Optical Coherence Tomography-Derived Anatomical Criteria for Functionally Significant Coronary Stenosis Assessed by Fractional Flow Reserve

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Background: For the identification of functionally significant coronary artery disease, there have not been any dedicated optical coherence tomography (OCT) studies reported previously, although OCT can clearly detect coronary vessel lumina at higher resolution than intravascular ultrasound (IVUS).

Methods and Results: OCT and fractional flow reserve (FFR) measurements were performed in 62 intermediate coronary lesions in 59 patients. FFR was calculated as the ratio of distal coronary pressure divided by proximal coronary pressure during maximal hyperemia. FFR <0.75 was used as the threshold for diagnosing functionally significant stenosis. Minimal lumen area (MLA), minimal lumen diameter (MLD) and percent lumen area stenosis were measured by OCT. FFR values correlated significantly with OCT-derived MLA ($r=0.75$, $P<0.01$), MLD ($r=0.76$, $P<0.01$) and percent lumen area stenosis ($r=-0.77$, $P<0.01$). Receiver-operating characteristic curve suggested an OCT-derived MLA <1.91 mm² (sensitivity 93.5%, specificity 77.4%), MLD <1.35 mm (sensitivity 90.3%, specificity 80.6%) and percent lumen area stenosis >70.0% (sensitivity 96.8%, specificity 83.9%) as the best cutoff values for a FFR <0.75.

Conclusions: Anatomical measurements of coronary stenosis obtained by OCT show significant correlation with FFR. OCT has the potential to predict functionally significant stenosis, although the present OCT-derived parameters were smaller than those reported in previous IVUS studies. (*Circ J* 2012; **76**: 2218–2225)

Key Words: Fractional flow reserve; Intermediate coronary stenosis; Optical coherence tomography

In patients with coronary artery disease, the presence of myocardial ischemia is an important risk factor for adverse clinical outcome.¹ Although coronary angiography (CAG) is the standard method for evaluating coronary lesions,² visual estimation of lesion severity on CAG, even with quantitative CAG, is not guaranteed to accurately predict the presence of myocardial ischemia. Noninvasive stress tests before diagnostic CAG are often not performed, and the results are sometimes inconclusive.³ At present, several intracoronary modalities can be used, such as pressure wire, intravascular ultrasound (IVUS), and optical coherence tomography (OCT), to evaluate coronary lesions accurately. Fractional flow reserve (FFR) measured by pressure wire is an established index for invasively evaluating the functional significance of coronary

stenosis.⁴ The presence of inducible myocardial ischemia determines the potential benefit of the revascularization procedure.^{5,6} FFR-guided percutaneous coronary intervention (PCI) is associated with reduced major adverse cardiac events.^{7–9}

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Previous studies have demonstrated that the minimal lumen area (MLA) measured by IVUS correlates with FFR and that a MLA <3.0 mm² or <4.0 mm² is a useful threshold for predicting functionally significant stenosis with a FFR <0.75.^{10,11}

Recently, we used OCT, which has a 10-fold higher resolution than IVUS, to investigate coronary artery disease.^{12,13} With its excellent resolution, OCT provides not only detailed mor-

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phological information, but also clear anatomical quantitative information about coronary lesions. Furthermore, OCT is useful for risk stratification of PCI patients, including predicting the post-procedure no-reflow phenomenon.¹⁴ However, the relationship between anatomical quantitative measurement by OCT and FFR has not been investigated. The aims of this study, therefore, were to (1) investigate the relationship between quantitative OCT parameters and FFR, and (2) assess whether quantitative OCT measurements can predict the functional severity of coronary lesions evaluated by FFR.

Methods

Study Population

Between January 2007 and August 2011, 59 patients with 62 coronary lesions who had undergone both OCT and physiological assessment by pressure wire at diagnostic catheterization or before PCI were retrospectively examined. All patients were interviewed about their medical history and their cardiac function was evaluated by echocardiography (Simpson's method) before cardiac catheterization. They all had at least 1 target vessel with stenosis (>30% diameter stenosis by visual estimation) including de novo or in-stent restenosis lesions. We excluded multiple stenoses in the same epicardial coronary artery (tandem lesion, >2 stenoses in the same coronary artery by visual estimation), bypass graft disease, left main coronary artery disease, side-branch lesions, presence of collateral vessels, and thrombi-containing lesions. Written informed consent was given by all patients participating in the study.

Cardiac Catheterization

After intravenous administration of 8,000 IU heparin, a 5 or 6Fr catheter without side holes was seated in the coronary ostium via the transradial or transfemoral artery approach. After intracoronary administration of 2.0 mg of isosorbide dinitrate through a catheter, CAG was performed in multiple projections.

