Quantitative Coronary Angiography in Predicting Functional Significance of Stenoses in an Unselected Patient Cohort

JOZEF BARTŮNEK, MD, STANISLAS U. SYS, MD, PhD, GUY R. HEYNDRICKX, MD, PhD, FACC, NICO H. J. PIJLS, MD, PhD,* BERNARD DE BRUYNE, MD
Aalst, Belgium and Eindhoven, The Netherlands

Objectives. This study investigated the value of quantitative coronary angiography for predicting coronary flow reserve, as calculated from the transstenotic pressure gradient in a large, unselected patient cohort.

Background. In patients with extensive coronary artery disease, quantitative coronary angiographic findings fail to correlate with functional variables of coronary stenoses. New developments in pressure-monitoring wire technology permitted validation in humans of the concept of myocardial fractional flow reserve as assessed from coronary pressure measurements.

Methods. One hundred ten patients with normal left ventricular function were studied in the setting of coronary angioplasty. Quantitative coronary angiography was performed on-line using the ACA system. Myocardial and coronary fractional flow reserve were calculated from aortic and distal coronary pressures during maximal coronary hyperemia.

Results. When data before and after angioplasty were pooled, a curvilinear relation was found between myocardial fractional flow reserve and both diameter stenosis ($r = 0.79$) and minimal lumen diameter ($r = 0.82$), and a linear relation was found between myocardial fractional flow reserve and angiographic stenosis flow reserve ($r = 0.78$). Correlations between quantitative angiographic and pressure-derived indexes, although significant, were characterized by a large dispersion of the values of myocardial fractional flow reserve for a similar angiographic degree of stenosis. Nevertheless, the sensitivity and specificity of a minimal lumen diameter $<1.5$ mm to predict myocardial fractional flow reserve $<0.72$ were 96% and 89%, respectively. The corresponding values for a diameter stenosis $>50\%$ were 93% and 85%, respectively.

Conclusions. 1) In an unselected patient cohort, geometric indexes of stenosis severity derived from quantitative coronary angiography correlate significantly with physiologic variables, although these relations are imprecise in individual patients. 2) Nevertheless, the diagnostic accuracy of quantitative coronary angiography in predicting myocardial fractional flow reserve $<0.72$ is high and allows its use for clinical decision making in the individual patient during diagnostic or interventional procedures.

(J Am Coll Cardiol 1995;26:328-34)
Methods

Patients. The study included 110 patients (mean [±SD] age 58 ± 11 years) with normal global and regional left ventricular systolic function, scheduled for one-vessel coronary angioplasty. Patients with total occlusion or "functional" coronary occlusions (Thrombolysis in Myocardial Infarction [TIMI] flow grade 1 or 0) were excluded from the study.

Catheterization protocol. All patients were premeditated with diazepam (10 mg), and molsidomine (4 mg twice daily) was started 24 h before the protocol. After engaging the coronary ostium by a 7F or 8F guide catheter without side holes, a 0.015-in. (0.038-cm) fluid-filled pressure-monitoring guide wire (Premo wire, Advanced Cardiovascular Systems) was advanced up to the end of the catheter. The characteristics of the pressure-monitoring guide wire have been described previously (13). The side arm of the sheath, the guide catheter and the pressure monitoring guide wire were connected to fluid-filled pressure transducers (Spectranetic P23 Statham). All three were zeroed at midchest level. In 26 patients, a 0.018-in. (0.045-cm) fiber-optic pressure-monitoring wire (RadiMedical) was used for coronary pressure measurements (14). Before entering the coronary artery with the pressure-monitoring guide wire, the femoral sheath pressure, guiding catheter pressure and pressure-monitoring guide wire were compared to exclude any intrinsic pressure difference. The guide wire was advanced distally to the lesion under continuous pressure monitoring. Eight milligrams (right coronary artery) or 12 mg (left coronary artery) of papaverine were injected through the guide catheter to induce maximal coronary arteriolar vasodilation (18,19). Mean transstenotic pressure gradient was measured 30 to 40 s after injection of papaverine. Coronary angioplasty was performed using "monorail" balloon catheter systems. During balloon coronary occlusion, coronary wedge pressure was recorded. After completion of the angioplasty, rest and hyperemic transstenotic gradients were measured again in the same way as before the angioplasty. Figure 1 shows an example of pressure recordings performed at rest, during maximal hyperemia and during balloon coronary occlusion.

