

MEASUREMENT OF FRACTIONAL FLOW RESERVE TO ASSESS THE FUNCTIONAL SEVERITY OF CORONARY-ARTERY STENOSES

NICO H.J. PIJLS, M.D., PH.D., BERNARD DE BRUYNE, M.D., KATHINKA PEELS, M.D.,
PEPIJN H. VAN DER VOORT, M.D., HANS J.R.M. BONNIER, M.D., JOZEF BARTUNEK, M.D.,
AND JACQUES J. KOOLEN, M.D., PH.D.

Abstract Background. The clinical significance of coronary-artery stenoses of moderate severity can be difficult to determine. Myocardial fractional flow reserve (FFR) is a new index of the functional severity of coronary stenoses that is calculated from pressure measurements made during coronary arteriography. We compared this index with the results of noninvasive tests commonly used to detect myocardial ischemia, to determine the usefulness of the index.

Methods. In 45 consecutive patients with moderate coronary stenosis and chest pain of uncertain origin, we performed bicycle exercise testing, thallium scintigraphy, stress echocardiography with dobutamine, and quantitative coronary arteriography and compared the results with measurements of FFR.

Results. In all 21 patients with an FFR of less than 0.75, reversible myocardial ischemia was demonstrated

unequivocally on at least one noninvasive test. After coronary angioplasty or bypass surgery was performed, all the positive test results reverted to normal. In contrast, 21 of the 24 patients with an FFR of 0.75 or higher tested negative for reversible myocardial ischemia on all the noninvasive tests. No revascularization procedures were performed in these patients, and none were required during 14 months of follow-up. The sensitivity of FFR in the identification of reversible ischemia was 88 percent, the specificity 100 percent, the positive predictive value 100 percent, the negative predictive value 88 percent, and the accuracy 93 percent.

Conclusions. In patients with coronary stenosis of moderate severity, FFR appears to be a useful index of the functional severity of the stenoses and the need for coronary revascularization. (N Engl J Med 1996;334:1703-8.)

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IN patients with chest pain and stenosis of moderate severity as assessed by coronary angiography, evaluation and treatment are challenging. Often, many diagnostic tests are performed and no clear diagnosis of the cause of the chest pain results. In a considerable number of patients, coronary revascularization is performed without definite evidence that the coronary stenosis is causing the symptoms.^{1,2}

On the basis of pressure-flow analysis of coronary stenoses during maximal flow,^{3,4} the concept of myocardial fractional flow reserve (FFR) has been developed as an invasively determined index of the functional severity of coronary stenoses.⁵⁻¹⁰ FFR is defined as the maximal blood flow to the myocardium in the presence of a stenosis in the supplying coronary artery, divided by the theoretical normal maximal flow in the same distribution. This index represents the fraction of the normal maximal myocardial flow that can be achieved despite the coronary stenosis.

FFR can be derived easily from the ratio of the mean distal coronary-artery pressure to the aortic pressure during maximal vasodilatation.^{5,6} This index is independent of changes in systemic blood pressure and heart rate and is unaffected by conditions known to increase the base-line myocardial flow.⁷ In addition, FFR takes into account the contribution of the collateral blood supply to maximal myocardial perfusion.^{5,8} The normal value of the index is 1.0, regardless of the patient or the specific vessel studied.⁹ Furthermore, in selected patients undergoing percutaneous transluminal

coronary angioplasty an FFR of less than approximately 0.75 identified functionally important stenoses—that is, stenoses associated with inducible myocardial ischemia.^{9,10}

We investigated the usefulness of FFR in making clinical decisions concerning patients with ambiguous clinical symptoms, contradictory or inconclusive results of noninvasive testing, and moderate stenosis in one large coronary artery as determined angiographically.

METHODS

Study Patients

The study population consisted of 45 consecutive patients (28 men and 17 women) with a mean (\pm SD) age of 54 ± 8 years (range, 36 to 74). To be eligible for the study, each patient was required to have chest pain; an angiographically detectable stenosis of moderate severity (defined as approximately 50 percent by visual examination) in the proximal part of one major coronary artery; normal left ventricular function; and uncertainty about whether the chest pain was related to reversible ischemia caused by the moderate stenosis. The study protocol was approved by the institutional review board, and informed consent for all tests was obtained from all the participants.

