Hyperemic Stenosis Resistance Index for Evaluation of Functional Coronary Lesion Severity

Martijn Meuwissen, MD; Maria Siebes, PhD; Steven A.J. Chamuleau, MD; Berthe L.F. van Eck-Smit, MD; Karel T. Koch, MD; Robbert J. de Winter, MD; Jan G.P. Tijssen, PhD; Jos A.E. Spaan, PhD; Jan J. Piek, MD

Background—Both coronary blood flow velocity reserve (CFVR) and myocardial fractional flow reserve (FFR) are used to evaluate the hemodynamic severity of coronary lesions. However, discordant results between CFVR and FFR have been observed in 25% to 30% of intermediate coronary lesions. An index of stenosis resistance based on a combination of intracoronary pressure and flow velocity may improve the assessment of functional coronary lesion severity.

Methods and Results—Single photon emission computed tomography (SPECT) was performed in 151 patients with angina to determine reversible perfusion defects within one-week before cardiac catheterization. Coronary pressure and flow velocity was measured distal to 181 single coronary lesions with a mean diameter stenosis of 56% (range: 32% to 85%). Maximum hyperemia was induced by 15 to 20 μg IC adenosine to determine CFVR, FFR, and the hyperemic stenosis resistance index (h-SRv), defined as the ratio of hyperemic stenosis pressure gradient (mean aorta pressure-mean distal pressure) and hyperemic average peak-flow velocity. Receiver-operating-characteristic curves of CFVR, FFR, and h-SRv were calculated to evaluate the predictive value for presence of reversible perfusion defects on SPECT with the use of the area under curve (AUC). The AUC was significantly higher for h-SRv (0.90±0.03) compared with those for CFVR (0.80±0.04; P=0.024) and FFR (0.82±0.03; P=0.018), respectively. Agreement with SPECT was particularly higher (73%) than for CFVR (49%, P=0.022) or FFR (51%, P=0.037) in the group of lesions showing discordant results between CFVR and FFR.

Conclusion—These results indicate that hyperemic stenosis resistance index is a more powerful predictor of reversible perfusion defects than CFVR or FFR. (Circulation. 2002;106:441-446.)

Key Words: coronary disease ■ coronary blood flow ■ myocardial perfusion scintigraphy ■ stenosis ■ ischemia

Several intracoronary physiological parameters have been introduced to improve discrimination of functional coronary lesion severity during cardiac catheterization.1 Of these parameters, myocardial fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) are the most frequently used. These indices show a good agreement with noninvasive stress testing at cutoff values varying between 1.7 and 2.2 for CFVR and between 0.68 and 0.78 for FFR.1 However, these parameters are affected by the confounding influence of microvascular disease, hemodynamic conditions in cases of CFVR, and transient changes in maximal hyperemic flow.1-3 Moreover, in 27% of our patients with an intermediate coronary stenosis, we have found conflicting outcomes between CFVR and FFR, based on their respective cutoff values for clinical decision-making.4 The purpose of this study was to test the hypothesis that stenosis resistance index, by incorporating both intracoronary pressure and flow velocity measurements, is more accurate in identifying functionally significant coronary lesions than traditional hemodynamic parameters derived from either flow velocity or pressure alone.

Methods

A total of 151 consecutive patients (age 60.0±10.7 years) with anginal complaints and 1- or 2-vessel coronary artery disease who were eligible for PTCA were included. Part of this patient group was used for evaluation of FFR and CFVR.4 Exclusion criteria were: 2 or more stenosis in 1 coronary vessel, severe renal disease, significant left main coronary artery stenosis, atrial fibrillation, recent myocardial infarction (<6 weeks), previous coronary artery bypass grafting, or visible collateral development. The Institutional Ethics Committee approved the study protocol. All patients gave informed written consent.

Myocardial Perfusion Scintigraphy

Patients were scheduled for single photon emission computed tomography (SPECT) with the use of ±500 MBq of 99mTc-methoxyisobutylisonitrile (MIBI) or Tetrofosmin (Myoview) during the week before the cardiac catheterization, according to a 2-day stress-rest protocol. All antianginal medication was discontinued for at least 48 hours before the stress test. Patients were asked to

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fast on the day of the SPECT and to abstain from any caffeine-related products 24 hours before the stress test. Stress was induced by dipyridamole (0.56 mg/kg intravenously for 4 minutes) or adenosine (140 μg/kg per minute intravenously for 6 minutes). For both stress and rest tests, SPECT imaging was started 45 minutes to 1 hour after injection of the radioactive-labeled tracer. SPECT images were acquired with a 3-headed γ camera (Siemens) that produces 60 views (6° shift per view) in a 64×64-pixel matrix by use of a 360° noncircular orbit.

