Noninvasive Evaluation of Coronary Collateral Arterial Flow by Coronary Computed Tomographic Angiography

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Background—Coronary collateral flow is an alternative source of myocardial perfusion in patients with totally occluded coronary arteries. Clinical evaluation of collateral flow has been limited by the need of invasive measurements. We investigated whether noninvasive coronary computed tomographic angiography can evaluate the angiographic extent of coronary collateral flow.

Methods and Results—We enrolled 325 coronary computed tomographic angiography cases with angiographically confirmed chronic total occlusion (median age, 63 years; men 83%). Transluminal attenuation gradient (TAG), which reflects the kinetics of contrast media in coronary artery, of an entire artery as well as of a distal vessel was assessed to evaluate the flow in entire vessel and distal vessel. TAGs were validated against visually assessed angiographic collateral connection and Rentrop grading. TAG of an entire artery increased consistently according to the angiographic extent of collateral flow (P<0.001). Well-developed collaterals, defined by highest collateral connection and Rentrop grades (n=103), could be predicted by TAG of an entire artery (cutoff, ≥7.6 Hounsfield units/10 mm; c-statistics, 0.72; sensitivity, 65%; specificity, 73%; positive predictive value, 52%; negative predictive value, 82%). TAG of a distal vessel could discriminate the antegrade (n=143) and retrograde (n=182) flows in distal artery (cutoff, 0.0 Hounsfield unit/10 mm; c-statistics, 0.88; sensitivity, 78%; specificity, 85%; positive predictive value, 87%; negative predictive value, 75%).


Key Words: collateral circulation ▪ coronary artery disease ▪ multidetector computed tomography
subsequent diagnostic coronary angiography <8 weeks (median, 14 days). Angiographic definition of chronic total occlusion (CTO) was used: complete absence of luminal continuity in major epicardial coronary artery accompanied by interruption of antegrade flow or minimal contrast penetration through the lesion without distal vessel opacification. Patients with recent myocardial infarction <90 days, uncompensated heart failure, and left main disease were not included. Patients with angiographic subtotal occlusion (antegrade Thrombolysis in Myocardial Infarction grade 2 flow, 99% stenosis), previous history of bypass surgery, or CTO in a small branch were excluded to establish the effect of collateral flow on the artery distal to total occlusion. Coronary CT angiography was performed using 64-slice (n=174) or 128-slice (n=184) CT scanner. Among 128-slice scanner cases, 33 cases acquired by ultrafast spiral flash were excluded to avoid bias related to axial scan time. Finally, 325 patients were enrolled into analysis (Figure 1). The institutional review board committee approved the study protocol.

**Coronary CT Angiography**

A 64-slice (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan) or 128-slice scanner (SOMATOM Definition Flash; Siemens Medical Solution, Forchheim, Germany) was used. Oral metoprolol was administered to patients with a heart rate ≥65 beats per minute. Sublingual nitroglycerin (0.6 mg) was administered before image acquisition. A bolus of 80 mL of nonionic contrast medium (Iomeron, 400 mg iodine/mL; Bracco, Milan, Italy) was injected intravenously at a flow rate of 4 mL/s followed by an injection of 30 mL of 30:70 contrast medium–saline mixture and an injection of saline 30 mL. Scan was initiated by an automated bolus tracking system with a delay of 14 seconds after attaining a measured threshold of 100 Hounsfield units (HU) in the ascending aorta.

The scan mode of 64-slice multidetector spiral computed tomography was retrospective-gated helical mode without the use of ECG pulsing. Scan parameters were tube voltage, 120 kV; tube current, 400 mA; gantry rotation time, 350 ms; pitch, 0.22 to 0.25; and detector collimation, 64×0.5 mm. Volume image data set was reconstructed by 0.5-mm slices. For 128-slice scanner, retrospective ECG-gated helical technique was used with the full radiation dose window set at 68% to 78% of the R-R interval in patients with heart rate <65 beats per minute, and 200 to 400 ms after the R peak in patients with a higher heart rate. Scan parameters were tube voltage, 120 kV; tube current, 400 mA; gantry rotation time, 280 ms; pitch, 0.22 to 0.24; and detector collimation 2×64×0.6 mm resulting in 2×128×0.6-mm sections by means of the z axis flying focal spot technique. Image data set was reconstructed by 0.6-mm slices. The axial scan time was

