Clinical Potential of Intravascular Ultrasound for Physiological Assessment of Coronary Stenosis

Relationship Between Quantitative Ultrasound Tomography and Pressure-Derived Fractional Flow Reserve

Atsushi Takagi, MD; Yukio Tsurumi, MD; Yasuhiro Ishii, MD; Kazuhiro Suzuki, MD; Masatoshi Kawana, MD; Hiroshi Kasanuki, MD

Background—Little is known regarding intravascular ultrasound (IVUS) criteria to determine the functional severity of coronary stenosis. Recently, fractional flow reserve (FFR) has emerged as a lesion-specific index of the functional severity of a coronary stenosis that is independent of systemic hemodynamic variability. The present study was undertaken to determine the IVUS parameters for the physiological severity of coronary stenosis.

Methods and Results—Fifty-one lesions in 42 patients were evaluated by means of quantitative coronary angiogram, IVUS, and intracoronary pressure measurements. The FFR was calculated as the ratio of the distal coronary pressure divided by the proximal coronary pressure under hyperemia. We considered a value of the FFR <0.75 as significant in determining inducible ischemia, according to the previous studies. The minimal luminal area (MLA) and the area stenosis were measured by IVUS. By regression analysis, the MLA showed a positive correlation with the FFR value ($r^2=0.62$, $P<0.0001$). The area stenosis had a significant inverse correlation with the value of FFR ($r^2=0.60$, $P<0.0001$). The IVUS thresholds that maximized the sensitivity and specificity were MLA <3.0 mm$^2$ (sensitivity, 83.0%; specificity, 92.3%) and area stenosis >0.6 (sensitivity, 92.0%; specificity, 88.5%). The combination of both criteria (MLA <3.0 mm$^2$ and area stenosis <0.6) without exception met a value of the FFR <0.75.

Conclusions—Anatomic parameters obtained by IVUS showed a significant correlation to the FFR values. The present study demonstrated that the combination of the MLA and area stenosis measured by IVUS can be an anatomic predictor for the physiological impact of coronary epicardial stenosis. 

Key Words: pressure blood flow ultrasonics

Intravascular ultrasound (IVUS) is a widely accepted modality that can accurately measure the lumen size and vessel size in the setting of coronary intervention. Even though various ultrasonic parameters have been demonstrated to determine the morphological significance of coronary lesions, little is known regarding IVUS criteria for the physiological significance of coronary stenosis. Decision-making without any functional assessment of whether there should be intervention for the stenotic lesion is difficult but is often required in catheterization laboratories.

Coronary pressure and coronary flow measurements obtained by sensor-tipped guidewires have been used to assess the physiological significance of the coronary stenosis. Several studies using coronary flow velocity have attempted to determine the cutoff values of the IVUS parameters in assessing functional severity. Recently, a new concept of the fractional flow reserve (FFR), which is independent of the hemodynamics and specific to epicardial stenosis, has emerged. To date, few data are available regarding the relationship between the IVUS parameters and the FFR, an alternative physiological parameter of coronary stenosis. Accordingly, we sought to evaluate the relationship between the IVUS parameters and the FFR values in patients with coronary artery disease and to clarify whether or not IVUS has the clinical potential to assess the functional severity of coronary stenosis.

Methods

Study Patients

Fifty-one lesions in 42 patients were studied consecutively by quantitative coronary angiography (QCA), IVUS, and intracoronary pressure measurements at diagnostic catheterization or before a catheter intervention. Each vessel studied had an isolated stenosis. Clinical data regarding body weight, height, left ventricular function, and the incidence of prior myocardial infarction were collected individually. Written informed consent for all procedures was obtained from each patient, and the Investigational Review Board of
Cardiac Catheterization
Cardiac medications were not discontinued before catheterization. A guiding catheter without side holes was seated at the coronary ostium. After administration of 5000 IU heparin IV, 2.5 mg of isosorbide dinitrate was given through a guiding catheter, and coronary angiograms were obtained from multiple projections.

