Plaque Characteristics on Coronary CT Angiography Associated with the Positive findings of Fractional Flow Reserve and Instantaneous Wave-free Ratio.

Chihiro Aoshima, MD[1], Shinichiro Fujimoto, MD, PhD[1], Yuko O. Kawaguchi MD, PhD[1], Tomotaka Dohi, MD, PhD[1], Yuki Kamo, MD[1], Kazuhisa Takamura, MD, PhD[1], Makoto Hiki, MD, PhD[1], Yoshiteru Kato MD[1], Iwao Okai MD, PhD[1], Shinya Okazaki MD, PhD[1], Kanako K. Kumamaru, MD, PhD[2], Shigeki Aoki , MD, PhD[2], Hiroyuki Daida, MD, PhD[1]

1. Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

2. Department of Radiology, Juntendo University Graduate School of Medicine, Tokyo, Japan

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Conflict of interest

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Correspondence to:

Shinichiro Fujimoto, MD, PhD

Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine

2-1-1 Hongo Bunkyo-ku, Tokyo 113-8421, Japan

Telephone number: +81-3-5802-1056

FAX number: +81-3-5869-0627

E-mail: s-fujimo@tj8.so-net.ne.jp

Abstract

Background:

Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are useful in determining indications for revascularization of coronary artery disease (CAD). Although the discordance of FFR and iFR was noted in approximately 20%, this cause has not been well established. We investigated patient background and features on coronary CT angiography (CCTA) showing not only FFR- and iFR-positive findings but also discordance between FFR≤0.8 and iFR≤0.89.

Methods：

Subjects were consecutive 83 cases with 105 vessels in which stenosis of 30-90% was detected at one vessel of at least 2mm or more in the major epicardial vessels and FFR and iFR was performed within subsequent 90 days, among suspected CAD which underwent CCTA. The factors affecting not only FFR-and iFR- positive findings respectively but also discordance between FFR and iFR were evaluated using logistic regression analysis on per-patient and per-vessel basis.

Results:

FFR- and iFR-positive findings were observed in 42 vessels (40.0%) and 34 vessels (32.3%) respectively. Discordance between FFR≤0.8 and iFR≤0.89 was observed in 22 vessels (21.0%) of 21 patients. In multivariate logistic analysis, LAD (OR, 3.55; 95%CI, 1.20-11.71; p=0.0217) and lumen volume/myocardial weight (L/M) ratio (OR, 0.93; 0.86-0.99, p=0.0290) were significant predictors for FFR positive findings. For iFR positive findings, LAD (OR, 3.86; 95%CI, 1.12-13.31; p=0.0236) was only significant predictor. In FFR≤0.8 and iFR>0.89 group (15 vessels, 14.3%), positive remodeling (PR) (OR 5.03, 95％CI:1.23-20.48, p=0.0205) were significant predictors. In FFR>0.8 and iFR≤0.89 group (7 vessels, 6.7%), there were no significant predictors.

Conclusions：

On CCTA characteristics, a relevant predictor for FFR positive findings included low L/M ratio. PR were significant predictor in FFR-positive, iFR-negative patients among those with discordance between the FFR and iFR.

Key words

coronary CT angiography; fractional flow reserve; instantaneous wave-free ratio; plaque characteristics

Introduction

When assessing revascularization for coronary artery disease, it is necessary to evaluate the degree of functional stenosis. Currently, fractional flow reserve (FFR) is routinely used as an index of functional ischemia [1,2].

Recently, instantaneous wave-free ratio (iFR), in which the diastolic wave-free period involving the minimum/stable vascular resistance was used, not requiring maximum hyperemia in comparison with FFR, was developed. iFR was demonstrated to be equivalent to FFR for evaluating whether revascularization is indicated, and the clinical usefulness of iFR has been established [3,4]. This may facilitate functional assessments by a simpler procedure.

There is a strong correlation between the FFR and iFR [5]. On the other hand, discordance between the two parameters was reported in approximately 20% of patients, regarding an FFR of ≤0.8 and an iFR of ≤0.89 as positive. However, the mechanism remains to be clarified [6-8].

Coronary computed tomography angiography (CCTA) facilitates the assessment of the degree of coronary artery stenosis and plaque morphology. Many studies have reported its clinical usefulness [9,10]; while its quantification property and objectivity remain controversial [11]. We developed new plaque-analyzing software to more

objectively evaluate plaque properties using a clustering procedure [12].

In this study, we examined the patient background and CCTA characteristics analyzed using this new software related to not only FFR- and iFR-positive findings but also the discordance between FFR and iFR.

