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Physiologic Assessment of Jailed Side Branch Lesions Using Fractional Flow Reserve

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OBJECTIVES This study was performed to evaluate the feasibility of the physiologic assessment of jailed side branches using fractional flow reserve (FFR) and to compare the measured FFR with the stenosis severity assessed by quantitative coronary angiography (QCA).

BACKGROUND It is not well-known which side branches should be treated after stent implantation at main branches and how to assess the functional significance of these lesions.

METHODS Ninety-seven jailed side branch lesions (vessel size >2.0 mm, percent stenosis >50% by visual estimation) after stent implantation at main branches were consecutively enrolled. The FFR was measured using a pressure wire at 5 mm distal and proximal to the ostial lesion of the jailed side branch.

RESULTS The FFR measurement was successful in 94 lesions. Mean FFRs were 0.94 ± 0.04 and 0.85 ± 0.11 at the main branches and jailed side branches, respectively. There was a negative correlation between the percent stenosis and FFR ($r = -0.41$, $p < 0.001$). However, no lesion with <75% stenosis had FFR <0.75. Among 73 lesions with ≥75% stenosis, only 20 lesions were functionally significant.

CONCLUSIONS The FFR measurement in jailed side branch lesions is both safe and feasible. Quantitative coronary angiography is unreliable in the assessment of the functional severity of jailed side branch lesions, and measurement of FFR suggests that most of these lesions do not have functional significance. (J Am Coll Cardiol 2005;46:633–7) © 2005 by the American College of Cardiology Foundation

The bifurcation coronary lesion is one of the most challenging lesion subsets in interventional coronary angioplasty. Treatment of this lesion is associated with low procedural success and high complication and restenosis rates (1–4). Because interventionists are stenting longer lesions than before and are treating more and more lesions than ever, because of the development of the drug-eluting stent, more side branches are included in the stented segments. In addition, even with drug-eluting stents, which have dramatically reduced the restenosis rates (5–7), bifurcation lesions still have a relatively high restenosis rate, especially at the ostium of the side branches (8–10).

There have been various studies on how to treat bifurcation lesions (1–4,8–10), yet it is still not clear which side branches should be treated after stent implantation of the main branch lesion and how the functional significance of these lesions ought to be assessed. Furthermore, a simple morphologic analysis may not be able to accurately assess the functional significance of jailed side branch lesions.

Fractional flow reserve (FFR) is an easily obtainable lesion-specific parameter for the physiologic evaluation of epicardial coronary artery stenosis that takes into account the interaction between the anatomic stenosis and the area of perfusion supplied by a specific coronary artery (11–13). The FFR is being increasingly used to assess the functional significance of coronary artery stenosis and to guide in the decision to intervene in ambiguous and complex lesions (14–20).

Therefore, this study was preformed to evaluate the safety and feasibility of the physiologic assessment of jailed side branches with a pressure wire. Furthermore, we compared the measured FFR with the stenosis severity assessed by quantitative coronary angiography (QCA) to examine whether morphologic stenosis in these lesions correlates with functional stenosis.

METHODS

Study population. Patients with de novo coronary bifurcation lesions with jailed side branches after successful stenting of the main branch were prospectively and consecutively enrolled. Jailed side branches needed to have Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 with an ostial stenosis >50%, vessel size >2 mm, and lesion length <10 mm by visual estimation. Patients were

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Abbreviations and Acronyms

FFR = fractional flow reserve
QCA = quantitative coronary angiography
TIMI = Thrombolysis In Myocardial Infarction

excluded if any one of the following was present: left main stenosis, totally occluded lesion, infarct-related artery or angiographically visible thrombus, diffuse or significant distal lesion at a side branch, significant lesion at a main branch proximal to stented segment, regional wall motion abnormalities of the stented artery and jailed side branch segments, left ventricular ejection fraction ≤40%, primary myocardial disease, left ventricular hypertrophy, serum creatinine ≥2 mg/dl, predilation of side branch before the main branch stent implantation, or contraindications to adenosine.

This study was approved by the Institutional Review Board of Seoul National University Hospital, and all patients gave informed consent to participate in the study.