Quantitative Coronary Angiography
QCA was performed by an independent analyzer blinded to the results of IVUS and FFR using a computer-assisted, automated edge-detection algorithm (AWOS, Siemens). The external diameter of the contrast-filled catheter was used as the calibration standard. Minimal luminal diameter (MLDQCA), vessel diameter of the reference segment (reference diameter rQCA), and the percent diameter stenosis at end diastole were measured from the worst-view trace. Lesion length was measured as the distance between the proximal and distal shoulders in the projection demonstrating the stenosis with the least foreshortening.

IVUS Analysis
IVUS studies were performed with a 30-MHz IVUS catheter (UltraCross, 3.2F, Boston Scientific Corp/Cardio Vascular Imaging System, Inc) immediately after coronary angiograms. This system incorporated a single-element transducer that rotates at 1800 rpm. Additional intracoronary isosorbide dinitrate was given immediately before IVUS examination. The transducer was pulled back from the distal coronary artery through the target stenosis and to the proximal portion. Images were recorded on S-VHS tapes for offline analysis. Quantitative analysis of the IVUS images was performed by a skilled interpreter blinded to the FFR results and using computerized planimetry (Tape Measure, INDEC Systems). Luminal cross sections were measured at the most stenotic site (minimal luminal area, MLAIVUS) and at the reference vessel. The reference segments were the largest lumen at the proximal 10 mm. The area stenosis was calculated as (reference luminal area minus MLA)/reference luminal area.

Intracoronary Pressure Measurements and the Calculation of FFR
For distal coronary pressure measurement, a 0.014-in pressure wire (Pressure Guide, Radi Medical System) was advanced distally to the stenosis. The proximal coronary pressure was recorded by the guiding catheter. After intracoronary injection of papaverine (10 mg in the right and 12 mg in the left coronary artery), care was taken to disengage the guiding catheter from the coronary ostium to preclude any wedging of the catheter in the vessel and therefore to allow the maximum hyperemic perfusion. Both distal and proximal pressures were measured simultaneously during papaverine-induced hyperemia.

FFR was calculated as the ratio of the mean distal pressure divided by the proximal pressure during hyperemia, as previously reported.8,9 A value of the FFR <0.75 was considered significant for the physiological criterion, based on earlier studies.9,10

Statistical Analysis
Statistical analysis was performed with Stat View 4.5 (Abacus Concepts). The results were given as mean±SD. Differences between continuous variables were analyzed by Student’s t test. A probability value <0.05 was considered statistically significant. In the scattergrams, the relationship and variability between FFR and the IVUS or QCA parameters were analyzed by polynomial regression test. Multivariate regression analysis was used to select the best QCA and IVUS determinants of FFR.

Table 1.

Patient and Lesion Demographics

<table>
<thead>
<tr>
<th>Patients (n=42)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>37 (88.0)</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.0±10.4</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>29 (69.0)</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>162.4±8.7</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>65.2±11.7</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>55.5±7.8</td>
</tr>
<tr>
<td>Lesion (n=51)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending, n (%)</td>
<td>25 (49.0)</td>
</tr>
<tr>
<td>Right coronary artery, n (%)</td>
<td>20 (39.2)</td>
</tr>
<tr>
<td>Circumflex artery, n (%)</td>
<td>6 (11.7)</td>
</tr>
<tr>
<td>Reference diameter rQCA, mm</td>
<td>3.00±0.47</td>
</tr>
<tr>
<td>% Diameter stenosis rQCA</td>
<td>46.1±21.8</td>
</tr>
<tr>
<td>MLDQCA, mm</td>
<td>1.63±0.73</td>
</tr>
<tr>
<td>Lesion lengthQCA, mm</td>
<td>14.2±7.5</td>
</tr>
<tr>
<td>Lesion severityQCA</td>
<td></td>
</tr>
<tr>
<td>Mild stenosis (&lt;30%), n (%)</td>
<td>15 (29.4)</td>
</tr>
<tr>
<td>Intermediate stenosis (30% to 70%), n (%)</td>
<td>26 (51.0)</td>
</tr>
<tr>
<td>Severe stenosis (&gt;70%), n (%)</td>
<td>10 (19.6)</td>
</tr>
<tr>
<td>Reference lumen area MLAIVUS, mm²</td>
<td>9.26±2.72</td>
</tr>
<tr>
<td>MLAIVUS, mm²</td>
<td>3.89±2.02</td>
</tr>
<tr>
<td>Area stenosis MLAIVUS</td>
<td>0.55±0.24</td>
</tr>
</tbody>
</table>

Values are mean±SD where appropriate.

