Validation of Collateral Fractional Flow Reserve by Myocardial Perfusion Imaging

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**Background**—Collateral fractional flow reserve (FFR_{coll}) is an index to quantify collateral blood flow, derived from coronary pressure measurements. Although well defined theoretically, its direct validation by myocardial perfusion imaging has not been established so far. Validating this index by myocardial perfusion imaging is the main aim of this study.

**Methods and Results**—Twenty-four consecutive patients with stable angina and single left anterior descending artery stenosis underwent simultaneous measurement of aortic pressure (P_a), coronary wedge pressure (P_w), and central venous pressure (P_v) during balloon inflation. FFR_{coll} was calculated and compared with the extent and severity of the defect during coronary occlusion using \(^{99m}\)Tc-sestamibi imaging at balloon inflation of the respective coronary artery. Although the pressure-derived collateral indexes (P_a/P_w and FFR_{coll}) ranged widely, they were closely correlated with extent and severity scores of the nuclear occlusion images and superior to the ECG for that purpose. Of all parameters, FFR_{coll} correlated best with the severity score at imaging (r = −0.88), followed by the P_a/P_w ratio (r = −0.74) or P_v alone (r = −0.69).

**Conclusions**—FFR_{coll}, calculated from coronary pressure during balloon occlusion, is highly correlated with the extent and severity of the defect at myocardial perfusion of the territory of the occluded artery and can be used for quantitative assessment of collateral blood flow in conscious humans. (Circulation. 2002;105:1060-1065.)

**Key Words:** collateral circulation ■ blood flow ■ perfusion ■ imaging ■ pressure

Many studies have emphasized the importance of collateral blood flow in coronary artery disease.1–5 Pijls et al6–8 recently described the theoretical basis and experimental validation of a method that enables the assessment of recruitable collaterals at coronary artery occlusion by the simultaneous measurement of mean arterial (P_cru), coronary wedge (P_w), and central venous pressure (P_v). According to those studies, maximum recruitable collateral flow reserve (Qc) can be quantitatively expressed as a fraction of normal maximum myocardial perfusion (Q^m): Qc/Q^m = (P_cru − P_w)/(P_a − P_w).

The index Qc/Q^m is called the pressure-derived collateral fractional flow reserve (FFR_{coll}) and has also been called the pressure-derived collateral flow index (CFI_p) by some other authors.9 This index is independent of changes in heart rate, blood pressure, and other hemodynamic variables and has been proved to be of clinical importance to predict future ischemic events.6,7 However, until now, this concept has not been validated in humans directly by perfusion imaging. Validation of the concept of collateral fractional flow reserve in humans by relating it to myocardial perfusion imaging was the main aim of this study.

**Patients**

The population consisted of 24 male patients with stable angina and normal left ventricular function who were scheduled for elective PTCA of a single stenosis in the proximal (n = 8) or mid (n = 16) left anterior descending artery.

Patients with a history of myocardial infarction, diabetes mellitus, severe hypertension, ST-segment abnormalities on the surface ECG, and atrial fibrillation or bundle-branch block were excluded. Written informed consent was obtained in all patients before the study. The hospital ethics committee approved the study protocol.

**Cardiac Catheterization and Coronary Pressure Measurement**

All patients received aspirin (80 mg daily) and ticlopidine (200 mg daily) at least 2 weeks before coronary angioplasty. No further restrictions with respect to drug treatment were made. A 6F multipurpose catheter was introduced into a femoral vein and advanced to the right atrium for central venous pressure recording. A 6F guiding catheter was introduced into a femoral artery and advanced into the ostium of the coronary artery. A 0.014-inch pressure monitoring guide wire (PressureWire; Radi Medical Systems) was set at zero, calibrated, and advanced across the target lesion, and myocardial fractional flow reserve (FFR_{myo}) was obtained at maximum vaso-
dilation, with continuous infusion of 140 μg/kg per minute of ATP in the side channel of the venous sheath. While ATP infusion was maintained, the balloon catheter was positioned in the lesion and inflated for at least 3 minutes. During balloon inflation, mean arterial pressure (P_a), coronary wedge pressure (P_w), and 12-lead ECG were recorded. P_a/P_w, and collateral fractional flow reserve (Qc/Q⁎) was calculated by Equation 1 and correlated to the perfusion abnormality on ⁹⁹mTc-sestamibi occlusion images and to the degree of ST elevation on the ECG during balloon occlusion. Next, an optimum intervention was performed and FFRmyo was determined again at the end of the procedure.