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**Figure 1.** Patients with ≥1 total occlusion in major coronary artery by clinically indicated coronary computed tomographic (CT) angiography were validated by subsequent diagnostic coronary angiography <8 wk. Patients with angiographic subtotal occlusion or inadequate images were excluded. A total of 33 cases acquired by ultrafast spiral flash 128-slice CT scanner was excluded to avoid bias related to axial scan time between 64- and 128-slice CT scanners. CTO indicates chronic total occlusion; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.
6 to 8 seconds in both 64- and 128-slice scanners. Cardiovascular radiologists interpreted the images on a dedicated workstation (iNtuition; Terarecon, Foster City, CA).

Transluminal Attenuation Gradient
TAG was assessed as described previously.17–19 In brief, cross-sectional images perpendicular to the vessel centerline were reconstructed for each major coronary artery. Luminal cross-sectional area (in mm²) and radiological attenuation (in HU) were measured at 5-mm intervals from the ostium (TAG of an entire artery, TAGall) or just distal to CTO segment (TAG of a distal vessel, TAGdistal) where the vessel cross-sectional area fell <2.0 mm². TAGall and TAGdistal were devised to reflect the flow in the whole vessel and flow in distal vessel, respectively. The contour of the region of interest and the vessel centerline were manually corrected if necessary. TAG was defined as the linear regression coefficient between measured intraluminal radiological attenuation (in HU) and vessel length (per 10 mm; Figure 2).

Coronary Angiography
Coronary angiography was performed using standard techniques with the use of intracoronary nitroglycerin. Collateral flow was assessed by 2 experienced interventional cardiologists blinded to other imaging data. In case of disagreement, a third cardiologist was invited to reach an agreement. The diameter and angiographic flow of collateral vessels were semiquantitatively assessed using the collateral connection grade (0=no continuous connection; 1=continuous thread-like connection; 2=continuous and small branch-like connection) and the Rentrop grade (0=no visible filling of collaterals; 1=filling of side branches; 2=partial filling of epicardial segment; 3=complete filling of epicardial segment).22,23 Well-developed collateral was defined by collaterals having both collateral connection grade 2 and Rentrop

Figure 2. The concept of transluminal attenuation gradient (TAG) for the evaluation of coronary artery flow. Arrows indicate the extent and direction of flow. A to D, Coronary arteries with stenosis but without total occlusion. TAG of an entire artery (TAGall) decreases according to the severity of coronary artery stenosis. E to H, Coronary arteries with total occlusion. TAGall reflects the whole coronary artery flow and converges to 0 according to the functional extent of collateral flow. TAG of a distal vessel (TAGdistal) reflects both the function and direction of distal artery flow. TAGdistal has positive or negative value according to the direction of collateral flow. The absolute value of TAGdistal is higher in poorly developed collateral than in well-developed collateral.
grade 3. The direction of collateral flow in distal artery was visually determined by the most predominating flow.

Statistical Analysis
Analysis was performed on a per-patient basis unless indicated otherwise. Continuous variables are compared between groups using Mann–Whitney U or Kruskal–Wallis test. Relationships between continuous variables among ordinal groups were tested by Jonckheere–Terpstra test for trend. Optimal cutoff of variables was estimated by Youden J statistics. The predictive performance of variables was calculated and compared with each other by receiver operating characteristics analysis and DeLong method. The inter-rater agreement and reproducibility of TAG and collateral grading were validated in 21 randomly selected vessels using Bland–Altman analysis and Cohen weighted κ. R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) was used. A 2-tailed P <0.05 was considered statistically significant.

Results
Patients
The median age of study population was 63 years, and 83% of patients were men. The majority of patients had stable angina or silent ischemia (91%) and also had multivessel disease (70%). Two-dimensional echocardiography was performed in 318 patients (98%). Regional wall abnormality was found in 188 patients (58%), but most patients showed preserved left ventricular systolic function (Table 1).

