Combination of Lesion Stenosis and Myocardial Supply Area Assessed by Coronary Computed Tomography Angiography for Prediction of Myocardial Ischemia

Manabu Kashiwagi,1 MD, Hironori Kitabata,1 MD, Atsushi Tanaka,2 MD, Yu Arita,1 MD, Akira Taruya,1 MD, Yukiko Shimamoto,3 MD, Yasunori Yamamoto,1 MD, Kazuya Mori,1 MD, Tsuyoshi Nishiguchi,3 MD, Kosei Terada,1 MD, Shingo Ota,1 MD, Takashi Tanimoto,1 MD, Takashi Kubo,2 MD, and Takashi Akasaka,2 MD

Summary
Recent clinical studies revealed that anatomical information assessed by coronary computed tomography angiography (CTA) may be used effectively to diagnose coronary artery disease (CAD). However, a physiological assessment, demonstrating myocardial ischemia, is required to justify a therapeutic strategy for CAD. This study aimed to investigate whether using CTA to assess myocardial supply area can improve the prediction of myocardial ischemia.

We analyzed 201 vessels with moderate (luminal narrowing ≤ 50%, < 70%) and severe (luminal narrowing ≥ 70%, < 99%) stenosis on CTA from 174 patients, who were suspected of having stable angina and underwent measurement of fractional flow reserve (FFR). The myocardial area supplied by the coronary artery, distal to the stenosis, was evaluated with CTA, as reported previously (modified Alberta Provincial Project for Outcome Assessment in Coronary Heart score) and was classified into 3 groups (large, medium, and small).

Both percentage area stenosis and myocardial supply area were significantly correlated with FFR (r = −0.46, \( P < 0.01 \), and \( r = −0.45, \ P < 0.01 \)). Among patients who had coronary plaques, with moderate stenosis and a small myocardial supply area, only 3 of 42 lesions (7%) were identified as ischemic; deviation from the ischemic threshold (FFR = 0.80) was \( P < 0.01 \). The combined assessment of lesion stenosis and myocardial supply area, using CTA, improved the prediction of myocardial ischemia significantly compared to lesion stenosis alone (77% versus 59%, \( P < 0.01 \)).

Adding the assessment of myocardial supply area to standard CTA might help predict myocardial ischemia in patients with stable angina pectoris.

Key words: Fractional flow reserve, Stable angina pectoris

Coronary computed tomography angiography (CTA) allows us to assess coronary atherosclerotic plaque noninvasively.1-4) The associated anatomical information, including severity of stenosis, lesion characteristics, and coronary plaque locations, could help diagnose coronary artery disease (CAD) and make an appropriate decision about therapeutic strategy.5-7) Recent studies have indicated that coronary artery interventions should be limited to coronary lesions with hemodynamically significant stenosis, emphasizing the importance of evaluating myocardial ischemia.8-10) Several studies have shown that CTA can predict the presence of obstructive CAD with high sensitivity and negative predictive value, but low positive predictive value and specificity.11,12) CTA may over- or underestimate a lesion’s functional severity based solely on the severity of obstruction. Therefore, it is reasonable to perform cardiac scintigraphy or stress echocardiography before invasive coronary angiography. To resolve this problem, fractional flow reserve derived from coronary computed tomography angiography (FFRCT), and computed tomography perfusion (CTP) imaging, have recently been developed as techniques to predict and evaluate myocardial ischemia.13-15) However, FFRCT has not been available in all institutions, while CTP requires additional contrast agent and radiation exposure.

Fractional flow reserve (FFR) is invasive, but is currently one of the standard and conventional methods for evaluating myocardial ischemia.16) We previously reported that FFR was correlated not only with the severity of coronary artery stenosis, but also with the myocardial supply area.17) Therefore, this study aimed to investigate...
whether additional assessment of myocardial supply area by CTA can improve the prediction of hemodynamically significant stenosis.

**Methods**

**Study population:** Patients undergoing CTA examinations who were suspected of having stable angina pectoris and were admitted to Shingu Municipal Medical Center or Wakayama Medical University Hospital were included in this study retrospectively. The presence of coronary artery stenosis was defined as a plaque with ≥ 50% obstruction of the luminal area in any coronary segment on CTA. Lesions associated with an old myocardial infarction, left main coronary artery stenosis, coronary artery bypass graft, serial stenosis in the same epicardial coronary artery, or collateral circulation were excluded. Demographic and clinical data were collected retrospectively and assessed, as in previous report. The Institutional Ethics Committee approved this study, which was carried out according to the Declaration of Helsinki.