Electrocardiographic Assessment of Ischemia Severity
A standard 12-lead surface ECG was recorded at baseline and during 3 minutes of inflation, as shown in Figure 1. The sum of ST-segment elevation in all 12 leads was determined and defined as ΣST.

Myocardial Perfusion Imaging During Balloon Inflation
In all patients, 740 to 1110 MBq of ⁹⁹mTc-sestamibi was injected intravenously into a large antecubital vein during initial balloon inflation, as shown in Figure 1. Data acquisition was performed 1 to 2 hours after the PTCA procedure. SPECT imaging delineating myocardial perfusion abnormality during balloon inflation was obtained with a wide-field-of-view rotating gamma camera (ZLC-7500, Siemens Co, Ltd) equipped with a low-energy, high-resolution parallel hole collimator on the 140-KV photo peak with a 30% window. The camera was rotated through a 180° arc in an elliptical orbit around the patient’s thorax from 40° right anterior oblique to 40° left posterior oblique at 6° increments for 30 seconds each. Data were collected in a 64×64 array with a pixel size of 4.5 mm. Transaxial slices were reconstructed with a filtered back-projection algorithm with a Butterworth and Winner filter without attenuation and scatter correction. Short-axis tomograms were reconstructed from the transaxial slices. Polar maps of regional distribution of sestamibi were displayed. Polar maps were normalized for peak myocardial activity and compared with our normal limits. Pixels with tracer uptake <2.5 SD below mean normal values were considered abnormal. Two types of polar maps were generated for area at risk images. In the so-called extent map, the abnormal area on each short-axis slice was first multiplied by a correction factor that corrects the spatial distortion and allows for differences in myocardial slice mass from apex to base. Corrected abnormal area was then summed to obtain the total extent of ischemia, expressed as a percentage of the left ventricular surface (extent score). In the so-called severity map, the value of each pixel was computed such that if the pixel is within normal limits, it gets a value of 1. If below, it gets a fractional value linearly dependent on how far it falls below normal limit. The severity score is then calculated as the average pixel value in the abnormal area multiplied by the number of the abnormal pixels. Therefore, severity score specifically represents the severity of hypoperfusion in relation to normally perfused myocardium at maximum vasodilatation and conceptually corresponds to FFR<sub>coll</sub>.10–12

Statistical Analysis
The distribution of continuous variables is expressed as mean±SD. Linear regression analysis was used to compare these indexes and correlation coefficients expressed. A value of P<0.05 was considered to be significant.

Results

Procedural Results
Successful intervention could be performed in all patients, and no complication occurred in any. Twelve patients were treated by balloon angioplasty only, and in 12 patients, a stent was used because of a suboptimal result (either by angiography or pressure measurement).

Coronary pressure measurement and determination of P<sub>a</sub> could be obtained easily in all patients. Drift was minimum in all of them (1.2±0.5 mm Hg during complete procedure). FFRmyo increased from 0.67±0.16 before to 0.93±0.06 after intervention. The individual pressure data of each patient are mentioned in Table 1. P<sub>a</sub>, P<sub>w</sub>, and P<sub>a</sub>/P<sub>w</sub> all showed a large interindividual variation (P<sub>a</sub>/P<sub>w</sub>, 94.6±25.9 mm Hg; range, 44 to 157; P<sub>a</sub>, 15.9±9.1 mm Hg; range, 4 to 37; and P<sub>w</sub>, 5.4±2.4 mm Hg; range, 3 to 12), as did the pressure-derived collateral flow indexes (P<sub>a</sub>/P<sub>w</sub>, 0.17±0.08; range, 0.05 to 0.30; FFR<sub>coll</sub>, 0.12±0.08; range, 0.02 to 0.28).

Adequate myocardial perfusion imaging could be performed in all patients, and in the extent and severity score, a large interindividual variability was present (extent score, 0.51±0.13; range, 0.25 to 0.6; severity score, 116.1±51.8; range, 24 to 185). A representative example of angiograms, coronary pressures, and myocardial perfusion imaging in one patient is shown in Figures 2 through 4.

Correlation of Pressure-Derived Collateral Indexes and ⁹⁹mTc-Sestamibi Defect Extent and Severity
The relation between pressure-derived indexes and radionuclide indexes is shown in Figure 5. All pressure indexes are significantly inversely correlated to imaging indexes. The best relation is found for collateral fractional flow reserve followed by the P<sub>a</sub>/P<sub>w</sub> ratio. As expected from theory of both nuclear indexes, the severity score was significantly better than the extent score. Both collateral fractional flow reserve and severity score by nuclear imaging express recruitable collateral blood flow as a fraction of normal maximum blood flow, and the correlation between both indexes is the highest of all (R=-0.88).