Calculation of fractional flow reserve. The functional significance of the coronary stenosis was assessed by the myocardial and the coronary fractional flow reserves calculated from coronary pressure measurements. The experimental basis of the concept of fractional flow reserve has been published in detail elsewhere (12). The fractional flow reserve is defined as the maximal achievable flow in the presence of a coronary narrowing expressed as a ratio of its normal expected value. By definition, the normal fractional flow reserve is 1. Fractional flow reserve can be calculated separately for the myocardium (myocardial fractional flow reserve [FFR_{myo}]), which takes into account both anterograde and collateral flow, and for the epicardial coronary artery (coronary fractional flow reserve [FFR_{cor}]), which takes into account only anterograde coronary flow. Fractional flow reserves are calculated as follows:

$$FFR_{myo} = 1 - \Delta P/(P_{as} - P_{r}) = P_c/P_{as}$$

$$FFR_{cor} = 1 - \Delta P/(P_{as} - P_o),$$

Figure 1. Simultaneous tracings of aortic pressure ($P_{ao}$), distal coronary pressure ($P_c$) and coronary wedge pressure ($P_w$) used for the calculations of fractional flow reserves. At rest (left), transstenotic pressure gradient is 15 mm Hg. During maximal hyperemia (middle), the pressure gradient reaches 38 mm Hg. Myocardial fractional flow reserve is 0.58. During coronary occlusion (right), coronary wedge pressure was 34 mm Hg and coronary fractional flow reserve was 0.41 (see text for calculations).
where $\Delta P = \text{mean transstenotic pressure gradient } (P_{ao} - P_c)$ during maximal hyperemia; $P_{ao} = \text{mean aortic pressure measured by the guide catheter at maximal hyperemia}; P_c = \text{mean central venous pressure at maximal hyperemia}; P_w = \text{distal coronary pressure during balloon inflation or coronary wedge pressure}. The difference between myocardial and coronary fractional flow reserve represents the collateral contribution to the maximal myocardial perfusion. Both myocardial and coronary fractional flow reserve were calculated before angioplasty. After angioplasty, only myocardial fractional flow reserve was assessed. Balloon coronary occlusive pressure is needed to calculate coronary fractional flow reserve and is determined mainly by collateral perfusion, which in turn depends on the severity of the lesion before, but not after, angioplasty. Therefore, calculations of coronary fractional flow reserve were not performed after angioplasty.

**Quantitative angiographic analysis.** Visualization of the stenosis was performed in multiple projections to avoid, as much as possible, overlapping of side branches and foreshortening of the relevant segment. Quantitative assessment of stenosis geometry was performed on-line using the ACA system as described previously (20). Briefly, a guiding catheter was used as a calibration device. The relevant coronary stenosis was analyzed from end-diastolic digitized images. A center line was drawn automatically within a manually defined segment. A computer-assisted estimation of the original dimensions at the site of the obstruction was used to define the interpolated reference diameter, obstruction diameter and stenosis length. From these geometric variables, percent diameter stenosis, minimal lumen diameter and stenosis flow reserve (4) were calculated and averaged from two projections.

**Statistical analysis.** Data are presented as mean value ± SD. A paired $t$ test was used to compare paired data. Linear regression analysis was performed when appropriate. For pooled data, nonlinear regression analysis was used to describe the relation between myocardial fractional flow reserve and both minimal lumen diameter and percent diameter stenosis (SPSS Statistical PackageP + 4.0, using the Levenberg-Marquardt algorithm). A $p$ value $>0.05$ was considered non-significant.

**Results**

Coronary pressure measurements were obtained in all 110 patients before angioplasty. Quantitative assessment of lesion geometry was obtained in 105 patients. Clinical characteristics and a coronary lesion profile of the study cohort are given in Table 1. In 97 patients, balloon angioplasty was performed effectively. After angioplasty, both pressure measurements and quantitative angiographic assessment of the segment were achieved in 52 patients.

**Myocardial versus coronary fractional flow reserve.** Figure 2 illustrates the linear correlation between myocardial and coronary fractional flow reserve. Myocardial fractional flow reserve almost uniformly overestimated coronary fractional flow reserve. As expected, collateral contribution (area between the regression line and the line of identity) progressively increased with lesion severity. The intercept of this relation equaled 0.3, which indicates that in the present patient cohort with normal left ventricular function, the contribution of collateral circulation to maximal myocardial flow approximates 30% when anterograde flow is interrupted (coronary fractional flow reserve 0).