Study procedure. Coronary stenting of the main branch was performed with standard interventional techniques. After successful stenting, 200 μg nitrate was administered and a reference image was obtained. Pressure measurements were performed using a 0.014-inch pressure guidewire (PressureWire, Radi Medical Systems, Uppsala, Sweden) as previously described (13). The FFR was measured at 5 mm distal to the jailed side branch ostial stenosis to assess the severity of stenosis and at 5 mm proximal to the lesion in the main branch to evaluate the influence of the proximal lesion. Hyperemia was induced with intracoronary bolus administration (80 μg), followed by an intracoronary continuous infusion (240 μg/min) of adenosine. Intracoronary adenosine was infused through the guiding catheter. Only the distal pressure was monitored during adenosine infusion, and when the distal pressure reached a minimum, infusion was stopped and the FFR was measured immediately. The lower FFR value at each site was used in the analysis. Lesions with FFR <0.75 were considered to have functionally significant stenosis.

Quantitative coronary angiography (Quantcor QCA, version 4.0, Pie Medical Imaging, Maastricht, the Netherlands) was performed by a single experienced technician who was blinded to the FFR value. Minimal luminal diameter, percent stenosis, and reference vessel diameter of side branches were measured.

The decision to treat the side branch lesion was up to the operator's discretion after the measurement of FFR. Clinical follow-up was performed at one month after stent implantation, and every two to three months thereafter.

Statistical analysis. Data are presented as means ± standard deviations for continuous variables and frequency for categorical variables. Comparisons of continuous variables were performed using the Student or paired *t* test. Analyses of discrete variables were performed using the chi-square test. Correlations between the FFR and percent stenosis were analyzed using the Spearman correlation analysis. Receiver-operating characteristic curve analysis was used to examine the increase in percent stenosis as a predictor of the functional significance of a lesion (FFR <0.75). The resulting sensitivity and specificity were calculated. All statistical analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois), and a p value of <0.05 was considered statistically significant.

RESULTS

From June 2003 to August 2004, 97 lesions in 92 patients were consecutively enrolled. Among these lesions, FFR measurements of 94 lesions (97%) in 89 patients were successfully obtained. The FFR measurements could not be obtained for three lesions because of one case of type C side branch dissection and two cases of wiring failure. Clinical characteristics and baseline angiographic data are summarized in Table 1.

Most lesions were located in the diagonal branches (78%). The mean percent stenosis, reference vessel diameter, and lesion length of jailed side branch lesions were 79 ± 11%, 2.23 ± 0.45 mm, and 7.0 ± 3.3 mm, respectively (Table 2). Mean FFR measured in the main branches, proximal to jailed side branches, was 0.94 ± 0.04 (range, 0.86 to 1.0), whereas the mean FFR measured in the jailed side branches, distal to the ostial lesion, was 0.85 ± 0.11 after intracoronary 80-μg bolus adenosine administration and 0.84 ± 0.12 with 240-μg/min adenosine continuous infusion. Adenosine continuous infusion induced better hyperemia in jailed side branches ($p = 0.02$). Because an FFR <0.75 has been shown in previous studies to suggest significant functional stenosis (11–13), we divided the lesions into two groups according to the FFR of the side branch lesions (0.75). We found that there were no significant differences between the two groups in terms of lesion location, bifurcation type, and FFR at main branch (0.95 ± 0.03 vs. 0.94 ± 0.04, $p = 0.15$).

Although there was a negative correlation between percent stenosis and FFR ($r = -0.41$, $p < 0.001$) (Fig. 1), no

Table 1. Clinical and Angiographic Data of the Patients (n = 89)

Age, yrs	62 ± 9
Male	64 (72%)
Risk factors	
Diabetes mellitus	30 (32%)
Hypertension	55 (59%)
Hypercholesterolemia	15 (16%)
Current smoker	30 (32%)
Stable angina/unstable angina	35 (37%)/34 (36%)
Left ventricular ejection fraction, %	60 ± 7
Multi-vessel disease	46 (39%)
Stents in main vessel (n = 96)	
Drug-eluting stents	82 (85%) (CYPHER 70, TAXUS 12)
Diameter, mm	3.0 ± 0.3
Length, mm	28.9 ± 11.3

Table 2. Angiographic Characteristics of Jailed Side Branch Lesions (n = 94)

Lesion location	
Diagonal branch	71 (76%)
Obtuse marginal branch	19 (20%)
Posterior descending artery	3 (3%)
Posterolateral branch	1 (1%)
Bifurcation type (ICPS classification)	
1	55 (58%)
2	12 (13%)
3	17 (18%)
4	10 (11%)
Quantitative coronary angiography (before/after stenting)	
Minimal luminal diameter, mm	1.21 ± 0.46/0.45 ± 0.25
Reference diameter, mm	2.23 ± 0.40/2.23 ± 0.45
Percent stenosis, %	45 ± 20/79 ± 11
Lesion length, mm	6.7 ± 2.9/7.0 ± 3.3