Study Protocol

All medications were stopped for seven days, except that patients were allowed to take 80 mg of aspirin daily. Within 48 hours after the end of the seven-day period, bicycle exercise testing, thallium scintigraphy, stress echocardiography with dobutamine, and coronary arteriography with intracoronary-pressure measurements and the calculation of FFR were performed in all patients. The clinical decision to perform myocardial revascularization (percutaneous transluminal coronary angioplasty or bypass surgery) was made when the FFR was less than 0.75, a value selected on the basis of the results of earlier studies.^{9,10} In the patients in whom revascularization procedures were performed, all the noninvasive tests that had yielded positive results were repeated within six weeks after the procedure. None of the patients had previously undergone any form of revascularization.

Exercise Testing and Thallium Scintigraphy

Bicycle exercise testing was performed at an initial workload of 20 W, which was increased by 20 W every minute. A 12-lead electro-

From the Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands (N.H.J.P., K.P., P.H.V., H.J.R.M.B., J.J.K.), and the Cardiovascular Center, Aalst, Belgium (B.B., J.B.). Address reprint requests to Dr. Pijls at the Department of Cardiology, Catharina Hospital, P.O. Box 1350, 5602 ZA Eindhoven, the Netherlands.

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cardiogram was recorded continuously. The test was considered positive when horizontal or downsloping ST depression of at least 0.1 mV was recorded 80 msec after the J point by two adjacent leads. At peak exercise, 2.0 mCi (73 MBq) of thallium chloride Tl 201 was administered in a large antecubital vein. Exercise was maintained for one more minute, and then planar imaging was performed in the three standard views.¹¹ After three hours, 1.0 mCi (37 MBq) of thallium chloride Tl 201 was injected again, and redistribution images were obtained.¹² All the images obtained by thallium scintigraphy were evaluated independently by two experienced reviewers unaware of any other study data.

Dobutamine Stress Echocardiography

Stress echocardiography with dobutamine was performed by a four-screen comparison technique showing identical views.^{13,14} An intravenous infusion of dobutamine was started at a rate of 10 μ g per kilogram of body weight per minute and was increased by 10 μ g per kilogram per minute every three minutes until either wall-motion abnormalities were observed or a maximal rate of 50 μ g per kilogram per minute was reached. In patients who did not reach 90 percent of their age-adjusted maximal heart rates and had no objective signs of ischemia, 1 mg of atropine was administered intravenously while the dobutamine infusion was continued.¹⁵ The occurrence of wall-motion abnormalities was evaluated as previously described^{16,17} by two independent echocardiographers unaware of any other study data.

Pressure Measurements and Calculation of FFR

At the time of catheterization, a 6-to-8-French coronary catheter was introduced into one femoral artery and advanced into the ostium of the coronary artery. A 0.46-mm (0.018-in.) fiberoptic pressure-monitoring guide wire (Pressureguide, Radi Medical, Uppsala, Sweden) was set at zero, calibrated, advanced through the catheter, introduced into the coronary artery, and positioned distal to the stenosis as previously described.^{9,10,18-20} Adenosine was then infused intravenously (140 μ g per kilogram per minute) to induce maximal coronary blood flow, corresponding with minimal distal coronary pressure.²¹⁻²⁴ When steady-state hyperemia was achieved, FFR was calculated as the ratio of the mean distal intracoronary pressure measured by the wire to the mean arterial pressure measured by the coronary catheter, as described previously.^{5,6,9}

If the FFR was 0.75 or higher, no revascularization procedure was performed. If the FFR was below 0.75, myocardial revascularization was recommended. If the lesion was suitable for coronary angioplasty, that procedure was performed during the same session, and FFR was measured again 15 minutes after successful angioplasty. If the lesion was not considered suitable for coronary angioplasty (i.e., because of stenosis of the left main coronary artery or a long ostial stenosis of the left anterior descending coronary artery), coronary bypass surgery was performed within four weeks.

Quantitative Coronary Arteriography

Quantitative coronary arteriography was performed in all patients in two orthogonal views.²⁵ The percent stenosis, area of stenosis, reference diameter of the adjacent normal segment, and minimal luminal diameter were calculated as the mean of the values obtained in the two views.