**Scanning and imaging protocol of CTA:** CTA was carried out in accordance with the Society of Cardiovascular Computed Tomography’s Guidelines for the performance of coronary computed tomographic angiography, using two different computed tomography platforms (Lightspeed VCT, GE Healthcare, US; BrillianceCT64, Philips Electronics, NL). The scan parameters were: 64 × 0.625 mm collimation, a tube current of 400-800 mA, and a tube voltage of 120 kV. Sublingual nitrates were administered prior to scanning in all patients. All patients with a heart rate > 70 bpm received oral or intravenous beta-blockers before the CT scan. A 65 mL bolus of contrast media was injected intravenously, at a flow rate of 3.5-4.5 mL per second, followed by a 30 mL saline injection at the same flow rate.

**Analysis of CTA parameters:** The CTA data was analyzed by two experienced readers. Quantitative measurements were performed based on the concordance of two observers. The outer vessel area and lumen area were assessed by cross-sectional images. Percentage area stenosis was calculated as the ratio between the plaque area and the outer vessel area at the site of maximal luminal narrowing. Coronary plaque with moderate stenosis was defined as present stenosis ≥ 50% and < 70%, while severe stenosis was defined as ≥ 70% and < 99%; these correspond to grades 3 and 4 of the recommended quantitative stenosis grading in the previous guideline. Calcium depositions were classified as long (> 3 mm), short (≤ 3 mm), or none. Assessment of myocardial supply area: The extent of myocardial area supplied by the coronary artery, distal to the stenosis, was assessed by CTA using the modified Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) score. This score is based on a scoring system developed at the Green Lane Hospital, with modifications from pathologic and cardiac magnetic resonance imaging data. Regarding the stenosis location and vessel dominance, the left ventricle is divided into several regions, according to pathological studies in humans that evaluated the relative proportion of myocardium perfused by each coronary artery. The myocardial supply area is quantified and expressed as a percentage of the entire left ventricle (3.25%-47.75%) (Figure 1). Because the myocardial supply area by modified APPROACH score has 39 sections, we divided the values recorded into each of 13 sections. As a result, there were three groups, small (≤ 15.75%), medium (> 15.75%, < 28%), and large supply area (≥ 28%). An independent observer, blinded to the clinical characteristics and the FFR value, assessed the score of each lesion. The myocardial supply area was evaluated by angiographic view and volume rendering of CTA. Representative cases are shown in Figures 2, 3.

**FFR and QCA measurement:** FFR measurement and quantitative coronary angiography (QCA) analysis were carried out as previously reported. Intracoronary pressure was measured using a 0.014-inch pressure guidewire (Pressure wire, St. Jude Medical, St. Paul, MN). The pressure wire was calibrated and advanced to the tip of the guiding catheter to equalize the pressure/temperature signals. The wire was then introduced into the coronary artery, and positioned distal to the assessed stenosis. The proximal coronary pressure was recorded by the guiding catheter. FFR was calculated as the mean distal coronary pressure, measured by the pressure guidewire, divided by the mean aortic pressure, measured simultaneously by the guiding catheter, during maximal hyperemia. Maximal hyperemia was induced by continuous intravenous infusion of adenosine 5'-triphosphate, administered at 150-180 μg/kg/minute via the forearm or femoral vein, as in previous studies. The FFR was considered diagnostic of ischemia at a threshold of ≤ 0.80. QCA analysis was performed by standard techniques with an automated edge-detection algorithm (CASS-5, Pie Medical, Maastricht, Netherlands). After selection of the optimal projection, displaying the most severe stenosis, the minimum lumen diameter, and reference vessel diameter were measured. The percent diameter stenosis was calculated as the ratio of the minimum lumen diameter to the reference vessel diameter.

**Statistical analysis:** Statistical analysis was performed using JMP pro version 13 for Macintosh (SAS Institute, Cary, NC, USA). Results are expressed as mean value ± standard deviation for approximately normally distributed variables, and median [interquartile range] for skewed variables. Spearman’s rank correlation test was used to analyze the correlation between two variables. The difference between stenosis severity alone and the combination of stenosis severity and supply area for predicting myocardial ischemia was tested by McNemar’s test. The Wilcoxon signed-rank test was used to assess the deviation of median FFR values from 0.8. A P-value < 0.05 was considered statistically significant.

**Result**

**Baseline characteristics:** We analyzed 201 coronary lesions from 174 patients. The baseline characteristics are shown in Table I. The median interval between the CTA and FFR measurement was 20 [13-35] days, and there was no cardiovascular event between examinations. Forty-
eight patients did not have hemodynamically significant stenosis in any vessel.

