INTERVENTIONAL CARDIOLOGY AND SURGERY

Fractional flow reserve for the prediction of cardiac events after coronary stent implantation: results of a multivariate analysis

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Objective: To determine the prognostic value of fractional flow reserve (FFR) measurements after coronary stent implantation including multiple clinical and angiographic parameters collected in one centre.

Methods: 119 consecutive patients were enrolled who had a stent implanted with the use of a pressure wire as a guidewire. Patients were followed up for at least six months. Any death, myocardial infarction, and target vessel revascularisation were considered major adverse cardiac events (MACE). Multivariate logistic regression was used to determine adjusted odds ratios (OR) and 95% confidence intervals (CI) for FFR and covariates.

Results: Complete follow up data were available for all 119 patients. Pre-interventional FFR increased from 0.65 (0.15) to 0.94 (0.06) ($p < 0.0001$) after stent implantation. Eighteen MACE (15%) occurred during follow up including 15 (12.6%) target vessel revascularisations. Final FFR was significantly higher in patients without than in patients with an event (0.95 (0.05) *v* 0.88 (0.08), p = 0.001). In the multivariate logistic regression analysis, only final FFR < 0.95 (OR 6.22, 95% CI 1.79 to 21.62, p = 0.004) and reduced left ventricular function (OR 0.95, 95% CI 092 to 0.99, p = 0.021) remained as significant independent predictors for MACE.

Conclusion: These results including multiple parameters underline that FFR after coronary stenting is a strong and independent predictor for subsequent cardiac events after six months' follow up.

Compared with angioplasty alone, coronary stenting reduced the restenosis rate in a large patient group.[1] However, in-stent restenosis appears to be difficult and expensive to treat.[2 3] Therefore, it is clinically important to identify patients with a favourable clinical outcome and who are not expected to obtain further benefit from additional interventional treatment. Fractional flow reserve (FFR) is a functional index of stenosis severity recently introduced into clinical practice. FFR is defined as the maximum achievable blood flow to the dependent myocardium of a coronary artery in the presence of a stenosis divided by normal maximum flow if the stenosis would not be present. The concept of FFR has been described and validated extensively.[4–7]

FFR can be easily obtained by a pressure guidewire at maximum hyperaemia during cardiac catheterisation. In patients with single vessel disease undergoing balloon angioplasty FFR has been shown to have additional predictive value to angiographic parameters.[8] Recently, the prognostic value of FFR after coronary stent implantation has been proved in a multicentre registry (FFR registry).[9] However, a registry is limited with respect to the number of variables that can be collected from multiple participating centres. Thus, the purpose of the present study was to assess in patients undergoing coronary stent implantation in a single centre the prognostic impact of FFR on cardiac events adjusted for all available risk factors.

METHODS

Patients

Patients with elective stent implantation and a final FFR measurement were enrolled in the analysis. A subset of these patients (88 of 119, 75%) was part of the FFR registry.[9] All patients had to be symptomatic or present with objective ischaemia in a stress test. Patients with acute coronary syndromes and chronic total occlusions were excluded. All patients received bare metal stents.

Interventional procedure and pressure measurements

Patients were premedicated with acetylsalicylic acid 100 mg/day. Before the intervention, 7000 IU heparin was administered. A 6 or 8 French guiding catheter was inserted and a 0.014 inch pressure guidewire (PressureWire, Radi Medical Systems, Uppsala, Sweden or WaveWire, JoMed, Helsingborg, Sweden) was passed through the target lesion with the tip > 3 cm distal to the stenosis. Both aortic and distal coronary pressure were measured at rest and at maximum hyperaemia induced by intracoronary bolus injections of 30–150 μg adenosine. Stents were implanted according to local practice with an implantation pressure of 12–14 bar. FFR was determined before intervention and was repeated when coronary angiography documented a good angiographic result ($< 10\%$ residual diameter stenosis by visual analysis). The final FFR was measured when stable haemodynamic conditions were documented after the last balloon inflation. If FFR was not normalised after stent implantation FFR was again measured proximally to the stent to identify a possible pressure drop within the stented segment. All patients received clopidogrel 75 mg/day for four weeks.