Definition of Inducible Ischemia Based on the Results of the Noninvasive Tests

Despite the excellent sensitivity and specificity of thallium exercise testing and stress echocardiography in patients with angiographically important coronary stenosis, these tests are known to be less accurate in patients with atypical chest pain or only moderate coronary stenoses on angiography.^{12,17,26-29} It is thus difficult to establish the value of any new method to assess the functional severity of coronary artery disease, because there is no single unequivocal or gold standard. This is especially true of our study population with moderate stenoses.

To overcome this problem, we compared the value of the new invasive index, FFR, with that of the information derived from a combination of noninvasive indexes. We postulated that functionally important stenoses (indicative of potentially inducible myocardial ischemia) were present if and only if at least one of the noninvasive tests had a

Table 1. Characteristics of the Patients, Results of Noninvasive Tests, and Quantitative Angiographic Measurements.*

VARIABLE	STUDY GROUP	
	FFR \geq 0.75 (N = 24)	FFR <0.75 (N = 21)
Sex (M/F)	13/11	15/6
Age (yr)	55 \pm 9	54 \pm 8
Affected artery (no. of patients)		
Left main	1	1
Left anterior descending	10	14
Left circumflex	4	2
Right coronary	9	4
Reference diameter (mm)	3.31 \pm 0.67	3.10 \pm 0.63
Percent stenosis	44 \pm 9	41 \pm 8
Minimal luminal diameter (mm)	1.94 \pm 0.47	1.78 \pm 0.41
Exercise test and thallium scanning		
Heart rate		
Beats/min	146 \pm 18	162 \pm 19 [†]
Percentage of age-adjusted rate	95 \pm 12	104 \pm 12
Positive exercise tests (no.)	2	16
Positive thallium scans (no.)	1	12
Stress echocardiography		
Heart rate		
Beats/min [‡]	149 \pm 11	147 \pm 13
Percentage of age-adjusted rate	98 \pm 7	95 \pm 8
Positive tests (no.)	0	10
Treatment		
Medicine only	24	1
Angioplasty	0	13
Bypass surgery	0	7

*Plus-minus values are means \pm SD.

[†]P = 0.033 for the comparison with the group with an FFR of 0.75 or higher.

[‡]Adequate stress-echocardiographic images could not be obtained in four patients.

clearly positive result and reverted to normal after successful coronary angioplasty or bypass surgery.

We further postulated that there was no functionally important stenosis (and therefore no inducible ischemia) if and only if all the noninvasive tests were negative. Patients with one or more positive results of noninvasive testing but in whom the FFR exceeded 0.75 were considered to have false negative results with respect to FFR.

Composite information from sequentially performed noninvasive tests has a diagnostic accuracy of almost 100 percent, according to sequential Bayesian considerations.³⁰⁻³⁵ FFR values (\geq 0.75 or <0.75) were compared with the composite test results.

Statistical Analysis

Angiographically determined indexes of stenosis and heart rate were compared between the two study groups by the two-tailed Student unpaired t-test. P values of less than 0.05 were considered to indicate statistical significance. All numerical data are presented as means \pm SD.

RESULTS

Clinical Results

The characteristics of the patients, the results of noninvasive testing, and the angiographic data are shown in Table 1. All the patients had normal electrocardiograms while resting. There was no difference in the percentage of stenosis or the minimal luminal diameter between the patients with an FFR below 0.75 and those with higher values. Figure 1 shows representative coronary angiograms and coronary-pressure tracings typical of those used to calculate FFR.

The FFR was 0.75 or higher in 24 patients, and in these patients revascularization was not performed. The FFR was less than 0.75 in 21 patients. In 20 of

these 21, coronary angioplasty or bypass surgery was performed (in 13 and 7 patients, respectively); all non-invasive tests that had previously been positive were then repeated, and the results all reverted to normal. In one patient with an FFR of 0.40 and a stenosis in the proximal portion of the left anterior descending coronary artery, revascularization was recommended, but the patient declined to undergo the procedure.

In the patients who underwent coronary angioplasty, FFR was measured again 15 minutes after the pro-

cedure. In every case it increased to a value greater than 0.75 (mean [\pm SD], 0.87 ± 0.06 ; range, 0.77 to 0.96), in accordance with the normal results of noninvasive testing.

