Clinical Significance of Fractional Flow Reserve for Evaluation of Functional Lesion Severity in Stent Restenosis and Native Coronary Arteries*

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Objective: Fractional flow reserve (FFR) is a valid surrogate for hemodynamic significance in stenotic native coronary arteries, but its validity in patients with coronary stent restenosis is unknown.

Design: Prospective.

Setting: University hospital.

Patients: We studied 42 patients (mean age ± 1 SD, 62 ± 10 years) with stent restenosis and 57 patients (mean age, 61 ± 12 years) with a native coronary lesion. All patients demonstrated a single coronary lesion of intermediate severity (stenosis diameter, 40 to 70%). Determination of FFR and quantitative angiography of the stenosis were performed.

Results: Stenosis diameter was comparable in both groups (native, 52 ± 11%; stent, 52 ± 9%; not significant [NS]). FFR was lower in stent restenosis (0.77 ± 0.15 vs 0.82 ± 0.12, p < 0.05) and more often pathologic with an FFR < 0.75 (48% vs 26%, p < 0.05) compared to native coronary stenosis. However, the area under the receiver operating characteristic curve for native stenosis was 0.82 (95% confidence interval [CI], 0.71 to 0.94) and for stent restenosis was 0.84 (95% CI, 0.71 to 0.97; NS). In patients with an FFR > 0.75, there was no adverse coronary event that was related to the stented lesion in the subsequent 6 months.

Conclusions: The threshold of stenosis diameter of coronary lesions for pathologic FFR measurement (FFR < 0.75) is similar for stent restenosis and native coronary stenosis. Thus, FFR measurement seems to be applicable for decision making in patients with stent restenosis.

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Key words: coronary artery stenosis; fractional flow reserve; stent restenosis

Abbreviations: AUROC = area under the receiver operating characteristic; CI = confidence interval; FFR = fractional flow reserve; NS = not significant; SPMS = stress perfusion myocardial scintigraphy

Coronary artery stenting has become a standard procedure in patients undergoing percutaneous coronary intervention. However, within 6 months, approximately 15 to 20% of patients have stent restenosis and require repeat target-vessel revascularization. Even quantitative coronary angiography cannot reliably predict whether a stent restenosis induces ischemia. Especially in stenosis of intermediate severity (40 to 70%), noninvasive stress testing, eg, stress perfusion myocardial scintigraphy (SPMS) or stress echocardiography, is used for clinical decision making.

Fractional flow reserve (FFR) can be invasively measured in the catheter laboratory as a simple, reliable, and reproducible index of functional stenosis severity. An FFR value < 0.75 reliably identifies stenosis of native coronary arteries associated with inducible ischemia. Although FFR is reported to be a valid surrogate for SPMS in stenotic native coronary arteries, its utility in patients with coronary stent restenosis is unknown. Stent restenosis differs from native coronary lesions in its morphology, histology, and geometry. In a previous study, we examined the value of FFR compared to SPMS in patients with coronary stent restenosis. FFR measurement, SPMS, and quantitative angiography of the stent stenosis were performed in all
patients. FFR showed a good diagnostic accuracy for the detection of reversible perfusion defects in SPMS, with the best cut-off value of 0.75 for FFR. We concluded that an FFR value of 0.75 is not only valid for diagnosing significant native coronary stenosis but also for stent restenosis. Thus, FFR measurement seems to be applicable for decision making in patients with stent restenosis.

In contrast to native coronary lesions, which may have an eccentric and complex cross-sectional geometry, stent restenosis is thought to have a less complex lesion geometry. Therefore, the lesion severity threshold for inducing ischemia may be higher in stent restenosis than in a native lesion. The aim of the present study was to examine the value of FFR in intermediate coronary stent restenosis compared to intermediate native coronary artery stenosis.