Correlation Between Electrocardiographic Abnormality and ⁹⁹mTc-Sestamibi Defect Extent and Severity
The relations between ΣST and collateral indexes derived from pressure measurement as well as between ΣST and radionuclide were weaker in comparison to those between radionuclide indexes and pressure indexes. The relevant data are shown in Table 2.
Discussion

The conceptual basis of calculating maximum myocardial, coronary, and collateral blood flow by coronary pressure measurement and the concept of fractional flow reserve (FFR) was first described by Pijls et al in 1993. Since then, a number of studies have been performed to validate myocardial and coronary fractional flow reserve in models, animals, and humans. However, direct quantitative

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ES indicates extent of hypoperfusion at nuclear imaging; SS, severity of hypoperfusion at nuclear imaging.

Figure 2. Angiograms of left anterior descending artery in a 53-year-old man with stable angina before and after stenting.
comparison of collateral blood flow, calculated by pressures in this way, versus myocardial perfusion imaging in humans has not been performed thus far. This study shows that a close correlation is present between collateral fractional flow reserve, calculated from coronary pressure measurement, and the extent and severity of hypoperfusion of the territory supplied by the occluded artery in relation to normally perfused myocardium.

Assessment of FFR\textsubscript{coll} in the catheterization laboratory is easy during coronary intervention. In conscious humans, a close correspondence between Qc/QN and clinical and angiographic parameters such as the presence of chest pain, ischemic ST elevation, coronary wedge pressure, and collateral grading of contralateral artery has been demonstrated.\textsuperscript{8} A value of FFR\textsubscript{coll} below or above 0.25 or a value of P\textsubscript{w}/P\textsubscript{a} below or above 0.30 has been found to be strongly associated with presence or absence of ischemia on the ECG during coronary artery occlusion.\textsuperscript{8,15,16} In our study, the values of FFR\textsubscript{coll} and P\textsubscript{w}/P\textsubscript{a} were somewhat lower than in several previous studies,\textsuperscript{7,14,16,17} and ischemia was present at balloon occlusion in almost all patients. This probably is due to the fact that average stenosis severity was somewhat less than in most other studies and, as a consequence, collaterals were less developed. Piek et al\textsuperscript{16,17} showed that the presence of recruitable collaterals during coronary occlusion resulted in a higher coronary wedge-to-aortic pressure ratio. However, the gold standard of ischemia in all these studies used binary criteria. As for the quantitative point of view, Mohri et al\textsuperscript{18} demonstrated a weak yet significant positive correlation between the magnitude of collateral flow velocity signals detected by Doppler flow wire and distal occlusion pressure. Seiler et al\textsuperscript{9,19} also demonstrated linear correlation between velocity-derived collateral flow indexes and pressure-derived collateral flow indexes. Our study is the first report showing the linear relation between FFR\textsubscript{coll} and myocardial perfusion during coronary occlusion. In this study, the relation between the scintigraphic defect severity and FFR\textsubscript{coll} was better than those for P\textsubscript{w} or P\textsubscript{w}/P\textsubscript{a}. This finding supports the previous report by Pijls et al\textsuperscript{7} showing that FFR\textsubscript{coll} was found to be a more accurate marker of PTCA-induced electrocardiographic changes than the coronary wedge pressure and P\textsubscript{w}/P\textsubscript{a}, although the latter value is easier to obtain because it is not necessary to measure central venous pressure. Furthermore, this study clearly demonstrates that severity score is the best nuclear index to approximate FFR\textsubscript{coll} because myocardial perfusion pressure during coronary balloon occlusion influences both extent of hypoperfusion and severity of hypoperfusion, which is represented more precisely by severity score rather than by extent score. Our data quantitatively relate FFR\textsubscript{coll} to the perfusion of distal coronary beds during balloon occlusion.

**Figure 3.** Pressure tracings of the patient in Figure 2. Before PTCA, a large pressure gradient is present and fractional flow reserve is calculated to be 0.67 (left). During balloon inflation, P\textsubscript{w}/P\textsubscript{a} decreases to 0.12 and because central venous pressure was 4 mm Hg during balloon inflation (not shown), collateral fractional flow reserve equals 0.08 (middle). After stenting, optimum functional result is achieved and even during maximum hyperemia there is no inducible gradient, resulting in a myocardial fractional flow reserve of 1.0 (right).