Comparison of FFR with the Results of Noninvasive Tests

The relation between FFR and the results of the non-invasive tests is shown in Figure 2. In all 21 patients with an FFR below 0.75, signs of myocardial ischemia could be induced by at least one noninvasive test. All

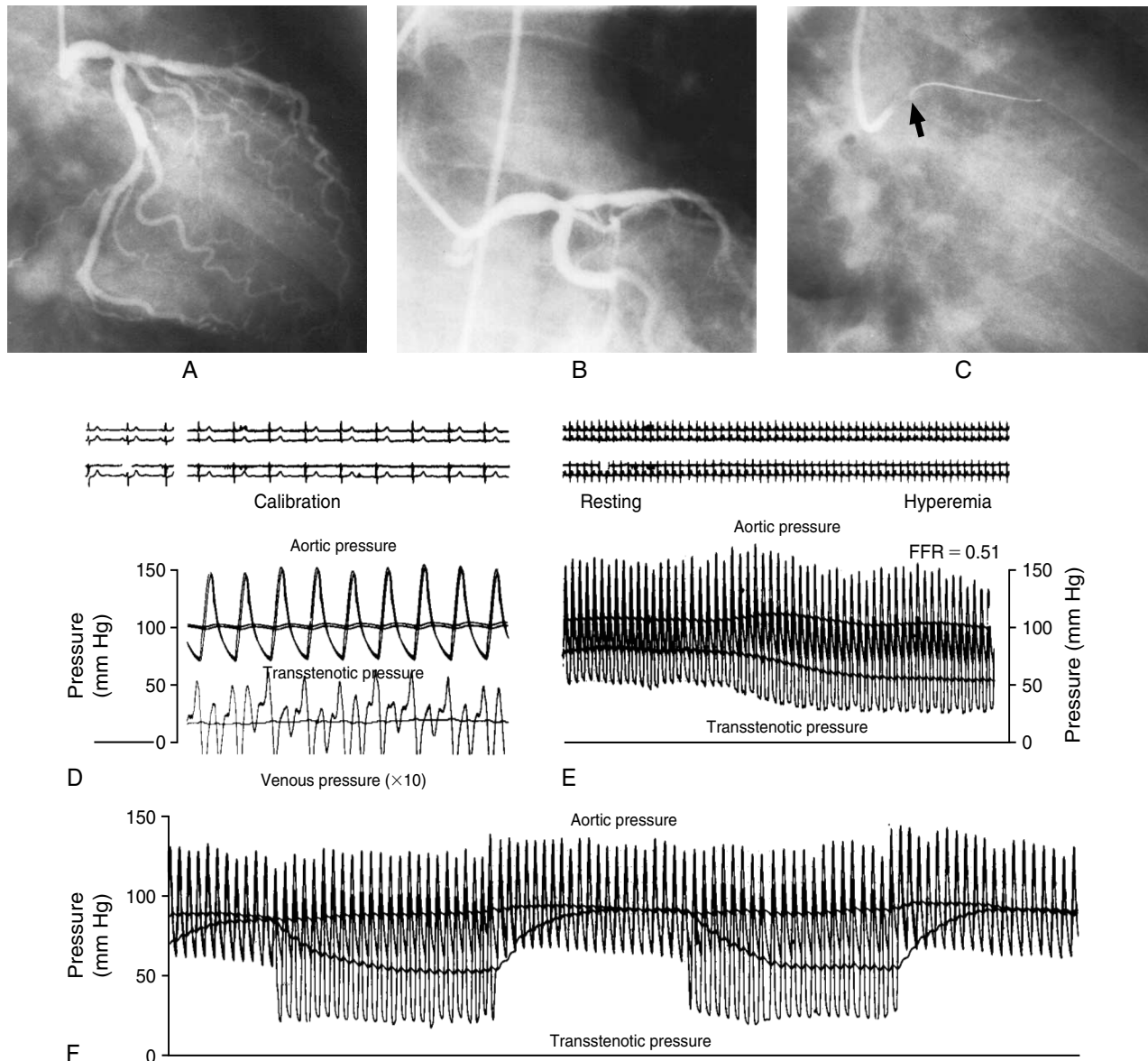


Figure 1. Coronary Angiograms and Simultaneously Obtained Recordings of Aortic and Transstenotic Pressure in a 65-Year-Old Woman.

