Improved Assessment of Coronary Stenosis Severity Using the Relative Flow Velocity Reserve

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Background—Myocardial fractional flow reserve (FFR) is based on pressure measurements. We have now sought to establish a Doppler-based concept of relative flow velocity reserve (RFVR) for the functional assessment of stenosis severity in epicardial coronary arteries. A clear threshold value to discriminate the functional severity of a coronary stenosis does not exist for coronary flow velocity reserve (CVR) based on intracoronary Doppler measurements. In contrast, the concept of FFR, which is based on intracoronary pressure measurements, has been extensively validated. An FFR value below 0.75 reliably indicates a significant stenosis.

Methods and Results—RFVR is calculated as the ratio between distal CVR in the stenosed target vessel and distal CVR in a nonstenotic reference vessel. In 21 patients, RFVR was determined in 24 target vessels by use of intracoronary adenosine and correlated to the FFR, determined as the ratio of mean poststenotic to aortic pressures, in the target vessel. Stenosis severity was classified according to quantitative coronary angiography analysis. Reference diameter was 3.0±0.4 mm (mean±SD), and area stenosis was 74±15% (range, 40% to 95%). CVRs in the target and reference vessels were 2.1±0.5 and 2.6±0.7, respectively. FFR ranged from 0.49 to 0.99 (mean, 0.81±0.15) and RFVR from 0.53 to 1.0 (mean, 0.82±0.13). Poststenotic CVR did not correlate with either percent area stenosis (r=0.27, P=NS) or FFR (r=0.33, P=NS). In contrast, FFR as well as RFVR showed a curvilinear relation to percent area stenosis (r=0.89, P<0.0001 and r=0.79, P<0.0001, respectively). There was a close linear correlation between FFR and RFVR (r=0.91, P<0.0001).

Conclusions—RFVR correlates closely to FFR and to percent area stenosis, whereas the correlation of CVR with FFR and percent area stenosis is rather poor. RFVR is a promising new concept for assessment of coronary stenosis severity and clinical decision making based on Doppler measurements. (Circulation. 1998;98:40-46.)

Key Words: catheterization ■ stenosis ■ blood flow velocity ■ angioplasty ■ diagnosis

The use of an intracoronary Doppler wire for the measurement of coronary flow velocity has been validated extensively in the in vitro and in vivo setting. On the basis of this experience, intracoronary Doppler measurements are gaining more and more attention in clinical decision making. Smaller studies as well as larger trials have demonstrated that coronary interventions can be guided by physiological measurements and that the restenosis rate can be predicted on the basis of intracoronary Doppler measurements. Nevertheless, a clear-cut threshold value for CVR to determine the functional severity of a coronary stenosis does not exist. Reported threshold values of CVR for clinical decision making range from as low as 1.8 to 3.0, depending on the individual study group. The wide scatter of threshold values has created a relative uncertainty among those groups currently using the technology and has deterred those who were about to implement physiological measurements. Such doubts were augmented further when correlations between poststenotic CVR and measurements of stenosis severity based on angiographic as well as intravascular ultrasound measurements turned out to be rather weak. Part of the explanation for such weak correlations can be attributed to the fact that poststenotic coronary flow reserve is determined not only by epicardial stenosis severity but also by structural and functional changes in the microvasculature. In the clinical situation, it is hard to differentiate which of these factors is responsible for the reduction in CVR.

Recently, the value of intracoronary Doppler measurements for assessment of coronary stenosis severity has been challenged by the concept of myocardial FFR, which is based on intracoronary pressure measurements. This concept has been thoroughly and extensively validated. In contrast to the concept of the CVR, the concept of FFR has presented a clear threshold value. An FFR value <0.75 indicates a hemodynamically significant stenosis with high accuracy and reproducible induction of myocardial ischemia on the basis of stress tests and thallium scintigraphy.