Angiographic Analysis

Quantitative angiographic analysis (QCA) was performed by standard techniques with an automated edge-detection algorithm (CASS-5, Pie Medical, Maastricht, the Netherlands) by an independent investigator (K.K.) who was unaware of the clinical presentations, results of FFR measurements, and OCT findings. Image calibration was performed with a contrast-filled catheter. The external diameter of the catheter was used as the calibration standard. Coronary end-diastolic frames from matched views obtained by angiography were analyzed with an automated contour detection system. Reference lumen diameter, minimal lumen diameter (MLD), and lesion length were measured. Percent diameter stenosis was calculated as the reference lumen diameter minus the MLD divided by the reference lumen diameter.

FFR Measurement

To measure distal coronary pressure, a 0.014-inch pressure guidewire (Pressure wire 5 or Certus, St. Jude Medical, Uppsala, St. Paul, MN, USA) was advanced across the stenosis, and the pressure sensor was positioned as distal to the coronary stenosis as possible. Proximal coronary pressure was recorded by the guiding catheter. Maximal hyperemia was induced by continuous adenosine triphosphate (ATP: $150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) infusion via the femoral vein. In the case of an intermediate FFR measurement of 0.75–0.80 or uncertain maximal hyper-

emia, the dose of ATP was increased to $180 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. FFR is calculated as the mean distal coronary pressure (measured with the pressure guidewire) divided by the mean aortic pressure (measured simultaneously via a 5 or 6Fr catheter) during maximal hyperemia. Based on the results of earlier studies,^{4,15} the stenosis was considered functionally significant with FFR <0.75. At the end of the FFR measurement, the pressure guidewire was manually pulled back slowly from the most distal to the most proximal part of the artery during induced steady-state maximal hyperemia in all patients. When the pressure sensor was pulled back into the guiding catheter, both pressures were checked to exclude transducer drift. If there was a difference >5 mmHg between the pressure of the guiding catheter and the pressure of the guidewire, the FFR values were corrected by manual recalculation.

OCT Imaging Acquisition

We used a time-domain OCT system (TD-OCT, M2, LightLab Imaging, Inc, Westford, MA, USA).¹² For the TD-OCT procedure, the z-offset was adjusted before acquisition of every image while holding the image wire between 2 fingers and advancing it distal to the target stenosis. All OCT procedures used the conventional occlusion technique. The targeted coronary artery was occluded using an occlusion balloon catheter (OBC) at the proximal site of the targeted stenosis followed by flushing with lactate Ringer's or low-molecular-weight dextran from the tip of the OBC at a rate of 0.5 ml/s. The refraction index was adjusted to each flushing solution used. All OCT images were obtained using the automatic pullback function at a rate of 1.0 mm/s. The frame rate of image acquisition was 15.6 frames/s.

OCT Quantitative Analysis

Analysis of OCT images was performed with proprietary LightLab software for offline analysis (LightLab Imaging) by an independent investigator (K.I.) who was unaware of the QCA data and the results of FFR measurements. Data were imported to the workstation in the LightLab database format. The lumen contour was obtained using an automated detection algorithm available in LightLab, and additional manual corrections were performed if necessary. MLA was defined as the smallest lumen area along the length of the target lesion, and MLD was defined as the smallest lumen diameter from 1 intimal leading edge to another along any line passing through the center of the lumen. The reference lumen area was defined as the site with the largest lumen either proximal or distal to the stenosis within the same segment (within 10 mm of the stenosis with no major intervening branches), and the mean reference lumen area was calculated as the distal plus proximal reference lumen areas divided by 2. Percent luminal area stenosis was defined as the relative decrease in luminal area of the target lesion when compared with the reference lumen area in the same vessel segment. Percent luminal area stenosis was calculated as the mean reference lumen area minus the MLA divided by the mean reference lumen diameter. Lesion length was defined as the length between the proximal and distal references measured by the duration of the pullback and the pullback speed of the imaging catheter.

Statistical Analysis

Statistical analysis was performed using SPSS (version 11.0, SPSS Inc, Chicago, IL, USA). Values are expressed as mean $\pm$ standard deviation for continuous variables or as number and percentage for categorical variables. The relationship and variability between FFR and quantitative OCT parameters in the

Table 1. Patients' Characteristics (n=59)

Men, n (%)	49 (79.0)
Age, years	66.9±10.9
Body height, cm	164.1±7.7
Body weight, kg	66.3±11.4
Body mass index	24.5±3.1
Ejection fraction, %	58.8±7.3
Dyslipidemia, n (%)	45 (76.3)
Hypertension, n (%)	51 (86.4)
Diabetes mellitus, n (%)	34 (57.6)
Hemodialysis, n (%)	2 (3.4)
Current smoking, n (%)	34 (57.6)
Familial history, n (%)	11 (18.6)
Previous myocardial infarction, n (%)	22 (37.2)

Values are presented as mean±SD or n (%).