Standard filtered-back projection was performed without applying attenuation correction. Stress and rest tomographic images were displayed side by side in the short axis, horizontal long axis, and vertical long axis reconstruction. A panel of experienced nuclear medicine physicians evaluated the scintigraphic images as previously described. Stress and rest images were semiquantitatively scored as having a normal, dubious, mild, moderate, or severe defect. Improvement of defect classification of >1 class was considered reversible, indicative of myocardial ischemia. Results were dichotomized into reversible or nonreversible defects. The result was considered positive when a reversible defect was allocated to the perfusion territory of the coronary artery of interest.

Cardiac Catheterization
All antianginal and antiplatelet medication was continued until cardiac catheterization. Lorazepam (1 mg) was orally administered before the procedure. Cardiac catheterization was performed by percutaneous femoral approach. All patients received a bolus of heparin (7500 IU intravenously) at the beginning of the procedure. Additional heparin was administered if the procedure lasted >90 minutes. Nitroglycerin (0.1 mg intracoronary) was administered before coronary angiography and every 30 minutes throughout the procedure.

Hemodynamic Measurements
All hemodynamic signals were obtained at baseline and during maximum hyperemia induced by a bolus of intracoronary adenosine, 15 μg for the right coronary artery and 20 μg for the left coronary artery. Injections were repeated and means of pressure and velocity were used for further calculations. Throughout the procedure, mean aortic pressure was measured continuously via the guiding catheter. In the target vessel, intracoronary pressure distal to the stenosis was measured with a 0.014-in pressure-monitoring guidewire (RADI Medical Systems). Directly after the intracoronary pressure measurements, the pressure wire was exchanged with a Doppler-tipped guidewire (JOMED). The Doppler sensor was manipulated until an optimal and stable blood flow velocity signal was obtained distal to the lesion.

Data Analysis
Percent diameter stenosis, reference diameter, and minimal lumen diameter were obtained by quantitative analysis of the coronary angiograms, with the use of a validated automated contour detection algorithm (QCA-CMS version 3.32, MEDIS). The saline-filled guiding catheter was used for calibration. End-diastolic cine frames from 2 or more views were analyzed per lesion and the most severe one in percent stenosis was used.

FFR was calculated as the ratio of mean distal to mean aortic pressure during maximum hyperemia. CFVR was calculated as the ratio of hyperemic to baseline average peak flow velocity (APV). A velocity-based index of coronary stenosis resistance during hyperemia (h-SRv) was calculated as mean stenosis pressure gradient (ΔP) divided by APV.

Statistical Analysis
Continuous variables were expressed as mean±SD and compared with the use of an unpaired Student’s t test (SPSS for Windows, version 10.0). A Mann-Whitney test was used for nonnormally distributed continuous data and a Fisher’s exact test for categorical data. Receiver operating characteristic (ROC) curve analysis was used to compare the diagnostic performance of derived hemodynamic parameters to outcomes of SPECT. The area under the curve (AUC) for h-SRv, FFR, and CFVR was compared by use of the software package ROC Curve Analyzer (written by R.M. Centor and J. Keightley, University of Virginia). The best cutoff value for h-SRv was defined as the highest sum of sensitivity and specificity.

<table>
<thead>
<tr>
<th>Medication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>117 (78)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>105 (70)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>94 (62)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>34 (23)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>86 (57)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>143 (95)</td>
</tr>
</tbody>
</table>

Values are given as n (%).

Results
Clinical and Angiographic Characteristics
A summary of the clinical profile of all 151 patients is shown in Table 1. Most patients had moderate to severe anginal complaints (17% Braunwald class I to II, 57% Canadian Cardiovascular Society [CCS] class 3, 20% CCS class 2, and 7% CCS class 1). No relationship with false CFVR or false FFR values was observed with any of the medications used in the study group. Angiographic and hemodynamic characteristics are listed in Table 2 for lesions with and without reversible perfusion defect. Prevalence of reversible perfusion deficits in this study population of 181 lesions was 29%.

Diagnostic Performance of Stenosis Resistance Index Compared With FFR and CFVR
Figure 1 shows the ROC curves for the three derived hemodynamic parameters. The AUC was significantly higher for h-SRv (0.90±0.03) compared with that for CFVR (0.80±0.04; P=0.024) or FFR (0.82±0.03; P=0.018). Sensitivity and specificity for h-SRv was 79% and 90%, respectively. The predictive accuracy for h-SRv was significantly higher (87%) than that for CFVR (75%, P=0.005) or FFR (75%, P=0.007).

