Fractional Flow Reserve in Patients With Prior Myocardial Infarction

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Background—Fractional flow reserve (FFR), an index of coronary stenosis severity, can be calculated from the ratio of hyperemic distal to proximal coronary pressure. An FFR value of 0.75 can distinguish patients with normal and abnormal noninvasive stress testing in case of normal left ventricular function. The present study aimed at investigating the value of FFR in patients with a prior myocardial infarction.

Methods and Results—In 57 patients who had sustained a myocardial infarction ≥6 days earlier, myocardial perfusion single photon emission scintigraphy (SPECT) imaging and FFR were obtained before and after angioplasty. The sensitivity and specificity of the 0.75 value of FFR to detect flow maldistribution at SPECT imaging were 82% and 87%. The concordance between the FFR and SPECT imaging was 85% (P<0.001). When only truly positive and truly negative SPECT imaging were considered, the corresponding values were 87%, 100%, and 94% (P<0.001). Patients with positive SPECT imaging before angioplasty had a significantly lower FFR than patients with negative SPECT imaging (0.52±0.18 versus 0.67±0.16, P=0.0079) but a significantly higher left ventricular ejection fraction (63±10% versus 52±10%, P=0.0009) despite a similar degree of diameter stenosis (67±13% versus 68±16%, P=NS). A significant inverse correlation was found between LVEF and FFR (R=0.29, P=0.049).

Conclusions—The present data indicate (1) that the 0.75 cutoff value of FFR to distinguish patients with positive from patients with negative SPECT imaging is valid after a myocardial infarction and (2) that for a similar degree of stenosis, the value of FFR depends on the mass of viable myocardium. (Circulation. 2001;104:157-162.)

Key Words: infarction ■ coronary disease ■ ischemia ■ scintigraphy ■ pressure

Fractional flow reserve (FFR), an index of coronary stenosis severity, is the ratio of hyperemic myocardial blood flow in the stenotic territory to hyperemic myocardial blood flow in that same territory without stenosis.1 This ratio of 2 flows can be calculated from the ratio of distal coronary pressure divided by aortic pressure during maximal hyperemia.1–3 For a given patient and a given status of the microvascular circulation, the value of FFR is highly reproducible whatever the prevailing hemodynamics and left ventricular (LV) contractility.4 In patients with normal LV function, a well-defined cutoff value of 0.75 has been shown to accurately distinguish stenoses capable of inducing myocardial ischemia (FFR<0.75) from those that are not (FFR≥0.75).5–11

An important prerequisite of the principle of pressure-derived FFR is to achieve maximal arteriolar vasodilation, ie, to obtain the pressure measurements under conditions of minimal myocardial resistance. Although maximal hyperemia can be achieved pharmacologically in noninfarcted myocardial regions,12–15 it remains unknown whether this is the case in (partially) infarcted territory. With respect to FFR, there are 2 main differences between a region with and a region without prior myocardial infarction (MI): first, the mass of viable myocardium, depending on the artery, is smaller for a similar degree of stenosis; second, infarct-related resistive-vessel dysfunction may blunt maximal hyperemic response. Therefore, it is questionable whether the 0.75 cutoff value of FFR is valid for clinical decision-making in patients with a prior MI.

Accordingly, the goal of the present study was to determine whether the FFR value of 0.75 may apply to patients with prior MI. Therefore, the occurrence of residual reversible flow maldistribution at adenosine MIBI scan were correlated before and after revascularization with pressure-derived FFR measurements in patients with a prior MI in the distribution area of the artery under study.

Methods

Patients

Fifty-seven patients were included in the study if they fulfilled the following criteria: (1) documented MI ≥6 days before the study; (2) no totally akinetic territory depending on the infarct-related artery by
visual assessment of the LV angiogram; (3) normally contracting segments in regions other than that of the prior MI; (4) scheduled coronary angioplasty of the infarct-related artery only; and (5) interpolated reference diameter at the level of the target stenosis of ≥2.5 mm.

All patients underwent myocardial perfusion single photon emission computed tomography (SPECT) imaging at rest and during adenosine-induced hyperemia within 3 days before and within 12 days after revascularization. Intracoronary pressure measurements were obtained immediately before and immediately after the planned angioplasty procedure.

The study protocol was approved by the Medical Ethical Committees of the OLV Hospital, Aalst, Belgium, and of the Catharina Hospital, Eindhoven, Netherlands. Informed consent was obtained from all patients.