Materials and methods

Study population

CCTA examinations using 320-row CT were performed on 1,905 consecutive patients with suspected coronary artery disease of unidentified types between December 1, 2015 and October 31, 2018. Of the 1,905 patients, 514 had stenosis of 30-90% in a major epicardial vessels of at least 2 mm in diameter. Invasive coronary angiography was scheduled in 298 of those 514 patients within 90 days. A total of 97 consecutive patients who consented to undergo FFR and iFR assessments within 90 days were enrolled in the study. Of 97 patients, the stenosis rate of the lesion exceeded 90% on invasive coronary angiography in 9, 3 withdrew consent, ventricular tachycardia occurred during FFR measurement in 1, and acute coronary syndrome developed between CCTA and FFR in 1. Excluding these patients, 105 vessels in 83 consecutive patients were included in the study. Exclusion criteria included patients with renal insufficiency (eGFR

<60mL/min/1.73m2), bronchial asthma requiring long term steroid therapy, contraindications to iodinated contrast and known CAD.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of Juntendo University Hospital (No. 19-077).

CCTA Acquisition

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 mmHg, bronchial asthma, symptomatic heart failure, or advanced atrioventricular block) did not receive these drugs (13). For all patients, 0.6mg (2 push) of nitroglycerin were sprayed into the mouth.

The following devices were used: Aquilion ONE ViSION Edition^{TM} or Aquilion ONE GENESIS Edition^{TM} (320-ADCT, Canon 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 kVp except for patients whose body mass index exceeded 30 kg/m^2, who were scanned at 120 kVp. Mean tube current was calculated with automatic exposure control with a target standard deviation (SD) of 22. With a slice width of 0.5 mm and a 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. Coronary artery calcium score (CACS) was performed by the following parameters: 120 kV, 150 mA, and 3-mm thickness to calculate Agatston score [14,15]

Prospective CTA mode was used for all patients. The contrast agent iohexol (Omnipaque 350 mg/ml I; Daiichi Sankyo Company, Tokyo, Japan) was injected for 12 sec at 18.0 mg I/kg/s, followed by injection of 30 mL of saline at the same rate as contrast agent injection.

Real prep scanning with bolus tracking at the ascending aorta level was performed every 0.5 sec beginning 10 sec after the start of contrast agent injection. Scanning was

started 6 sec after when the contrast agent reached to 300HU at the ascending aorta. The reconstruction slice thickness was 0.5 mm and the increment was 0.25. A convolution kernel of FC04 used with iterative reconstruction technique (FIRST). The reconstruction slice thickness was 0.5 mm. Radiation doses were estimated and compared using the extended Dose Length Product (DLPe) from 320-detector row CT [16]. The effective dose was calculated by multiplying the DLPe by 0.028, based on ICRP 103 [17].

CCTA Plaque analysis

After reconstruction at the optimal phase within the R–R interval, CT images were anonymized and then transferred to a workstation with dedicated plaque analyses software (Sure Plaque Research Version, Canon medical systems, Japan). The vessel volume and lumen volume were calculated automatically, if necessary, corrected manually for the centerlines, inner vessel wall, and outer vessel. Based on the calculated vessel volume and lumen volume, the plaque analysis (necrotic area, fibrous area, calcified area) by labeling method [12], Maximum plaque burden ((maximum plaque area / vessel area)*100), %diameter stenosis and minimum lumen area (MLA) were evaluated. Positive remodeling (PR) was defined as the remodeling index>1.1 [18, 19].

A coronary plaque was defined as a structure of >1 mm^2 in the area located within the vessel walls. A calcified lesion was defined as a structure with a CT attenuation number of ≥130 HU on the plain image or ≥130 HU on the contrast-enhanced image. Calcified plaque was defined as an atherosclerotic plaque wholly manifesting as calcium density. A partially calcified plaque was defined as atherosclerotic plaque in which there were 2 visible plaque components, of which 1 was calcified. A noncalcified plaque was defined as an atherosclerotic plaque that was wholly devoid of calcium density.

Measurement of lumen volume/myocardial weight (L/M) ratio

CT images were transferred to a workstation to measure the weight of the cardiac muscle (SYNAPSE VINCENT, FUJIFILM Medical Co., Ltd., Japan). The cardiac muscle weight for each target vessel was calculated by a segmentation algorithm based on the Voronoi method using dedicated software (myocardial analysis, FUJIFILM Medical Co., Ltd., Japan). A mathematical algorithm called the Voronoi diagram was applied in conjunction with a calculation to select a dominant perfusion area for each coronary artery branch from a point where the coronary artery contacted the left ventricular myocardium. The cardiac muscle weight in the dominant perfusion area was

automatically calculated when the target coronary artery was finally specified [20, 21]. Lumen volume/myocardial weight (L/M) ratio was calculated the ratio of the lumen volume of target coronary arteries to left ventricle myocardial mass.

Invasive coronary angiography, FFR, iFR

Coronary angiography was performed using 5–7 French guide catheters without side holes by femoral or radial approach. In each vessel, percent stenosis was calculated for the most significant lesion as the ratio of the minimum lumen diameter within the lesion divided by the expected normal coronary diameter using visual assessment. A vessel was considered significant if there was more than 1 segment with >50% luminal stenosis.