**Correlation between flow reserve and coronary lesion geometry.** Before angioplasty, myocardial fractional flow reserve ranged from 0.27 to 0.76 (mean 0.5 ± 0.18) and coronary fractional flow reserve from 0.05 to 0.73 (mean 0.36 ± 0.19) (Table 2). Before angioplasty, diameter stenosis ranged from 40% to 86% (mean 60 ± 14%), minimal lumen diameter from 0.45 to 1.48 mm (mean 0.96 ± 0.45 mm) and stenosis flow reserve as assessed from quantitative coronary angiography from 0.3 to 3.6 (mean 1.8 ± 1.2). Significant linear relations were found between percent diameter stenosis and myocardial fractional flow reserve, between minimal lumen diameter and myocardial fractional flow reserve and between angiographic stenosis flow reserve and myocardial flow reserve. Weaker

Table 1. Clinical Characteristics and Coronary Lesion Profile of 110 Study Patients

<table>
<thead>
<tr>
<th>No. (% of Ps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>No. of vessels diseased</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>No. of lesions analyzed (before and after angioplasty)</td>
</tr>
<tr>
<td>%DS</td>
</tr>
<tr>
<td>&lt;30</td>
</tr>
<tr>
<td>31-40</td>
</tr>
<tr>
<td>41-50</td>
</tr>
<tr>
<td>51-60</td>
</tr>
<tr>
<td>61-70</td>
</tr>
<tr>
<td>&gt;70</td>
</tr>
</tbody>
</table>

$DS = \text{diameter stenosis}; Ps = \text{patients}.$

Figure 2. Relation between coronary fractional flow reserve (FFRcor) and myocardial fractional flow reserve (FFRmyo).
Table 2. Angiographic Indexes of Stenosis Severity and Myocardial and Coronary Fractional Flow Reserve

<table>
<thead>
<tr>
<th></th>
<th>Myocardial Fractional Flow Reserve</th>
<th>Coronary Fractional Flow Reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r Value</td>
<td>SEE</td>
</tr>
<tr>
<td>Minimal lumen diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>0.65*</td>
<td>0.13</td>
</tr>
<tr>
<td>After PTCA</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>0.82*</td>
<td>0.12</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>0.58*</td>
<td>0.14</td>
</tr>
<tr>
<td>After PTCA</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>$-0.79^*$</td>
<td>0.13</td>
</tr>
<tr>
<td>Stenosis flow reserve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>0.61†</td>
<td>0.13</td>
</tr>
<tr>
<td>After PTCA</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>0.78*</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*p < 0.001. †p < 0.01. ‡p < 0.05. DS = percent diameter stenosis; $\text{FFR}_{\text{myo}}$ ($\text{FFR}_{\text{cor}}$) = coronary (myocardial) fractional flow reserve; MLD = minimal lumen diameter; NA = not applicable; PTCA = percutaneous transluminal coronary angioplasty; SFR = angiographic stenosis flow reserve.

correlations were observed between percent diameter stenosis and coronary fractional flow reserve, between minimal lumen diameter and coronary fractional flow reserve and between angiographic flow reserve and coronary fractional flow reserve.

After angioplasty, myocardial fractional flow reserve ranged from 0.72 to 1 (mean 0.88 ± 0.07), diameter stenosis from 2% to 40% (mean 24 ± 11%), minimal lumen diameter from 1.62 to 2.99 mm (mean 2.02 ± 0.7 mm) and stenosis flow reserve from 3.9 to 5 (mean 4.2 ± 1.2). No significant correlation was found between angiographic indexes and myocardial or coronary fractional flow reserve.

When preangioplasty and postangioplasty results were considered together (Table 2, Fig. 3), a curvilinear relationship was found between diameter stenosis and myocardial fractional flow reserve (Table 2) and between minimal lumen diameter and myocardial fractional flow reserve (Table 2). A linear relation was found between angiographic stenosis flow reserve and myocardial fractional flow reserve (Table 2).

Discriminative power of quantitative coronary angiography to detect functionally significant lesions. Sensitivity, specificity and diagnostic accuracy of minimal lumen diameters <1.5 mm to predict a myocardial fractional flow reserve <0.72 were 96%, 89% and 92%, respectively. The corresponding values for a diameter stenosis >50% were 93%, 85%, and 89%, respectively.