Materials and Methods

Patients

A total of 42 consecutive patients with an intermediate stent restenosis in a native coronary vessel and 57 consecutive patients with an intermediate native coronary lesion were included. Patients with stent restenosis were recruited from a consecutive group of patients who were routinely invited for control angiography 6 months after coronary stenting, irrespective of their clinical presentation. All patients demonstrated a single coronary lesion of intermediate severity (stenosis diameter, 40 to 70%) as assessed potentially flow limiting by angiography. Exclusion criteria were factors that could impair the correct measurement of FFR of one single lesion (eg, two or more stenoses in a coronary vessel, severe left main coronary artery stenosis, de novo stenosis of the stented native coronary artery at control angiography after coronary stenting, prior bypass surgery, visible collateral development, complete occlusions of the target vessel, and side branch involvement) or ethical considerations that an FFR measurement in a special condition could be potentially dangerous for the patient (eg, severe left main coronary artery stenosis, acute coronary syndromes or urgent coronary revascularization, recent myocardial infarction). There were no patients with drug-eluting stents. After control angiography, stent patients were followed up clinically for an additional 6 months.

Quantitative Coronary Angiography

Digitized coronary angiograms were analyzed off-line using a computer-assisted, automated edge-detection system. The percentages of stenosis diameter, reference diameter, and minimal lumen diameter were obtained by quantitative analysis. The guiding catheter was used for calibration. End-diastolic cine frames from two or more views were analyzed per lesion, and the most severe lesion in stenosis percentage was used. Angiograms were analyzed without knowledge of clinical data or FFR results.

FFR Measurement

Immediately after diagnostic coronary angiography, coronary pressure measurement at maximum hyperemia was performed. The coronary artery was selectively engaged with a 6F catheter without side holes, and 0.2 mg nitroglycerin was administered intracoronary. A 0.014-inch pressure guide wire (RADI Medical Systems; Uppsala, Sweden) was set at zero, advanced into the coronary artery, and positioned distal to the stenosis to be measured. FFR was determined during maximum hyperemia by the ratio $P_d/P_A$, where $P_d$ represents mean coronary pressure distal to the stenosed segment measured by the pressure wire, and $P_A$ represents mean aortic pressure measured by the guiding catheter. Maximum hyperemia was induced by intracoronary adenosine ($\geq 30$ $\mu$g in the right coronary artery and $\geq 40$ $\mu$g in the left coronary artery).

Statistical Analysis

Values are presented as mean values $\pm 1$ SD. All variables were tested for normal distribution by the Kolmogorov-Smirnov test. Student $t$ test was used for comparisons of continuous variables, and $X^2$ test was used to compare categorical data. The area under the receiver operating characteristic curve (AUROC) was utilized for discrimination. Agreement with stenosis diameter was determined for FFR, for which we used the clinically applied threshold of 0.75.3,4,7–10 The best cut-off value for stenosis diameter to predict a $\text{FFR} < 0.75$ was defined as the highest sum of sensitivity and specificity. All statistical tests were two tailed, and a p value $< 0.05$ was considered statistically significant.

Results

Patients With Native Coronary Artery Stenosis

Fifty-seven patients (mean age, 61 $\pm$ 12 years) with native coronary artery stenosis were studied by angiography (Table 1). Twenty patients (35%) had prior myocardial infarction. The mean percentage of stenosis diameter was $52 \pm 11\%$ (range, 40 to 70%) as measured by quantitative coronary angiography. FFR measurement was successfully performed in all patients without complications. FFR averaged $0.82 \pm 0.12$ and was $< 0.75$ in 15 patients.

Patients With Stent Restenosis

Forty-two patients (mean age, 62 $\pm$ 10 years) were studied by control angiography 5.3 $\pm$ 1.6 months after coronary stent implantation (Table 1). Thirteen

<table>
<thead>
<tr>
<th>Table 1—General Patient Characteristics*</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td>Dyslipidemia</td>
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</tbody>
</table>

*Data are presented as mean $\pm 1$ SD or No. (%).
patients (31%) had prior myocardial infarction. The mean percentage of in-stent diameter stenosis was 52 ± 9% (range, 40 to 70%) as measured by quantitative coronary angiography. FFR measurement was successfully performed in all patients without complications. FFR averaged 0.77 ± 0.15 and was < 0.75 in 20 patients. In the 22 stent patients with an FFR > 0.75, there was no adverse coronary event that was related to the stented lesion in the subsequent 6 months.