Table 2. Lesion Characteristics (n=62)

Lesion location	
Left anterior descending, n (%)	37 (59.7)
Right coronary artery, n (%)	16 (25.8)
Circumflex artery, n (%)	9 (14.5)
QCA parameters	
Reference diameter, mm	3.17±0.51
% Diameter stenosis, %	58.2±17.0
Minimum lumen diameter, mm	1.30±0.56
Lesion length, mm	20.2±12.2
Physiological parameter	
Fractional flow reserve	0.72±0.14

Values are presented as mean±SD or n (%).
QCA, quantitative coronary angiography.

Table 3. OCT Parameters (n=62)

Minimum lumen area, mm ²	1.90±0.94
Minimum lumen diameter, mm	1.33±0.38
Proximal reference lumen cross-sectional area, mm ²	6.79±1.74
Distal reference lumen cross-sectional area, mm ²	5.82±1.76
Mean reference lumen cross-sectional area, mm ²	6.30±1.72
Lumen area stenosis, %	68.9±15.4
Lesion length, mm	18.74±9.71

Values are presented as mean±SD.
OCT, optical coherence tomography.

scattergrams were analyzed using Pearson's correlation coefficient test. A receiver-operating characteristic curve was used to determine the best cutoff values of quantitative OCT parameters to predict an FFR <0.75. The best cutoff value was defined as the value with the highest sum of sensitivity and specificity. P<0.05 was considered statistically significant.

Results

Patients' Characteristics

The patients' characteristics are summarized in **Table 1**. A total of 34 patients (57.6%) had diabetes mellitus and 51 (86.4%) had hypertension. The average ejection fraction was 58.8±7.3%.

Lesion Characteristics

The study vessels and lesion locations are shown in **Figure 1**. The left anterior descending artery (LAD) was the most common studied vessel (37 lesions, 62.7%). Offline QCA was per-

Figure 1. Studied vessels and lesion location. Lesions (n=62) included 37 in the left anterior descending artery (LAD), 9 in the left circumflex coronary artery (LCX) and 16 in the right coronary artery (RCA).

formed for all study lesions (Table 2). The average reference vessel diameter, MLD, diameter stenosis and lesion length were 3.17 ± 0.51 mm, 1.30 ± 0.56 mm, $58.2 \pm 17.0\%$, and 20.2 ± 12.2 mm, respectively.

Quantitative OCT Measurement

All OCT image acquisitions were successfully performed without serious complications. The results of quantitative OCT measurements are summarized in Table 3. Mean MLA, reference lumen area, percent lumen area stenosis and lesion length

were 1.90 ± 0.94 mm² (range, 0.52–4.55 mm²), 6.30 ± 1.72 mm² (range, 3.74–11.40 mm²), $68.9 \pm 15.4\%$ (range, 10.4–90.0%) and 18.74 ± 9.71 mm (range, 5.3–39.2 mm), respectively.

FFR Measurement

Coronary pressure was successfully measured, and FFR was calculated in all cases. There were 4 cases (6.5%) of pressure drift and the FFR values were corrected by manual recalculation. In 12 cases (20.3%) of an intermediate FFR value (0.75–0.80) or uncertain maximal hyperemia, we increased the dose

of ATP up to $180 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, but FFR values did not change from negative (FFR ≥ 0.75) to positive (<0.75) in any case. The overall median FFR was 0.72 ± 0.14 (range, 0.35–1.0). FFR <0.75 was observed in 31 lesions (50.0%).

FFR and QCA Measurement

FFR correlated positively with MLD ($r=0.66$, $P<0.01$) and negatively with percent diameter stenosis ($r=-0.67$, $P<0.01$).

