Coronary Flow Reserve Calculated From Pressure Measurements in Humans
Validation With Positron Emission Tomography

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Background Experimental studies have shown that fractional flow reserve (defined as the ratio of maximal achievable flow in a stenotic area to normal maximal achievable flow) can be calculated from coronary pressure measurements only. The objectives of this study were to validate fractional flow reserve calculation in humans and to compare this information with that derived from quantitative coronary angiography.

Methods and Results Twenty-two patients with an isolated, discrete proximal or mid left anterior descending coronary artery stenosis and normal left ventricular function were studied. Relative myocardial flow reserve, defined as the ratio of absolute myocardial perfusion during maximal vasodilation in the stenotic area to the absolute myocardial perfusion during maximal vasodilation (adenosine 140 μg·kg⁻¹·min⁻¹ intravenously during 4 minutes) in the contralateral normally perfused area, was assessed by ¹⁸F-labeled water and positron emission tomography (PET). Myocardial and coronary fractional flow reserve were calculated from mean aortic, distal coronary, and right atrial pressures recorded during maximal vasodilation. Distal coronary pressures were measured by an ultrathin, pressure-monitoring guide wire with minimal influence on the transstenotic pressure gradient. Minimal obstruction area, percent area stenosis, and calculated stenosis flow reserve were assessed by quantitative coronary angiography. There was no difference in heart rate, mean aortic pressure, or rate-pressure product during maximal vasodilation during PET and during catheterization. Percent area stenosis ranged from 40% to 94% (mean, 77±13%), myocardial fractional flow reserve from 0.36 to 0.98 (mean, 0.61±0.17), and relative flow reserve from 0.27 to 1.23 (mean, 0.60±0.26). A close correlation was found between relative flow reserve obtained by PET and both myocardial fractional flow reserve (r=0.87) and coronary fractional flow reserve obtained by pressure recordings (r=0.86). The correlations between relative flow reserve obtained by PET and stenosis measurements derived from quantitative coronary angiography was markedly weaker (minimal obstruction area, r=0.66; percent area stenosis, r=−0.70; and stenosis flow reserve, r=0.68).

Conclusions Fractional flow reserve derived from pressure measurements correlates more closely to relative flow reserve derived from PET than angiographic parameters. This validates in humans the use of fractional flow reserve as an index of the physiological consequences of a given coronary artery stenosis. (Circulation. 1994;89:1013-1022.)

Key Words • angiography • tomography • rate-pressure product

Visual interpretation of the coronary angiogram still remains the most widely used method to assess coronary lesion severity despite its well-known interobserver variability¹-³ and its poor correlation with actual pathology of the lesion.⁴-⁶ Quantitative coronary angiography provides accurate measurements on individual coronary lesions for comparative and evolutionary analyses. However, reliable functional evaluation of coronary stenosis by quantitative coronary angiography remains restricted to carefully selected segments and is only applicable in a minority of patients with coronary artery disease.⁷ Functional information therefore becomes necessary for appropriate clinical decision making, especially on coronary lesions with difficult interpretation at angiography (postangioplasty segments, bifurcation lesions, ostial lesions, overlapping side branches, left main disease, etc) or in lesions of intermediate severity. Several functional methods based on coronary flow ratios⁸-¹⁵ or on the maximal achievable flow during arteriolar vasodilation¹⁶,¹⁷ have been proposed. In addition to some theoretical shortcomings, their widespread use has been hampered by time-consuming procedures, limited applicability, and the need for expensive equipment and off-line calculations or processing.