Discussion

The results of the present data can be summarized as follows: 1) In an unselected patient cohort scheduled for percutaneous transluminal coronary angioplasty, a significant overall correlation existed between quantitative angiographic measurements of the lesion and pressure-derived calculations of flow reserve. These correlations are characterized by a wide dispersion of the data so that angiographic indexes poorly predict the absolute value of fractional flow reserve in individual patients. 2) Nevertheless, the diagnostic accuracy of a minimal lumen diameter <1.5 mm and a diameter stenosis >50% in detecting lesions associated with myocardial fractional flow reserve <0.72 is high.

Angiographic versus functional approaches. Experimental data (21-24) and previous studies in humans reported statistically significant correlations between angiographic and functional measures of stenosis severity as assessed by technologically diverse measures, including rest transstenotic pressure gradient (13,25), myocardial videodensitometry (7,10), Doppler velocity measurements (6,8,9,11) and positron emission tomography (26,27). Folland et al. (28) studied 227 patients scheduled for coronary angioplasty and demonstrated a very poor relation between changes in coronary artery stenosis assessed by angiography and the improvement in exercise capacity of the patients. These investigators explained this finding by inherent technical variability and insensitivity of angiography to detect small, but functionally important, changes in cross-sectional area. In the present study, a curvilinear relation was found between myocardial fractional flow reserve and both percent diameter stenosis and minimal lumen diameter. A linear relation was found between myocardial fractional flow reserve and angiographic stenosis flow reserve. However, a large scatter around fitted curves was observed.

Methodologic considerations. Several methodologic factors may explain the large individual variations observed in the present study and must be considered when interpreting these data. 1) Angiography and pressure-derived myocardial fractional flow reserve are fundamentally different approaches, because quantitative coronary angiography is lesion specific and myocardial fractional flow reserve depends on more global conditions (i.e., lesion severity, collateral perfusion and myocardial resistance during hyperemia). 2) Angiographic measurements were performed in an unselected patient cohort. Overlapping side branches, the emergence of a side branch immediately before or after a stenosis, foreshortening of the
BARTUNEK ET AL.

QUANTITATIVE CORONARY ANGIOGRAPHY AND MYOCARDIAL FLOW RESERVE

Changes in lumen area after mechanical disruption associated with balloon angioplasty (30). Because angiography is a projection method, dimensions derived from irregular wall boundaries will tend to overestimate the true cross-sectional area. Recent studies (31-33), however, have suggested that both preangioplasty and postangioplasty geometric assessments by edge detection yielded better reproducibility and smaller variation between different views than videsodensitometric measurements. In addition, the small range of values obtained after balloon angioplasty may explain the absence of a significant relation between functional and angiographic variables. 4) The administration of papaverine has been demonstrated to increase minimal lumen area (7). This can induce changes in stenosis hemodynamic variables at the time of hyperemic transstenotic pressure gradient measurements, whereas angiographic assessment is performed under baseline conditions. Yet, to minimize the possible coronary vasodilatation induced by higher shear stress (34) during hyperemic flow, and to avoid vasospasm during wire manipulation, all patients received pretreatment with oral molsidomine. 5) Minimal lumen diameter, percent diameter stenosis and lesion length are the major determinants of the physiologic impact of an epicardial lesion on the underlying myocardium. However, other factors, such as entrance and exit angles, blood viscosity, lesional roughness and eccentricity (35) and coronary flow pulsatility were not accounted for and may affect the value of flow reserve for a given degree of stenosis. 6) The concept of myocardial fractional flow reserve assumes that, during intracoronary administration of papaverine, myocardial resistance becomes negligible as compared with that of the epicardial stenosis. In patients with both an epicardial stenosis and a significant impairment of resistive vessel function, myocardial resistance during administration of papaverine cannot be neglected. In the latter patients, pressure-derived myocardial fractional flow reserve is expected to be higher than that in patients with normal vasodilatory capacity.

Quantitative coronary angiography for clinical decision making. Despite the wide dispersion of the individual values some practical implications can be stated. All but three lesions with a minimal lumen diameter >1.5 mm were associated with myocardial fractional flow reserve >0.72 (sensitivity 96%). Preliminary data have shown that a myocardial fractional flow reserve >0.72 is uniformly associated with normal findings on the exercise electrocardiogram (ECG) (16,17). In contrast, 89% of lesions with a minimal lumen diameter <1.5 mm had a myocardial fractional flow reserve <0.72. Similarly, only four patients with a diameter stenosis >50% had a myocardial fractional flow reserve >0.72, whereas 11 (15%) with a diameter stenosis <50% had a myocardial fractional flow reserve <0.72. These cutout values of minimal lumen diameter and percent diameter stenosis are very close to the corresponding angiographic values with the highest diagnostic accuracy to predict the occurrence of angina or abnormal findings on the exercise ECG, as reported by Rensing et al. (36).