Relation Between Angiographic Results and FFR

Angiographic and FFR data are given in Table 2. The percentage of stenosis diameter was not different in patients with native coronary stenosis and stent restenosis (52 ± 11% vs 52 ± 9%, not significant [NS]). However, FFR was significantly lower in patients with stent restenosis (0.77 ± 0.15 vs 0.82 ± 0.12, p < 0.05) and more often pathologic FFR < 0.75 (48% vs 26%, p < 0.05) compared to patients with native coronary stenosis. Patients with stent restenosis had a lower minimal lumen diameter (1.28 ± 0.56 mm vs 1.50 ± 0.55 mm, p < 0.05) and a lower vessel reference diameter (2.36 ± 0.77 mm vs 2.82 ± 0.84 mm, p < 0.05) compared to patients with native coronary stenosis.

Receiver operating characteristic curves were constructed for stenosis diameter to predict a hemodynamically relevant (FFR < 0.75) lesion. Figure 1 shows the receiver operating characteristic curves for native coronary stenosis (left, A) and stent restenosis (right, B). The area under the ROC (AUROC) for native stenosis was 0.82 (95% confidence interval [CI], 0.71 to 0.94), indicating good discriminatory power. The best cutoff value for the percentage of stenosis diameter was 57% and had a sensitivity of 80% and a specificity of 83% to predict an FFR < 0.75. In stent restenosis, FFR showed also good discriminatory power, with an AUROC of 0.84 (95% CI, 0.71 to 0.97). A stenosis diameter percentage of 55% had a sensitivity of 81% and a specificity of 81% to predict an FFR < 0.75. The difference of the AUROC curves for native stenosis and stent restenosis was NS.

**Table 2—Angiographic Parameters***

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Native Coronary Stenosis (n = 57)</th>
<th>Stent Restenosis (n = 42)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right coronary artery</td>
<td>16 (28)</td>
<td>12 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>31 (54)</td>
<td>23 (55)</td>
<td>NS</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>10 (18)</td>
<td>7 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>52 ± 11</td>
<td>52 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>1.50 ± 0.55</td>
<td>1.28 ± 0.56</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.82 ± 0.84</td>
<td>2.36 ± 0.77</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>FFR</td>
<td>0.82 ± 0.12</td>
<td>0.77 ± 0.15</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>FFR &lt; 0.75</td>
<td>15 (26)</td>
<td>20 (48)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) or mean ± 1 SD.

**Discussion**

The major finding of this study is that the threshold stenosis diameter of coronary lesions for pathologic FFR measurement (FFR < 0.75) was similar for stent restenosis and native coronary stenosis. Thus, FFR measurement seems to be applicable for decision making in patients with stent restenosis.

In a study14 using dipyridamole stress echocardiography, complex coronary lesion morphology was found to be more frequently associated with pathologic findings than simple coronary lesions despite similar stenosis diameter. In contrast to native coronary lesions, which may have an eccentric cross-sectional geometry, stent restenosis is thought to have a more homogenous and less complex lesion geometry.11,12 Usually, a stent structure that is either round or oval is covered by a relatively smooth neointimal layer. However, in a previous myocardial scintigraphy study,2 we could not support the hypothesis that stent restenosis requires a higher angiographic stenosis diameter than native coronary lesions to result in reversible perfusion defects at SPMS. The threshold stenosis diameter of coronary lesions for reversible perfusion defects during SPMS was similar for stent restenosis and native coronary lesions. The diagnostic accuracy of angiographic variables to assess the hemodynamic significance of intermediate lesions was low in both stent and native lesions. In the present study, FFR measurement could confirm this finding, that the threshold stenosis diameter of hemodynamic relevant intermediate coronary lesions was not different in stent restenosis and native coronary stenosis.