Recently, Pijls et al¹⁸ provided a theoretical and experimental basis for determining relative maximal flow or fractional flow reserve of both the epicardial vessel and the myocardium from pressure measurements during maximal vasodilation. Advantages of this parameter compared with absolute and relative coronary flow reserve were independence of pressure changes, simple derivation from pressure recordings, and, most important, inclusion of the contribution of collateral flow to total myocardial perfusion. Moreover, because normal fractional flow reserve is well defined and equal to 1 for every patient, every coronary artery, and every myocardial distribution, a diminished value of

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fractional flow reserve can be interpreted unequivocally without a normal reference distribution. Recently, our laboratory described and validated a novel angioplasty guide wire that allowed monitoring of distal coronary pressure without additional procedure time or patient risk.19

The purpose of the present study was (1) to validate in humans the calculation of myocardial fractional flow reserve and (2) to compare the information derived either from pressure measurements or from quantitative coronary angiography with myocardial perfusion assessment by 15O-labeled water and positron emission tomography (PET).

Methods

Study Population

The study population consisted of 22 patients (18 men; mean age, 56±8 years; range, 36 to 78 years) admitted because of anginal chest pain caused by an isolated, discrete lesion of the proximal or mid left anterior descending coronary artery in the absence of other lesions on the coronary angiogram. All patients had normal ECG and normal global and regional left ventricular systolic function on a biplane left ventricular angiogram. They were scheduled for elective percutaneous transluminal coronary angioplasty (PTCA) because of significant ST-T depression either during a bicycle stress test or during a spontaneous episode of angina pectoris. Patients were selected on the basis of the ideal suitability of their lesion for quantitative coronary angiography. All cardiac medications were stopped at least 48 hours before admission. Molsidomine 4 mg TID was started on the day of admission. The study was approved by the Ethics Committee of the O.L.V. Hospital, Aalst, Belgium, and of the University Hospital Saint-Luc, Brussels. All patients gave their informed consent to participate in the study. They successively underwent a PET study (day 1) and PTCA (day 2) with quantitative coronary angiography and intracoronary pressure measurements. On day 1, all patients underwent a bidimensional echocardiographic examination at rest and during adenosine infusion (140 μg · kg⁻¹ · min⁻¹) to test their tolerance to adenosine and to rule out left ventricular cavity dilation and wall thinning, which could have led to erroneous sampling during PET studies.

PET Studies

Preparation of Radionuclides

15O-water was produced by irradiating natural oxygen with 28-MeV protons from the cyclotron (Cyclone 30). 31K was produced by the 30Ar-K reaction on argon gas. Irradiation was carried out with an 18-MeV beam of 30-MeV protons.

Tomographic Procedure

Myocardial perfusion images were obtained with an ECAT III (911/01, CTI Inc, Knoxville, Tenn) one-ring device, the characteristics of which have been described previously.20 Measurements were performed with a stationary ring, and images were reconstructed with a Hann filter, giving an in-plane resolution of 8 mm full width at half maximum (FWHM). The collimator aperture was set at 30 mm, resulting in a slice thickness of 15 mm FWHM. Regular calibration of the tomography versus a well counter was performed by measuring a uniform cylindrical phantom (diameter, 20 cm) filled with a solution of 68Ge. All patients were studied after fasting overnight. The patients were carefully positioned in the tomograph. Serial transmission scintigrams at different levels were obtained to select an adequate midventricular cross-sectional plane and to allow for subsequent correction for photon attenuation. All transmission scintigrams were viewed before collection of emission data to verify proper positioning of the patient. The selected imaging plane corresponded to a midventricular plane. Correct positioning was maintained throughout the study with the use of a light beam and indelible felt pen marks on the patient’s torso. Soon after transmission scintigrams were recorded, 15 mCi of H215O was administered intravenously as a slow bolus over a 30-second period with an infusion pump (model 4420, FWHM R Sage Instruments). Thirty serial images were acquired for 180 seconds (15 for 2 seconds and 15 for 10 seconds). The use of water for quantifying myocardial blood flow necessitates the injection of another isotope because water is a freely diffusible tracer taken up by both the ventricular walls and the blood pool. Five minutes after the end of the H215O acquisition, 5 to 8 mCi of 31K (t1/2, 462 seconds) was injected intravenously over a 20-second period with an infusion pump. Beginning with tracer injection, 35 serial images were acquired in a decay-compensated mode for 20 minutes. The last three images of 240 seconds each were used to delineate the regions of interest used for the H215O imaging processing (Fig 1). Thirty minutes after the end of the K acquisition, adenosine was infused intravenously (140 μg · kg⁻¹ · min⁻¹). ECG, heart rate, and invasive brachial arterial pressure were recorded and digitized on line. The same sequence of tomographic acquisition as the one previously described then was performed during arteriolar vasodilation: H215O injection and acquisition followed by K injection and acquisition.