Given the above limitations of poststenotic CVR, an RFVR based on Doppler measurements might be more helpful in clinical decision making. In principle, factors such as hypertension, diabetes, hypercholesterolemia, and smoking will affect the microcirculation of the myocardium more or less to
the same extent. Also, values of CVR measured in normal vessels are not different among the perfusion territories of the three major coronary arteries.15,16 Thus, reduction of CVR on the basis of microcirculatory disease can be assumed to be similar in all three vessels. Additional reductions in CVR in one vessel versus another can then be attributed to the severity of the epicardial stenosis.

The present study sought to establish the concept of RFVR compared with FFR. In addition, the study tested whether the concept of RFVR might be superior to simple poststenotic CVR measurements for on-site clinical decision making during cardiac catheterization.

Methods

Study Population
The study included 21 patients with a mean age of 61±8 years (range, 50 to 78 years) who underwent coronary angiography for routine clinical indication (Table 1). There were 16 men and 5 women. All patients were symptomatic with typical or atypical angina pectoris. Angina pectoris was classified as grade CCS II in 9 patients and grade CCS III in 12 patients. Eighteen patients had 1-vessel and 3 patients had 2-vessel disease. All patients gave written informed consent to obtain pressure and flow velocity measurements.

To be eligible for the study, patients had to fulfill the inclusion criteria. Patients had to have an angiographic area stenosis ≥40% in the target vessel. In addition, an ipsilateral or contralateral reference vessel had to be reached by the Doppler wire to obtain the respective reference measurements. The reference vessel was defined as a major coronary artery without a coronary stenosis or with a coronary stenosis of <40% area reduction. In addition, a 7F or 8F guiding catheter without side hole had to be inserted in the reference or target vessel without damping of the aortic pressure signal. A good, stable position of the flow wire signal had to be obtained for reliable measurements. Patients with previous infarction in the perfusion territory of the target or reference vessel were excluded. In addition, patients with diffuse coronary atherosclerosis, tandem stenotic lesions, or lesions >2 cm long were excluded from the study.

TABLE 1. Patient (n=21) and Vessel (n=24) Characteristics

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<td>RCA</td>
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LAD indicates left anterior descending coronary artery. LCx indicates left circumflex artery.

Coronary Angiography
Selective coronary angiography was performed by the Judkins technique with ≥4 projections of the left coronary arteries and ≥2 for the RCA by use of the BICOR system (Siemens). All coronary angiograms were reviewed by an observer blinded to the results of the Doppler measurements. A bolus intracoronary injection of 0.2 mg of nitroglycerin was administered at least 3 minutes before angiography. Assessment of coronary stenosis severity was performed in the worst-view projection. Quantification of stenosis severity was performed with the use of off-line caliper measurements (MEDIS, Reiber), as described previously.17

Intracoronary Doppler Measurements
Intracoronary Doppler measurements were performed with the use of a 0.014-in Doppler wire (Flowire, Cardiometrics) connected to a stationary flow module (FloMod, Cardiometrics). The Doppler wire was advanced to the midportion of the respective reference vessel, and after a stable baseline signal was obtained, baseline parameters were recorded. Then, adenosine (12 µg for the RCA and 18 µg for the left coronary artery) was injected as an intracoronary bolus, and peak hyperemic conditions were recorded. The Doppler wire was withdrawn and repositioned in the target vessel ≥2 cm distal to the stenosis. Again, a stable baseline signal was secured before baseline parameters were recorded 3 to 5 minutes after intracoronary administration of 0.2 mg of nitroglycerin. Then, CVR was determined after adenosine injection as described above. All measurements were performed twice. In case of disagreement, a mean value was calculated from two consecutive measurements. All data were stored continuously on a videotape system (S-VHS, Sony) for playback and off-line analysis.18 RFVR was defined as the ratio of distal CVR in the target vessel to distal CVR in the nonstenosed reference vessel.