Follow up and major adverse cardiac events

Follow up information was obtained by telephone and outpatient visits. Major adverse cardiac events (MACE) were

Abbreviations: FFR, fractional flow reserve; LV, left ventricular; MACE, major adverse cardiac events

Table 1 Patients' characteristics

Characteristic	Mean (SD) or %
Age (years)	62 (10)
Men	75%
Risk factors	
Diabetes mellitus	26%
Hypertension	79%
Hypercholesterolaemia	83%
Smoking	38%
Family history	39%
Prior MI	56%
Unstable angina	29%
Ejection fraction (%)	63 (13)
Restenotic lesion	11%
Target vessel	
LAD	39%
LCx	24%
RCA	36%
Vessel involvement	
1 vessel disease	20%
2 vessel disease	33%
3 vessel disease	47%
Lesion type	
Type A	23%
Type B1	12%
Type B2	37%
Type C	28%

LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; RCA, right coronary artery.

defined as any death, myocardial infarction, or target vessel revascularisation within six months. If more than one event occurred, the first event was used for the analysis. Angiography was not repeated except in patients presenting again with symptoms or objective signs of ischaemia.

Quantitative coronary angiography

The angiograms were recorded in biplane projections after intracoronary injection of 0.25 mg of glyceryl trinitrate. Qualitative analysis was based on American Hospital Association/American College of Cardiology classifications.[10] Quantitative data were analysed by computer according to a validated edge detection algorithm taking the guiding catheter as reference.

Statistical analysis

Potential predictors for MACE comprised post-interventional FFR and other demographic and clinical patient characteristics. Values were expressed as proportions or as mean (SD). Univariate variables on a $p < 0.20$ level were screened to identify potential predictors. For the comparison of continuous variables before and after stent implantation, unpaired Student's *t* test (normal distribution) or Wilcoxon signed rank test (skewed distributions) were used. In the comparison of groups with and without MACE, Fisher's exact test was used for categorical variables and unpaired Student's *t* test (normal distribution) or Mann-Whitney-Wilcoxon U test (skewed distributions) for continuous variables. Multivariate stepwise logistic regression analysis was applied to identify independent predictors at a $p < 0.05$ level. Adjusted odds ratios with 95% confidence intervals were used to quantify the independent prognostic impact of predictors.

Statistical analysis was done with the software package SPSS 11.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Patients

This study group consisted of 119 patients with a mean age of 62 (10) years. Table 1 lists the patients' characteristics.

Angiographic parameters and FFR data

Stents were successfully implanted in all patients. Table 2 shows angiographic parameters and FFR results. Mean stent length was 18 (9) mm (range 8 to 54 mm). One, two, and three stents were implanted in 91 (76.5%), 21 (17.5%), and 7 (5.9%) patients, respectively. No patient was lost to clinical follow up. An FFR $\geqslant$ 0.95 was achieved in 66 of 119 patients (55%).

Major adverse cardiac events

During the six month follow up period, 18 MACE occurred including five deaths. One patient died following subacute stent thrombosis seven days after the intervention. This patient had a reduced FFR after stent implantation (0.79). One patient died suddenly six months after the intervention. He was awaiting heart transplantation, having an ejection fraction of 16%. His post-interventional FFR was 1.00. Another patient died of a left main dissection during a target lesion revascularisation. The FFR of the index procedure was 0.95. One patient had a fatal anterior myocardial infarction five months after percutaneous coronary intervention for a lesion of the left anterior descending artery (final FFR 0.88). One patient died suddenly five months after the intervention. She had impaired left ventricular (LV) function (ejection fraction 33%) and a final FFR of 0.93. One patient developed a non-fatal Q wave MI after a stent thrombosis (final FFR 0.86). Fifteen patients underwent target vessel revascularisation.

Prognostic value of predictors

As tables 3 and 4 show, only the variables unstable angina, vessel involvement, post-interventional FFR, LV function, and numbers of stents implanted were significant at $p < 0.20$ in the univariate variable screening and were considered as potential predictors in the multivariate analysis (table 5). In this analysis, only post-interventional FFR < 0.95 and LV function were significant ($p < 0.05$) and independent predictors. Post-interventional FFR < 0.95 increased the risk of MACE about sixfold compared with FFR $\geqslant$ 0.95. An increase of 1% in LV function was associated with a 5% relative risk reduction with respect to MACE.

Table 2 Angiographic and pressure data before and after stent implantation

	Before	After	p Value
MLD (mm)	0.85 (0.43)	3.01 (0.69)	<0.0001*
Mean reference diameter (mm)	2.88 (0.69)	3.11 (0.71)	<0.0001*
DS (%)	70 (14)	−2 (15)	<0.0001*
FFR	0.65 (0.15)	0.94 (0.06)	<0.0001†
Lesion length (mm)	11 (6)		
Stent length (mm) (range)	18 (9) (8 to 54)		
Number of stents	1.29 (0.57)		

Data are mean (SD).
**t* Test for paired samples; †Wilcoxon signed rank test.
DS, diameter stenosis, FFR, fractional flow reserve; MLD, minimum lumen diameter.