Analysis of Tomographic Data and Calculation of Myocardial Perfusion

After random coincidence subtraction, normalization of sinograms, and correction for attenuation, the reconstructed images (256×256 pixels) were corrected for dead time and isotope decay. Three large regions of interest representing 4 to 5 cm² each were drawn on the images of the 31K study (Fig 1, panel A). These three regions then were copied on all H215O dynamic images to construct the corresponding tissue and blood pool time-activity curves. When copied, each region of interest was checked for appropriate location around the blood pool image (Fig 1, panel B) and for correspondence to the myocardial wall activity of the normalized subtraction image (Fig 1, panel D). Myocardial perfusion was calculated from H215O tomographic images by fitting arterial input function and tissue time-activity curves to a single tissue compartment tracer kinetic model for H215O studies. The method has been validated in experimental animals by different groups,21-23 including ours.24 Relative myocardial perfusion reserve25 of the anterior segment was defined as the ratio of the maximal achievable absolute flow in the anterior region (depending on the stenotic left anterior descending coronary artery) to the maximal achievable absolute flow in the lateral region (depending on the normal left circumflex coronary artery). Because in this particular group of patients the left circumflex coronary artery was normal, myocardial relative perfusion reserve defined in this way and assessed by PET can be considered as equivalent to myocardial fractional flow reserve, defined as the ratio of maximal stenotic to normal maximal flow in the left anterior descending coronary artery—dependent myocardium, as will be discussed extensively later.

Quantitative Coronary Angiography

The stenosed coronary segment was analyzed with the automated coronary analysis program26 implemented on biplane Optimus 200 radiographic equipment (Philips Medical Systems BV, Best, The Netherlands). Briefly, a path line was automatically detected within a manually defined coronary segment on an end-diastolic frame. The absolute diameter of the stenosis was determined using the empty catheter as a scaling device. Care was taken to film successively the empty guiding catheter and the stenotic segment in the center of the radiographic field to minimize pincushion distortion. A computer estimation of the original dimension at the site of
obstruction was used to define the interpolated reference area, obstruction area, and stenotic length. From these geometric data, percent diameter and area stenosis, minimal obstruction area, and stenosis flow reserve were averaged from at least two orthogonal or nearly orthogonal projections.

**Pressure Measurements**

**Catheterization Protocol**

An 8F introduction sheath was inserted in the femoral artery, and 8F or 7F Judkis guiding catheters were used to cannulate the coronary ostium. The side arm of the femoral sheath and the guiding catheter each were connected to a Spectranetic P23 Statham pressure transducer. To measure the mean distal coronary pressure, a 0.015-in, fluid-filled, pressure-monitoring guide wire (Preme, Advanced Cardiovascular Systems) was used. The characteristics of the wire have been described in detail previously. The pressure-monitoring guide wire was flushed with heparinized saline and attached by two three-way high-pressure stopcocks to a third pressure transducer. The side arm of the distal stopcock was connected to an inflator filled with heparinized saline for flushing the wire. The three pressure transducers were zeroed at mid chest level. Through a 7F pigtail catheter, a high-fidelity tipped manometer was advanced into the right atrium. Central venous pressure was continuously recorded. The pressure-monitoring guide wire first was advanced up to the tip of the guiding catheter, where mean and phasic pressures were recorded simultaneously. The pressure-monitoring guide wire was advanced through the stenotic segment while continuously recording the phasic pressure of the femoral sheath, the guiding catheter, and the pressure-monitoring guide wire. Mean transtenotic pressure gradient, mean aortic pressure, and mean right atrial pressure were recorded simultaneously under baseline conditions and during maximal vasodilation induced by a 4-minute intravenous infusion of adenosine (140 μg · kg⁻¹ · min⁻¹). The mean coronary wedge pressure was measured at the end of the first balloon inflation. PTCA was performed with a monorail balloon catheter system. No complication resulted from the study protocol. An example of sequential pressure recordings is given in Fig 2.