Reproducibility and Agreement of Measurements
By Bland–Altman analysis, the intrarater and inter-rater limits of agreement of TAG were 0.5 HU/10 mm (95% confidence interval [CI], −0.2 to 1.3) and −0.2 HU/10 mm (95% CI, −1.1 to 0.8). Weighted κ for intrarater and inter-rater variability was 0.83 (95% CI, 0.65–1.00) and 0.78 (95% CI, 0.58–0.98) for Rentrop grade; 0.79 (95% CI, 0.60–0.98) and 0.79 (95% CI, 0.59–0.98) for collateral connection grade; and 0.82 (95% CI, 0.58–1.00) and 0.91 (95% CI, 0.74–1.00) for direction of collaterals.

Assessment of the Functional Extent and Direction of Collateral Flow by Invasive Coronary Angiography
Half of the total occlusion was found in right coronary artery (n=157; 48%). The directions of flow in distal artery were antegrade in 178 vessels (44%) and retrograde in 228 vessels (56%). Well-developed collateral was found in 103 vessels (32%) and showed mostly retrograde flow in distal artery (n=75; 73%; Table 2).

Assessment of the Functional Extent of Collateral Flow by TAG
Representative cases are shown in Figure 3A to 3D. TAG all increased consistently according to the angiographic Rentrop

Table 1. Clinical Characteristics
<table>
<thead>
<tr>
<th>Clinical factors</th>
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<tr>
<td>Age</td>
<td>63 (55–69)</td>
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<tr>
<td>Male sex</td>
<td>270 (83)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>24.8 (23.2–26.6)</td>
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<tr>
<td>Hypertension</td>
<td>213 (66)</td>
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<td>Diabetes mellitus</td>
<td>129 (40)</td>
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<td>Smoking</td>
<td>126 (39)</td>
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<tr>
<td>Stroke</td>
<td>23 (7)</td>
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<td>Coronary artery disease</td>
<td></td>
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<tr>
<td>Stable angina</td>
<td>245 (75)</td>
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<tr>
<td>Silent ischemia</td>
<td>49 (15)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>31 (1)</td>
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<tr>
<td>1-vessel disease</td>
<td>99 (31)</td>
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<tr>
<td>2-vessel disease</td>
<td>105 (32)</td>
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<tr>
<td>3-vessel disease</td>
<td>121 (37)</td>
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<tr>
<td>Laboratory tests</td>
<td></td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>14.0 (13.0–15.0)</td>
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<tr>
<td>Creatinine, g/dL</td>
<td>1.0 (0.9–1.1)</td>
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<tr>
<td>Electrocardiography*</td>
<td></td>
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<tr>
<td>Sinus rhythm</td>
<td>323 (99)</td>
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<tr>
<td>Junctional or paced rhythm</td>
<td>2 (0)</td>
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<tr>
<td>Q wave</td>
<td>83 (26)</td>
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<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>Left ventricular ejection fraction, %</td>
<td>60 (52–64)</td>
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<tr>
<td>Left ventricular ejection fraction, &lt;40%</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Regional wall motion abnormality</td>
<td>188 (58)</td>
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*Left bundle branch block was found in 1 patient. Anterior and inferior Q waves were found in 31 and 52 patients, respectively.

Table 2. Angiographic Assessment of Collateral Flow
<table>
<thead>
<tr>
<th>Location of occlusive lesion*</th>
<th>LAD</th>
<th>LCX</th>
<th>RCA</th>
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<tr>
<td></td>
<td>110 (34)</td>
<td>58 (18)</td>
<td>157 (48)</td>
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<tr>
<td>Collateral flow</td>
<td></td>
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<tr>
<td>Direction of flow in distal coronary artery</td>
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<td></td>
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<tr>
<td>Antegrade</td>
<td>143 (44)</td>
<td></td>
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<tr>
<td>Retrograde</td>
<td>182 (56)</td>
<td></td>
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<td>Rentrop grade classification</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>68 (21)</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>136 (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>121 (37)</td>
<td></td>
<td></td>
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<tr>
<td>Collateral connection grade</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>49 (15)</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>134 (41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>142 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-developed collateral†</td>
<td>103 (32)</td>
<td></td>
<td></td>
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</tbody>
</table>

