Role of Variability in Microvascular Resistance on Fractional Flow Reserve and Coronary Blood Flow Velocity Reserve in Intermediate Coronary Lesions

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Background—Fractional flow reserve (FFR) and coronary blood flow velocity reserve (CFR) represent physiological quantities used to evaluate coronary lesion severity and to make clinical decisions. A comparison between the outcomes of both diagnostic techniques has not been performed in a large cohort of patients with intermediate coronary lesions.

Methods and Results—FFR and CFR were assessed in 126 consecutive patients with 150 intermediate coronary lesions (between 40% and 70% diameter stenosis by visual assessment). Agreement between outcomes of FFR and CFR, categorized at cut-off values of 0.75 and 2.0, respectively, was observed in 109 coronary lesions (73%), whereas discordant outcomes were present in 41 lesions (27%). In 26 of these 41 lesions, FFR was <0.75 and CFR≥2.0 (group A); in the remaining 15 lesions, FFR was ≥0.75 and CFR<2.0 (group B). Minimum microvascular resistance, defined as the ratio of mean distal pressure to average peak blood flow velocity during maximum hyperemia, showed a large variability (overall range, 0.65 to 4.64 mm Hg·cm⁻¹·s⁻¹) and was significantly higher in group B than in group A (2.42±0.77 versus 1.91±0.70 mm Hg·cm⁻¹·s⁻¹; P=0.034).

Conclusions—Our findings demonstrate the prominent role of microvascular resistance in modulating the relationship between FFR and CFR and emphasize the importance of combined pressure and flow velocity measurements to evaluate coronary lesion severity and microvascular involvement. (Circulation. 2001;103:184-187.)

Key Words: coronary disease ■ blood flow ■ microcirculation

Coronary angiography is considered the gold standard for the diagnosis of coronary artery disease, although its value is limited in evaluating the functional significance of intermediate coronary lesions. Intracoronary physiological parameters have been introduced to assess functional coronary lesion severity during cardiac catheterization. These parameters, myocardial fractional flow reserve (FFR) and coronary flow velocity reserve (CFR), have excellent agreement with noninvasive stress testing at cut-off values of 0.72 to 0.75 for FFR and 1.7 to 2.0 for CFR, which would suggest agreement between outcomes of FFR and CFR in the same patient. However, discordant pressures depend on flow across the stenosis, which is determined by both epicardial and microvascular resistance. A change in the latter affects distal pressure and flow in opposite directions. Therefore, discordance between the results of these diagnostic techniques can be expected in patients with intermediate coronary lesions.

Methods

Study Population
FFR and CFR were assessed in 126 consecutive patients with stable angina (Canadian Cardiovascular Society classes I through III) who had 150 intermediate coronary lesions (40% to 70% diameter stenosis on visual assessment). Patients were included when they had ≥1 vessel with a single coronary lesion that was eligible for angioplasty. Exclusion criteria were severe renal disease, severe vavular disease, previous coronary artery bypass grafting, recent myocardial infarction (<6 weeks), or collateral development. Patients with diabetes mellitus, hypertension, left ventricular hypertrophy, or restenosis were not excluded from this study. The Institutional Ethics Committee of the University of Amsterdam approved the study protocol. All patients gave written informed consent.

Cardiac Catheterization
Cardiac catheterization was performed following routine procedures, and quantitative measurements of coronary stenosis dimensions were obtained using an automated contour detection algorithm (MEDIS). Throughout the procedure, nitroglycerin (0.1 mg IC) was administered every 30 minutes, heart rate was monitored, and aortic pressure was measured via the guiding catheter.

Hemodynamic Measurements
Intracoronary pressure was measured with a 0.014-inch pressure-monitoring guidewire (RADI Medical), which was first calibrated, equaled with the aortic pressure in the guiding catheter, and then positioned with the pressure-sensor ~3 cm distal to the coronary...
lesion in the target vessel. Mean aortic and distal pressures were obtained during baseline measurements, and maximum hyperemia was induced by a bolus injection of intracoronary adenosine (15 µg for the right and 20 µg for the left coronary artery). FFR was calculated as the ratio of the mean distal pressure to the mean aortic pressure during maximum hyperemia.