**Calculation of Fractional Flow Reserve and Coronary Resistance**

Fractional flow reserve is coronary flow reserve expressed as a fraction of its normal expected value and is therefore defined as the maximal achievable flow in the stenosed epicardial vessel or in the myocardium depending on the stenosed coronary artery (coronary fractional flow reserve and myocardial fractional flow reserve, respectively) divided by the maximal achievable flow if the epicardial coronary artery were normal. The theoretical and experimental basis of determining maximal coronary, myocardial, and collateral blood flow by pressure measurements has been published recently. Based on a schematic representation of the coronary circulation, the fractional flow reserve for the myocardium (FFRmyo) and for the epicardial vessel (FFRvess) can be calculated as:

\[
\text{FFR}_{\text{myo}} = 1 - \frac{\Delta P}{P_a - P_s}
\]

\[
\text{FFR}_{\text{vess}} = 1 - \frac{\Delta P}{P_a - P_s}
\]

where \( \Delta P \) is the transtenotic pressure gradient, \( P_a \) is the mean aortic pressure, \( P_s \) is the mean right atrial pressure, and \( P_w \) is the mean coronary wedge pressure, all pressures being measured during maximal arteriolar vasodilation.
Myocardial vascular resistances in the stenotic territory (R) and the normal contralateral territory (Rn) were calculated as

\[ R = \frac{(P_d - P_s)}{Q} \]

\[ R_n = \frac{(P_{ao} - P_s)}{Q_n} \]

since, in the normal epicardial vessel

\[ P_d = P_{ao} \]

\[ R_n = \frac{(P_{ao} - P_s)}{Q_n} \]

where \( P_{ao} \) is the mean aortic pressure, \( P_d \) is the distal coronary pressure, \( P_s \) is the mean right atrial pressure, \( Q \) is the myocardial flow in the stenotic area, and \( Q_n \) is the myocardial flow in the normal area.

**Statistics**

The results are given as mean ± 1 SD. Linear regression was calculated between relative flow reserve data as derived from PET (as dependent variable) and myocardial fractional flow reserve values, hyperemic pressure gradients, and indices derived from quantitative coronary angiography (as independent variable). A logarithmic regression was calculated between relative flow reserve data and resting pressure gradients. A stepwise polynomial regression was calculated between relative flow reserve data and coronary fractional flow reserve data. Statistical analysis of hemodynamic data was performed with two-factor ANOVA with repeated measurements. Multiple comparisons between pairs of means were performed according to the Student-Newman-Keuls test. Statistical analysis of myocardial vascular resistance was performed with paired t tests. Results were considered statistically significant at \( P < .05 \).

**Results**

**Clinical and Hemodynamic Results**

All lesions could be crossed easily with the pressure-monitoring guide wire, and PTCA was performed without the need of another guide wire.

The hemodynamic data during PET and catheterization are summarized in Table 1. During PET, there was no significant difference between mean aortic pressure under baseline conditions and during adenosine-induced maximal vasodilation. Similarly, at catheterization, no significant difference was noted between mean aortic pressure at rest and during adenosine infusion. More important, during maximal vasodilation, mean aortic pressure did not differ significantly during PET data acquisition and during catheterization. Adenosine infusion induced a significant increase in heart rate during