Study limitations. Although the patients in the present study were not selected for having a lesion ideally suited for

![Graph](image-url)

Figure 3. Angiographic indexes and myocardial fractional flow reserve (FFRmyo) after pooling preangioplasty and postangioplasty data. Top, Relation between percent diameter stenosis and myocardial fractional flow reserve. Middle, Relation between minimal lumen diameter and myocardial fractional flow reserve. Bottom, Comparison between angiographic (Anglo) stenosis flow reserve and myocardial fractional flow reserve. $D_{50}$ and $MLD_{50}$ = values of diameter stenosis and minimal lumen diameter, respectively, resulting in the equation: $FFR_{myo} = \text{minimal FFR}_{myo} + (\text{maximal FFR}_{myo} - \text{minimal FFR}_{myo})/2$. 

stenotic segment, poststenotic dilation and marked irregularities of the segment adjacent to the lesion are often present in unselected patients (29). These angiographic factors are potential sources of errors that might reduce the accuracy of quantitative assessment of the stenotic segment. 3) The edge detection method is theoretically not ideal for assessing...
quantitative coronary angiography, all were scheduled for percutaneous transluminal coronary angioplasty. This explains the predominance of patients with single-vessel disease and represents a potential selection bias. In addition, all patients had normal left ventricular function. The concept of fractional flow reserve has not yet been validated in vessels supplying (partially) infarcted myocardium. These potential selection biases preclude the extrapolation of the present findings to patients with diffuse three-vessel disease or with a previous myocardial infarction.

Single versus multiple dimensions of stenoses. The fluid dynamic equations (21) describe the factors responsible for the resistance of a given narrowing. Minimal lesion dimensions, percent diameter stenosis and the length of the lesion all affect this resistance and, thus, the physiologic significance of a stenosis. One could, therefore, expect that the larger the number of geometric variables taken into account, the closer the relation would be with functional assessment of the narrowing. Actually, these theoretic considerations were not confirmed in the present study. Myocardial fractional flow reserve correlated better with minimal lumen diameter (which takes into account only one single measurement) than with percent diameter stenosis (taking into account two measurements: minimal diameter and "normal" reference diameter) and stenosis flow reserve (which, in addition, takes into account lesion length). This suggests that multiple measurements, by amplifying the effect of measurement errors leads paradoxically to a weaker functional depiction of the narrowing.

Myocardial, coronary and collateral fractional flow reserves. Myocardial fractional flow reserve reflects both anterograde and collateral contribution to maximal myocardial flow. In contrast, coronary fractional flow reserve takes into account only anterograde flow. The difference between myocardial and coronary fractional flow reserve represents the collateral contribution to hyperemic myocardial perfusion (collateral fractional flow reserve). As seen in Figure 2, the difference between the regression line and the line of identity increases when myocardial fractional flow decreases, which suggests a progressive increase in the contribution of collateral flow to total hyperemic myocardial perfusion. When coronary fractional flow reserve equals 0, that is, in the absence of anterograde flow, the collateral contribution to maximal myocardial perfusion averaged 30% of the normal expected value of hyperemic myocardial perfusion with preserved left ventricular function in the present series of patients.

Clinical implications. Several clinical implications can be derived from the results of the present study: 1) Although quantitative coronary angiography correlates significantly with the physiologic significance of coronary stenoses, no single quantitative angiographic variable is accurate enough to predict the absolute value of fractional flow reserve in individual patients. 2) Nonetheless, the potential of quantitative coronary angiography to discriminate between functionally significant and nonsignificant lesions is high, even in this unselected patient cohort. In the vast majority of patients, a minimal lumen diameter >1.5 mm, or a diameter stenosis <50%, was associated with a myocardial fractional flow reserve >0.72, indicating the absence of a physiologically significant lesion. In contrast, the vast majority of lesions with a minimal diameter <1.5 mm, or a diameter stenosis >50%, were associated with a myocardial fractional flow reserve <0.72. Although not all lesions are optimally suited for quantitative coronary angiography, our results suggest that quantitative angiographic measurements in the catheterization laboratory may be useful for on-line clinical decision making in unselected patients.

We are grateful to the nursing staff of the catheterization laboratory for their careful and patient assistance. The secretarial help of Josefa Cano is greatly appreciated.

References