The patient had moderately severe stenosis of the left main and left anterior descending coronary arteries (Panels A and B, respectively). The pressure recordings in Panel D were obtained with the sensor located at the tip of the coronary catheter to verify that equal pressures were obtained at that location by both the catheter and the guide wire. Subsequently, the fiberoptic wire was advanced across the stenosis in the left main coronary artery and a large resting gradient (22 mm Hg) was found (Panel E), which increased further after an intravenous infusion of adenosine. At steady-state maximal hyperemia, the aortic pressure was 101 mm Hg and the transstenotic pressure 52 mm Hg, resulting in an FFR of 0.51, which indicated that the stenosis was functionally important. Panels C and F show how the wire was slowly advanced across the stenosis and then withdrawn, indicating the site and severity of the stenosis exactly and reproducibly. The arrow in Panel C indicates the location of the pressure sensor.

positive tests in this group were repeated after revascularization, and the results reverted to normal.

In 21 of the 24 patients with an FFR of 0.75 or higher, all the noninvasive tests were negative. Of the remaining three patients, two had positive exercise electrocardiograms and one had a positive thallium scan. In these

three patients the FFR method yielded false negative results, because evidence of inducible ischemia was present despite an FFR of 0.75 or higher. The overall sensitivity, specificity, positive and negative predictive values, and accuracy of FFR were 88, 100, 100, 88, and 93 percent, respectively.

Clinical Follow-up of Patients with FFR of 0.75 or Higher

Myocardial revascularization was not performed in the patients with an FFR of 0.75 or higher. Seventeen were treated with aspirin alone, and seven with a combination of aspirin and a calcium-channel blocker. At follow-up visits four weeks later, the functional class of these patients, when measured according to the classification system of the Canadian Cardiovascular Society, had improved substantially, from 2.8 to 1.3. After a mean follow-up of 14 ± 5 months (range, 5 to 21), there were no ischemic events in any of these patients, no revascularization was necessary, and 17 were asymptomatic.

DISCUSSION

Our study supports the concept that FFR reliably indicates functionally significant coronary stenoses. This index performed well as compared with standard noninvasive tests for myocardial ischemia. Decisions made on the basis of the FFR resulted in excellent clinical outcomes in the patients in whom unnecessary revascularization was averted. Such decisions are often difficult in patients with coronary stenoses of moderate severity.

In most patients with coronary artery disease, the decision to perform revascularization procedures should be based not only on the coronary anatomy but also on the functional severity of a lesion.³⁶⁻³⁸ This is especially true in patients with narrowings of intermediate severity demonstrated on coronary angiograms. If, when such a lesion is present, myocardial ischemia can be clearly demonstrated by exercise or pharmacologic stress testing, revascularization is appropriate when medical therapy fails to control symptoms.^{37,38} In some patients, however, noninvasive tests are inconclusive. Moreover, both exercise thallium scintigraphy and stress echocardiography have limited sensitivity in such patients. When chest pain persists despite repeatedly negative tests, confusion often arises about the clinical importance of the lesions.^{1,2} Therefore, it would be useful to have a measurement that is easily obtainable at the time of diagnostic coronary angiography that would indicate clearly whether the coronary stenosis is responsible for reversible ischemia.

Myocardial FFR is such an index of the effect of an epicardial coronary-artery stenosis on maximal myocardial perfusion.⁵⁻¹⁰ In previous studies of selected patients undergoing percutaneous transluminal coronary angioplasty, a cutoff FFR value of approximately 0.75 distinguished lesions associated with inducible ischemia from other lesions, and there was minimal overlap between the two groups.^{9,10} Our study extends previous observations by assessing the clinical application of FFR. The results indicate that FFR performed well in assessing the functional severity of coronary stenoses.