| Table 1. Hemodynamic Data of Patients During Positron Emission Tomography and During Catheterization |
|-------------------------------------------------|-------------------------------------------------|
| MAP                                             | Positron Emission Tomography | Catheterization |
| **MAP**                                         | **Positron Emission Tomography** | **Catheterization** |
| **MAP**                                         | **Positron Emission Tomography** | **Catheterization** |
| Rest                                            | 94 ± 14 mm Hg                  | 105 ± 18 mm Hg* |
| Hyperemia                                       | 96 ± 13 mm Hg                  | 102 ± 13 mm Hg |
| HR                                              | Rest                            | 63 ± 10 bpm      |
| Hyperemia                                       | 87 ± 17 bpm†                   | 87 ± 15 bpm†     |
| RPP                                             | 5955 ± 1379                    | 7579 ± 2465 mm Hg · bpm* |
| Hyperemia                                       | 8392 ± 2279†                   | 8884 ± 2215 mm Hg · bpm† |
| RAP                                             | Rest                            | NM               |
| Hyperemia                                       | NM                              | 5 ± 1 mm Hg      |

MAP indicates mean aortic pressure; HR, heart rate; RPP, rate-pressure product; RAP, mean right atrial pressure; NM, not measured; and bpm, beats per minute.

*\( P < .05 \) vs the corresponding value during positron emission tomography; †\( P < .05 \) vs the corresponding value at rest.
PET and during catheterization. However, during maximal arteriolar vasodilation, heart rate was not significantly different during PET and during catheterization. Rate-pressure product during maximal hyperemia was comparable during PET and during catheterization.

Mean right atrial pressure measured invasively during catheterization varied from 2 to 7 mm Hg at rest and from 2 to 8 mm Hg during intravenous infusion of adenosine.

Fig 3 shows the calculated individual values of myocardial resistance in the perfusion area depending on the stenotic vessel and in the perfusion area depending on the normal vessel. At rest, that is, under normal autoregulatory conditions, myocardial resistance was lower in the stenotic than in the normal territory (66±33 versus 86±26 mm Hg·mL⁻¹·min⁻¹ per gram of tissue, P<.05). However, during suppression of autoregulatory tone by intravenous adenosine, no significant difference was observed between the normal and stenotic territories (36±15 versus 32±11 mm Hg·mL⁻¹·min⁻¹ per gram of tissue, P=NS).

Myocardial Perfusion Quantitation Versus Pressure Measurements and Fractional Flow Reserve Calculations

Relative flow reserve in the anterior segment assessed by PET was decreased and varied from 0.27 to 1.23 (mean, 0.60±0.26). Myocardial and coronary fractional flow reserve as calculated from pressure measurements in the anterior segment ranged, respectively, from 0.36 to 0.98 (mean, 0.61±0.17) and from 0.24 to 0.98 (mean, 0.46±0.25). Myocardial fractional flow reserve assessed by pressure measurements correlated closely with relative flow reserve by PET (r=.87, Fig 4A). The mean difference between myocardial fractional flow reserve values and relative flow reserve values was −0.049±0.092 (Fig 4B). The correlation remained identical when, in the equation calculating myocardial fractional flow reserve, an arbitrary value of 5 mm Hg was introduced instead of the actual mean right atrial pressure (r=.87). A good correlation was found between relative flow reserve by PET and coronary fractional flow reserve by pressure measurements (r=.86, Fig 5A). The latter relation was best fitted by a quadratic equation showing a divergence from the line of identity in the range of severe stenoses. The mean difference between the value of relative flow reserve and coronary fractional flow reserve was +0.13±0.11 (Fig 5B). A poor inverse correlation was found between relative flow reserve as derived from PET and transstenotic pressure gradient at rest (r=−.61). However, during vasodilation, transtenotic pressure gradient closely correlated with relative flow reserve (r=−.86, Table 2).

Myocardial Perfusion Estimates Versus Quantitative Coronary Angiography

Minimal obstruction area ranged from 0.52 to 5 mm² (mean, 1.5±1.3 mm²), diameter stenosis ranged from 22% to 77% (mean, 55±14%), area stenosis ranged from 40% to 94% (mean, 77±13%), and calculated stenosis flow reserve ranged from 1.03 to 4.6 (mean, 2.9±1.1). As shown in Table 2 and Fig 6, measurements derived from quantitative coronary angiography correlated less with relative flow reserve than did myocardial and coronary fractional flow reserves and transstenotic pressure gradient during hyperemia.