**CTA, QCA and FFR data:** The CTA, QCA, and FFR data for the culprit lesion are summarized in Table II. Percentage stenosis by CTA was significantly correlated with percentage diameter stenosis by QCA \( (r = 0.77, P < 0.01) \). Sixty-eight coronary plaques were classified as severe stenosis, and 119 lesions demonstrated ischemia on FFR examinations (Figure 4). Both percentage stenosis and myocardial supply area were significantly correlated with FFR, respectively \( (r = -0.46, P < 0.01, \text{ and } r = -0.45, P < 0.01) \) (Figure 5).

**Prediction of myocardial ischemia:** Although more than three quarters (87%) of lesions with severe stenosis demonstrated ischemia, only about 45% of lesions with moderate stenosis were ischemic (Figure 6). In particular, in coronary plaques with moderate stenosis and a small myocardial supply area, only three lesions (7%) were identi-
fied as ischemic. If the lesion was positive with (1) severe stenosis or (2) moderate stenosis with a myocardial supply area of greater than medium size, the diagnostic accuracy for predicting myocardial ischemia by CTA was significantly improved compared to moderate stenosis alone, according to McNemar’s test \((P < 0.01)\) (Table III). Among 39 non-ischemic, moderate stenotic lesions with a small myocardial supply area, target lesion revascularization was required in one lesion during a long follow-up period (655 [325-1268] days). The relationship between stenosis severity/myocardial supply area assessment and FFR is summarized in Figure 6. Deviation from the ischemic threshold \((\text{FFR} = 0.80)\) was \(P < 0.01\), \(P < 0.01\), \(P = 0.96\), and \(P < 0.01\), respectively. Among three types of calcium deposition (none, small and large), diagnostic accuracy was not significantly different in prediction of myocardial ischemia \((73.9%, 80.6%\) and \(77.5%, P = 0.63\)).

### Table I. Patient Characteristics

| Variable | \(n\) |
|----------|-------|
| Patients, \(n\) | 174 |
| Age, years | 68 ± 9 |
| Men | 133 (76) |
| Body mass index, kg/m\(^2\) | 24 ± 4 |
| Coronary risk factor | |
| Hypertension | 136 (78) |
| Diabetes mellitus | 74 (43) |
| Dyslipidemia | 116 (67) |
| Smoking | 87 (50) |
| Family history | 34 (20) |
| The number of stenosis vessels | |
| 0 | 48 (28) |
| 1 | 79 (45) |
| 2 | 36 (21) |
| 3 | 11 (6) |
| CTA data | |
| Heart rate at scanning | 64 ± 9 |
| Arrhythmia | 21 (12) |
| Duration between CTA and Angiography, days | 20 [13 - 35] |

Data presented are mean ± SD, median [interquartile range] or number (%). CTA indicates computed tomography angiography.

### Table II. Lesion Characteristics

| Variable | \(n\) |
|----------|-------|
| Vessel number, \(n\) | 201 |
| Target vessel | |
| Left anterior descending artery | 113 (56) |
| Left circumflex artery | 43 (21) |
| Right coronary artery | 45 (22) |
| CTA data | |
| Outer vessel area, mm\(^3\) | 17.7 ± 5.1 |
| Luminal area, mm\(^3\) | 6.0 ± 2.6 |
| \% stenosis | 65.5 ± 11.5 |
| Severe stenosis | 68 (34) |
| Calcium deposition | |
| Long (\(>3\) mm) | 41 (20) |
| Short (\(≤3\) mm) | 71 (35) |
| None | 89 (44) |
| Modified APPROACH score | 29.0 ± 13.4 |
| QCA data | |
| Minimum lumen diameter | 1.40 ± 0.52 |
| Reference vessel diameter | 3.57 ± 0.65 |
| \% diameter stenosis | 61.0 ± 12.4 |
| Fractional flow reserve | 0.75 ± 0.13 |
| Ischemia | 119 (59) |

Data presented are mean ± SD or number (%). CTA indicates computed tomography angiography; and QCA, quantitative coronary angiography.

### Discussion

In the present study, we demonstrated that additional assessment of myocardial supply area by CTA could improve the prediction of myocardial ischemia. In our population, more than half the lesions detected by CTA were not hemodynamically significant. Therefore, the assessment of stenosis severity alone could overestimate the presence of CAD.