The best cutoff value for h-SRv was determined as 0.8 mm Hg/cm per second. Values were labeled as positive outcomes (predictive of presence of reversible ischemia) if they were above this cutoff and as negative otherwise. The
number of false outcomes for h-SRv was almost half of that for FFR or CFVR, with most of the gain in accuracy achieved in a reduction of false-positive predictions (Table 3). Notably, significant differences in predictive accuracy were obtained in those lesions with discordant outcomes between FFR and CFVR, ie, groups B and C (Figure 2). For these groups combined, h-SRv achieved an accuracy of 74% compared with 49% for CFVR ($P=0.022$) and 51% for FFR ($P=0.037$).

On the basis of a table summarizing all 16 possible combinations of positive or negative outcomes for SPECT, h-SRv, FFR, and CFVR, 6 combinations were selected in which h-SRv correctly predicted the SPECT outcome, but FFR or CFVR did not. The average pressure drop-velocity relationships of these subgroups further elucidate the functional distinctions achieved by h-SRv (Figure 3). The relationships are presented for lesions in which predictions were discordant between FFR and CFVR (groups B and C, top and middle panels) or concordant (groups A and D, bottom panel). In each panel, the curve representing lesions with a true negative h-SRv (ie, correctly indicating the absence of reversible perfusion defects, right curve) had a lower pressure gradient at any given flow velocity than the corresponding curve of the hemodynamically more severe lesions with a true positive h-SRv (left curve).

### Discussion

An index of stenosis resistance, based on the ratio of pressure gradient and flow velocity measured during maximal hyperemia (h-SRv), had a significantly higher predictive power to identify reversible perfusion defects as detected by SPECT than traditional hemodynamic parameters based on only flow velocity (CFVR) or pressure measurements (FFR). This gain in accuracy was predominantly achieved in cases of intermediate lesions with conflicting predictive outcomes between FFR and CFVR, in which decision-making would depend on whether a pressure or flow wire was used for hemodynamic assessment.

### Traditional Methods for Stenosis Evaluation

Conventional methods of hemodynamic evaluation of functional stenosis severity in the catheterization laboratory involve the assessment of pressure-derived FFR, which predicts the fraction of maximal flow that can still be achieved in the

### TABLE 2. Angiographic and Hemodynamic Data of All Coronary Lesions

<table>
<thead>
<tr>
<th></th>
<th>Reversible Defect (n=52)</th>
<th>No Reversible Defect (n=129)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis, %</td>
<td>64.1±10</td>
<td>53.8±8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>1.05±0.42</td>
<td>1.34±0.37</td>
<td>0.001</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.90±0.67</td>
<td>2.88±0.64</td>
<td>0.8</td>
</tr>
<tr>
<td>CFVR</td>
<td>1.75±0.68</td>
<td>2.50±0.72</td>
<td>0.0001</td>
</tr>
<tr>
<td>b-APV, cm/s</td>
<td>14±8</td>
<td>18±8</td>
<td>0.002</td>
</tr>
<tr>
<td>h-APV, cm/s</td>
<td>24±14</td>
<td>43±15</td>
<td>0.0001</td>
</tr>
<tr>
<td>b-Pd, mm Hg</td>
<td>78±24</td>
<td>91±13</td>
<td>0.0001</td>
</tr>
<tr>
<td>FFR</td>
<td>0.62±0.18</td>
<td>0.82±0.11</td>
<td>0.0001</td>
</tr>
<tr>
<td>h-Pa, mm Hg</td>
<td>96±15</td>
<td>94±12</td>
<td>0.3</td>
</tr>
<tr>
<td>h-Pd, mm Hg</td>
<td>60±21</td>
<td>77±15</td>
<td>0.0001</td>
</tr>
<tr>
<td>h-SRv, mm Hg/cm per second</td>
<td>2.45±2.44</td>
<td>0.44±0.34</td>
<td>0.0001</td>
</tr>
<tr>
<td>h-ΔP, mm Hg</td>
<td>36±18</td>
<td>17±10</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values are mean±SD. b indicates baseline; h, hyperemia; APV, average peak flow velocity; Pa, aortic pressure; Pd, distal pressure; and ΔP, pressure gradient.