Results

Patient and Lesion Characteristics
Fifty-one coronary arteries in 42 patients were studied (Table 1). Mean patient height was 162.4±8.7 cm, and the mean body weight was 65.2±11.7 kg. Twenty-five lesions were located in the left anterior descending, 20 in the right, and 6 in the circumflex coronary arteries. The mean percent diameter stenosis was 46.1±21.8% (range, 8% to 81%). Half of the lesions studied (26 of 51) were characterized as intermediate stenosis (percent diameter stenosis, >30%, <70%). The mean MLDQCA was 1.63±0.73 mm, and the mean reference diameter rQCA was 3.00±0.47 mm.

In 6 cases, an IVUS catheter was surrounded by plaque over 360°, and ST change was observed. In these cases, the area of the IVUS catheter was considered the MLAIVUS. The mean MLAIVUS was 3.89±2.02 mm² (range, 1.47 to 8.06 mm²). The mean reference lumen area was 9.26±2.72 mm² (range, 3.69 to 14.66 mm²), and the mean area stenosis was 0.55±0.24 (range, 0.02 to 0.84).

Measurement of the FFR
In all cases studied, coronary pressure was successfully measured without serious complications. The mean FFR value was 0.72±0.20 (range, 0.34 to 1.0). There were 25 lesions associated with an FFR value <0.75, which was considered to be physiologically significant.

QCA Versus FFR
There were no differences in the reference diameter rQCA between the vessels with FFR value <0.75 and those with...
FFR ≥0.75. Lesion length was also similar in both groups (Table 2). The 25 lesions associated with FFR <0.75 were much more severe in QCA parameters than those with FFR >0.75. There was a positive relationship between FFR and MLDQCA (r²=0.661, P<0.0001) and an inverse relationship between FFR and percent diameter stenosis QCA (r²=0.582, P<0.0001) (Figure 1A and 1B). The QCA thresholds that maximized the sensitivity and the specificity for FFR <0.75 were MLD QCA, 1.5 mm (sensitivity, 92.0%; specificity, 92.3%) and percent diameter stenosis QCA, 60 (sensitivity, 88.0%; specificity, 88.5%).

**IVUS Versus FFR**

The correlation between IVUS parameters and FFR values was examined (Figure 1C and 1D). Regression analysis demonstrated a significant inverse relationship between MLA IVUS and FFR values (r²=0.62, P<0.0001). The area stenosis also showed a strong inverse correlation to the FFR (r²=0.60, P<0.0001). By multivariate regression analysis, the most independent determinant of FFR among MLA IVUS, area stenosis IVUS, MLD QCA, and percent diameter stenosis QCA was area stenosis measured by IVUS (Table 3). Compared with the value of the FFR <0.75, the sensitivity and specificity curves for the IVUS measurements were observed as in Figure 2. The best agreement with the FFR was found when the area stenosis IVUS was >0.60 (sensitivity, 92.0%; specificity, 88.5%). Another evaluation revealed that the best ultrasound cutoff point was 3.0 mm² for MLA IVUS (sensitivity, 83.0%; specificity, 92.3%). Twenty-two vessels with an MLA IVUS, <3.0 mm² and area stenosis IVUS, >0.60 all presented FFR values <0.75. On the contrary, when the IVUS parameters were both above those cutoff points, 21 of 23 vessels demonstrated FFR measurements ≥0.75 (Figure 3).