To date, several trials have reported that providing coronary intervention for hemodynamically ischemic coronary lesions proven by FFR and/or myocardial scintigraphy, rather than anatomically stenotic lesions on coronary angiography, is crucial for better patient outcomes.\(^{8,10}\) Stenosis severity and the minimum lumen area of a coro-

---

**Figure 3.** Representative cases of moderate stenotic lesion with ischemia. Intermediate stenosis was seen in a mid-portion of LAD, which had large-sized diagonal branches. Because the myocardial supply area was large (31.8%), the FFR value was below the ischemic threshold (FFR = 0.72). Yellow arrow indicates culprit site; LAD, left anterior descending artery; D, diagonal artery; and LCx, left circumflex artery.
Figure 4. Patient populations. Patients were divided into four groups, severe stenosis, and moderate stenosis with a large, medium, or small supply area. In particular, of the lesions with moderate stenosis and a small myocardial supply area, only three were considered ischemic.

Figure 5. Relationships between FFR and CTA parameters. FFR was significantly correlated with percentage plaque area (r = -0.46, P < 0.01) and myocardial supply area (r = -0.45, P < 0.01). FFR indicates fractional flow reserve; and CTA, computed tomography angiography.

nary lesion are considered predictive of ischemia. Indeed, intravascular coronary imaging devices, optical coherence tomography and intravascular ultrasound, in particular, are used to predict myocardial ischemia.

CTA has been established as a screening examination for CAD. Despite the relatively high levels of radiation exposure involved, CTA is less invasive than coronary angiography. Moreover, its negative predictive value is extremely high. However, evaluating the severity of coronary artery stenosis by CTA has not become established because of its low spatial resolution. This means that it is impossible to predict the physiological significance of coronary stenosis based on CTA information alone; therefore, myocardial scintigraphy and/or stress echocardiography are usually combined to avoid unnecessary and invasive coronary angiography.

Recently, FFR\textsubscript{CT} and CTP imaging have been developed to resolve this problem. FFR\textsubscript{CT} is a method for as-
Figure 6. Frequency of myocardial ischemia and FFR among four groups. A: $P < 0.05$; Severe versus Moderate/Large, Moderate/Large versus Moderate/Medium, $P < 0.01$; comparison of other groups. B: Deviation from the ischemic threshold (fractional flow reserve = 0.80) was $P < 0.01$, $P < 0.01$, $P = 0.96$, and $P < 0.01$, respectively. Data are presented as a box plot with median, 25th and 75th percentiles (box), and 10th to 90th percentiles (whiskers). FFR indicates fractional flow reserve.

| Table III. | Prediction for Ischemia by CTA Findings |
|------------|----------------------------------------|
|            | Severity of stenosis alone              |
|            | Correct | Incorrect | Total |
| Combination of severity of stenosis and myocardial supply area | |
| Correct    | 116 (58) | 39 (19) | 155 (77) |
| Incorrect  | 3 (1)   | 43 (21) | 46 (23) |
| Total      | 119 (59) | 82 (41) | 201 (100) |

Data presented are number (%). CTA indicates computed tomography angiography.

We have demonstrated that FFR is influenced not only by the severity of coronary artery stenosis, but also by the myocardial supply area. Many investigators have demonstrated the usefulness of $\text{FFR}_{\text{CT}}$ and its high diagnostic accuracy. However, extra time is required to obtain results because the data have to be sent to a host computer for a specific calculation. Therefore, $\text{FFR}_{\text{CT}}$ is not available in all institutions. CTP imaging, on the other hand, requires the additional use of contrast-enhancing agents and radiation exposure and is a relatively time-consuming method.

We have demonstrated that FFR is influenced not only by the severity of coronary artery stenosis, but also by the myocardial supply area. In a previous study, the myocardial supply area was assessed by coronary angiography based on the modified APPROACH score. Therefore, the angiographic view of CTA was used for its assessment in this study. Our results show that the combined evaluation of severity of coronary artery stenosis and myocardial supply area could correctly diagnose patients who were suspected of having angina pectoris. Lesions with moderate stenosis and a small supply area were usually not significant ischemic lesions. In contrast, lesions with a myocardial supply area greater than medium size could be positive for ischemia. Furthermore, the possibility that lesions with severe stenosis cause myocardial ischemia is high. This result might help preclude unnecessary examinations in cases where a moderate stenosis has a relatively narrow supply area, reducing medical costs. Indeed, in our population, target lesion revascularization was required in only one case during a long follow-up period. Optimal medical therapy, rather than invasive coronary intervention, is encouraged for patients with a small degree of ischemia. Therefore, noninvasive examinations before coronary angiography and optimal medical therapy are recommended in these cases.

Limitations: Several limitations may be associated with the present study. The study population was relatively small, and our results may not be applicable to all patients with CAD. We collected data retrospectively, so selection bias might exist. We did not calculate Agaston calcium score. Therefore, severity of calcium deposition might influence the evaluation of coronary artery stenosis. Lastly, we used two different CT scanners.