Myocardial Perfusion Scintigram
SPECT was performed on 2 separate days: after adenosine stress (140 μg·kg⁻¹·min⁻¹) and at rest with gating. Imaging was obtained after intravenous injection of 99mTc sestamibi (900 MBq). Emission data were obtained in the step mode (25 seconds per step with the high-energy collimator) over a 180° circular orbit (64 stops), and images were reconstructed by filtered backprojection (frequency cutoff 0.66) in the short-axis, vertical, and horizontal long-axis views (Vertex Epic dual-head ADAC gamma camera). Tracer uptake on stress and rest images was scored semiquantitatively on a 4-point scale (1 = normal, 2 = 50% to 75%, 3 = <50%, 4 = absent uptake) in the 16-segment model. SPECT imaging was considered positive for reversible flow maldistribution when defect extent and/or severity was larger on the stress images than the residual rest defect. SPECT imaging was considered negative when no reversible adenosine-induced perfusion defect could be observed in addition to the fixed defect related to myocardial scar. Those perfusion studies that reverted from positive before revascularization to negative after revascularization were considered truly positive.

Catheterization and Coronary Angiography
Global LV ejection fraction (LVEF) was calculated from the right anterior oblique projection of the LV angiogram obtained at diagnostic catheterization. For the angioplasty, a 6F or 7.5F arterial guiding catheter and by the pressure-monitoring wire were identical. The side arm of the arterial introducer and the guiding catheter to ensure that the pressures recorded by the guiding catheter was used a scaling device. The values obtained in 2 incidences were averaged.

A 0.014-in pressure-monitoring guidewire (PressureWire, Radi Medical, or WaveWire, Endosonics) was advanced to the tip of the guiding catheter to ensure that the pressures recorded by the guiding catheter and by the pressure-monitoring wire were identical. The wire was then advanced distal to the stenosis and placed in the distal part of the vessel. Once the distal coronary pressure (Pd) was measured through the 6F or 7F guiding catheter without side holes. The side arm of the arterial introducer and the guiding catheter were connected to fluid-filled pressure transducers zeroed at mid chest level. After intracoronary administration of 0.2 mg of isosorbide dinitrate, an angiogram of the vessel under study was taken in ≥2 different projections. Quantitative coronary angiography of the stenosis was performed as described by Reiber et al. Therefore, 2 orthogonal projections were studied to calculate the interpolated reference diameter, the minimal luminal diameter, and the percent diameter stenosis. The guiding catheter was used as a scaling device. The values obtained in 2 incidences were averaged.

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Results
Table 1 summarizes the clinical characteristics of the patients. Angiographic and coronary hemodynamic data are given in Table 2. The delay between the MI and catheterization was 20±27 days (range 6 to 570 days). The delay between the first SPECT and the catheterization was 1±2 days (range from a few hours to 12 days). The delay between the catheterization and the second SPECT was 7±8 days (range 2 to 27 days).

Relation Between FFR and SPECT Imaging
In all 57 patients, SPECT, FFR, and quantitative coronary arteriography were obtained both before and after angioplasty. Figure 2 shows the FFR values in patients before and after angioplasty in relation to the results of SPECT. Before angioplasty, SPECT was positive for reversible flow maldistribution in 43 patients (75%) and negative in 14 (25%). After angioplasty, SPECT was positive in 4 patients (7%) and negative in 54 (93%).
In 3 patients (5%), SPECT was positive before and remained positive after revascularization. The FFR in these patients increased from 0.56 to 0.88, from 0.74 to 0.83, and from 0.35 to 0.73, respectively, before and after stenting. The percent diameter stenosis in these patients decreased from 46% to 6%, from 78% to 2%, and from 65% to 8%, respectively, before and after angioplasty.

In 1 patient, SPECT was negative before and became positive after stenting. In this patient, FFR increased from 0.32 to 0.90 and diameter stenosis decreased from 88% to 0% before and after angioplasty, respectively.

In 13 patients, SPECT was negative before and remained negative after angioplasty. In these patients, FFR increased from 0.70 ± 0.14 to 0.92 ± 0.05 (P < 0.001) and diameter stenosis increased from 67 ± 16% to 10 ± 7% (P < 0.001) before and after angioplasty, respectively.