Intracoronary Pressure Measurements
Intracoronary pressure measurements were performed with the use of a 0.014-in fiberoptic pressure monitoring wire (Pressureguide, Radi Medical) connected to a pressure console (Radi Medical). The pressure wire was set at 0, calibrated, advanced through the catheter, and positioned distal to the stenosis, as described previously.19 Then, adenosine (12 µg for the RCA and 18 µg for the left coronary artery) was injected as an intracoronary bolus to induce maximal hyperemia, which is associated with minimal distal coronary pressure.20,21 At hyperemia, FFR was calculated as the ratio of mean distal coronary pressure, as measured by the wire, to mean arterial pressure, as measured by the coronary catheter.13

To avoid any bias, intracoronary pressure and Doppler measurements were taken sequentially in a randomized fashion. Nitroglycerin (0.2 mg) was administered ≥5 minutes before Doppler or pressure measurements were taken.

Data Analysis
A curvilinear regression was calculated between percent area stenosis and FFR (as independent variables) and CVR (as dependent variable). In addition, a curvilinear regression was calculated between percent area stenosis (as independent variable) and FFR and RFVR (as dependent variables, respectively). Furthermore, a linear regression was calculated between FFR (as independent variable) and RFVR (as dependent variable). Statistical analysis of hemodynamic data was performed by use of paired t tests. An additional comparison between FFR and RFVR was performed according to Bland and Altman.22 Data analysis was performed with the use of the standard statistical software program Sigma-stat (Jandel Scientific). All values are presented as mean±SD. A P value of <0.05 was regarded as significant.

Results
A typical example of 1 patient with a significant stenosis in the midportion of the RCA is given in Figure 1a. The LAD was taken as a reference vessel. Images of the Doppler recordings could be integrated into the angiographic images.
Clinical and Hemodynamic Results
All target lesions could be crossed with both pressure and flow wires. In 6 cases, the distal position of the pressure wire could be reached only with the help of a multiprobing catheter. When an additional PTCA was performed, an additional floppy wire was used. There were no significant differences between mean aortic pressure and heart rate under baseline conditions and adenosine-induced maximal vasodilation during flow velocity and pressure measurements. A bolus injection of adenosine did not induce a significant change compared with baseline parameters.

Quantitative Coronary Angiography
Results of each lesion are given in Table 2. Reference diameter ranged from 2.4 to 3.9 mm (mean, 3.0±0.4 mm), and lesion diameter ranged from 0.7 to 2.6 mm (mean, 1.5±0.5 mm). Percent diameter and area stenosis represent calculated values. Diameter stenosis ranged from 22.5% to 77.6% (mean, 50.5±14.3%) and area stenosis from 40% to 95% (mean, 73.5±14.9%).

Intracoronary Doppler and Pressure Measurements
A total of 24 target lesions were investigated. For the 9 LAD target lesions, the RCx served as a reference vessel in 8 cases and the RCA in 1. For the 9 LCx and 6 RCA target lesions, the LAD served as a reference vessel (Table 1). Individual data from each measurement are given in Table 2. CVR in the reference vessel ranged from 1.9 to 4.5 (mean, 2.6±0.7) and in the target vessel from 1.3 to 3.3 (mean, 2.1±0.5). FFR ranged from 0.49 to 0.99 (mean, 0.81±0.15) and RFVR from 0.53 to 1.0 (mean, 0.82±0.13).

Poststenotic CVR did not correlate with either percent area stenosis (r=0.27, P=0.21; Figure 2) or FFR (r=0.33, P=0.33; Figure 3). In contrast, a good inverse correlation was found between FFR and percent area stenosis (r=0.89, P<0.0001; Figure 4) as well as between RFVR and percent area stenosis (r=0.79, P<0.0001; Figure 5). Both correlations were best fit by a quadratic equation, demonstrating a more scattered appearance in the range of intermediate
lesions. There was a highly significant linear correlation between RFVR and FFR ($r = 0.91$, $P < 0.0001$; Figure 6, top). The mean difference between the value of RFVR and FFR was 0.86.3 (Figure 6, bottom).

**Discussion**

The present study demonstrates a close correlation between RFVR and the angiographically determined percent area stenosis and FFR. In contrast, CVR per se correlates neither with percent area stenosis nor FFR. The concept of RFVR is based on Doppler flow measurements and appears to be promising in the assessment of coronary stenosis severity. Therefore, RFVR and not CVR per se is recommended for on-site clinical decision making in assessing the functional role of a coronary stenosis.

