Diastolic Fractional Flow Reserve to Assess the Functional Severity of Moderate Coronary Artery Stenoses
Comparison With Fractional Flow Reserve and Coronary Flow Velocity Reserve

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Background—Coronary blood flow occurs mainly during the diastolic phase of each cardiac cycle and is mainly dependent on diastolic driving pressure, especially in the left anterior descending coronary artery (LAD). We hypothesized that calculation of the ratio of the diastolic driving pressure of a stenotic LAD to its normal value, namely diastolic FFR (d-FFR), might provide precise insight into the mechanism of FFR for assessment of the functional severity of the stenosis. We compared d-FFR with FFR, coronary flow reserve (CFR), and exercise myocardial thallium scintigraphy in an lesion of intermediate severity.

Methods and Results—The study population consisted of 46 consecutive patients with a moderate stenosis in the LAD in whom simultaneous measurements of aortic pressure, left ventricular pressure, and coronary pressure distal to the stenosis were obtained. Coronary flow velocity was successfully measured with a Doppler guidewire in 37 of the 46 patients. Values for FFR, d-FFR, and CFR in the noninvasive test–positive group were significantly lower than those in the negative group. With cutoff values of 0.75, 0.76, and 2.0 for FFR, d-FFR, and CFR, sensitivities were 83.3%, 95.8%, and 88.2% and specificities were 100%, 100%, and 95.0%, respectively.

Conclusions—The close similarity of the sensitivity and specificity of FFR and d-FFR, around almost identical cutoff values (0.75 versus 0.76), confirms the physiological validity of FFR as a clinical standard. In clinical practice, FFR remains the index of choice for assessment of the functional severity of moderate coronary artery stenoses.

Key Words: ischemia ■ coronary artery disease ■ hemodynamics

Angiograms provide only a 2-dimensional coronary luminal silhouette and have many limitations, especially in intermediate lesions (ie, those with percent diameter stenosis of 40% to 70%). Physiological assessment of the severity of the coronary lesion is critical for clinical decision making. The recent miniaturization of pressure and velocity sensors has allowed the simultaneous measurement of intracoronary flow velocity and transstenotic pressure gradients. A number of parameters derived from direct pressure and flow measurements have been clinically evaluated, such as coronary flow velocity reserve (CFR), instantaneous hyperemic diastolic velocity-pressure slope index, and pressure-derived fractional flow reserve (FFR). It was reported that an FFR of <0.75 is associated with inducible myocardial ischemia, as documented with bicycle exercise testing, thallium scintigraphy, and dobutamine-stressed echocardiography, and that the specificity and sensitivity of FFR are 100% and 88%, respectively. However, FFR is conventionally obtained through the calculation of the ratio of mean blood pressure distal to a coronary stenosis to the mean aortic pressure during maximal hyperemia. In the present study, we calculated diastolic coronary driving pressure (dp-cor) from the difference between the diastolic coronary artery pressure and the diastolic left ventricular pressure. The calculation of diastolic FFR (d-FFR) in the left anterior descending coronary artery (LAD) seems to be a theoretically correct and rational concept, because the greater part of coronary blood flow takes place during the diastolic phase of each cardiac cycle, particularly in the LAD. We hypothesized that the ratio of dp-cor for a stenotic coronary artery to its normal value might provide insight into the mechanism of FFR for the assessment of the functional severity of the stenosis, especially in a lesion of intermediate severity. We therefore compared FFR with d-FFR and CFR against the results of exercise myocardial thallium scintigraphy.
Methods

Subjects
The present study included 46 consecutive patients who were hospitalized with a complaint of chest pain, who fulfilled defined inclusion criteria, and in whom simultaneous measurements, of adequate quality for analysis, could be obtained of aortic pressure, left ventricular pressure, and coronary pressure distal to the stenosis. Patients were eligible for the present study if they had a single stenosis in the proximal or mid portion of the LAD, but enrollment was restricted to patients with an intermediate lesion (40% to 70%). Patients who had the following clinical conditions were excluded from the study: (1) left main trunk disease, (2) 2- or 3-vessel disease, (3) anemia, (4) prior myocardial infarction in the flow-distribution territory of the LAD, (5) diabetes mellitus, (6) left ventricular hypertrophy or significant valvular heart disease, or (7) prior CABG. We also excluded patients (8) for whom we could not obtain informed consent. In 37 of the 46 patients, a Doppler guidewire was used simultaneously. All cardiac medications except for aspirin were discontinued 24 hours before the study.