Discussion

Feasibility of Fractional Flow Reserve Calculation

This study confirms the feasibility of fractional flow reserve calculation in humans. The pressure-monitoring guide wire adequately fulfills its dual role as a mean coronary pressure measurement device and part of the therapeutic angioplasty system. The pressure-monitoring guide wire has the same overall technical character-

![Fig 3](image-url)
istics as most of the presently available angioplasty guide wires. Therefore, manipulation of the wire into the coronary tree is easy and safe. No complication related to manipulation of this guide wire was encountered in this series of selected patients or in a larger series of unselected patients.28 The additional time needed to perform the measurements is limited to a few minutes and could be diminished further by using short-acting vasodilatory drugs such as papaverine or adenosine administered intracoronarily. In this study, intravenous adenosine was selected because no intracoronary drugs could be administered during PET. The transstenotic pressure gradient during maximal vasodilation can be read directly from the pressure-monitoring screen, and the calculation of fractional flow reserve can be done with a pocket calculator in a few seconds. In this validation study, right atrial pressure was monitored invasively throughout the study. Mean right atrial pressure did not change during maximal vasodilation or during balloon coronary occlusion. Hence, the value of mean right atrial pressure could be estimated clinically or set at an arbitrary value. This would further simplify the procedure, since all data needed for fractional flow reserve calculation could be derived from routine coronary angioplasty measurements.

Rationale of Validating Fractional Flow Reserve by PET Measurements of Relative Flow Reserve

The fractional flow reserve is the ratio of maximal achievable flow in the stenotic area to the maximal achievable flow in that same area in the presence of a normal epicardial vessel. The relative flow reserve is the maximal achievable absolute flow in the stenotic area divided by the maximal achievable absolute flow in a contralateral area depending on a normal coronary artery. Fig 7 illustrates the rationale of comparing fractional and relative flow reserve in a model of isolated left anterior descending coronary artery stenosis. In that particular case, fractional and relative myocardial flow reserves should be identical. Therefore, validation of the concept of myocardial fractional flow reserve against relative flow reserve as derived from PET is justified provided that four conditions are fulfilled: (1) the absence of significant narrowing in the left circumflex and right coronary arteries, which was confirmed by two experienced angiographers in the present study. (2) The myocardial vascular resistance in the perfusion territory of the circumflex and the left anterior descending coronary arteries should be identical during maximal vasodilation. As shown in Fig 3, our results confirm that myocardial resistance in the lateral and anterior myocardial segments decreased to a similar level during adenosine infusion although they were significantly different under baseline condition. (3) Relative flow reserve determination and fractional flow reserve calculation should be performed under similar hemodynamic conditions. Although both relative and fractional myocardial flow reserves have been shown to be independent of driving pressure,18,25 it seems reasonable in a validation study to perform both measure-

### Table 2. Correlation Between Relative Flow Reserve (y) as Derived From Positron Emission Tomography and Either Pressure-Derived Indices or Data Derived From Quantitative Coronary Angiography (x)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation Coefficient</th>
<th>SEE</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial fractional flow reserve</td>
<td>.87</td>
<td>.13</td>
<td>y=1.22x−0.17</td>
</tr>
<tr>
<td>Coronary fractional flow reserve</td>
<td>.86</td>
<td>.14</td>
<td>y=0.71x²+0.37</td>
</tr>
<tr>
<td>Resting transstenotic pressure gradient</td>
<td>−.61</td>
<td>.22</td>
<td>y=0.98−0.14logx</td>
</tr>
<tr>
<td>Hyperemic transstenotic pressure gradient</td>
<td>−.86</td>
<td>.14</td>
<td>y=1.02−0.021x</td>
</tr>
<tr>
<td>Obstruction area</td>
<td>.66</td>
<td>.20</td>
<td>y=0.40+0.14x</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>−.68</td>
<td>.20</td>
<td>y=1.28−0.012x</td>
</tr>
<tr>
<td>Area stenosis</td>
<td>−.70</td>
<td>.19</td>
<td>y=1.65−0.014x</td>
</tr>
<tr>
<td>Stenosis flow reserve</td>
<td>.68</td>
<td>.20</td>
<td>y=0.16x+0.14</td>
</tr>
</tbody>
</table>
ments under similar hemodynamic conditions. During hyperemia, mean aortic pressure, heart rate, and rate-pressure product were similar during PET and during invasive measurements. Furthermore, all medications were withheld at least 48 hours before PET except Molsidomine and Aspirine. (4) The method used as the gold standard to assess myocardial perfusion should be highly reliable. The methodology of myocardial perfusion assessment used in our laboratory has been validated against microspheres in dogs. The correlation was found to be excellent ($r = 0.97$, systematic error = 26 mL/min per 100 g), with flow values ranging from 40 to 680 mL/min per 100 g.