**CVR Versus RFVR**

On the basis of experimental studies, correlations between morphological and functional parameters of stenosis severity are

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<th>Lesion Diameter, mm</th>
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<th>Mean Poststenotic Pressure, mm Hg</th>
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LCx indicates left circumflex artery.
excellent. Thus, the functional significance of an epicardial stenosis can be derived from anatomic data, which are much easier to obtain via coronary angiography than physiological parameters. With the development of the Doppler wire, these concepts could be reevaluated more easily in the clinical setting. Correlation between morphological and functional parameters of an epicardial stenosis in the clinical setting has, however, been poor, independently of whether stenosis severity was measured by quantitative coronary angiography or by intravascular ultrasound. Such poor correlations are not surprising, however, because poststenotic CVR is determined by both the epicardial stenosis and the microcirculation. Particularly in mild to moderate stenoses, the microvasculature plays a dominant part in the regulation of coronary resistance. Thus, values of poststenotic CVR scatter widely, depending on the status of the microcirculation. With increasing severity of the epicardial stenosis, the influence of the microcirculation for the determination of CVR is weaker. Thus, in the individual patient, the contribution of each factor for the reduction of flow velocity reserve can hardly be foreseen. The correlation between percent area stenosis and CVR is improved only with high-grade stenoses. In this respect, it is not surprising that a cutoff value for distal CVR around 2.0 indicates a hemodynamically significant epicardial coronary stenosis with high accuracy. Furthermore, it is not surprising that correlations between distal CVR measurements and thallium scintigraphy have correlated well with PET measurements and percent area stenosis. RFVR correlates much more closely than poststenotic CVR to stenosis severity within a wide range of percent area stenoses. In agreement with the present results, Kern and coworkers demonstrated that the precision of poststenotic CVR to assess lesion-specific flow impairment is improved when relative CVR with reference to an adjacent normal vessel is used. However, the correlation coefficient between relative CVR and percent diameter stenosis was only 0.44, in contrast to 0.79 in the present study. These differences are most
likely related to the fact that only intermediate lesions were included in the study by Kern and coworkers. In contrast, high-grade stenoses were also included in the present study, and it is expected that data points at the end of the stenosis severity spectrum improve the correlation.

RFVR Versus FFR
To the best of our knowledge, this is the first report correlating RFVR with FFR by use of intracoronary measurements. The correlation between these relative flow reserves has been excellent, with a coefficient of 0.91. A similar correlation of relative flow reserves has been found in validation studies for FFR. In agreement with the present study, the correlation between FFR and RFVR as derived from PET measurements in the study by de Bruyne et al yielded a correlation coefficient of 0.87 in 22 patients. The slightly lower correlation coefficient is most likely related to the design of that particular study, because PET and pressure measurements were performed on 2 consecutive days. On the basis of this experience, it can be anticipated that myocardial vascular resistance in the perfusion territory of target and reference vessels is similar under conditions of maximal hyperemia. This interpretation is supported by other data from Uren and coworkers. In their experimental studies, a similar curvilinear correlation between FFR, using a newly designed pressure wire, and percent area stenosis was demonstrated, with a correlation coefficient of 0.84.

The excellent correlation between FFR and RFVR seems to be most important for future investigations using the Doppler wire as a tool for clinical decision making. For FFR, a clear threshold value of 0.75 exists below which a functionally significant epicardial stenosis with evidence of exercise-induced ischemia is reliably diagnosed. In contrast, a clear threshold value for poststenotic CVR to facilitate clinical decision making does not exist. Although the results of the DEBATE study were very promising, it used both Doppler and angiographic criteria for decision making. If our present concept of RFVR is confirmed in a larger patient population, a similar clearly defined threshold value for Doppler measurements can be expected. Additional validations with respect to other noninvasive methods for the detection of myocardial ischemia, ie, exercise tests, thallium scans, or stress echocardiography, must be performed in future investigations.