Noninvasive Tests
Symptom-limited bicycle exercise testing was performed at an initial workload of 25 W and was increased by 25 W every 3 minutes. A 12-lead ECG was continuously recorded. At peak exercise, 3 mCi thallium chloride was administered intravenously. Exercise was maintained for 1 additional minute. Within 10 minutes after the termination of exercise, stress planar images were acquired in the anterior, left lateral, and left anterior oblique views, followed by the acquisition of cardiac SPECT images. After 3 to 4 hours, redistribution planar and SPECT images were obtained. When chest pain was accompanied by ST-segment depression of $>0.2$ mV on bicycle exercise testing or reversible ischemia was detected with SPECT at baseline and after exercise, the noninvasive test was judged to be positive.

Cardiovascular Catheterization
After the intravenous administration of 5000 IU heparin, a 6F guiding catheter, without side holes, was advanced up to the left coronary ostium through the right brachial artery. Isosorbide dinitrate (5 mg) was administered through the inserted catheter. Lesion severity was evaluated with an online analysis system that operated on digital images (DLK-II; GE Medical Systems). A 4F pigtail catheter was placed in the left ventricle through the right radial artery to measure left ventricular pressure. A 2.6F intravascular ultrasound (IVUS) catheter (Discovery; Boston Scientific) was used to calculate the percent area stenosis of the lesion. Distal coronary flow velocity and pressure were obtained simultaneously with a 0.014-in Doppler guidewire (FloWire; Endosonics) and a 0.014-in pressure guidewire (WaveWire; Endosonics). Care was taken to position the 2 wire transducers at the same site.

Translesional Pressure Gradient Measurements
The pressure measurements with the WaveWire were processed with the use of the WaveMap (Endosonics), and mean aortic and mean distal coronary pressures were displayed simultaneously on the analog display of the WaveMap. The pressure signal was calibrated to the normal atmosphere before insertion. When the sensor was in place close to the tip of the guiding catheter and equal pressures were not observed at that location, a normalization procedure was performed to superimpose the 2 pressures at that point. All pressure measurements were completed within 10 minutes, and after the final measurement, the WaveWire was pulled back close to the tip of the guiding catheter. If a pressure difference of $>5$ mm Hg was observed, the coronary pressure distal to the stenosis was recalculated, with this drift taken into account.

Figure 1. From top to bottom: ECG, coronary flow velocity distal to stenosis (Velocity), aortic pressure (Ao), coronary pressure measured with WaveWire (Endosonics) (LAD), and left ventricular pressure (LV).

Aortic and Left Ventricular Pressure Measurements
Aortic pressure (guiding catheter) and left ventricular pressure (pigtail catheter) were obtained with 2 separate fluid-filled pressure transducers (1290C; Hewlett Packard) zeroed at mid chest level. All measurements, including aortic pressure, left ventricular pressure, poststenotic coronary pressure, and coronary flow velocity, were obtained simultaneously, both at rest and during maximal vasodilation, and were induced by the infusion of $150 \mu g \cdot kg^{-1} \cdot min^{-1}$ ATP IV (Figure 1).

Translesional Coronary Flow Velocity Measurements
The quadrature/Doppler signals were processed with the FloMap (Endosonics). The Doppler transducer was advanced distal to the stenosis by $5$ artery diameter lengths, to avoid placement in any side branches. The flow velocity measurements distal to the stenosis were obtained under baseline conditions and during hyperemia. CFR was computed as the ratio of the average peak flow velocity ($cm/s$) during hyperemia to baseline average peak flow velocity.$^7,^8$

Simultaneous Assessment of Aortic Pressure, Poststenotic Coronary Pressure, Left Ventricular Pressure, and Coronary Flow Velocity Measurements
All measurements were continuously acquired with a personal computer with a 12-bit analog-to-digital converter at a sampling frequency of 250 Hz (MP100 systems and Acqknowledge; BIOPACK Systems, Inc) (Figure 2).

Data Analysis
As shown in Figure 2, we used the results obtained here to calculate the dp-corr, which is the coronary distal pressure minus left ventricular pressure during diastole. With the difference in aortic pressure and left ventricular pressure during diastole, we calculated the driving pressure of the theoretically normal coronary artery (dp-aor). The diastolic intervals for analysis were defined manually from the peak pressure point of the dp-aor to the sudden drop point of the dp-corr due to myocardial contraction.

Calculation of FFR and d-FFR
FFR was calculated as the ratio of mean coronary distal pressure, as measured with the WaveWire, to mean arterial pressure, as measured...
with the guiding catheter, at maximal hyperemia. The d-FFR was defined as the ratio of dp-cor for a stenotic coronary artery to its dp-aor value (Figure 3); both intervals of the dp-cor and dp-aor obtained at maximal hyperemia were integrated (Figure 4), and d-FFR was derived by dividing dp-cor by the dp-aor (Figure 4).