Table 3 Clinical characteristics of patients with and without major adverse cardiac events (MACE) within six months of follow up

	MACE (n = 18)	No MACE (n = 101)	p Value
Age (years)	61 (10)	62 (11)	0.574*
Men (%)	78%	74%	1.0†
Risk factors			
Hypertension	83%	78%	0.761†
Diabetes	39%	24%	0.242†
Smoking	28%	40%	0.498†
Family history	33%	40%	0.827†
Hypercholesterolaemia	94%	81%	0.403†
Prior MI	56%	57%	1.0†
Restenotic lesion	11%	12%	0.831†
Unstable angina	44%	26%	0.15†
Vessel involvement			0.133‡
1 vessel disease	17%	21%	
2 vessel disease	17%	36%	
3 vessel disease	67%	44%	
Lesion type			0.483‡
Type A	25%	22%	
Type B1	0%	14%	
Type B2	44%	36%	
Type C	31%	28%	

**t* Test for unpaired samples; †Fisher exact test; ‡Mann-Whitney-Wilcoxon U test.

DISCUSSION

This study showed that FFR after stent implantation is a strong and independent predictor for the development of adverse cardiac events during a follow up of six months.

Since the beginning of the stent era several attempts have been made to identify risk factors for an impaired outcome after stent implantation. Most of the recent studies dealt with different clinical and morphologic parameters.[11] To overcome the well known limitations of coronary angiography,[12] intravascular ultrasound was used to improve the result of interventional procedures. But randomised trials with intravascular ultrasound failed to show a clinical benefit for this adjunctive method.[13]

FFR is the ratio of the maximum achievable coronary blood flow in the presence of a given stenosis and maximum achievable blood flow if all epicardial obstructions were absent. FFR has shown its relative robustness to changes in physiological conditions such as heart rate and blood pressure.[4] In a large series of patients FFR was of prognostic value in patients with intermediate stenoses.[8] It was shown that patients with an FFR $>$ 0.75 and a deferred intervention had a better outcome than patients receiving a planned intervention. Recently the results of the FFR registry have been published showing the prognostic impact of FFR measurement after stent implantation.[9] The potential mechanisms contributing to the strong association between FFR and outcome have been discussed extensively. However, owing to the design of a registry with multiple participating centres, the number of variables that can be evaluated is limited.

By using this centre's database more clinical and angiographic parameters that are known to affect outcome after coronary interventions could be considered in the analysis. However, the final FFR remained the most powerful predictor, underlining the results of the FFR registry. Another, weaker predictor in this analysis was a reduced LV ejection fraction. It is known that an impaired ejection fraction is associated with an unfavourable outcome for patients with coronary artery disease.[14] To represent a real world patient cohort, these patients were not excluded from our analysis.

Compared with the FFR registry[9] mortality in the present study was rather high. Three of the five deaths reported in the FFR registry were among the 88 patients included there. Two more patients died among the additional 31 patients in the present analysis. But, as mentioned above, we did not exclude any patient to affect the analysis.

This study has several limitations. Firstly, as in most registries, the patient population was very heterogeneous. No restrictions were made with regard to comorbidity. Thus,

Table 4 FFR data and angiographic variables in patients with and without MACE within six months of follow up

	MACE (n = 18)	No MACE (n = 101)	p Value
Pressure variables			
FFR pre-PCI	0.61 (0.17)	0.66 (0.15)	0.323*
FFR post-stent	0.88±0.08	0.95 (0.05)	0.001*
FFR <0.95	14/18 (78%)	39/101 (39%)	0.004†
Angiographic variables			
LV function (%)	57 (18)	64 (12)	0.083*
Lesion length (mm)	10 (9)	11 (6)	0.347*
Reference diameter pre-PCI (mm)	2.60 (0.69)	2.92 (0.68)	0.317‡
MLD pre-PCI (mm)	0.82 (0.31)	0.86 (0.45)	0.718‡
MLD post-stent (mm)	2.98 (1.14)	3.02 (0.59)	0.893‡
Stent length (mm)	20 (9)	17 (9)	0.281*
DS pre-PCI (%)	68 (9)	71 (14)	0.323‡
DS post-stent (%)	−1.9 (19)	−1.8 (15)	0.997*
Number of stents implanted	1.3 (0.6)	1.4 (0.5)	0.123*

**t* Test for unpaired samples; †Fisher exact test; ‡Mann-Whitney-Wilcoxon U test.
LV, left ventricular; PCI, percutaneous coronary intervention.