Limitations
As opposed to FFR, RFVR cannot be determined in patients with 3-vessel disease. It is, however, our experience that the critical question of intermediate lesion assessment seldom applies to patients with 3-vessel disease. Usually, this question arises in patients with 1- or 2-vessel disease in whom a reference vessel is present. Even in a patient with 3-vessel disease, RFVR can be determined after the culprit lesion has been treated successfully.

Another limitation is related to the presence of myocardial infarction in the perfusion territory of the epicardial artery in which the Doppler measurements are performed. Certainly, a large transmural myocardial infarction will alter CVR and thus affect RFVR substantially. The presence of transmural myocardial infarction or severe microvascular disease also limits the application of pressure measurements because it leads to an underestimation of the epicardial stenosis due to inadequate hyperemic vasodilation. As defined by the inclusion and exclusion criteria, a similar patient population was examined in the present study.

At present, the current analysis is limited to a small and rather select group of patients. The validity of the concept, therefore, must be examined in a larger patient population. It is expected that the correlation coefficient will decrease when more patients are included. In addition, the correlation will most likely worsen when the range of coronary stenoses is limited to intermediate stenoses between 40% and 75%. A third factor that might weaken the correlation may be related to the presence of diffuse disease in the reference vessel, which could potentially lead to a reduction in reference CVR and thus to an underestimation of target-lesion severity. It seems reasonable to test these potential limitations in a subgroup analysis of larger clinical trials. Nevertheless, the current data are in good agreement with previous data from others. Also, Kern and coworkers demonstrated significant improvement of diagnostic accuracy in assessment of coronary stenoses when using RFVR rather than poststenotic CVR.

Given the close correlation between RFVR and FFR, it can be expected that a similarly sharp cutoff threshold for RFVR for procedural decisions may exist. The published sharp cutoff value of FFR was obtained in a highly selected group of patients. Flow restrictions and ischemia, however, are graded, continuous processes without an inherent sharp threshold. For RFVR, a similar threshold would therefore need to be determined by rigorous selection of well-defined patients with stress ischemia, as was done during validation of FFR for purposes of interventional decisions.

The proposed concept of RFVR relies on the assumption that the microcirculations of the stenotic and reference vessels behave similarly. Although risk factors for coronary artery disease will affect the coronary circulation homogeneously, a homogeneous behavior of the microcirculation in the stenotic and reference vessels appears unlikely at first, because even with homogeneous risk factors, 1 epicardial conduit artery has a significant atherosclerotic lesion, whereas, by definition, the reference vessel has not. However, even if the microcirculation is also affected by atherosclerotic/fibrotic alterations in a stochastic manner, similarly to that of the epicardial vessels, the measured flow velocity values in the present study integrate over many microcirculatory units such that any alterations are averaged and thus comparable between the poststenotic and reference microcirculations. Several previous studies, including our own, found similar values for CVR in the perfusion territories of the 3 major vessels and thus support the assumption of a homogeneous microcirculation.

When functional factors such as α-adrenergic coronary vasoconstriction during exercise or after PTCA are superimposed on the coronary microcirculation, the poststenotic and the reference vascular territories may behave differently. The present study, however, was performed during strict resting conditions and with adequate doses of adenosine to ensure maximal vasodilation.
Clinical Perspective

Assessment of the functional significance of a given coronary stenosis is most often based on the results of noninvasive exercise tests. However, in a large percentage of patients, these noninvasive tests cannot be used for clinical decision making because they have not been performed or the results are inconclusive, contradictory, or dubious. Thus, an on-site diagnostic tool to evaluate functional stenosis significance is more than desirable. FFR, as derived from pressure measurements, is a well-validated and accepted concept to assess such functional stenosis significance. So far, acceptance of CVR to assess stenosis severity has been hampered by controversial findings and variable threshold values among different interventional centers. This is due in part to the significant influence of hemodynamic variables on flow velocity reserve. In contrast, the concept of RFVR circumvents the above problems and may serve as a valid and more accurate measure of stenosis severity in the clinical setting. It may turn out that there is no absolute cutoff value for CVR and that we are dealing with a floating threshold value that has to be determined individually for every patient.

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