Myocardial, Coronary, and Collateral Fractional Flow Reserves

This study establishes the accuracy of fractional flow reserve calculation from intracoronary pressure measurements in humans as an index of the physiology of a coronary lesion. In the present patient population with isolated disease of the left anterior descending coronary artery, a close linear correlation was found between fractional flow reserve of the myocardium as derived from pressures and the relative coronary flow reserve as derived from PET over a wide range of stenosis severity (Fig 4). Theoretically, the presence of the pressure-monitoring guide wire (diameter, 0.38 mm) through severe lesions could induce an artificial increase in transstenotic pressure gradient and, hence, an underestimation of the actual myocardial fractional flow reserve; however, this is not supported by our data (Fig 4B). In patients with normal left ventricular function and very tight coronary lesions, the transstenotic pressure gradient depends more on the retrograde (collateral) flow than on the anterograde flow. Therefore, in these tight stenoses, the presence of the guide wire through the lesion will not induce a large overestimation of the actual pressure gradient since, even without the guide wire, the pressure gradient is very large. The concept of fractional flow reserve allows calculation of the relative maximal flow of the coronary artery and the myocardium. The myocardial fractional flow reserve incorporates the relative maximal antegrade flow (provided by the epicardial artery) and the relative maximal flow provided by the collateral circulation under conditions of arteriolar dilatation. In contrast, coronary fractional flow reserve only represents the relative maximal antegrade flow during maximal vasodilation. As a consequence, the difference between myocardial and coronary fractional flow reserves represents the relative maximal achievable collateral flow, ie, collateral fractional flow reserve. In the present study, we did not intend to validate coronary and collateral fractional flow reserves because only global myocardial perfusion can be assessed by $H_2^{15}$O and PET. This explains why the fit through the observed values of coronary fractional flow reserve plotted against relative flow reserve values diverged from the line of identity in the range of severe stenoses when collateral circulation starts to play an increasing role (Fig 5).
Comparison With Quantitative Coronary Angiography