### Table 2. Comparison of Angiographic and Ultrasonic Parameters Between Vessels With FFR <0.75 and FFR ≥0.75

<table>
<thead>
<tr>
<th></th>
<th>FFR &lt;0.75 (n=25)</th>
<th>FFR ≥0.75 (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference diameter QCA, mm</td>
<td>2.92±0.58</td>
<td>3.08±0.33</td>
<td>0.2143</td>
</tr>
<tr>
<td>MLD QCA, mm</td>
<td>1.01±0.29</td>
<td>2.22±0.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Diameter stenosis QCA</td>
<td>64.1±13.0</td>
<td>28.8±12.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lesion length QCA, mm</td>
<td>14.5±7.3</td>
<td>14.0±7.9</td>
<td>0.8247</td>
</tr>
<tr>
<td>Reference lumen area QCA, mm²</td>
<td>9.61±2.55</td>
<td>8.91±2.88</td>
<td>0.3620</td>
</tr>
<tr>
<td>MLA IVUS, mm²</td>
<td>2.36±0.84</td>
<td>5.41±2.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Area stenosis IVUS</td>
<td>0.74±0.10</td>
<td>0.36±0.18</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD.

### Table 3. Multivariate Correlates of FFR

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient</th>
<th>Standard Regression Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD QCA</td>
<td>0.153</td>
<td>0.554</td>
<td>0.0295</td>
</tr>
<tr>
<td>% Diameter stenosis QCA</td>
<td>0.001</td>
<td>0.078</td>
<td>0.7381</td>
</tr>
<tr>
<td>MLA IVUS, mm²</td>
<td>0.003</td>
<td>0.034</td>
<td>0.8408</td>
</tr>
<tr>
<td>Area stenosis IVUS</td>
<td>−0.350</td>
<td>−0.422</td>
<td>0.0066</td>
</tr>
</tbody>
</table>

Multiple R² value for model=0.716, F=29.054.
Discussion

To the best of our knowledge, this is the first article to determine the IVUS parameters for the physiological severity of coronary stenosis assessed by FFR. Two major findings can be drawn from our study: (1) The IVUS measurements showed a significant relationship to the FFR values and (2) the IVUS cutoff points of the MLA_{IVUS} 3.0 mm$^2$ and the area stenosis 0.60 had a potential to predict an FFR estimation below or above the ischemic threshold.

In the previous studies, FFR was measured during hyperemia achieved by adenosine.$^8,^{10–12}$ In the present study, we used intracoronary papaverine, which has been shown to be an equal alternative hyperemic agent.$^13$ Papaverine may cause ventricular arrhythmia; however, no serious complications were observed in the present study except for moderate QT prolongation in 2 cases, which normalized spontaneously within 1 minute.

Although automated quantitative analysis has been developed to minimize observer variability and maximize reproducibility,$^{14}$ it is well recognized that the angiogram still has limitations in evaluating the geometry of the coronary arteries$^{15–17}$ and in assessing the functional severity of coronary stenosis.$^{18}$ To date, 2 major techniques for physiological assessment are available in the catheterization laboratories: coronary flow velocity measurements and intracoronary pressure measurements. Coronary flow measurements with the concept of coronary flow reserve (CFR) have been shown to be of great clinical impact on the physiological assessment of coronary stenosis.$^{19}$ It has been validated that the CFR by Doppler wire has a good correlation with the noninvasive evidence of ischemia$^{20}$ and clinical events after catheter intervention.$^{21}$ However, a variety of factors, such as heart rate, blood pressure, myocardial viability, status of resistance

Figure 2. Representation of sensitivity (■) and specificity (●) as functional cutoff values over whole spectrum of A, MLA_{QCA}; B, % diameter stenosis_{QCA}; C, MLA_{IVUS}; and D, area stenosis_{IVUS}. Best agreement with ischemic threshold of FFR was found when abnormal MLA_{IVUS} was 3.0 mm$^2$ (sensitivity, 83.0%; specificity, 92.3%). Another evaluation revealed that best ultrasound cutoff point was 0.60 for area stenosis_{IVUS} (sensitivity, 92.0%; specificity, 88.5%). Similar results were obtained in QCA criteria: MLA_{QCA} < 1.5 mm (sensitivity, 92.0%; specificity, 88.0%) and % diameter stenosis_{QCA} < 60 (sensitivity, 88.0%; specificity, 88.5%).