*Left anterior descending coronary artery; LCX, left circumflex artery; and RCA, right coronary artery.
†Well-developed collateral is defined by collaterals showing both Rentrop grade 3 and collateral connection grade 2. Most of vessels with well-developed collaterals showed retrograde flow in distal artery (73%).
Figure 3. Representative cases of noninvasive collateral flow evaluation. Curved or straight multiplanar reconstruction of coronary computed tomographic (CT) angiography, invasive coronary angiography (CAG), and the results of transluminal attenuation gradient (TAG) are shown. Red dotted line indicates direction of collateral flow; white dotted line, chronic total occlusion (CTO) segment; yellow arrowhead, vessel distal to CTO; pink arrowhead, collateral vessels; green graph, intraluminal attenuation; blue arrow, TAG of an entire artery; and pink arrow, TAG of a distal vessel. Movies of CAG and CT showing collateral vessels are available in the Data Supplement. A, CTO at mid left anterior descending coronary artery (LAD) and septal collateral with Rentrop grade 2, collateral connection grade 1 antegrade flow (see Movies I–III in the Data Supplement). B, CTO at mid LAD and right ventricular (RV) branch collateral with Rentrop grade 2, collateral connection grade 1 retrograde flow (see Movies IV–VI in the Data Supplement). C, CTO at proximal LAD and collateral between posterolateral (PL) branch and diagonal branch with Rentrop grade 3, collateral connection grade 2 antegrade flow (see Movies VII–IX in the Data Supplement). D, CTO at proximal right coronary artery (RCA) and apical collateral with Rentrop grade 3, collateral connection grade 2 retrograde flow (see Movies X–XII in the Data Supplement). PDA indicates posterior descending; and HU, Hounsfield unit.
grade or collateral connection grade \( (P < 0.001 \) by Kruskal–Wallis and Jonckheere–Terpstra test; all; Figure 4A and 4B). TAG\textsubscript{all} showed moderate predictive performance for well-developed collateral: optimal cutoff, \( > -7.6 \) HU/10 mm; sensitivity, 65.1\% (95\% CI, 55.0–74.2\%); specificity, 73.2\% (95\% CI, 66.1–78.3\%); positive predictive value, 52.3\% (95\% CI, 43.3–61.2\%); negative predictive value, 81.7\% (95\% CI, 75.6–86.9\%); and \( c \)-statistics, 0.720 (95\% CI, 0.667–0.768; Figure 4C).

Assessment of the Direction of Flow in Distal Artery by TAG

Vessels with retrograde flow in distal artery showed significantly higher TAG\textsubscript{distal} compared with vessels with antegrade flow in distal artery \( (P < 0.001 \) by Mann–Whitney test; Figure 5A). TAG\textsubscript{distal} showed fair predictive performance for retrograde flow in distal artery: optimal cutoff, \( > 0.0 \) HU/10 mm; sensitivity, 77.5\% (95\% CI, 70.7–83.3\%); specificity, 85.3\% (95\% CI, 78.4–90.7\%); positive predictive value, 87.0\% (95\% CI, 80.9–91.8\%); and \( c \)-statistics, 0.875 (95\% CI, 0.834–0.909).