Pressure measurements were performed using a 0.014-inch pressure guide wire (Verrata Pressure Guide Wire, Volcano Corp., San Diego, CA) and software (s5x™ Imaging System, Volcano Corp., SanDiego, CA). The pressure wire was calibrated and equalized with the aortic pressure before being placed distal to the stenosis and in the distal third of the coronary artery being interrogated.

iFR was first calculated as the mean pressure distal to the stenosis during the diastolic wave-free period divided by the mean aortic pressure during the diastolic

wave-free period. The onset of diastole was identified from the dicrotic notch, and the diastolic window was calculated beginning at 25% of the extent of diastole and extending to 5 ms before the end of diastole. This time was chosen to reflect the wave-free period in diastole when resistance is naturally minimized. All analyses were fully automated; that is, there was no need for manual selection of data time points. A iFR value of ≤0.89 was chosen to define hemodynamically significant stenosis [3, 4].

FFR was then measured as the mean distal coronary pressure (Pd) divided by the mean aortic pressure (Pa) during maximal hyperemia. In brief, FFR was measured with a coronary pressure guidewire at maximal hyperemia induced by adenosine triphosphate (ATP) administered at 140 μg/kg/min for at least 2 minutes through a large forearm vein using an infusion pump until the heart rate began increasing and the Pd/Pa ratio remained steady. Pressure wire pullback was performed to check for FFR at each lesion segment and to check for pressure drift. If a Pd/ Pa ratio <0.98 or >1.02 at the catheter tip was documented, the protocol mandated repeat assessment. An FFR value of ≤0.8 was chosen to define hemodynamically significant stenosis [3, 4].

Nitroglycerin was used by injecting 0.5 mg into the right coronary artery and 1 mg into the left coronary artery before coronary angiography.

Definition of risk factors

Hypertension was defined as either systolic or diastolic blood pressure ≥140/90 mmHg or use of antihypertensive medications. Diabetes mellitus was defined as fasting blood sugar ≥7.0 mmol/L (126 mg/dl) or postprandial blood sugar ≥11.0 mmol/L (200 mg/dl) or hemoglobin A1c ≥6.5% (47.5 mmol/mol) or use of anti-diabetic medications. Dyslipidemia was defined as total cholesterol ≥5.7 mmol/L (220 mg/dl), low-density lipoprotein cholesterol >3.6 mmol/L (140mg/dl), fasting triglycerides ≥1.7 mmol/L (150 mg/dl), high density cholesterol < 1.0 mmol/L (40mg/dl) or use of lipid-lowering medications. Smokers were defined as those patients who had smoked during the past 1 year from the time of CCTA acquisition.

Statistical analysis

Continuous data were expressed as the mean ± standard deviation (SD). Categorical data are expressed as frequencies (percentage). Predictors for FFR, iFR positive findings and discordance between FFR and iFR were determined by univariate and multivariate logistic regression analyses. P-values of less than 0.05 were considered significant. Statistical analyses were performed using JMP Software for Windows (SAS Institute Inc., USA).

Results

Patient and Image characteristics

One-hundred five vessels in 83 patients were analyzed. The mean age was 67.1±9.7 years old and the mean calcium score was 482.5±676.5. The baseline patient characteristics are listed in Table 1A.

The mean heart rate at the time of image acquisition was 54.5±5.6 bpm and nitrates were used for all patients. The tube voltage was 120 KVp in 10 patients and the mean effective dose was 5.7±3.2 mSv. Image characteristics are provided in Table 1B.

Vessel characteristics

Of the 105 vessels, 17 were in RCA vessels (16.2%), 70 were in LAD vessels (66.7%), and 18 were in LCX vessels (17.1%), and the FFR was ≤0.80 in 42 vessels (40.0%), iFR was ≤0.89 in 34 vessels (32.3%). The 105 vessels included 34 vessels with positive remodeling (32.4%).

The plaque classification of the lesions was non-calcified plaques in 30 vessels (28.6%), partially calcified plaques in 32 vessels (30.5%), and calcified plaques in 43 vessels (41.0%). Discordance of FFR and iFR was observed in 15 cases (14.3%) with

FFR ≤ 0.80 and iFR ≻ 0.89, and in 7 cases (6.7%) with FFR>0.80 and iFR ≤ 0.89 (Table 1C).

Analysis for patient-based prediction of positive findings on FFR and iFR

In 83 patients, we investigated patient-based relevant factors for positive findings on the FFR using univariate logistic regression analysis. There was no significant relevant factor (Table 2A). We also examined patient-based relevant factors for positive findings on the iFR. However, there was no significant relevant factor (Table 3A).