FFR and OCT Measurement

FFR correlated significantly with OCT-measured MLA ($r=0.75$, $P<0.01$), MLD ($r=0.76$, $P<0.01$) and percent luminal area stenosis ($r=-0.77$, $P<0.01$) (Figure 2). The best cutoff value of the OCT-measured MLA for predicting FFR <0.75 was 1.91 mm^2 (sensitivity: 93.5%; specificity: 77.4%; positive predictive value (PPV): 80.6%; negative predictive value (NPV): 92.3%; accuracy: 85.4%; area under the curve (AUC): 0.904; and 95% confidence interval (CI): 0.829–0.978). The best

cutoff value of the OCT-measured MLD was 1.35 mm (sensitivity: 90.3%; specificity: 80.6%; PPV: 84.4%; NPV: 84.6%; accuracy: 85.5%; AUC: 0.917; and 95% CI: 0.851–0.984), and the best cutoff value of the OCT-measured percent luminal area stenosis was 70.0% (sensitivity: 96.8%; specificity: 83.9%; PPV: 85.7%; NPV: 96.3%; accuracy: 90.3%; AUC: 0.940; and 95% CI: 0.883–0.997) (Figure 3). The 23 vessels with MLA >1.91 mm² and percent luminal area stenosis <70% all presented a negative value (ie, FFR ≥0.75). In contrast, when the OCT-derived MLA and percent luminal area stenosis were both under those cutoff points, 28 (90.3%) of 31 vessels demonstrated a positive FFR value <0.75 (Figure 4).

Discussion

The major findings of the present study are: (1) OCT-measured parameters showed a significant correlation with FFR values and (2) anatomically based OCT identified the best cutoff values for predicting FFR <0.75 were MLD <1.35 mm, MLA <1.91 mm² and percent luminal area stenosis >70.0%, all of which were associated with the functional severity of coronary stenosis. However, the best cutoff values of MLA and MLD measured by OCT in the present study were smaller than those reported in previous IVUS studies.^{10,11}

Several studies have reported a good correlation between FFR and IVUS-derived MLA for assessing coronary lesion severity. Since the late 1990s, an IVUS-derived MLA <3.0 mm² or <4.0 mm² has been suggested as a threshold for detecting functionally significant stenosis with FFR <0.75.^{10,11} Therefore, we also defined coronary lesions with FFR <0.75 as functionally significant stenosis.^{4,15}

In contrast, a recent study¹⁶ with a larger study population than previously demonstrated an IVUS-derived MLA <2.4 mm² as the best cutoff point for FFR <0.80, currently defined by consensus.⁹ This suggests that the cutoff value of MLA corresponding to FFR <0.75 is <2.4 mm², even with IVUS.

Moreover, the anatomic measurements of coronary lesions obtained using IVUS differ according to vessel size. Several studies investigating the IVUS parameters that correspond to functionally significant coronary stenosis have demonstrated different cutoff values of IVUS-derived MLA (range, 2.0–4.0 mm²) according to the reference lumen area (range, 5.5–11.9 mm²). On the other hand, the cutoff values of percent luminal stenosis were consistently 60–70%.^{10,11,16–21} The reference lumen area of 6.30 mm² in the present study was relatively small, which might have led to the smaller OCT-derived MLA cutoff value of 1.91 mm². However, the cutoff value of lumen area stenosis of 70% corresponded to previous IVUS reports.

Several studies have reported that coronary lumen dimensions measured by OCT are smaller than those measured by IVUS.^{22,23} Yamaguchi et al evaluated the in vivo differences between IVUS and OCT for human coronary lumen dimensions and found that MLA was significantly smaller when measured by OCT with occlusion technique than when measured by IVUS (mean difference, 0.4 mm²).²² Gonzalo et al also reported the lumen area measured by OCT with and without occlusion as much smaller than that measured by IVUS (mean difference of 1.67 mm² with occlusion technique and 1.11 mm² with non-occlusion technique).²³ Several explanations of this phenomenon are proposed. The IVUS catheter may stretch small arteries (Dotter effect), because of its large size (3Fr [1.0 mm]) compared with an OCT image wire (0.016 inches [0.41 mm]), producing an artificially larger vessel size. Intra-

		Percent luminal area stenosis, %	
		>70	≤70
MLA, mm ²	<1.91	FFR <0.75 : 28 FFR ≥0.75 : 3	FFR <0.75 : 1 FFR ≥0.75 : 4
	≥1.91	FFR <0.75 : 2 FFR ≥0.75 : 0	FFR <0.75 : 0 FFR ≥0.75 : 23

Figure 4. Combination of OCT-derived cutoff values. Combining both criteria of OCT-derived MLA and percent luminal area stenosis showed a high potential to predict the presence or absence of functionally significant coronary artery stenosis. OCT, optical coherence tomography.

coronary perfusion pressure may be reduced during balloon inflation followed by continuous injection at a rate of 0.5 ml/s to eliminate red blood cells, and the pressure reduction may generate smaller artificial vessel dimensions during OCT image acquisition. The greater resolution of OCT enables optimal definition of the lumen-plaque border compared with IVUS imaging. Finally, slight z-offset drift during OCT image acquisition may lead to misreading measurement of vessel dimensions. Therefore, the cutoff value of OCT-derived MLA, especially when performed with the occlusion technique, for predicting functionally significant stenosis should be smaller than IVUS-derived MLA. The cutoff value of an OCT-derived MLA of <1.91 mm² for functionally significant stenosis is feasible. Moreover, the effect of the MLA on functional significance should differ according to the reference vessel size for each lesion. We need to take into consideration not only MLA but also percent luminal area stenosis. The combination of MLA and percent luminal area stenosis criteria could provide more accurate assessment of significant coronary stenosis.