**Figure 4.** Polar map display of \textsuperscript{99m}Tc-sestamibi imaging in the patient from Figures 2 and 3 with tracer injected during balloon inflation. Severe perfusion defect is shown in the anteroseptal wall and apex. Defect score in this patient was 0.56; severity score, 173.
99mTc-Sestamibi Occlusion Image as the Standard for Ischemia

In this study, we used 99mTc-sestamibi occlusion images as the gold standard of perfusion abnormality. 99mTc-sestamibi is a well-known myocardial perfusion imaging tracer and is widely used for the assessment of extent of myocardial ischemia and infarction. 20, 21 99mTc-sestamibi remains relatively fixed in myocardial cells after initial extraction with minimum delayed redistribution. 22 Therefore, it could be used to delineate the collateral flow relative to nonobstructed myocardium and the distribution of the occluded artery during balloon inflation of at least 3 minutes as in this study.

Restoration of hyperemic reperfusion flow after balloon deflation does not significantly alter the original distribution of the tracer when injected during coronary occlusion, as demonstrated by Sinusas et al. 23 and De Coster et al. 24 in open chest dogs. The use of 99mTc-sestamibi imaging as a measure of myocardial ischemia severity during coronary occlusion not only in the setting of acute coronary syndrome but also during controlled coronary artery occlusion, as in our model, has also been validated before. 25–29

Another method for assessing collateral circulation is the presence of ECG ST-segment change during balloon inflation. 30 Also in this study, the sum of ST elevation showed significant negative correlation with fractional collateral flow reserve and positive correlation with defect severity of occlusion images. However, these correlations were weak in comparison with the quantitative relation between collateral fractional flow reserve and defect severity of the occlusion image.

**Limitations**

In this study, 99mTc-sestamibi imaging was used as the gold standard of perfusion during transient coronary occlusion. Recirculation of 99mTc-sestamibi in the blood pool immediately after balloon deflation, at a time of reactive hyperemia, could be

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**TABLE 2. Correlation Coefficients Between the Different Hemodynamic Indexes and Extent (ES) and Severity (SS) of Hypoperfusion at Nuclear Imaging**

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<th>SS (sestamibi)</th>
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<td>$-0.785^{‡}$</td>
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<td>$P_w/P_a$</td>
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<td>$\text{FFR}_{\text{coll}}$</td>
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*P<0.05; †P<0.01; ‡P<0.001.
a confounding factor. Because we continued the occlusion for 3 minutes after injection of $^{99m}$Tc-sestamibi, longer than in previous studies, and because of the high initial extraction of this tracer as discussed above, it can be assumed that delayed redistribution did not play a major role in this study.

Furthermore, unlike PET, perfusion abnormalities could only be assessed relative to normal myocardium. But that was not a true limitation because $\text{FFR}_{\text{coll}}$ also expresses maximum recruitable collateral blood flow as a ratio to normal maximum flow and not as an absolute flow.

Furthermore, attenuation and scatter are technically difficult to correct by SPECT. These problems for the quantification by SPECT tend to decrease the estimated scintigraphic perfusion abnormality, resulting in underestimation of truly existing hypoperfusion during balloon occlusion. To minimize this limitation, only men with a single stenosis in the left anterior descending artery were included in this study to minimize regional differences of attenuation and scatter.

As a method of analysis for the quantification of hypoperfusion by SPECT, in this study, we used well-validated scintigraphic estimates of extent and severity of ischemia as described above. It should be noted that the extent score is not only determined by the magnitude of collateral flow but also by the location of the stenosis and the extent of the perfusion territory. The severity score, on the other hand, is more specific for collateral flow because this index incorporates the information about magnitude of hypoperfusion. This explains the better correlation of this latter nuclear index with $\text{FFR}_{\text{coll}}$.

Finally, our study contains only a limited number of patients and with normal left ventricular function. Therefore, the relation between scintigraphic defect and pressure-derived collateral indexes obtained in this study cannot be extended to the other populations such as patients with old myocardial infarction, without further validation.

Conclusions
This study validates that collateral fractional flow reserve measured by a pressure wire is closely related to myocardial perfusion during balloon occlusion as directly assessed by perfusion imaging. Therefore, it corroborates the concept of assessing collateral blood flow by pressure measurement and provides a useful method for quantitative assessment of collateral blood flow in conscious humans.

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Validation of Collateral Fractional Flow Reserve by Myocardial Perfusion Imaging
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