Since the length of the lesion and the reference and stenotic diameters can be determined by quantitative coronary angiography, functional information can be derived from these anatomic data by applying the fluid dynamic equation.\textsuperscript{27,29,30} The link between the anatomic and functional approaches has been clearly validated in an animal model instrumented with flowmeters and in which a stenosis was created by external compression of a coronary artery\textsuperscript{27} or with precision-drilled plastic cylinders placed to create intraluminal stenoses.\textsuperscript{29} In these instrumented dogs, percent area reduction correlated well with absolute and relative coronary flow reserves. Moreover, it was suggested that arteriographic stenosis flow reserve is a more specific functional measure of stenosis severity than direct measurement of absolute coronary flow reserve by flowmeter because the effects of physiological variables other than stenosis severity are eliminated.\textsuperscript{25} In the present study, the correlations between indices derived from quantitative coronary angiography and relative flow reserve (PET) were markedly weaker than the correlation between relative flow reserve (PET) and fractional flow reserve, even though the lesions had been selected for their suitability for quantitative coronary angiography (Table 2 and Fig 6). Stenotic models with smooth boundaries and nondiseased reference segments are not necessarily equivalent to clinical practice with irregular atheromatous lesions containing thrombus material and abnormal reference segments. Furthermore, in these animal experiments, only antegrade flow in the epicardial coronary artery was assessed, whereas myocardial fractional flow reserve reflects both antegrade and retrograde (collateral) flows. Previous studies in humans suggest that coronary stenoses determined quantitatively correlate closely with functional parameters when coronary obstruction is produced by discrete, limited coronary artery disease.\textsuperscript{31,32} In contrast, in patients with diffuse coronary disease, angiographic parameters poorly correlate with coronary flow reserve because of the difficulty in determining the actual severity of the lesion by angiography.\textsuperscript{33,34} In the present study, quantitative coronary angiography was performed without intracoronary nitrate and under baseline flow conditions, whereas PET and pressure measurements were performed under conditions of maximal hyperemic flow. Increased shear stress during hyperemia could have led to endothelium-dependent changes in diameters of the coronary artery.\textsuperscript{35} The rationale of administering oral Molsidomine to all patients was to minimize the coronary vasodilation during PET, pressure measurements, and angiography as well as to offset as much as possible the flow-dependent changes in coronary diameters. It should be acknowledged, however, that a better correlation between perfusion data and quantitative coronary angiographic measurements might have been observed under identical flow conditions.

Comparison With Other Functional Approaches of Coronary Stenosis Severity

Absolute coronary flow reserve defined as the ratio of hyperemic to resting flow\textsuperscript{36,38} has been considered the standard for the functional status of a coronary artery. In addition to the practical limitations discussed above, diminished absolute coronary flow reserve can reflect a decrease in maximal flow, an increase in resting flow, or a combination of both. Since heart rate, mean arterial pressure, contractility, and left ventricular preload can affect resting or hyperemic flow, changes in these parameters may result in altered absolute flow reserve for a given stenosis.\textsuperscript{39-42} Because stable hemodynamic resting conditions are difficult to obtain during catheterization and angioplasty, as observed in our own data (Table 1), proper interpretation of absolute flow reserve measurements is often impossible. Relative flow reserve might be measured quantitatively by PET and perfusion tracers is the ratio of maximal flow in a stenotic territory to the maximal flow in a contralateral normal territory. It avoids the problem of variability in resting flow because another part of the heart serves as an internal control area. It is, however, restricted to patients with at least one normally perfused territory. Determining fractional flow reserve from pressure measurements alone has the additional advantage of not requiring an adjacent normally perfused area because the pressure measurements are performed only in the stenotic artery. Fractional flow reserve calculation therefore can be applied in patients with three-vessel disease. It is independent of hemodynamic changes occurring during the procedure and can be calculated easily without prolonging the catheterization. Finally, the uniqueness of the concept of fractional flow reserve is its ability to distinguish between the relative contribution of the epicardial vessel and the collateral circulation to the maximal achievable myocardial perfusion. Large-scale clinical application of the concept depends on the availability of ultrathin, pressure-monitoring guide wires.

Recently, Mancini et al\textsuperscript{43,44} proposed the instantaneous hyperemic flow versus pressure slope index as an alternative to conventional coronary flow reserve indices. This index has been shown to be slightly more sensitive in detecting stenoses than was traditional coronary flow reserve, to be strongly correlated with subendocardial coronary conductance, and to be independent of heart rate, contractility, and volume loading. Preliminary human application already has been performed,\textsuperscript{45} but wide applicability in the clinical setting is unlikely unless a Doppler velocity probe\textsuperscript{46} and a high-fidelity pressure transducer\textsuperscript{47} can be combined on the same PTCA guide wire.

Conclusions

This study validates in humans the concept of fractional flow reserve calculation from pressure measurements as an index of the severity of epicardial coronary stenoses. Since calculation of myocardial fractional flow reserve only requires a pressure-monitoring guide wire and a bolus of short-acting coronary vasodilatory drug, it should be readily obtainable to evaluate angioplasty segments and lesions of intermediate severity.

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