Table 5 Multivariate analysis: independent predictors with odds ratios (OR) and 95% confidence intervals (CI)

	OR	95% CI	p Value
FFR <0.95	6.22	1.79 to 21.62	0.004
LV function (%)	0.95	0.92 to 0.99	0.021

patients with a severely reduced LV function were included. On the other hand, this patient cohort represents a population that is treated daily. The second and major limitation of this study is that it was based on observational data and therefore has the potential of confounding. Although it is clear that reduced post-interventional FFR is an independent predictor of future cardiac event risk, this study did not address the question of whether additional intervention in patients with low post-interventional FFR resulted in a reduced MACE risk.

Furthermore, the statistical power of this study with respect to other covariables may be limited by the single centre approach. The trend among several clinical parameters known to affect long term outcome in patients with coronary artery disease was a higher coronary event rate at six months in the FFR registry but not in the present study. Although diabetic patients had a higher event rate in the present study than in the FFR registry this difference did not reach significance because of the limited sample size.

Given the prognostic impact of a reduced FFR after stenting it is important to distinguish whether a persistent hyperaemic gradient is due to incomplete stent deployment, to abnormalities within the adjacent segments, or to diffuse disease more proximal or distal to the treated lesion. Such diffuse disease is often not apparent angiographically but may result in a significant pressure drop when blood flow is increased by stenting the most severe lesion. Recently is has been shown that diffuse atherosclerosis without focal stenoses at angiography may cause a graded continuous pressure fall over the whole arterial length.[15] In the present study we did not systematically assess the FFR in the whole artery, since we used intracoronary adenosine. Although stents were implanted with a good angiographic result (mean (SD) residual stenosis −2 (15)%) it cannot be totally excluded that the stented segment or dissections not seen by angiography were responsible for a low FFR. However, since this was a registry and the results were not anticipated, no efforts were undertaken to improve a reduced FFR by subsequent interventions.

As a consequence of this study it is preferable to perform a pressure pullback curve during sustained hyperaemia, induced by intravenous adenosine, to obtain a complete analysis of the vessel after the intervention. Only by those means can possible pressure drops within or outside the stent be reliably identified with the need for further interventions.

Conclusion

This study based on data from a single centre shows that FFR after coronary stenting is a strong and independent predictor for the risk of subsequent MACE at six months. Since more potential predictors were considered in this analysis than in the FFR registry, these data clearly confirm the predictive value of FFR after stenting.

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REFERENCES

1 **Holmes DR**, Hirshfeld J, Faxon D, *et al.* ACC expert consensus document on coronary artery stents. *J Am Coll Cardiol* 1998;**32**:1471–82.
2 **Baim DS**, Levine MJ, Leon MB, *et al.* Management of restenosis within the Palmaz-Schatz coronary stent. *Am J Cardiol* 1993;**71**:364–6.
3 **Macander PJ**, Roubin GS, Agrawal SK, *et al.* Balloon angioplasty for treatment of in-stent restenosis: feasibility, safety, and efficacy. *Cathet Cardiovasc Diagn* 1994;**32**:125–31.
4 **De Bruyne B**, Bartunek J, Sys SU, *et al.* Simultaneous coronary pressure and flow velocity measurements in humans: feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation* 1996;**94**:1842–9.
5 **De Bruyne B**, Pijls NH, Heyndrickx GR, *et al.* Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and animal validation. *Circulation* 2000;**101**:1840–7.
6 **Pijls NH**, Van Gelder B, Van der Voort P, *et al.* Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 1995;**92**:3183–93.
7 **Pijls NH**, van Son JA, Kirkeeide RL, *et al.* Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993;**87**:1354–67.
8 **Bech GJ**, De Bruyne B, Pijls NH, *et al.* Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001;**103**:2928–34.
9 **Pijls NHJ**, Klauss V, Siebert U, *et al.* Coronary pressure measurement after stenting predicts adverse events at follow-up. *Circulation* 2002;**105**:2950–4.
10 **Smith SC Jr**, Dove JT, Jacobs AK, *et al.* ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)—executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation* 2001;**103**:3019–41.
11 **Lee SG**, Lee CW, Hong MK, *et al.* Predictors of diffuse-type in-stent restenosis after coronary stent implantation. *Catheter Cardiovasc Interv* 1999;**47**:406–9.
12 **Isner JM**, Kishel J, Kent KM, *et al.* Accuracy of angiographic determination of left main coronary arterial narrowing: angiographic-histologic correlative analysis in 28 patients. *Circulation* 1981;**63**:1056–64.
13 **Mudra H**, Di Mario C, de Jaegere P, *et al.* Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS study). *Circulation* 2001;**104**:1343–9.
14 **Gheorghiade M**, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation* 1998;**97**:282–9.
15 **De Bruyne B**, Hersbach F, Pijls NHJ, *et al.* Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but ''normal'' coronary angiography. *Circulation* 2001;**104**:2401–6.