Analysis for vessel-based prediction of positive findings on FFR and iFR

In 105 vessels, we investigated vessel-based relevant factors for positive findings on the FFR using univariate logistic regression analysis. A low lumen volume/vessel volume (odds ratio (OR), 0.94; 95%CI, 0.89-0.98; p=0.0066), high plaque volume/vessel volume (OR, 1.05; 95%CI,1.00-1.10; p=0.0296), high maximum plaque burden (OR, 1.07; 95%CI, 1.01-1.15; p=0.0171), low MLA (OR, 0.58; 95%CI, 0.41-0.86; p=0.0296), LAD (OR,5.11; 95%CI, 1.89-13.86; p=0.0005), and low L/M ratio (OR, 0.90; 95%CI, 0.84-0.96; p<0.0001) were significant relevant factors (Table 2B). In multivariate analysis among significant factors, LAD (OR, 3.55; 95%CI,

1.20-11.71; p=0.0217) and L/M ratio (OR, 0.93; 0.86-0.99, p=0.0290) were significant relevant factors (Table 2C).

In these vessels, we also examined vessel-based relevant factors for positive findings on the iFR. As demonstrated for the FFR, a low lumen volume/vessel volume (OR, 0.90; 95%CI, 0.85-0.95; p=0.0001), high plaque volume/vessel volume(OR, 1.11; 95%CI, 1.05-1.18; p<0.0001), high maximum plaque burden (OR, 1.07; 95%CI, 1.00-1.14; p=0.0344), low MLA (OR, 0.61; 95%CI, 0.41-0.90; p=0.0030), LAD (OR, 4.24; 95%CI, 1.47-12.20; p=0.0034), and low L/M ratio(OR, 0.92; 95%CI, 0.86-0.98; p=0.0014) were significant relevant factors (Table 3B). In multivariate analysis among significant factors, LAD (OR, 3.86; 95%CI, 1.12-13.31; p=0.0236) was only significant relevant factor (Table 3C).

Analysis for prediction of discordance case between FFR and iFR

In 15 FFR-positive, iFR-negative vessels, we investigated vessel-based relevant factors for iFR-negative findings in the FFR-positive group using univariate logistic regression analysis. The presence of PR (OR, 5.03; 95%CI, 1.23-20.48; p=0.0205), a high lumen volume/vessel volume (OR, 1.08; 95%CI, 1.00-1.17; p=0.0437), and low plaque volume/vessel volume (OR, 0.91; 95%CI, 0.84-0.98; p=0.0071) were significant

relevant factors (Table 4A). PR (OR, 5.32; 95% CI, 0.98-28.94; p = 0.0415) was a significant factor in the multivariate analysis (Table 4A).

In 7 FFR-negative, iFR-positive vessels, we examined vessel-based relevant factors for iFR-positive findings in the FFR-negative group. Although a low lumen volume/vessel volume (OR, 0.88; 95%CI, 0.78-1.00; p=0.0351) and high plaque volume/vessel volume (OR, 1.14; 95%CI, 1.01-1.29; p=0.0230) were significant relevant factors (Table 4B), no significant factors were found in the multivariate analysis (Table 4B).

Discussion

In this study, we examined the CCTA characteristics influencing FFR and iFR. We found the following: 1. significant relevant factors for FFRpositive findings included LAD, and low L/M ratio while significant relevant factor for iFR positive findings included only LAD; and 2. FFR was discordant with iFR in approximately 20% of the patients, regarding an FFR of ≤0.8 and iFR of ≤0.89 as positive. In these patients, FFR-positive, iFR-negative findings were more common. The underlying reason for this that the iFR positive rate is lower than the FFR positive rate. Significant relevant factors

for the discordance included the presence of PR. In contrast, no significant factors for iFR-positive, FFR-negative findings included.

In this study, significant vessel-based relevant factors for FFR-positive and, iFR-positive findings included LAD, Furthermore, there was no significant patient-based relevant factor for FFR- or iFR-positive findings. LAD often has a more extensive perfusion area than other coronary trees, therefore a reduction in the pressure is large even if the degree of stenosis is the same. This is the reason why LAD was associated with the positive of both FFR and iFR [22]. However, a low L/M ratio was a significantly relevant factor for only FFR-positive finding in multivariate analysis. A recent study reported that a low L/M ratio is associated with a low FFR [23]. It has been reported that coronary artery volume and myocardial mass have a very tight linear relationship in an animal model without arteriosclerosis based on Allometric scaling low. Therefore, it is considered that the variation of L/M ratio, which is corrected by the myocardial mass of the lumen volume that reflects the coronary artery volume, most represents the degree of ischemia. The reason that L/M ratio was not a significant factor for iFR-positive findings could be that iFR was associated with plaque volume and diffuse lesion, which may be a confounding factor for L/M ratio. Although a previous study [23] investigated patient-based factors, we calculated the myocardial weight for a