In 40 patients, SPECT was positive before and became negative after revascularization. In these patients, FFR increased from 0.51 ± 0.19 to 0.91 ± 0.05 (P < 0.001) and diameter stenosis decreased from 67 ± 13% to 13 ± 7% (P < 0.001). Because SPECT reverted from positive before to negative after angioplasty, such positive results can be considered true positives and such negative results true negatives.

When the patient population as a whole before and after angioplasty is considered, the sensitivity, specificity, and positive and negative predictive values of the 0.75 value of FFR were 82%, 87%, 81%, and 91%, respectively. The concordance between the FFR and the results of SPECT was 85% (κ = 0.67, P < 0.001; Figure 3).

When only the truly positive and the truly negative SPECT results were considered, the corresponding values were 87%, 100%, 89%, and 94% (κ = 0.87, P < 0.001; Figure 3).

Figure 4 shows the sensitivity and specificity curves of FFR in detecting a positive SPECT. The value of FFR for which sensitivity and specificity are equal (88%) was 0.78. The difference in the area under the receiver operating characteristic curves obtained for the cutoff value of 0.75 and of 0.78 did not show any statistically significant differences in the accuracy of these 2 threshold values.

Relation Between FFR, Global LV Function, and Stenosis Severity
As shown in Figure 5, patients with positive SPECT before angioplasty had a significantly lower FFR but a significantly higher LVEF than patients with a negative SPECT (0.52 ± 0.18 versus 0.67 ± 0.16, P = 0.0079, and 63 ± 10% versus 52 ± 10%, P = 0.0009, respectively) despite a similar degree of diameter stenosis (67 ± 13% versus 68 ± 16%, P = NS). A weak but significant inverse correlation was found between LVEF and FFR (r = 0.29, P = 0.0495, Figure 6) and between DS and FFR (r = 0.54, P < 0.001).

Discussion
The accuracy of the FFR value of 0.75 for identifying coronary stenoses capable of inducing myocardial ischemia is
well established for stenoses supplying normal myocardial regions.5–11 The present data demonstrate that even in the presence of a prior MI in the distribution area of the stenosis, a pressure-derived FFR value of 0.75 accurately distinguishes patients with and without residual reversible flow maldistribution in the partially infarcted myocardial area. Because the patients in this study had sustained an MI $6$ days before the measurements, however, the results of the present study should not be applied to FFR measurements obtained in the acute phase of an infarction.

Postinfarction Ischemia

Several studies have underscored the prognostic importance of residual reversible perfusion defects in partially infarcted areas.19–23 In patients with a recent MI, the occurrence of cardiac events is often related to coronary reocclusion, which cannot be predicted by angiography.24 It is therefore generally accepted that postinfarction stress-induced reversible ischemia warrants revascularization. Because in the postinfarction setting the accuracy of noninvasive testing is poor and because the majority of patients undergo coronary angiography before hospital discharge after MI without complete noninvasive workup, it is desirable to determine in the catheterization laboratory whether a given stenosis detected at angiography is capable of inducing residual myocardial ischemia. The present data actually extend the validity of the 0.75 threshold value of FFR as a surrogate for noninvasive stress testing to patients with a prior MI.

Because detecting reversible myocardial ischemia in partially infarcted territories is difficult, we focused on truly positive and truly negative SPECT results. Considering the relatively limited accuracy of SPECT in detecting residual ischemia after infarction, we considered as truly positive and truly negative SPECT only the tests that were positive before angioplasty and reverted to negative after angioplasty. According to Bayesian considerations, the probability of such positive tests being truly positive and the probability of such negative tests being truly negative is very high.25–27 This approach provides us with an optimal test for comparing the results of pressure-derived FFR.7

Relation Between Stenosis Severity, FFR, and Mass of Viable Myocardium

Basal and hyperemic myocardial flows per gram of perfusible tissue are lower in infarcted regions than in regions remote from the infarction up to 6 months after MI.28,29 For similar degrees of stenosis, coronary flow velocity reserve is lower in regions with than in regions without prior MI both before and after angioplasty.29 The mechanisms responsible for a reduced basal flow remain speculative and include the

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**Table 1:**

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Concordance = 83%

K = 0.66; P=0.0001

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<td>n=35</td>
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Concordance = 94%

K = 0.87; P=0.0001

Figure 3. Concordance between FFR and SPECT imaging in patient population as a whole (top) and patients in whom SPECT imaging was truly positive and truly negative (bottom).