Figure 4. Box and whisker plots show median and interquartile (IQR) ranges as boxes and 1.5 IQR of lower or upper quartile as whiskers. C0 to C2 indicates collateral connection grades 0 to 2; and R1 to R3, Rentrop grades 1 to 3. A and B, Transluminal attenuation gradient of an entire artery \( \text{TAG}_\text{all} \) increased consistently according to the angiographic Rentrop grade or collateral connection grade \( (P < 0.001 \) by Kruskal–Wallis and Jonckheere–Terpstra test; all). C, Predictive performance of \( \text{TAG}_\text{all} \) cutoff \( > -7.6 \) Hounsfield units (HU)/10 mm was sensitivity 65.1\% (95\% confidence interval [CI], 55.0–74.2\%); specificity 72.5\% (95\% CI, 66.1–78.3\%); positive predictive value 52.3\% (95\% CI, 43.3–61.2\%); negative predictive value 81.7\% (95\% CI, 75.6–86.9\%); and \( c \)-statistics 0.720 (95\% CI, 0.667–0.768).

Figure 5. A, Vessels with retrograde flow in distal artery show significantly higher transluminal attenuation gradient of a distal vessel \( \text{TAG}_\text{distal} \) compared with vessels with antegrade flow in distal artery \( (P < 0.001 \) by Mann–Whitney test). B, Predictive performance of \( \text{TAG}_\text{distal} \) cutoff \( > 0.0 \) Hounsfield unit (HU)/10 mm was sensitivity 77.5\% (95\% confidence interval [CI], 70.7–83.3\%); specificity 85.3\% (95\% CI, 78.4–90.7\%); positive predictive value 87.0\% (95\% CI, 80.9–91.8\%); and \( c \)-statistics, 0.875 (95\% CI, 0.834–0.909).
The results of TAG all and TAG distal in relation to the functional extent of collateral flow were different according to the direction of flow in distal artery. TAG all increased consistently according to the Rentrop grade or collateral connection grade irrespective of the direction of collateral flow. TAG distal of vessels with antegrade flow in distal artery was mostly negative in value and also increased according to the Rentrop grade or collateral connection grade (P<0.05 by Kruskal–Wallis; Figure 6A–6D). However, TAG distal of vessels with retrograde flow in distal artery was mostly positive in value and showed a tendency of decrease according to Rentrop grade or collateral connection grade (P>0.05 by Jonckheere–Terpstra; Figure 6E–6H).

Figure 6. A to D, Transluminal attenuation gradient of an entire artery, which reflects the functional extent of collateral flow, increased consistently according to the Rentrop grade or collateral connection grade in both antegrade and retrograde flow subgroups (P<0.01 by Kruskal–Wallis and Jonckheere–Terpstra test; all). JT indicates Jonckheere–Terpstra test; and KW, Kruskal–Wallis test. E to H, TAG of a distal vessel (TAG distal), which reflects the direction of flow in distal vessel, was negative or positive in vessels with antegrade or retrograde flow, respectively. TAG distal converged to 0 according to the Rentrop grade or collateral connection grade (P<0.05 by KW; all; P<0.05 by JT in E and F). HU indicates Hounsfield unit.

80.9–91.8%); negative predictive value, 74.8% (95% CI, 67.4–81.3%); c-statistics, 0.875 (95% CI, 0.834–0.909; Figure 5B).
Discussion

Our study is the first of its kind to evaluate coronary collateral circulation by coronary CT angiography. Intracoronary attenuation-based analyses of CT enabled noninvasive functional assessment of coronary collateral flow and discrimination of the flow direction. Angiographically well-developed collateral vessels could also be predicted reasonably.

Well-developed collaterals are protective from myocardial ischemia, mitigate myocardial infarct, and improve survival.4-9 The presence of well-developed collaterals resulted in 36% reduced long-term mortality risk compared with poorly developed collaterals.24 Therefore, the evaluation of collateral flow would be important for long-term risk stratification in patients with total occlusion. Coronary CT angiography has been established for stenosis and functional imaging and showed high prognostic value for the prediction of future cardiovascular events.17-19,25-27 However, coronary CT angiography has not provided evaluation of collaterals mostly because of the limited spatial and temporal resolution.3 TAG can be measured in conventional 64-slice or higher CT scanners without additional radiation exposure, modification of CT acquisition protocols, or any sophisticated computational process.17-20 Therefore, TAG may extend the capability of coronary CT angiography into the evaluation of collateral flow and may improve the prognostic value of coronary CT angiography. The potential benefits of noninvasive collateral imaging now seem warranted.