target vessel using Voronoi's method and the L/M ratio for respective target vessels. On the other hand, CT-verified high risk plaque characteristics, such as PR and low attenuation plaque (LAP), were reported to be associated with a reduction in the FFR regardless of the degree of stenosis [24, 25-27]. However, in this study, no such result was obtained. We examined patients with moderate stenosis on CCTA, but approximately 80% had ≥50% (significant) stenosis. When the degree of stenosis is low, these plaque characteristics reduce the FFR or iFR [28]. On the other hand, when stenosis is advanced to some degree, the influence of the degree or extent of stenosis is marked, and the influence of these plaque characteristics may not be significant. Furthermore, in this study, we used plaque-analyzing software that we developed to analyze the plaque volume and morphology on CCTA [12]. This analysis facilitates the automatic calculation of the remodeling index, and differences in measurement among analyzers may be minimized. Usually, plaque morphology such as LAP were analyzed/classified using CT values alone. However, the CT value was reported to be affected by the concentration of contrast agent in the coronary artery lumen, stenosis level of coronary artery lesions tube voltage and so on [29-32]. This new analytical method facilitates a more objective classification of plaque morphology using a clustering procedure (labeling method) in addition to the CT number [12]. And when

using the method, perivascular adipose tissue and image noise are not counted as low attenuation plaque. In this study, we evaluated plaque morphology based on the necrotic core volume calculated using this analytical software, but not using the LAP, which has been used previously.

In this study, the FFR was discordant with the iFR in 22 vessels (21.0%) when using an FFR of ≤0.8 and iFR of ≤0.89 as criteria for positive findings. This was similar to the results of previous studies [6-8]. In this study, significant factors for FFR-positive, iFR-negative findings included the presence of PR. Recently, it has been reported that PR and spotty calcification were also independent predictors of an impaired FFR, but adverse plaque characteristics were not independently related to the vasodilator-free iFR [33]. As an underlying mechanism, there may be a difference in nitroglycerin- or adenosine-related vessel dilatation responses between the lesion site and healthy region [22,25]. In lesions with the characteristics of vulnerable plaques such as PR, endothelial dysfunction-related dilatation responses may be reduced in the presence of inflammatory insult or oxidative stress [34,35]. On the other hand, PR-related maximal stretching of smooth muscle cells may restrict dilatation responses. Moreover, a moderately stenotic lesion in the presence of PR is a phenomenon observed in the initial phase of coronary artery atherosclerosis, and the dilatation response of

microvascular vessels may be relatively maintained in many patients. In addition, many such lesions are eccentric; therefore, partial vascular elasticity is maintained at the healthy level, and vascular distortion related to Venturi effects at the stenotic site is marked. As a result, the degree of stenosis may become greater, increasing the rate of decrease in the FFR. With a maximum hyperemia-related increase in the flow volume, a reduction in the pressure mediated by Venturi effects may become more marked than at rest; the degree of distortion-related stenosis may become much greater [28,36]. Mechanisms other than nitroglycerin are specific to the FFR through maximum hyperemia. This supports the finding that the presence of PR was a significant factor in patients with an FFR-positive, iFR-negative pattern. On the other hand, significant relevant factors for FFR-negative, iFR-positive findings included a small lumen volume/vessel volume and large plaque volume/vessel volume in the univariate analysis. However, there was no significant relevant factors in the multivariate analysis.

The present findings have following clinical application. In the case of FFR-positive and iFR-negative, there is a high possibility that lesion has high risk plaque features while diffuse coronary atherosclerosis lesions has not progressed. Therefore, optimal medical therapy for stabilizing plaque would necessary. In the case of iFR-positive and FFR-negative, coronary atherosclerosis lesions may have

progressed in the diffuse and microcirculatory disturbance may have occurred, so revascularization would be positively considered.

Limitation

This study has some limitations. First, this was a single-center study, and the number of subjects was small. Second, the target vessel myocardial weight was calculated using Voronoi's method. However, it was calculated based on the perfusion ranges of only the main branch in LAD, RCA, and LCX; therefore, the influence of target vessel lateral branches was not considered.

Conclusion

On CCTA characteristics, while relevant factor for FFR positive findings included low L/M ratio, there was no relevant factor for iFR positive findings. Furthermore, in FFR-positive, iFR-negative patients among those with a discordance between the FFR and iFR, relevant factors included the presence of PR. In contrast, in FFR-negative, iFR-positive patients, there were no significant relevant factors.

Conflict of interest

Dr. Aoki has received a research agreement with Daiichi-Sankyo Company, Medi-Physics Co., FUJIFILM Toyama Chemical Co. and Bayer Holding Ltd. Dr. Daida has a research agreement from Canon Medical Systems Corporation, Daiichi-Sankyo Company and Medi-Physics Co. and he has received speakers' Bureau/Honoraria from FUJIFILM Toyama Chemical Co., Daiichi-Sankyo Company and ABBOTT JAPAN Co. that is not related to this study.