In a second study,13 we could show that FFR supports decision making in stent restenosis. The value of FFR measurement for the prediction of reversible perfusion defects on SPMS was evaluated in patients with stent restenosis. An FFR < 0.75 predicted hemodynamic significant stent restenosis with a sensitivity of 92%. Thus, the FFR cutoff value of 0.75 was valid also for stent restenosis. If FFR was > 0.75, a conservative approach in stent restenosis was justified.

There are several potential mechanisms that could explain the lower FFR and the higher percentage of pathologic FFR in patients with stent restenosis. An FFR < 0.75 predicted hemodynamic significant stent restenosis with a sensitivity of 92%. Thus, the FFR cutoff value of 0.75 was validated for stent restenosis. If FFR was > 0.75, a conservative approach in stent restenosis was justified.
the stenosis or the microvascular resistance. The higher prevalence, although not significant, of hypertension and diabetes in patients with native coronary stenosis can possibly serve as a confounding factor, because it is associated with a higher microvascular resistance, potentially leading to a higher FFR value. Lower FFR values are seen in case of a higher pressure gradient caused by a high flow rate through the stenosis, which may be attributed to the specific geometry of stent restenosis compared to native coronary lesions. Another explanation could be that the degree of stent restenosis was underestimated by angiography. It is well known from intravascular ultrasound studies\textsuperscript{12,16–18} that incomplete stent deployment, protruding struts, or dislocation of plaque at the entry or exit of the stent are often not recognized by angiography but can nevertheless be responsible for a pressure gradient across the stented segment. Finally, more diffuse occult disease in the remaining parts of the coronary artery might have contributed to decreased FFR in patients with stent restenosis.\textsuperscript{18}

Safe deferral of percutaneous coronary intervention based on an FFR $>0.75$ has been demonstrated in several studies with low event rates at follow-up. In a retrospective analysis by Bech et al,\textsuperscript{6} percutaneous coronary intervention was deferred in a group of 100 patients with intermediate stenosis if FFR was $>0.75$. The clinical event rate at 18-month follow-up was significantly lower than if the percutaneous coronary intervention had been performed as initially planned. This is confirmed by our findings that in stent patients with an FFR $>0.75$ there was no adverse coronary event that was related to the stented lesion at follow-up. FFR is also a strong independent predictor of adverse coronary events when measured directly after coronary stent implantation. Normalization of FFR after stenting (FFR $>0.95$) is accompanied by a event rate of 4.9\% at follow-up, with a strong inverse correlation between FFR after stenting and event rate.\textsuperscript{18}

It is well documented that the angiographic assessment of a coronary lesion correlates poorly with its functional significance, especially in intermediate lesions. Fischer et al\textsuperscript{19} demonstrated that neither visual assessment of an angiogram by experienced interventional cardiologists nor quantitative coronary angiography can accurately predict the functional significance of most moderate coronary stenosis. Considering these data, a decision to revascularize an intermediate coronary stenosis or stent restenosis should be based on noninvasive stress testing (eg, SPMS or stress echocardiography) or on functional invasive methods such as FFR to assess the functional severity of stent restenosis.

Performing noninvasive stress testing after angiography to determine whether a native coronary stenosis or stent restenosis should be dilated delays hospital discharge. The use of FFR may obviate the need for performing noninvasive stress testing, thus reducing duration and cost of hospitalization, which is not associated with an increase in clinical event rates at follow-up.\textsuperscript{3,8,20} Consequently, we suggest that the most effective way for managing coronary

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**Figure 1.** AUROC curve of FFR < 0.75 to detect hemodynamic relevant stenosis in patients with intermediate native coronary artery stenosis (left, A) and stent restenosis (right, B). The optimal cutoff value for stenosis diameter was chosen as the point with the highest sum of sensitivity and specificity.
stenosis or stent restenosis of intermediate severity is to measure FFR in the same session where coronary angiography is performed and to proceed with percutaneous coronary intervention if the FFR is < 0.75.

REFERENCES