After the intracoronary pressure measurements, the pressure-wire was exchanged with a 0.014-inch Doppler-tipped guidewire (FloWire, Endosonics) that was advanced to the same position distal to the target lesion. Baseline and hyperemic average peak flow velocities (APV) were obtained online (FloMap; Endosonics). CFR was calculated as the ratio of hyperemic to baseline APV. CFR was also obtained in an angiographically normal reference vessel, when present (n=116). The relative CFR (rCFR) was calculated for 139 lesions as the ratio between the CFR of the target vessel and that of the reference vessel. FFR and CFR values were categorized according to previously established cut-off values at 0.75 and 2.0, respectively.\(^2,4\) A velocity-based index of microvascular resistance during hyperemia (h-MRv) was determined as the ratio of mean distal pressure to APV during maximum hyperemia.

### Statistical Analysis
Data are expressed as mean±SD or n (%). Continuous data were compared using a paired or unpaired Student’s t test as appropriate, and a χ\(^2\) test was performed for categorical data using SPSS version 9.0 (SPSS Inc). \(P<0.05\) was considered statistically significant.

### Results
Figure 1A shows a scatterplot of FFR and CFR, together with the cut-off values used. Linear regression analysis demonstrated moderate relationships between FFR versus CFR (\(r=0.60, P<0.001\)) and FFR versus rCFR (\(r=0.64, P<0.001\)). Concordant outcomes between FFR and CFR were obtained in 109 of the coronary lesions (73%). Within these 109 lesions, FFR and CFR were below their respective cut-off values in 36 cases, whereas in 73 coronary lesions, both indices were above their threshold. Discordant outcomes between FFR and CFR were obtained in 41 coronary lesions (27%). CFR was ≥2.0 and FFR<0.75 in 26 cases (group A), whereas FFR was ≥0.75 and CFR<2.0 in 15 cases (group B). Agreement between dichotomized values of FFR and CFR revealed a \(κ\) of 0.42 (\(P<0.001\)). Figure 1B shows the average pressure gradient-flow velocity relation underlying the association between FFR and CFR for each group and illustrates the change of stenosis resistance between baseline and hyperemic conditions. The following results focus on the 2 groups with discordant outcomes.

There were no significant differences in clinical characteristics between patients with discordant outcomes (group A versus group B), except for the presence of hypertension, which was higher in group B (57% versus 22% in group A, \(P=0.015\)). Quantitative measurements of angiographic dimensions showed comparable reference diameters (2.99±0.63 mm versus 2.73±0.45 mm, \(P=0.17\)) and minimum lumen diameters (1.14±0.33 mm versus 1.23±0.21 mm, \(P=0.34\)) for coronary lesions in groups A and B, respectively. Percent diameter stenosis was slightly higher in group A (61±9% versus 55±7% in group B, \(P=0.018\)). Mean heart rate (70±11 bpm versus 68±12 bpm) and aortic pressure (100±19 mm Hg versus 95±12 mm Hg) during intracoronary measurements were similar both within and between patients in groups A and B, respectively.

Significant differences between the discordant groups were found for mean distal pressure at hyperemia, CFR and baseline APV for both the target and reference vessels, rCFR, and FFR (Table). Note that rCFR and FFR change in opposite directions between the 2 groups. For the entire study population, the h-MRv of the target vessel ranged from 0.65 to 4.64 mm Hg cm\(^{-1}\) s\(^{-1}\) (Figure 2A). It was significantly higher in group B compared with group A (Table and Figure 2B), but there was no difference in the h-MRv of the reference vessel between these 2 groups. Within group B, h-MRv was higher for the target than for the reference vessel (\(P=0.048\)).

### Discussion
In this study, we compared cut-off–based outcomes for FFR and CFR in intermediate lesions and found discordant results in 27% of the cases.
Hemodynamic Data of Coronary Lesions With Discordant Results in FFR and CFR

<table>
<thead>
<tr>
<th>Target vessel</th>
<th>CFR-target</th>
<th>Baseline APV, cm/s</th>
<th>h-APV, cm/s</th>
<th>FFR</th>
<th>h-MAP, mm Hg</th>
<th>h-MDP, mm Hg</th>
<th>h-MRv, mm Hg · cm⁻¹ · s⁻¹</th>
<th>Reference vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=26)</td>
<td>2.65±0.43</td>
<td>14.5±7.1</td>
<td>36.7±18.4</td>
<td>0.67±0.06</td>
<td>90.4±12.4</td>
<td>60.5±10.3</td>
<td>1.91±0.70</td>
<td>(n=24)</td>
</tr>
<tr>
<td>(n=15)</td>
<td>1.70±0.25*</td>
<td>22.4±11.5†</td>
<td>36.9±15.2</td>
<td>0.83±0.06*</td>
<td>96.5±19.1</td>
<td>80.1±17.1*</td>
<td>2.42±0.77†</td>
<td>(n=13)</td>
</tr>
<tr>
<td>CFR-reference</td>
<td>3.19±0.58</td>
<td>17.4±6.6</td>
<td>53.0±15.3</td>
<td>1.85±0.63</td>
<td>2.57±0.73†</td>
<td>22.9±9.2‡</td>
<td>1.91±0.82</td>
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<td>Group A</td>
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<td>Group B</td>
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<tr>
<td>FFR&lt;0.75</td>
<td>FFR≥0.75</td>
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<tr>
<td>(Group A)</td>
<td>(Group B)</td>
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</table>