### TABLE 3. Number of False Predictions of h-SRv, FFR, and CFVR Compared With SPECT Outcomes

<table>
<thead>
<tr>
<th></th>
<th>h-SRv</th>
<th>FFR</th>
<th>CFVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positive, n</td>
<td>13</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>False negative, n</td>
<td>11</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Total, n</td>
<td>24</td>
<td>46</td>
<td>46</td>
</tr>
</tbody>
</table>

which h-SRv correctly predicted the SPECT outcome, but FFR or CFVR did not. The average pressure drop-velocity relationships of these subgroups further elucidate the functional distinctions achieved by h-SRv (Figure 3). The relationships are presented for lesions in which predictions were discordant between FFR and CFVR (groups B and C, top and middle panels) or concordant (groups A and D, bottom panel). In each panel, the curve representing lesions with a true negative h-SRv (ie, correctly indicating the absence of reversible perfusion defects, right curve) had a lower pressure gradient at any given flow velocity than the corresponding curve of the hemodynamically more severe lesions with a true positive h-SRv (left curve).
presence of a stenosis compared with the case if the stenosis were absent, or of CFVR, which represents the ratio of maximal-to-baseline flow velocity distal to the stenosis. When evaluating FFR, only the ratio of distal to aortic pressure at maximal vasodilation is taken into account, regardless of the flow that passes through the stenosis or of the microvascular resistance. It has been described that FFR may indicate a false-negative result (above threshold) in cases of low maximal flow due to microvascular disease. Conversely, FFR may indicate a false-positive result (below threshold) in the case of a higher pressure gradient caused by a high-flow rate through the stenosis in the presence of a low microvascular resistance. Similarly, CFVR is defined as a flow velocity ratio, regardless of the concomitant pressure gradient or of the absolute values of flow. Its value inherently depends on frequently independent variations in baseline or maximal flow that may be caused by factors unrelated to stenosis severity. Hence, the limitation to only 1 of 2 interdependent signals, pressure or flow velocity, may be a source for potential inaccuracies in the assessment of functional stenosis severity for diagnostic purposes by FFR or CFVR. Furthermore, determination of both CFVR and FFR critically depends on the achievement of maximal vasodilation.

Recent developments in sensor technology that take advantage of the temperature sensitivity of the pressure sensor have resulted in the acquisition of data representing both FFR and CFR with a single pressure wire, and it is assumed that a combination of these 2 parameters may provide additional information about the functional severity of the lesion. However, we have recently shown a high prevalence (27%) of discordant outcomes between FFR and CFVR in coronary vessels with intermediate lesions because of a large variability in microvascular resistance during maximal vasodilation that affects FFR and CFVR in opposite directions.

Coronary stenosis resistance, and its inverse (conductance), has been evaluated in earlier studies, but technical limitations have hampered its assessment in humans. The instantaneous hyperemic diastolic flow velocity-pressure relation has been introduced to identify physiologically significant coronary lesions. This approach is rather complicated both in terms of instrumentation and analysis and does not compare favorably with FFR and CFVR. We have not evaluated this index because it requires the simultaneous acquisition of phasic pressure and flow velocity signals, which was not done in our study.

### Advantages of Stenosis Resistance Index

We found that hyperemic stenosis resistance index was the best predictor of reversible perfusion deficit in the territory supplied by the target vessel, as determined by SPECT compared with FFR or CFVR.

Starting with the pioneering work by Gould and Young et al, it has been demonstrated in vitro, in animals, and in patients that the relationship between stenosis pressure drop and flow or velocity is curvilinear and is described by \( \Delta P = aV + bV^2 \), where \( a \) and \( b \) are stenosis-specific constants and \( V \) is velocity. It is therefore understandable that the prediction of functional severity based on only 1 of the 2
interdependent variables that make up the pressure drop-flow velocity relationship will be less successful in prediction of perfusion deficits. Stenosis resistance index, by definition, takes both parameters into account as the ratio of pressure gradient to flow at hyperemia.

The pressure drop-velocity lines shown in Figure 3 demonstrate the effect of flow velocity on FFR. Despite the presence of reversible ischemia for groups C (middle panel, left curve) and A (bottom panel, left curve), FFR was negative (ie, suggestive of no perfusion deficit) because of a moderate hyperemic flow velocity. Similarly, although inducible ischemia was absent, FFR was positive in group B (top panel, right curve) and group D (bottom panel, right curve) because of a high hyperemic flow velocity. The latter suggests that a low distal pressure due to a large trans-stenotic pressure gradient does not by itself indicate a physiologically significant lesion. As was shown by Smalling et al, myocardial function remained unaffected despite a low perfusion pressure, suggesting that regional contractile function depends on blood flow rather than perfusion pressure.