ICPS = Institut Cardiovasculaire Paris Sud.

lesion with <75% stenosis had FFR <0.75 and wide variations in FFRs were shown even in lesions with ≥75% stenosis, suggesting not only that lesions with morphologic stenosis less than 75% did not show functional significance, but also that even lesions that on simple angiography seem to be severe actually have a wide range of functional significance when examined using FFR. Among 73 lesions with ≥75% stenosis, only 20 lesions (27%) had functionally significant stenosis (Table 3). In relatively large side branches (≥2.5 mm) with ≥75% stenosis (n = 21), 8 lesions (38%) had FFR <0.75.

The optimal cutoff value for percent stenosis to predict functionally significant stenosis was 85% (sensitivity, 0.8; specificity, 0.76), yielding an area under the curve of 0.85 (95% confidence interval, 0.76 to 0.94) (Fig. 2).

Among the 20 lesions with FFR <0.75, kissing balloon inflation was performed in 8 lesions. Clinical follow-up was available in all but one patient. Mean follow-up duration was 9.6 ± 4.6 months (range, 3 to 23 months). During

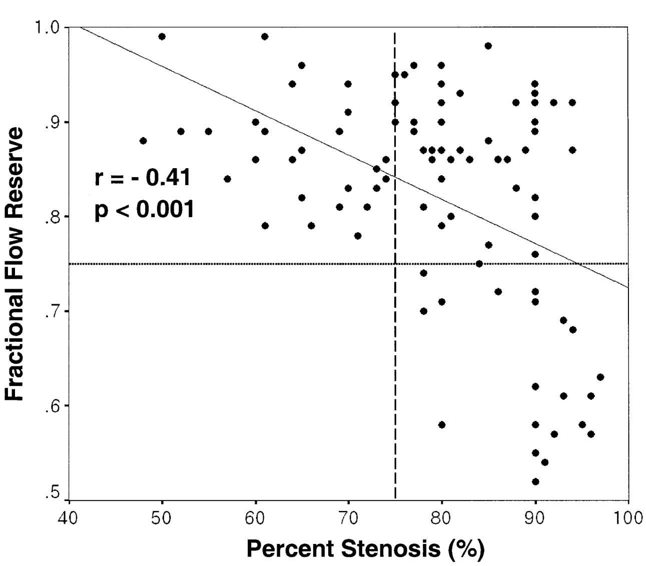

Figure 1. Correlation between fractional flow reserve and percent stenosis.

Table 3. Fractional Flow Reserve and Angiographic Percent Stenosis in Jailed Side Branches

	% Stenosis	
	≥50, <75	≥75
All lesions (n = 94)		
FFR <0.75	0	20 (27%)
FFR ≥0.75	20	53
Vessel size ≥2.5 mm (n = 28)		
FFR <0.75	0	8 (38%)
FFR ≥0.75	7	13

FFR = fractional flow reserve.

follow-up there were seven cases of target lesion revascularization. Six of them were caused by restenosis of the stent implanted in the main branch lesion. In patients with an initial FFR >0.75 in the side branch, there were no adverse events or target vessel revascularizations. Of the 20 side branch lesions with initial FFR <0.75, one patient had side branch target lesion revascularization that had not been treated initially. There was no death or myocardial infarction during follow-up.

DISCUSSION

The decision to intervene in a jailed side branch is a difficult one, and at present, there are no clear guidelines regarding how these lesions should be treated. Because FFR is a lesion-specific parameter that can measure the functional significance of a stenotic lesion, FFR may be useful in the decision to treat a jailed side branch lesion. This study shows, for the first time to our knowledge, that the physiologic assessment of a jailed side branch lesion, using a

