTA interpretation

For plaque detection, both cross-sectional and longitudinal curved multiplanar reformation images were analyzed. Coronary artery segments with a diameter ≥ 2 mm were evaluated for the degree of stenosis. The percent ratio of the stenotic lumen to the normal vessel diameter proximal or distal to the stenosis was obtained, and the percent degree of stenosis was determined. From still images taken from multiple projections, measurements were made in the angle showing the narrowest degree of stenosis. The degree of stenosis was evaluated by consensus of two experienced cardiologists who were unaware of the clinical data. Lesions with $>50\%$ stenosis were defined as

significant. If lesion stenosis were not assessable due to calcification, lesions were defined as significant.

ICA and FFR Techniques

ICA and FFR were performed according to standard clinical practice. Percent stenosis was calculated for the most significant lesion in each vessel in the angle showing the narrowest degree of stenosis. FFR was performed at the discretion of the operator. Pressure measurements were performed using a 0.014-inch pressure guide wire (Verrata Pressure Guide Wire, Volcano Corp., San Diego, CA or PressureWire Certus, St. Jude Medical Systems, Upssala, Sweden). The pressure wire was calibrated and equalized with aortic pressure. FFR was calculated at steady-state hyperemia after intracoronary isosorbide dinitrate (0.5-1 mg) and intracoronary papaverine hydrochloride (left coronary: 12 mg, right coronary: 8 mg) or intravenous ATP (140 µg/kg/min) injection.

TAG measurements

TAG values were obtained for the major epicardial vessels having 2 mm or more each in RCA, LAD and LCX using automatic analysis software [7]. Where a calcified

lesion is present, when the CT value of the lumen is plotted for measurement of TAG, the CT value may be markedly different. Because of this, the analysis results of the TAG value may influence the regression line. Plotted values beyond the CT value of the concentration of the contrast medium among the values plotted by automatic analysis software were removed manually and the regression line was calculated. This was defined as excluded-TAG.

Chronic total occlusion lesions, LCX-dominant RCA, LAD and LCX which showed 50% or more stenosis in LMT were excluded from the analyses.

Statistical Analysis

Statistical analyses were performed using Statview J-5.0 for Windows (HULINKS Inc., Tokyo, Japan) and MedCalc Version 12.2.1. (Mariakerke, Belgium). Numerical data were expressed as the mean \pm standard deviation. One-factor ANOVA was employed for comparisons between groups to determine the statistical significance of differences. Groups were compared independently using Scheffé analysis. The incremental diagnostic prediction ability of TAG for functionally significant stenosis was calculated using receiver operating characteristic (ROC) analysis and the area under

the curve (AUC). Values at $p < 0.05$ were considered statistically in all instances.

Results

Patient characteristics

Patient characteristics are shown in Table 1.

Comparison of normal coronary TAG for 3 major coronary arteries

Vessels having lesions with $\leq 25\%$ stenosis were defined as normal coronary vessels.

The TAG values in the normal vessels were -8.3 ± 5.0 (HU/cm) for the RCA (n=32), -23.3 ± 4.3 for the LAD (N=9) and -20.6 ± 10.0 for the LCX (n=32). The value for RCA was significantly the highest ($p < 0.001$) (Figure 1).

Comparison of TAG base in stenosis degree for 3 major coronary arteries

The TAG values in three major coronary arteries with stenosis degrees of $\leq 25\%$, 26-75% and $\geq 76\%$ were -8.3 ± 5.0 (n=32) vs -10.3 ± 7.2 (n=25) vs -10.0 ± 5.4 (n=4) in the RCA (Figure 2A), -23.3 ± 4.3 (n=9) vs -21.0 ± 11.5 (n=35) vs -23.5 ± 15.3 (n=10) in LAD (Figure 2B), and -21.1 ± 15.1 (n=32) vs -21.1 ± 15.1 (n=16) vs -17.7 ± 15.7 (n=6) in LCX (Figure 2C). There were no significant differences among the three groups based on

stenosis degree. In excluded-TAG, the TAG values in the three groups were -8.1 ± 5.1 (n=32) vs -9.1 ± 5.4 (n=25) vs -9.0 ± 5.1 (n=4) in the RCA (Figure 3A), -21.9 ± 4.9 (n=9) vs -17.2 ± 7.9 (n=35) vs -16.3 ± 8.2 (n=10) in the LAD (Figure 3B), and -21.9 ± 8.6 (n=32) vs -21.6 ± 12.3 (n=16) vs -20.2 ± 9.7 (n=6) in the LCX (Figure 3C), which also showed no significant difference among the three groups.