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Tables

Table 1. (A) patient characteristics of all study patients

(B) Scan characteristics of all study patients

(C) Vessel characteristics of all target vessels

CACS, coronary artery calcium score; eGFR, estimated glomerular filtration rate; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; HbA1c, hemoglobin A1c; DLP, Dose Length Product; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; L/M ratio, Lumen volume/ Myocardial weight (mm^3/g); CCTA, coronary CT angiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; SD,

standard deviation; IQR, interquartile range

Table 2. (A) Predictors for FFR≤0.8 findings on a per patient basis by univariate logistic regression analysis.

(B) Predictors for FFR≤0.8 findings on a per vessel basis by univariate logistic regression analysis.

(C) Predictors for FFR≤0.8 findings on a per vessel basis by multivariate logistic regression analysis.

eGFR, estimated glomerular filtration rate; CACS, coronary artery calcium score; FFR, fractional flow reserve; LAD, left anterior descending artery; L/M ratio, Lumen volume/ Myocardial weight (mm^3/g); FFR, fractional flow reserve; iFR, instantaneous wave-free ratio

Table 3. (A) Predictors for iFR≤0.89 findings on a per patient basis by univariate logistic regression analysis.

(B) Predictors for iFR≤0.89 findings on a per vessel basis by univariate logistic regression analysis.

(C) Predictors for iFR≤0.89 findings on a per vessel basis by multivariate logistic regression analysis.

CACS, coronary artery calcium score; iFR, instantaneous wave-free ratio; LAD, left anterior descending artery; L/M ratio, Lumen volume/ Myocardial weight (mm^3/g)

Table 4. (A) Predictors of Discordance between FFR≤0.8 and iFR>0.89 on a per vessel basis by univariate and multivariate logistic regression analysis.

(B) Predictors of Discordance between FFR>0.8 and iFR≤0.89 on a per vessel basis by univariate and multivariate logistic regression analysis.

L/M ratio, Lumen volume/ Myocardial weight (mm^3/g); FFR, fractional flow reserve; iFR, instantaneous wave-free ratio

Figure 1. Representative patient with FFR-positive and iFR-negative (discordant) results.

CCTA revealed intermediate focal stenotic plaque with positive remodeling and spotty calcification in the LAD proximal portion (A). Invasive coronary angiography confirmed the findings on CCTA (B). Invasive FFR and iFR in the distal part of the lesion were 0.73 and 0.90, respectively. FFR was positive and iFR was negative. Lumen volume, vessel volume and plaque characteristics were analyzed by software Sure Plaque Research Version. Positive remodeling (remodeling index 1.19) was observed in this lesion (C).

LAD, left anterior descending artery; CCTA, Coronary computed tomography angiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio

Table1A. Patient characteristics of all study patients (n=83)

Age (y.o)	67.1±9.7	Labo data	
Male	53 (63.9%)	eGFR	75.6±19.2
Body mass index (kg/m2)	24.2±3.3	Total cholesterol(mmol/L)	4.8±1.1
coronary risk factor		Triglyceride(mmol/L)	1.7±1.0
Hypertension	53 (63.9%)	HDL cholesterol(mmol/L)	1.3±0.3
Dyslipidemia	60 (72.2%)	LDL cholesterol(mmol/L)	2.8±0.8
Diabetes mellitus	43 (51.8%)	HbA1c (%)	6.7±1.3
Current smoking	14 (16.9%)		
Agaston Score			
Total CACS (3 vessels)		total CACS ≤100	32 (38.6%)
Mean ± SD	482.5±676.5	100<total CACS≤400	20 (24.1%)
Median [IQR]	299.4[70.6, 763.5]	400<total CACS	31 (37.3%)
Target Vessel CACS		target vessel CACS≤50	32 (30.5%)
Mean ± SD	6.1±1.9	50<target vessel CACS≤100	22 (21.0%)
Median [IQR]	85.6[32.0, 275.1]	100<target vessel CACS	51 (48.6%)

Table1B. Scan characteristics of all study patients

Heart Rate (bpm)	54.5 ± 5.6
Nitrates Administered (%)	100% (83/83)
B blocker Administered (%)	None：18.1% (15/83)
	Oral：59.0% (49/83)
	Intravenous：3.6% (3/83)
	Oral & Intravenous：19.2% (16/83)
Scan range(mm)	120mm: 24 cases
	128mm: 2 cases
	130mm: 12 cases
	140mm: 41 cases
	160mm: 4 cases
DLP (mGy・cm)	203.4 ± 132.1
Effective dose (mSv)	5.7 ± 3.2
Tube Voltage (kV)	100kV:88.0% (73/83)
	120kV:12.0% (10/83)
Tube Current (mA)	546.9±19.1

Table1C. Vessel characteristics of all study vessels (n=105)