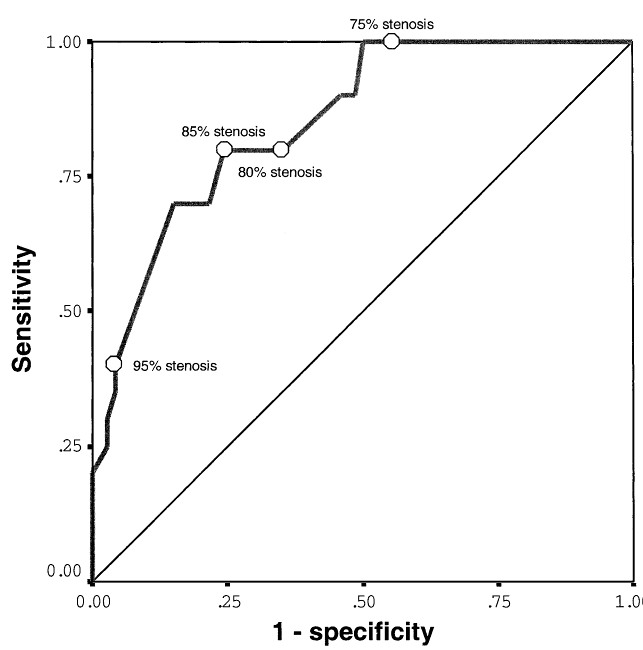

Figure 2. Receiver-operating characteristic curve using percent stenosis to predict functionally significant stenosis (fractional flow reserve <0.75) in jailed side branch lesions (area under the curve, 0.85; 95% confidence interval, 0.76 to 0.94)

pressure wire to assess its functional severity, is both safe and feasible. Furthermore, our data also show that there is discordance between the functional significance and the conventional morphologic stenosis severity measured by QCA.

Percutaneous coronary intervention for bifurcation lesions is technically difficult and is associated with relatively high complication and restenosis rates even with the use of drug-eluting stents (8–10). In addition, no study has proven the superiority of systematic double stenting over provisional stenting in these lesions. Therefore, the decision to treat both branches should be made on the precise assessment of the side branch lesion. However, the results of pre-intervention non-invasive tests are usually not helpful because of plaque shifting, which usually occurs after stenting of the main branch lesion.

The anatomic complexity and size variability of side branches make angiographic analysis difficult to use to accurately assess the functional significance of the jailed side branch lesions. Previous studies have validated the usefulness of FFR in angiographically ambiguous lesions (15–18). In ostial lesions, Ziaee et al. (17) compared angiographic severity with FFR and found that for lesions with >70% stenosis, FFRs were ≤0.75 in only 5 of 25 lesions. In the present study, no jailed side branch lesion with a QCA-assessed stenosis of <75% was functionally significant, and wide variations in FFRs were shown even in lesions with ≥75% stenosis. Only 27% of the lesions with ≥75% morphologic stenosis on QCA were functionally significant. In relatively large side branches (≥2.5 mm) with ≥75% stenosis, which are usually considered as the target for side branch intervention, only 38% of these lesions were functionally significant, suggesting that what you see is not always what you should widen. Taken together, our results suggest that some patients may be exposed to unnecessary high-risk interventions unless functional assessment of the lesion is performed.

It is not always easy to re-cross the side branch with a floppy guidewire after stent implantation at a main branch. In our study, FFR measurement was successful in 97% of lesions with a pressure-monitoring guidewire, and there were no serious complications related to the procedure except for one case of side branch dissection. These results suggest that the assessment of a jailed side branch lesion with a pressure wire is both feasible and safe.

The fate of untreated jailed side branches is reported to be benign (21–23). A recent study by Pan et al. (23) showed that the prognosis of side branches even with a dissection after balloon angioplasty was favorable. In our study, there was no death or myocardial infarction during the follow-up period, and one target lesion revascularization was performed in the side branch lesions with an initial FFR <0.75. All of the other revascularizations were caused by the progression of the main branch lesion. These findings suggest that results from previous studies that showed an excellent outcome after deferral of intervention based on FFR (15,24) could also be extended to jailed side branch lesions.

There are several limitations to this study. First, we used intracoronary bolus administration and intracoronary continuous infusion of adenosine to induce maximal hyperemia rather than intravenous adenosine infusion, which is currently the widely used protocol. However, our previous study showed that the hyperemic efficacy of intracoronary adenosine infusion was better than intracoronary bolus adenosine administration and comparable with intravenous adenosine infusion (25). Second, FFR reflects the degree of stenosis of all lesions located proximal to the pressure sensor. Although the mean FFR just proximal to the jailed side branch was 0.94 ± 0.04, influence of the proximal lesion to the side branch FFR cannot be excluded. Third, because intervention of a jailed side branch was performed at the discretion of the operator and the number of study patients was relatively small, the clinical follow-up results according to side branch FFR could not be evaluated. Our data warrant further study to evaluate the optimal treatment strategy of FFR-guided jailed side branch intervention in bifurcation lesions.

In conclusion, FFR measurement in jailed side branch lesions is both safe and feasible. Quantitative coronary angiography is unreliable in the assessment of the functional severity of jailed side branch lesions, and measurement of FFR suggests that most of these lesions do not have functional significance. This strategy may prevent unnecessary complex coronary interventions and related complications.

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