As previously demonstrated, the risk associated with

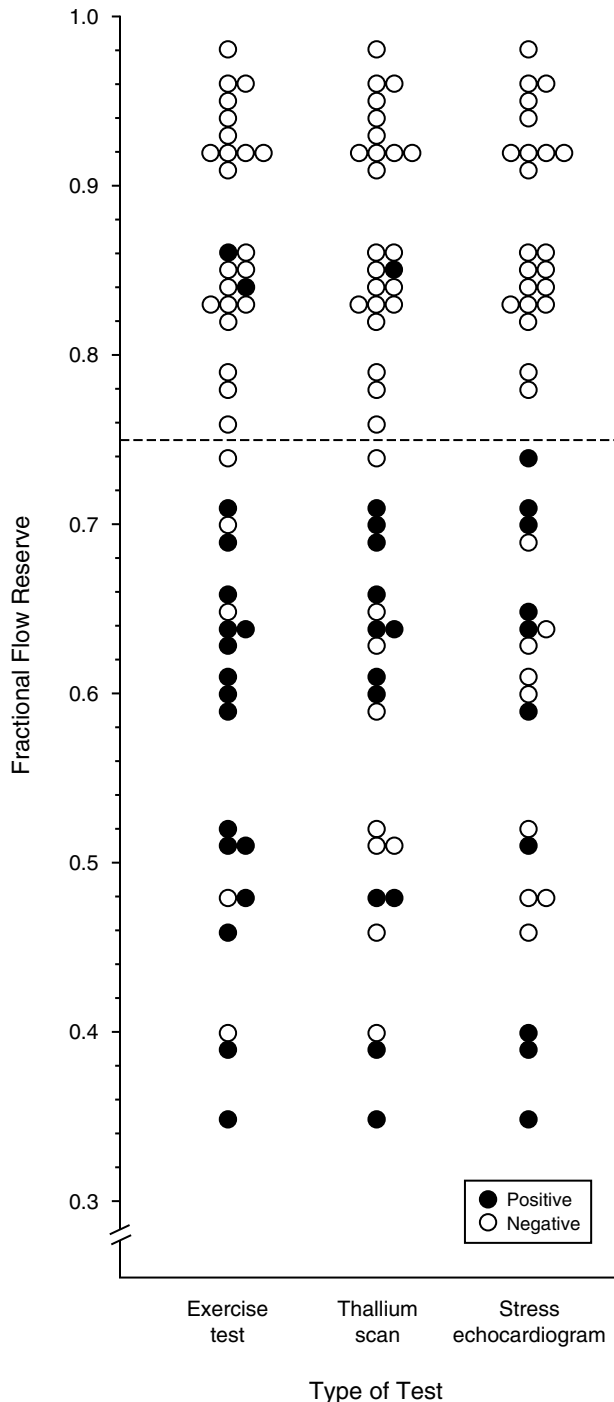


Figure 2. Relation between Myocardial FFR in the Study Patients and the Results of Three Noninvasive Tests.

The test results for each patient are shown on one line according to that patient's FFR. The dashed line representing an FFR of 0.75 indicates the cutoff between the two groups assessed in this study. Adequate stress-echocardiographic images could not be obtained in four patients.

advancing a sensor-tipped guide wire across a coronary stenosis is extremely low^{2,6,9,10,19,39,40} and is offset by the important clinical information gained, especially in the case of a moderate stenosis in the proximal portion of a large coronary artery. With such a stenosis, omitting an intervention that is indicated and performing one that is not indicated can both be harmful.

The calculation of FFR from measurements of pressure is limited by the presence of small-vessel disease, diffuse coronary artery disease, and left ventricular hypertrophy.^{5,6,9,10,41} These conditions restrict the increase in blood flow after pharmacologic vasodilatation and the corresponding decrease in distal coronary pressure. Under these conditions, therefore, the severity of the stenosis may be underestimated because of the limited increase in flow and the associated limitation in the pressure gradient. Also, in some patients exercise-induced vasospasm may occur during physical exercise.⁴² In those patients, the hyperemia induced by adenosine in the catheterization laboratory is not necessarily equivalent to exercise-induced maximal hyperemia in daily life. This mechanism could have played a part in the patients with positive exercise tests but FFR values of 0.75 or higher.

Our study indicates that measuring FFR during coronary arteriography is useful in determining whether an angiographically moderate stenosis is functionally important and may therefore be responsible for reversible myocardial ischemia. In this study, the accuracy of FFR for this purpose was equivalent to that of the information provided by a combination of all the noninvasive tests currently used. We therefore believe that myocardial FFR may be useful in making clinical decisions about revascularization procedures in patients with moderate coronary stenoses when other objective evidence of reversible ischemia is lacking.

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