Finally, we have to keep in mind that even IVUS for assessment of non-left main coronary arteries with intermediate coronary stenosis is classified as class IIb in the current ACC/AHA/SCAI PCI guidelines.²⁴ And the appropriate role of OCT on this issue has not been established yet. Anatomical parameters do not always predict functional significance, because the functional severity of a coronary lesion depends on not only the anatomical severity itself of the epicardial coronary lesion but also many other factors such as the lesion's location, the perfusion territory of each coronary vessel in where the target lesion exists, and so on. Our results also demonstrated that any OCT-derived cut off values had only moderate PPV. On the other hand, the NPVs of the OCT parameters were notably high. These results are consistent with a recent IVUS study.¹⁶ Intravascular imaging modalities, including IVUS and OCT, might have a higher potential for excluding the absence of ischemia rather than predicting the presence of ischemia.

Study Limitations

First, this was a retrospective study with a small sample population. Second, factors of epicardial coronary stenosis that disturb coronary flow are not only lesion dimension, but also lesion length. However, we used only dimensional parameters when analyzing the relationship between FFR and OCT measurement to simplify the evaluation of coronary stenosis. Fur-

thermore, lesion dimension influences coronary resistance more notably than does lesion length, because epicardial coronary resistance increases linearly according to lesion length and exponentially according to the extent of narrowing, based on Poiseuille's law.

Third, the cutoff values of OCT-derived coronary lesion parameters for predicting functionally significant stenosis may vary with the location of the coronary stenosis. In other words, the cutoff value of OCT-derived coronary lesion parameters might be affected by the reference vessel's size. For example, a proximal LAD lesion, which has a larger perfusion territory than other lesions, should provide the lowest FFR value if the severity of epicardial coronary stenosis is the same. However, because of the small numbers, we could not identify differences in cutoff values between lesions.

Fourthly, factors that cause deterioration of the microvasculature, such as diabetes mellitus and left ventricular hypertrophy, may affect the FFR value.^{25–28} In addition, accurate measurement of FFR depends on achieving maximal hyperemia in the myocardial territory subtended by the stenosis. Therefore, we tried to obtain maximal hyperemia in all cases by administering adequate amounts of ATP ($150\text{--}180\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).²⁹

Finally, we performed all OCT procedures by TD-OCT using the conventional occlusion technique. There are some limitations with regard to the complex procedure of TD-OCT, as well as technical matters, in a clinical setting. The influence of pressure reduction by balloon occlusion might differ according to lesion morphology, such as severely calcified lesions. The patient's condition during OCT image acquisition using occlusion balloon is quite different from the physiological state during FFR measurement. Therefore, it would be difficult to use the cutoff value of this study under other situations. Furthermore, the TD-OCT image wire is often positioned eccentrically, especially in curved vessel segments, even though centering of the image wire over the entire length of the target segments is very important for obtaining more reliable cross-sectional images. This eccentric position of the image wire may have affected the quantitative analysis by TD-OCT.³⁰

Frequency-domain OCT (FD-OCT) has been developed to overcome many of the technical limitations of the current TD-OCT system, including higher frame rates (100 frame/s), a wider scan diameter (10 mm), and a faster image acquisition rate (20 mm/s) without the loss of image quality. It can be delivered as a rapid exchange catheter over a conventional coronary guidewire.¹² Furthermore, FD-OCT may be able to provide better measurement of vessel dimensions than TD-OCT because its image acquisition method does not require proximal balloon occlusion.^{13,23,31} Hence, further investigations exploring the relationship between coronary dimensions assessed by FD-OCT and FFR are warranted. Our study had similar findings regarding the cutoff of percent lumen area stenosis to those of previous IVUS studies, which guarantees the accuracy of our results.

Conclusions

Anatomical severity of coronary artery stenosis assessed by TD-OCT correlates significantly with FFR values. Moreover, OCT-derived anatomical parameters have the potential to predict functionally significant stenosis with a FFR <0.75 , although the present values were smaller than those previously reported in IVUS studies.

Disclosures

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