Statistical Analysis
Results were expressed as mean±SD. Statistical analyses were performed with the SPSS software package. All indexes derived from pressure and velocity measurements and other continuous variables were compared between the noninvasive test–positive and –negative groups with the 2-tailed Student’s unpaired t test. The categorical variables were compared between the 2 groups by χ2 test. To compare both sensitivities and specificities of CFR, FFR, and d-FFR against the results of noninvasive tests, the receiver operator characteristic (ROC) curves were used. The best cutoff values were identified as the values with the highest sum of sensitivity and specificity. To compare the sensitivity and specificity of FFR, d-FFR, and CFR, the differences in the area under 3 respective ROC curves were compared.23

Results
Feasibility of Measurements
As shown in Table 1, FFR, d-FFR, and CFR values were obtained in 46 of 46 (100%), 46 of 46 (100%), and 37 of 37 (100%) patients, respectively.

Patient Characteristics
As shown in Table 1, of the total of 46 patients, 24 were positive on the noninvasive test and 22 were negative. Of the

TABLE 1. Clinical Characteristics of 2 Groups Defined by the State of Inducible Myocardial Ischemia

<table>
<thead>
<tr>
<th>Noninvasive Test</th>
<th>Positive (%)</th>
<th>Negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient total, n (%)</td>
<td>24/46 (52.2%)</td>
<td>22/46 (47.8%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>64.5±9.3*</td>
<td>56.9±7.2</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>20/4</td>
<td>19/3</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Smoking, n</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Serum cholesterol level, mg/dL</td>
<td>210.8±40.0</td>
<td>206.9±37.1</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>56.8±12.5</td>
<td>52.6±9.8</td>
</tr>
<tr>
<td>Area stenosis, %</td>
<td>60.0±15.7†</td>
<td>49.7±10.5</td>
</tr>
<tr>
<td>FFR</td>
<td>0.68±0.13*</td>
<td>0.87±0.05</td>
</tr>
<tr>
<td>d-FFR</td>
<td>0.59±0.16*</td>
<td>0.90±0.07</td>
</tr>
<tr>
<td>CFR (n=37)</td>
<td>1.83±0.78*</td>
<td>3.14±0.85</td>
</tr>
</tbody>
</table>

*P<0.01, †P<0.05.
37 patients in whom flow velocity was also measured, 17 were positive and 20 were negative. For patient characteristics, age alone was significantly higher in the noninvasive test–positive group than in the negative group.

Percent Diameter Stenosis and Percent Area Stenosis

As shown in Table 1, quantitative coronary angiography (QCA) revealed no significant difference in percent diameter stenosis between the noninvasive test–positive (56.8%) and –negative (52.6%) groups. IVUS showed that percent area stenosis was significantly higher in the noninvasive test–positive group than in the negative group (60.0±15.7% versus 49.7±10.5%, P<0.05), which concurs with other reports.24 The difference between QCA and IVUS may be due to disease of the reference segment for measurement of percent diameter stenosis that QCA fails to detect but IVUS does detect.

FFR, d-FFR, and CFR

The values for FFR, d-FFR, and CFR for both noninvasive test–positive and –negative groups are shown in Table 1. CFR, FFR, and d-FFR were significantly lower in the noninvasive test–positive group than in the negative group (P<0.01).

Figure 5 shows a comparison of the 3 ROC curves for d-FFR, FFR, and CFR used to discriminate noninvasive test–positive and –negative results.

**Table 2. Sensitivities and Specificities to Noninvasive Tests**

<table>
<thead>
<tr>
<th>Parameters (Cutoff Value)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR (2.0)</td>
<td>88.2</td>
<td>95.0</td>
</tr>
<tr>
<td>FFR (0.75)</td>
<td>83.3</td>
<td>100</td>
</tr>
<tr>
<td>d-FFR (0.76)</td>
<td>95.8</td>
<td>100</td>
</tr>
</tbody>
</table>