Incremental diagnostic value of TAG in coronary artery with intermediate stenosis for functionally significant coronary artery stenosis

Incremental values of TAG for functionally significant coronary artery stenosis were evaluated in 21 LAD vessels with intermediate stenosis in which FFR was performed. Nine of the 21 vessels had a positive FFR < 0.8. The optimal cut off values of TAG and excluded-TAG calculated from AUC by ROC analysis were -19.5 and -19.5, respectively. The area under the curve in the diagnosis of FFR < 0.8 in 21 LAD cases was 0.542 (95% CI: 0.314-0.758) for CT only, 0.694 (0.458-0.874) for CT+TAG, and 0.694 (0.458-0.874) for CT+excluded-TAG. Neither TAG nor excluded-TAG offered an incremental diagnostic value for functionally significant stenosis lesions in comparison with conventional CT findings (p=0.3767) (Figure 4). Representative cases of TAG and excluded-TAG are presented in Figure 5.

Discussion

The usefulness of TAG analyzed by single rotation imaging using 320-ADCT was investigated, with the following three major findings. Firstly, in non-LCX-dominant patients, the TAG value in the RCA without stenosis was significantly higher than those in the LAD and LCX. Secondly, in coronary CT images of actual clinical cases, no significant differences in the TAG values due to differences in the degree of stenosis were noted in any coronary artery vessels. Thirdly, when invasive FFR was used as a reference to evaluate functional stenosis, TAG measurement in the coronary artery with moderate stenosis did not significantly increase the diagnostic value of stenosis evaluation compared with conventional coronary CT.

A significantly higher blood flow in the RCA than in the LAD and LCX in non-LCX-dominant patients has been reported [8]. TAG on 320-ADCT reflects the difference in contrast medium concentration between coronary segments in the same time phase, and this may be dependent on the coronary blood flow velocity. Assuming that the diameter of the main epicardial coronary artery does not normally change, TAG is mostly related to coronary blood flow. In addition, as for RCA, at the systolic phase, the constriction from RV is smaller than that from LV. Thus, the blood flow is different

from that at the left coronary artery and this may influence the TAG value. The TAG value was significantly higher in the normal RCA in this study, and this finding makes sense. However, differences among the coronary vessels were not considered in most previous reports [2-6]. We suggest that it is necessary to set a cut-off value for each coronary vessel to evaluate TAG.

Theoretically, TAG may reflect coronary blood flow at rest [9]. Constant resting coronary blood flow is usually maintained by adjusting vascular resistance in microcirculation until the condition reaches severe stenosis exceeding 75% [10], based on which we established three groups – a severe stenosis group in which blood flow may have decreased even at rest, a moderate stenosis group in which blood flow was not reduced but the reserve was reduced, and a mostly normal mild-normal stenosis group – and compared the TAG values among the groups, but no significant difference was noted in any coronary branch among the three groups even in the group with severe stenosis that is assumed to influence the TAG value. When CCTA is imaged in a condition of hyperemia and the TAG is measured, the result may be different. However, this cancels out the merit of the ability to measure the TAG by conventional CCTA. Single rotation imaging using 320-row coronary CT is capable of TAG analysis in a single time-phase, and the acquisition protocol was consistent in all cases because this

was a single-center study. Differences in coronary blood flow within a specific time-phase may reflect the contrast medium concentration gradient, but when reduction of blood flow is not marked, the contrast medium concentration may rapidly become homogeneous in the entire coronary artery by continuous contrast medium injection. Moreover, the timing of filling the coronary artery with contrast medium is influenced by the cardiac output and blood pressure in individual patients. Therefore, even when an identical acquisition protocol is used, it is very difficult to consistently acquire images in the time phase in which blood flow is reflected as the contrast medium concentration gradient assumed to be kept for a very short time in actual clinical practice. Moreover, although coronary blood flow is influenced by the heart rate, blood pressure, and ventricular mass size[11], no significant difference was noted in the heart rate or blood pressure among the three groups. The ventricular mass size could not be investigated in this study.

In addition, high X-ray absorbents, such as calcification and stents, may influence the TAG value. Stented patients were excluded from this study. We performed analysis excluding calcified regions in cases with calcification, but the results did not change, as previously reported [4]. The acquisition timing is also a very important factor of TAG analysis on single rotation imaging using 320-ADCT, and it is not practical to always

identify the acquisition timing and acquire images in consideration of TAG analysis in actual clinical practice.