Despite the improved procedural success and long-term vessel patency enabled by novel techniques and drug-eluting stents, CTO still remains a major challenge in current percutaneous coronary interventions, and the benefits of CTO revascularization are also in debate.20,21 Considering the potential procedural complications and nonnegligible radiation dose that may be offset by an intrinsically protective role of well-developed collateral vessels, selective revascularization of CTOs subtending a large amount of viable myocardium or those having collateral circulation insufficient to prevent ischemia may be a reasonable approach. Additional evaluation of collateral flow by TAG to the standard interpretation of coronary CT angiography may refine the evaluation of complex coronary circulations in patients with CTO.31,32

TAG_all and TAG_dia showed similar patterns for both well-developed collateral and retrograde flow in distal artery. It is explained by the fact that most (73%) well-developed collateral flow showed retrograde flow in distal artery. Our result also explains how CTO could be predicted by the reversed attenuation gradient in distal vessel, which corresponds to negative TAG_dia in our study.33

Limitations

Our results represent single-center experience. Half of the patients with potential for CTO were excluded after coronary angiography, because noninvasive discrimination between CTO and subtotal occlusion is frequently challenging.31 TAG was compared with semiquantitative angiographic collateral assessment, which correlates weakly with invasively assessed collateral flow index.22 TAG was investigated in a cross-sectional study and was not validated against long-term clinical results. The potential effects of a non-CTO lesion on collateral flow, multiple collateral vessels, or nonflat nature of intracoronary time–density curve were not addressed by the current study. Although TAG has been successfully studied from CT images with multiple cardiac cycles, the lack of temporal uniformity might affect our results.7-15 Single-beat imaging using scanners capable of entire coronary tree coverage would be a better methodology to validate TAG against coronary collateral physiology.6,20

Conclusions

TAG, an intracoronary attenuation-based analysis of coronary CT angiography, could reflect the functional extent and direction of coronary collateral flow. Additional studies are needed to validate the potential of noninvasive collateral flow assessment against invasive measurement and clinical benefit.

Sources of Funding

This study was supported by Samsung Biomedical Research Institute grant G18B33211.

Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Total occlusion of coronary artery is not uncommon in patients with coronary artery disease. Myocardium subtended by totally occluded coronary artery is supplied by alternative source of blood flow named collateral vessels. In such patients, well-developed coronary collaterals are protective from myocardial ischemia, mitigate myocardial infarct, and improve survival. Despite the clinical importance, clinical evaluation of collaterals has been limited by the need of invasive measurements. Here we showed that intracoronary attenuation-based analyses of coronary computed tomographic angiography acquired by conventional 64-slice or higher computed tomographic scanners enables noninvasive functional assessment of coronary collateral flow. Additional functional evaluation of collateral flow to the standard interpretation of coronary computed tomographic angiography may refine evaluation and risk stratification of coronary circulations in patients with totally occluded coronary arteries.
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_Circ Cardiovasc Imaging_. 2014;7:482-490; originally published online April 3, 2014;
doi: 10.1161/CIRCIMAGING.113.001637
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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SUPPLEMENTAL MATERIAL

Case in Figure 3A:

Video 1: Left CAG showing mid LAD CTO.
Video 2: Right CAG showing faint antegrade septal collateral.
Video 3: Curved MPR showing septal collateral vessel between RCA and LAD.

Case in Figure 3B:

Video 4: Left CAG showing mid LAD CTO.
Video 5: Right CAG showing retrograde collateral from RV branch.
Video 6: Curved MPR showing RV branch collateral between RCA and LAD.

Case in Figure 3C:

Video 7: Left CAG showing proximal LAD CTO.
Video 8: Right CAG showing antegrade collateral from PL branch and diagonal branch.
Video 9: Curved MPR showing collateral between PL branch and diagonal branch.

Case in Figure 3D:

Video 10: Right CAG showing proximal RCA CTO.
Video 11: Left CAG showing retrograde collateral via apical collateral.
Video 12: Curved MPR showing apical collateral between LAD and RCA.