Discussion

FFR has emerged as an important clinical decision-making tool and is widely used in the assessment of the functional severity of intermediate stenoses, as an alternative to noninvasive testing for ischemia, and as the end point for coronary intervention. It is derived from the relationship between flow and resistance across the myocardial bed and represents the fraction of maximal blood flow that can still be obtained despite the presence of an epicardial coronary lesion.20 FFR has an unequivocal value of 1.0 in every normal coronary artery and is independent of changes in heart rate, blood pressure, and myocardial contractility and microvascular disease.22,25,26 An FFR cutoff value of 0.75 is thought to reliably distinguish functionally significant coronary stenoses.26–28 Because FFR is derived from the mean pressures of both systolic and diastolic phases, however, it does not fully reflect the diastolic contribution of coronary flow. Because coronary blood flow, especially in the LAD, takes place during the diastolic interval of the cardiac cycle, detailed analysis of the dp-cor in the LAD might provide an accurate insight into the mechanism of FFR. In particular, during hyperemia in the presence of moderate coronary stenosis, the actual increase in diastolic flow might be comparatively small, leading to a fall in the ratio of diastolic to systolic velocity. In flow velocity measurements in the 37 study patients, the ratio of diastolic to systolic velocity at baseline and hyperemia was 2.03±0.92 and 1.67±0.86, respectively (P=0.1). In such cases, theystolic fraction of coronary flow can be relatively high, and therefore the systolic interval fraction is composed of a larger proportion of the ratio compared with the diastolic interval fraction, particularly in the case of the left circumflex coronary artery and even more so in the right coronary artery. In addition, this diastolic predominance is less marked during hyperemia and even less so when a coronary stenosis is present. Therefore, and even though the principle of d-FFR is sound, the systolic component of coronary blood flow often cannot be neglected, in particular in the left circumflex and right coronary arteries.

Pijls et al22 pointed out that the specificity and sensitivity of FFR for myocardial ischemia detected with noninvasive tests were 100% and 85% to 95%, respectively, and in the present study, the specificity of FFR was 100% and sensitivity was 83.3%, around the 0.75 cutoff. It is encouraging that the cutoff value for d-FFR was 0.76, whereas the cutoff point for conventional FFR has been claimed to be 0.75 in a number of previous studies. The simple fact that the cutoff points are so similar is a strong confirmation of the physiological soundness of the principles that underlie the concept of FFR. FFR is generally considered to be independent of changes in heart rate, aortic pressure, and myocardial contractility. In the present study, we used d-FFR to identify the influences in left ventricular diastolic pressure and dp-cor and to predict the results of noninvasive testing. The diagnostic value of d-FFR is similar to that of classic FFR, because of
the similar cutoff values and diagnostic accuracy; that is, FFR is also independent of those influences.

Study Limitations
We divided all patients into binary positive or negative groups according to the results of noninvasive testing. However, it is well known that 201Tl SPECT with symptom-limited exercise bicycle testing has limited accuracy, with a sensitivity of no greater than 85% and specificity of ~90%. Therefore, discrepancies between the invasive parameters and the thallium testing could also be due to false-positive or false-negative thallium tests. The only way to know whether an abnormal perfusion scintigram is truly abnormal is to repeat the test after revascularization. In this case, the positive case that becomes negative can be considered truly positive, and the negative test that was negative before revascularization can be considered truly negative. Because noninvasive tests after revascularization were not available for all patients, we were unable to resolve this question in the present study.

Another limitation of the present study is that the acquisition of d-FFR is complex and therefore more vulnerable to measurement errors, although in here, all measurements were performed at least twice without difficulties. This can be important because the applicability of a parameter is also determined by the ease with which it can be obtained. Signal acquisition with the Doppler FloWire can sometimes be unstable, especially because the elevation of basal flow velocity during hyperemia may cause an abnormal CFR value. In some patients, effort-induced vasospasm may occur during exercise testing. The influence of effort-induced vasospasm cannot be excluded during noninvasive testing, because all cardiac medications except aspirin were stopped for 24 hours before the tests. In addition, the administration of nitroglycerin during the measurement of flow velocity and coronary pressure could eliminate the vasospastic mechanism. These 2 sets of diverse effects may modify the interpretation of our results.

We compared FFR and d-FFR with the results of noninvasive tests, but the latter obviously reflect the influence of epicardial coronary stenosis as well as of microvascular disease, which was difficult to exclude entirely from our results. Reference vessel CFR would confirm microvascular disease but that was not determined in the present study. One final limitation is that we investigated FFR and d-FFR only in the LAD.

Conclusion
We evaluated the functional impact of moderate coronary stenosis on myocardial perfusion by simultaneously measuring aortic pressure, distal coronary pressure, left ventricular pressure, and coronary flow velocity, and we compared the results of noninvasive testing with FFR, d-FFR, and CFR. The close similarity of the sensitivity and specificity of both FFR and d-FFR, around almost identical cutoff values, confirms the physiological soundness of the principles that underlie the concept of FFR. We believe that in clinical practice, FFR remains the index of choice for assessment of the functional severity of moderate coronary artery stenoses.

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