Conclusion

In this study, we demonstrated that the combined evaluation of coronary artery stenosis severity and myocardial supply area by CTA improved the prediction of significant obstructive lesions.
Disclosures

Conflicts of interest: None.

References

1. Hoffmann U, Nagurney JT, Moselewski F, et al. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. Circulation 2006; 114: 2251-60.

2. Achenbach S. Computed tomography coronary angiography. J Am Coll Cardiol 2006; 48: 1919-28.

3. Budoff MJ, Dowd D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary computed tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 2008; 52: 1724-32.

4. Meijboom WB, Meijjs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol 2008; 52: 2135-44.

5. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008; 359: 2324-36.

6. Choi JH, Kim EK, Kim SM, et al. Noninvasive discrimination of coronary chronic total occlusion and subtotal occlusion by coronary computed tomography angiography. JACC Cardiovasc Interv 2015; 8: 1143-53.

7. Opolski MP, Achenbach S, CT Angiography for revascularization of CTO: crossing the borders of diagnosis and treatment. JACC Cardiovasc Imaging 2015; 8: 846-58.

8. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenoses: 5-year follow-up of the DEFFER Study. J Am Coll Cardiol 2007; 49: 2105-11.

9. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360: 213-24.

10. van Nuenen LX, Zimmermann FM, Tonino PA, et al; FAME Study Investigators. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015; 386: 1853-60.

11. Rossi A, Papadopoulou SL, Pugliese F, et al. Quantitative computed tomographic coronary angiography: does it predict functionally significant coronary stenoses? Circ Cardiovasc Imaging 2014; 7: 43-51.

12. 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.

13. Gonzalez JA, Lipinski MJ, Flos L, Shaw PW, Kramer CM, Salerno M. Meta-analysis of diagnostic performance of coronary computed tomography angiography, computed tomography perfusion, and computed tomography- fractional flow reserve in functional myocardial ischemia assessment versus invasive fractional flow reserve. Am J Cardiol 2015; 116: 1469-78.

14. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012; 308: 1237-45.

15. Techasith T, Cury RC. Stress myocardial CT perfusion: an update and future perspective. JACC Cardiovasc Imaging 2011; 4: 905-16.

16. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 2001; 103: 2928-34.

17. Shiono Y, Kubo T, Tanaka A, et al. Impact of myocardial supply area on the transstenotic hemodynamics as determined by fractional flow reserve. Catheter Cardiovasc Interv 2014; 84: 406-13.

18. Ueda Y, Shiga Y, Idemoto Y, et al. Association between the presence or severity of coronary artery disease and pericardial fat, paracardial fat, epicardial fat, visceral fat, and subcutaneous fat as assessed by multi-detector row computed tomography. Int Heart J 2018; 59: 695-704.

19. Kashiwagi M, Tanaka A, Shimada K, et al. Distribution, frequency and clinical implications of napkin-ring sign assessed by multidetector computed tomography. J Cardiol 2013; 61: 399-403.

20. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2009; 3: 122-36.

21. Usui E, Lee T, Murai T, et al. Efficacy of multidetector computed tomography to predict periprocedural myocardial injury after percutaneous coronary intervention for chronic total occlusion. Int Heart J 2017; 58: 16-23.

22. Brandt PW, Partridge JB, Wattie WJ. Coronary arteriography: method of presentation of the arteriogram report and a scoring system. Clin Radiol 1977; 28: 361-5.

23. Kalbfleisch H, Hort W. Quantitative study on the size of coronary artery supplying areas postmortem. Am Heart J 1977; 94: 183-8.

24. Lee JT, Ideker RE, Reimer KA. Myocardial infarct size and location in relation to the coronary vascular bed at risk in man. Circulation 1981; 64: 526-34.

25. Ortiz Prez JT, Meyers SN, Lee DC, et al. Angiographic estimates of myocardium at risk during acute myocardial infarction: validation study using cardiac magnetic resonance imaging. Eur Heart J 2007; 28: 1750-8.

26. Seo MK, Koo BK, Kim JH, et al. Comparison of hyperemic efficacy between central and peripheral venous adenosine infusion for fractional flow reserve measurement. Circ Cardiovasc Interv 2012; 5: 401-5.

27. Gonzalez N, Escaned J, Alfonso F, et al. Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. J Am Coll Cardiol 2012; 59: 1080-9.

28. Shiono Y, Kitabata H, Kubo T, et al. Optical coherence tomography-derived anatomical criteria for functionally significant coronary stenosis assessed by fractional flow reserve. Circ J 2012; 76: 2218-25.

29. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003; 107: 2900-7.