We investigated whether or not TAG measurement increases the diagnostic value of moderate stenosis evaluation using conventional coronary CT and invasive FFR as a reference. It is possible that the cut-off value of TAG differed among the coronary vessels in this study. Thus, only cases in which invasive FFR was applied to the LAD were included. The addition of the TAG value tended to increase AUC compared with that on conventional CT alone, but no significant increase in the diagnostic value was noted. The major cause of this was that TAG reflects coronary blood flow at rest, as described above, and it may have no useful additional value for diagnosing moderate stenosis in which constant resting coronary blood flow may be maintained. In addition to TAG, the usefulness of perfusion CT [12] [13] and FFR-CT [14] [15] [16] as a functional stenosis evaluation method using coronary CT has recently been reported. Although TAG is the simplest method with which analysis can be performed within the conventional coronary CT acquisition range and short time among these, the fact that it is simple could be irrelevant as it did not offer an incremental diagnostic value in comparison with conventional CCTA. Recently, FFR-CT has markedly developed: analysis can be performed by conventional coronary imaging, and the analysis time is

shorter [17] [18]. It has also been reported that when invasive FFR was used as a reference, the diagnostic accuracy of FFR-CT was significantly higher than that of TAG [19] [20]. It was recently reported that the TAG-based contrast medium concentration gradient is a secondary result due to differences in coronary diameter [21]. Further study may be necessary with regard to the clinical significance of TAG measurement.

Limitation

There were some limitations in the present study. Firstly, this was a single-center retrospective study and the patient number was small. Especially, the incremental diagnostic value for functional stenosis diagnosis was evaluated in only 21 vessels. Since no usefulness of TAG was noted using the specified acquisition protocol at a single institution, further study on the use of TAG in actual clinical practice may be necessary. Secondly, the intra and inter reproducibility of TAG measurement was not determined. However, automatic analysis software was used for measurement, and its reproducibility has been reported [7]. Thirdly, we consider it important to investigate the clinical significance of TAG in real world protocols having favorable CCTA imaging as a major purpose. If a major purpose of the imaging is the evaluation of TAG, a shorter contrast bolus could be advantageous, but if this influences CCTA images, it could be counterproductive. However, we did not investigate the usefulness of TAG with

different protocols.

Conflict of interest

Dr. Daida has received speakers' Bureau/Honoraria from Astellas Pharma Inc., AstraZeneca K.K., MSD.K.K., Kyowa Hakko Kirin Company, Ltd., Kowa Pharmaceutical Company, Ltd., Daiichi-Sankyo Company, Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corp., Bayer Yakuhin, Ltd., as well as research funds from Kyowa Hakko Kirin Company Ltd., Philips Electronics Japan, Ltd. Astellas Pharma Inc., ABBOTT JAPAN CO., Ltd., Sanofi K.K., Eisai Co., Ltd., Shionogi & Co., Ltd., Daiichi-Sankyo Company, Ltd., Dainippon Sumitomo Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Bayer Yakuhin, Ltd., Pfizer Co., Ltd., Philips Electronics Japan, Ltd., FUJIFILM Corporation, Bristol-Myers Squibb Company, Boston Scientific Japan K.K., SANWA KAGAKU KENKYUSHO Co., Ltd., MSD.K.K.. and Toshiba Medical Systems that are unrelated to this project. All other authors have no potential conflict of interest.

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Table

Table 1. Plaque characteristics of all study patients

CAD: coronary artery disease, CCTA: coronary CT angiography, ICA: invasive

coronary angiography, DS: diameter stenosis

Figure legends

Figure 1. Comparison of normal coronary TAG for 3 major coronary arteries

TAG: transluminal attenuation gradient.

Figure 2. Comparison of TAG base on stenosis degree for RCA (A), LAD (B) and LCX.

(C)

TAG: transluminal attenuation gradient

Figure 3. Comparison of excluded-TAG base on stenosis degree for RCA (A), LAD (B) and LCX (C).

TAG: transluminal attenuation gradient

Figure 4. Incremental diagnostic value of TAG and excluded-TAG in coronary artery with intermediate stenosis compared to conventional CT findings for functionally significant coronary artery stenosis.

TAG: transluminal attenuation gradient

Figure 5. Representative case of TAG and excluded-TAG in LAD lesion performed with FFR.

CCTA revealed an intermediate stenotic lesion with calcification in LAD (A). Invasive coronary angiography confirmed the findings on CCTA (B) and invasive FFR was 0.70 (C). TAG (D) and excluded-TAG (E) were -13.46 and -7.52, respectively.

TAG: transluminal attenuation gradient, FFR: fractional flow reserve, CCTA: coronary CT angiography