Figure 3. A, Using QCA parameters, 22 vessels with MLD > 1.5 mm and % diameter stenosis < 45% showed FFR values > 0.75 without exception. B, Matching both IVUS criteria, MLA_{IVUS} and area stenosis_{IVUS}, showed a clinical potential in determination of presence or absence of inducible ischemia by FFR criterion of 0.75.
vessels, and myocardial hypertrophy influence coronary flow.\textsuperscript{6,10,22}

Previous studies have shown that the value of the FFR is independent of the hemodynamics\textsuperscript{6} or status of the resistance vessel and is specific to epicardial stenosis.\textsuperscript{8} Simultaneous measurements of coronary pressure and flow have demonstrated that CFR is sensitive to hemodynamics and that the FFR is unaffected by hemodynamic changes.\textsuperscript{6} Previous studies have also shown that the FFR has a good correlation with noninvasive assessments of ischemia, such as exercise-induced ECG changes or positron emission tomography.\textsuperscript{9,10}

The FFR value of 0.75 as the cutoff point has been shown to have high accuracy for identification of inducible ischemia with a narrow gray zone.\textsuperscript{23}

Whether IVUS-derived parameters may correspond to the physiological significance of the stenosis is still controversial. Moses et al\textsuperscript{8} showed that single tomographic measurements by IVUS had a weak correlation with the coronary physiological response. Conversely, Kern et al\textsuperscript{24} and Ge et al\textsuperscript{25} showed that the CFR improved and correlated with the severity of residual stenosis assessed by IVUS after subsequent catheter intervention. Similarly, Abizaid and colleagues\textsuperscript{26} reported that MLA $>4.0$ mm$^2$ corresponded to the CFR cutoff value of 2.0. To date, little is known regarding IVUS criteria to determine the functional severity of coronary stenosis. Recently, Hanekamp et al\textsuperscript{27} demonstrated a high concordance rate between IVUS and FFR for the purpose of evaluating optimal stenting. However, they did not determine the IVUS criteria for functional severity of the stenosis assessed by the value of FFR. In the present study, a significant relationship between the MLA$_{IVUS}$ and FFR was observed. A criterion of 3.0 mm$^2$ for the MLA$_{IVUS}$ demonstrated good specificity for an abnormal FFR value. Use of the measurements after the intervention and the difference in the reference vessel size in that study might explain the difference between their criteria and ours. There were exceptions to the relation that did not fit the regression line. In the present study, the reference lumen area$_{IVUS}$ ranged from 3.7 to 14.7 mm$^2$. Differences in the patients' physical makeup and the size of the individual coronary arteries might partially explain the discordance between the single cross-sectional values and functional severity. Therefore, we evaluated the physiological impact of the area stenosis in addition to the absolute value of the MLA. The area stenosis$_{IVUS}$ was the strongest independent determinant of the FFR values. The cutoff value for the area stenosis$_{IVUS}$ was 0.60 for FFR values under the ischemic threshold and was consistent with the previous study comparing the IVUS measurements with noninvasive physiological tests.\textsuperscript{27} The value of 0.60 agreed with the relationship between area stenosis and arteriographically determined relative CFR.\textsuperscript{19}

Moreover, the present study showed that the combined use of cutoff values for either the MLA$_{IVUS}$ or area stenosis$_{IVUS}$ was a potent predictor for an FFR value $<0.75$. In the present study, there was a discrepancy between the MLA$_{IVUS}$ and the MLA calculated by QCA. The angiographic projection used and the possible distortion in the IVUS images due to noncoaxial catheter position might explain the discordance between the IVUS and QCA values.\textsuperscript{17} Nevertheless, our criterion of 1.5 mm for MLD in predicting FFR $<0.75$ was quite similar to that in a previous clinical investigation.\textsuperscript{18}

**Clinical Implications**

The guidelines recommended that coronary intervention should be preceded by objective evidence of myocardial ischemia.\textsuperscript{28} Nevertheless, economic issues and facilities sometimes do not allow for the use of multimodalities. In the interventional revascularization procedure, it has been widely recognized that IVUS has an outstanding advantage in lesion morphology characterization, device selection, balloon sizing, and stent geometry.\textsuperscript{29–33} In addition, the present study thus suggested that IVUS has a clinical potential to assess the physiological severity of the lesion, and it may substantially reduce the overall cost and time for the decision and intervention.

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