The analysis of CFVR results deviating from SPECT outcomes is less obvious, because this index represents a ratio of velocities. For example, the high h-SRv stenoses of group B (left curve in the top panel of Figure 3) had a low hyperemic velocity, but also a low baseline velocity. Because of the >2-fold increase during vasodilation, the resulting CFVR was false-negative, suggesting an absence of perfusion defects despite an abnormal FFR outcome.

The bottom panel is of interest because both FFR and CFVR predict a functional stenosis severity that is not supported by the hemodynamic characteristics of the stenoses or corresponding SPECT results. For FFR, the velocity effect on pressure drop resulted in a value either above the threshold at a low stenosis resistance or below the threshold at a high stenosis resistance. The baseline velocities interfered again with a correct prediction of reversible ischemia by CFVR in these cases.

Hyperemic stenosis resistance index shares 2 advantages with FFR over CFVR: it is independent of baseline conditions and it possesses an unequivocal normal value in the absence of a stenosis. The normal value for h-SRv is 0, because there is no appreciable pressure gradient without a stenosis.

The evaluation of baseline stenosis resistance would be subject to factors that influence baseline flow, but more importantly, small errors in pressure measurement would translate into relatively large errors in stenosis resistance given the low-pressure gradients present at basal flow rates. Although hyperemic SRv, by definition, is also dependent on flow, it is less sensitive to transient variations in maximal flow. Whether microvascular dysfunction or an insufficient amount of adenosine induces limited maximal flow, stenosis pressure drop and velocity are affected in the same direction. Therefore, the effect on the stenosis resistance index partly cancels out, an advantage over FFR and CVFR.

**Study Limitations**
Measurement of both intracoronary pressure and flow velocity at present requires the sequential use of 2 sensor-equipped wires to avoid worsening the hemodynamic severity of the coronary lesion. Besides being relatively expensive and time-consuming, this approach requires that the location of sensors in sequential measurements be matched and that hemodynamic conditions remain stable. During the sequential measurements, heart rate and aortic pressure remained constant in our patients, indicating that external hemodynamic conditions during the separate measurements were stable. New developments of wire technology leading to incorporation of both a pressure and a Doppler velocity sensor in the tip of a single wire would facilitate simultaneous acquisition of these hemodynamic signals.

The merits of the hyperemic velocity-based stenosis resistance index may originate from the normalization of stenosis pressure drop by velocity. Obviously, if velocity is measured in a segment that, because of disease, is inappropriately narrow or wide, the outcome of resistance index calculation is affected, which may explain part of the false-positive and false-negative results of the new index. However, this cannot have been a major problem in this study, considering the high specificity and sensitivity. The perception that the measured and the hemodynamically representative velocity are not far apart is further supported by the fact that a significantly lower baseline flow velocity was detected in the group with perfusion deficit, compared with the one without (Table 2). This difference (4 cm/s) is probably related to the lower distal pressure and may result from an imperfect autoregulation, perfusion pressure-dependent oxygen consumption, or higher contribution of collateral flow. These are factors that inherently contribute to the value of CFVR.

It is possible that the predictive accuracy of hemodynamic parameters that assess a discrete lesion is influenced by undiscovered diffuse disease. Nevertheless, in the practical setting, this influence may be limited because the same approach was applied in other studies as well and led to significant outcomes. Moreover, the improved sensitivity and specificity of h-SRv follows from the AUC of the ROC curve and is not affected by the applied cutoff values used. It should be noted, however, that the results in terms of accuracy may be slightly biased by the fact that the threshold for h-SRv was calculated from data obtained in the present study, whereas thresholds for FFR and CVFR were taken as currently used clinically.

Possible influences of hemodynamic alterations (heart rate, aortic pressure, contractility) on this index have not been investigated. Further studies need to be performed to determine reproducibility and potential hemodynamic dependence of this parameter before its prognostic value for clinical use can be established. However, our initial results are very promising regarding the discriminatory power of h-SRv compared with CFVR or FFR.

**Clinical Implications**
The present study was performed in a large patient population, and is the first to show that the combination of directly measured stenosis pressure gradients and flow velocity during maximal hyperemia into an index of stenosis resistance has a significantly higher predictive power to assess functional coronary lesion severity, as determined by SPECT, compared with conventional parameters based on either...
intracoronary pressure or flow velocity. It thus represents a better characterization of the hemodynamic impediment due to the stenosis. It has a high potential to improve clinical decision-making in the catheterization laboratory, particularly in intermediate lesions with discordant results between FFR and CFVR, and especially once advancements in wire technology allow for the simultaneous measurement of velocity and pressure.

Acknowledgments
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References
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