Values are mean±SD. h indicates during hyperemia; MAP, mean aortic pressure; MDP, mean distal pressure; MRv, microvascular resistance index. *P<0.0001, †P<0.01 and ‡P<0.05 compared with group A.

The observed variability in microvascular resistance plays a prominent role in the discordance between the outcomes of FFR and CFR. It exists both across individuals and across perfusion territories, and it is related to variability in microvascular structure and is influenced by disease. However, our measurements do not allow differentiation between these 2 causes. Homogeneity in the structure and behavior of the microcirculation of the reference and stenotic vessels is a prerequisite for the concept of rCFR. The variability in h-MRv in our more diverse, large patient cohort (n=126) may explain the lower correlation between FFR and rCFR compared with the findings by Baumgart et al in a small group of patients (n=21).

In the presence of a stenosis, variability in microvascular resistance has an impact on the hemodynamic parameters used in the evaluation of the stenosis of the interrogated vessels, because both FFR and CFR are influenced by the combination of stenosis and microvascular resistance. As can be inferred from the electrical analog shown in Figure 2A. If h-MRv increases, CFR will decrease and FFR will increase, despite an anatomically fixed stenosis. In the absence of a stenosis, variability in h-MRv has little effect on FFR (≈1 by definition), but it would be reflected in CFR.

In the lesions in group A, both baseline APV and h-MRv were low, resulting in a CFR indicative of a nonsignificant coronary narrowing (>2.0). However, the hyperemic pressure gradient caused FFR to be <0.75. Despite an anatomically similar stenosis, the opposite is true for group B. Here, the discordance between FFR and CFR arises because of a low CFR, resulting from a high baseline APV, which can be explained by the higher oxygen demand of the heart in the presence of hypertension. These patients also had a significantly higher h-MRv, which kept hyperemic flow and, thus, the stenotic pressure gradient at a level commensurate with FFR >0.75.

The combination of stenosis (epicardial) and microvascular resistance at hyperemia affects both FFR and CFR and can lead to opposite outcomes in these physiological parameters with respect to their cut-off values, wherever they are chosen. Both distal pressure and flow velocity measurements, preferably simultaneous, are required to quantify this interaction. The latter point is a possible limitation of this study, because the intracoronary signals were obtained sequentially to avoid changes in stenotic characteristics due to the presence of 2 guidewires. However, external hemodynamic conditions, such as heart rate and aortic pressure, remained constant during the assessment of pressure and flow velocity, so one may expect reproducible responses to the vasodilatory stimulus.

Recent clinical studies suggest that PTCA can be safely deferred in patients with coronary lesions characterized by either FFR≥0.75 or CFR≥2.0. The present study shows that in about a quarter of patients with intermediate lesions, interventional procedures may be indicated or deferred, depending on whether a pressure- or flow velocity-derived parameter is used to reach the decision. However, a complete hemodynamic assessment rests on the separate evaluation of stenosis and microvascular resistance, which requires the measurement of both distal pressure and flow. The impact of

Figure 2. A, Frequency distribution of h-MRv measured in all target vessels (n=150). Inset shows a model of coronary circulation with stenosis resistance (R_s) in series with microvascular resistance (R_M). For a given R_s, distal pressure (P_d) and, therefore, FFR will be higher when R_M is elevated at hyperemia, but CFR will be lower. Q indicates coronary flow; P_a, aortic pressure; P_zf, zero-flow pressure; and ΔP, pressure gradient. B, Relative frequency of h-MRv obtained in groups with discordant outcomes in FFR and CFR. Vertical dashed and solid lines indicate median h-MRv for groups A and B, respectively.
combined measurements on clinical decision-making regarding coronary interventions remains to be determined.

References
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