Target vessel (%)		CACS (Target vessel)	213.2±334.1
LAD	70 (66.7%)	lumen volume / vessel volume (%)	40.4±8.5
LCX	18 (17.1%)	plaque volume /vessel volume (%)	59.9±10.3
RCA	17 (16.2%)	necrotic core area /vessel volume (%)	1.2±1.5
Characteristic of plaque		Max plaque burden	87.4±7.3
Non-calcified plaque	30 (28.6%)	plaque length (mm)	28.6±13.5
Partially calcified plaque	32 (30.5%)	Diameter stenosis(%DS) (%)	47.7±17.4
Calcified plaque	43 (41.0%)	Minimum lumen area (MLA) (mm2)	2.2±1.7
Vulnerable plaque			
Positive remodeling	34 (32.4%)	target L/M ratio (mm3/g)	15.7±10.9
Patient with FFR≤0.80	39 (47.0%)	Patient with stenosis >50% by CCTA	69(83.1%)
Vessel with FFR≤0.80	42 (40.0%)	Vessel with stenosis >50% by CCTA	72 (68.6%)
Patient with iFR≤0.89	30 (36.1%)	Vessel with FFR≤0.80 and iFR >0.89	15 (14.3%)
Vessel with iFR≤0.89	34 (32.4%)	Vessel with FFR > 0.80 and iFR≤0.89	7 (6.7%)

Table2A. Predictors for FFR≤0.8 findings on a per patient basis by univariate logistic regression analysis.

	OR	95%CI	P value
Age	1.00	0.95-1.04	0.9160
Male	1.02	0.42-2.50	0.9648
Body mass index (kg/m2)	1.08	0.95-1.24	0.2304
Coronary risk factor			
Hypertension	1.16	0.63-3.86	0.3360
Dyslipidemia	1.56	0.58-4.14	0.3728
Diabetes mellitus	0.79	0.33-1.88	0.5958
Current smoking	1.16	0.37-3.65	0.8045
Labo data			
eGFR	1.01	0.99-1.04	0.3021
Total cholesterol (mmol/L)	0.99	0.98-1.00	0.1841
Triglyceride (mmol/L)	0.99	0.99-1.00	0.0463
HDL cholesterol (mmol/L)	1.01	0.98-1.04	0.5787
LDL cholesterol (mmol/L)	1.00	0.98-1.01	0.6862
HbA1c (%)	0.80	0.55-1.15	0.2036
Agaston Score (3 vessels total)			
total CACS ≤100	0.81	0.33-1.97	0.6394
100<total CACS≤400	0.69	0.25-1.91	0.4709
400<total CACS	1.66	0.68-4.06	0.2684

Table2B. Predictors for FFR≤0.8 findings on a per vessel basis by univariate logistic regression analysis.

	OR	95%CI	P value
positive remodeling (%)	0.90	0.39-2.07	0.7981
lumen volume / vessel volume (%)	**0.94**	**0.89-0.98**	**0.0066**
plaque volume /vessel volume (%)	**1.05**	**1.00-1.10**	**0.0296**
necrotic core volume / plaque volume (%)	0.99	0.97-1.02	0.6869
Maximum plaque burden (%)	**1.07**	**1.01-1.15**	**0.0171**
plaque length (mm)	0.99	0.97-1.02	0.7258
Diameter stenosis(%DS) (%)	1.02	0.99-1.04	0.1910
Minimum Lumen Area (mm2)	**0.58**	**0.41-0.86**	**0.0009**
LAD	**5.11**	**1.89-13.86**	**0.0005**
L/M ratio (mm3/g)	**0.90**	**0.84-096**	**<0.0001**
Agaston Score (target vessel)			
target vessel CACS≤50	0.86	0.37-2.02	0.7286
50<target vessel CACS≤100	1.05	0.40-2.73	0.9221
100<target vessel CACS	1.10	0.50-2.40	0.8110

Table2C. Predictors for FFR≤0.8 findings on a per vessel basis by multivariate logistic regression analysis.

	OR	95%CI	P value
lumen volume / vessel volume (%)	0.97	0.87-1.08	0.5167
plaque volume /vessel volume (%)	0.99	0.91-1.08	0.7194
Maximum plaque burden (%)	1.0	0.92-1.11	0.8404
Minimum Lumen Area (mm2)	0.71	0.40-1.09	0.1214
LAD	**3.55**	**1.20-11.71**	**0.0217**
L/M ratio (mm3/g)	**0.93**	**0.86-0.99**	**0.0290**

Table3A. Predictors for iFR≤0.89 findings on a per patient basis by univariate logistic regression analysis.