Figure 4. Sensitivity and specificity curves of FFR to detect flow maldistribution at MiBI perfusion scan in population as a whole.

Figure 5. Values of LVEF, FFR, and diameter stenosis (DS) according to results of SPECT imaging. At similar degree of stenosis, patients with positive SPECT imaging have better preserved LVEF and lower FFR than patients with negative SPECT imaging, suggesting a larger amount of viable tissue. This corroborates that for same anatomic obstruction, value of FFR depends on mass of myocardium at risk.

Figure 6. Relationship between LVEF and FFR.

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prior MI and in patients with normal LV function. The presence of viable myocardium is unlikely to change. This explains the fact that 2 identical stenoses may have a different stenosis severity, FFR will be larger after than before MI, which is preserved despite the smaller amount of viable tissue to be supplied.

In the present study, an inverse relation was found between global LVEF and FFR. In addition, in patients with residual flow maldistribution, FFR was significantly lower and LVEF significantly higher in patients without residual reversible flow maldistribution, even though stenosis severity was similar in both groups. Taken together, these data illustrate the interrelationship between stenosis severity, epicardial blood supply, myocardial mass, and ischemic threshold: the smaller the infarcted area (and thus the better preserved the LVEF and the larger the reversible perfusion defect), the lower the FFR for a given degree of stenosis. Because after MI, the mass of viable tissue decreases in the perfusion territory supplied by a stenosis, adenosine-induced hyperemic flow and transstenotic gradient will be smaller, and thus, FFR will be larger, even though the stenosis remained unchanged. This implies that at unchanged stenosis severity, FFR will be larger after than before MI, illustrating the fact that 2 identical stenoses may have a different FFR, depending on their distribution area. Therefore, in case of prior MI, FFR does not underestimate stenosis severity. In contrast, FFR still represents the fraction of maximal flow to the remaining viable myocardium, which is preserved despite the presence of the stenosis (Figure 7). In fact, it is the angiogram that overestimates the functional severity after prior MI. Conversely, within the partially infarcted area, the perfusion pressure associated with flow maldistribution or ischemia of the remaining viable myocardial tissue is unlikely to change. This explains why the same cutoff value of FFR was found in patients with a prior MI and in patients with normal LV function.

Limitations

Patients were included in the study as early as 6 days after MI. This does not exclude the presence of ongoing myocardial30 and microvascular31 stunning. As long as 6 weeks after the acute ischemic episode, myocardial contractility and resistive vessel function may still improve.32 Therefore, it is likely that in some patients, hyperemic response to the vasodilators would have been more pronounced if they had been investigated after this delay of 6 weeks. Nevertheless, the time lag between SPECT imaging and the pressure measurements was very short, so it is unlikely that changes in resistive-vessel function between FFR measurements and SPECT imaging would cloud the results. In addition, most patients undergo a catheterization in the few days after the acute MI, so the setup of the present study reflects common practice. Therefore, the results of the present study support the use of FFR to decide on the appropriateness of revascularization of a residual stenosis when angiography is performed ≥6 days after MI. It should be emphasized that the assessment of stenosis severity should not be based on pressure-derived FFR in the acute or subacute phases of an MI, because resistive-vessel function is likely to undergo major changes during these phases.

The present study did not aim at investigating the role of intracoronary pressure measurements in assessing myocardial viability. Nevertheless, it might be speculated that in patients with a prior MI, a large increase in transstenotic pressure gradient or flow during adenosine could be a sign of the presence of viable myocardium, whereas the absence of vasodilatory response could be a sign of absent viability. This was suggested in previous studies showing a direct relationship between coronary flow reserve assessed immediately after primary angioplasty in acute MI and the degree of recovery of LV contractile function.33

Whether clinical decision-making based on FFR measurements in patients after MI is safe should be investigated in a larger prospective trial.

Summary

The present study demonstrates that the 0.75 threshold value of FFR distinguishes patients with positive from patients with negative SPECT imaging even after MI. Therefore, FFR can be used as a surrogate for noninvasive testing at predischarge coronary angiography after a prior MI for individual clinical decision-making. Indeed, FFR still defines to what extent myocardial perfusion will increase after reestablishment of the epicardial conductance. In contrast, pressure-derived FFR should not be used during the acute phase of an MI.

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