	OR	95%CI	P value
Age	1.00	0.96-1.05	0.9687
Male (%)	0.49	0.20-1.25	0.1354
Body mass index (kg/m2)	1.14	0.99-1.32	0.0563
Coronary risk factor			
Hypertension	1.21	0.32-2.11	0.6875
Dyslipidemia	1.89	0.65-5.48	0.2300
Diabetes mellitus	1.68	0.68-4.17	0.2598
Current smoking	0.66	0.19-2.3	0.5116
Labo data			
eGFR	1.00	0.97-1.02	0.8593
Total cholesterol(mmol/L)	0.99	0.98-1.00	0.1467
Triglyceride(mmol/L)	1.00	0.99-1.00	0.4545
HDL cholesterol(mmol/L)	0.98	0.95-1.02	0.3165
LDL cholesterol(mmol/L)	1.00	0.98-1.01	0.5429
HbA1c(%)	1.11	0.79-1.56	0.5530
Agaston Score (3 vessels total)			
total CACS ≤100	0.56	0.22-1.45	0.2244
100<total CACS≤400	0.69	0.24-2.06	0.5073
400<total CACS	2.31	0.92-5.83	0.0745

Table3B. Predictors for iFR≤0.89 findings on a per vessel basis by univariate logistic regression analysis.

	OR	95%CI	P value
1+log(CACS of target vessel)	1.10	0.88-1.38	0.3906
positive remodeling (%)	0.42	0.16-1.10	0.0673
lumen volume / vessel volume (%)	**0.90**	**0.85-0.95**	**0.0001**
plaque volume /vessel volume (%)	**1.11**	**1.05-1.18**	**<0.0001**
necrotic core volume / plaque volume (%)	1.23	0.94-1.60	0.1225
Maximum plaque burden (%)	**1.07**	**1.00-1.14**	**0.0344**
plaque length (mm)	1.01	0.98-1.04	0.6321
Diameter stenosis(%DS) (%)	1.02	0.99-1.04	0.1334
Minimum Lumen Area (mm^2)	**0.61**	**0.41-0.90**	**0.0030**
LAD	**4.24**	**1.47-12.2**	**0.0034**
L/M ratio (mm3/g)	**0.92**	**0.86-0.98**	**0.0014**
Agaston Score			
target vessel CACS≤50	0.60	0.24-1.53	0.2780
50<target vessel CACS≤100	0.74	0.26-2.09	0.5603
100<target vessel CACS	1.84	0.80-4.22	0.1451

Table3C. Predictors for iFR≤0.89 findings on a per vessel basis by multivariate logistic regression analysis.

	OR	**95%CI**	**P value**
lumen volume / vessel volume (%)	1.22	0.68-2.17	0.4072
plaque volume /vessel volume (%)	1.34	0.75-2.37	0.0609
Maximum plaque burden (%)	0.96	0.86-1.06	0.3830
Minimum Lumen Area (mm2)	0.72	0.42-1.26	0.2161
LAD	**3.86**	**1.12-13.31**	**0.0236**
L/M ratio (mm3/g)	0.97	0.90-1.04	0.3680

Table4A. Predictors of Discordance between FFR≤0.8 and iFR>0.89 on a per vessel basis by univariate and multivariate logistic regression analysis.

	univariate analysis			multivariate analysis		
	OR	95%CI	P-value	OR	95%CI	P-value
Positive remodeling (%)	**5.03**	**1.23-20.48**	**0.0205**	**5.32**	**0.98-28.94**	**0.0415**
plaque length (mm)	0.98	0.93-1.04	0.5280			
lumen volume / vessel volume (%)	**1.08**	**1.00-1.17**	**0.0473**	0.78	0.34-1.80	0.4062
plaque volume/vessel volume (%)	**0.91**	**0.84-0.98**	**0.0071**	0.72	0.32-1.62	0.1011
necrotic core volume / plaque volume (%)	0.84	0.53-1.32	0.4172			
plaque burden (%)	0.98	0.88-1.10	0.7664			
Diameter stenosis(%DS) (%)	1.00	0.95-1.04	0.8861			
Minimum Lumen Area (mm2)	1.46	0.72-2.95	0.2877			
Myocardial weight(g)	1.02	0.99-1.06	0.136			
L/M ratio (mm3/g)	1.05	0.95-1.17	0.2976			

Table4B. Predictors of Discordance between FFR>0.8 and iFR≤0.89 on a per vessel basis by univariate and multivariate logistic regression analysis.

	univariate analysis			multivariate analysis		
	OR	95%CI	P-value	OR	95%CI	P-value
Positive remodeling (%)	0.78	0.14-4.40	0.7743			
plaque length (mm)	1.01	0.97-1.07	0.5626			
lumen volume / vessel volume (%)	**0.88**	**0.78-1.00**	**0.0351**	2.36	0.70-8.03	0.1578
plaque volume/vessel volume (%)	**1.14**	**1.01-1.29**	**0.0230**	2.69	0.79-9.17	0.0991
necrotic core volume / plaque volume (%)	1.32	0.87-2.01	0.2145			
plaque burden (%)	1.07	0.94-1.21	0.2602			
Diameter stenosis(%DS) (%)	1.03	0.98-1.08	0.2122			
Minimum Lumen Area (mm2)	0.75	0.42-1.34	0.2776			
Myocardial weight(g)	1.02	0.98-1.07	0.2661			
L/M ratio (mm3/g)	0.97	0.88-1.06	0.3876			