Usefulness of Fractional Flow Reserve to Predict Clinical Outcome After Balloon Angioplasty

G. Jan Willem Bech, MD; Nico H.J. Pijls, MD, PhD; Bernard De Bruyne, MD, PhD; Kathinka H. Peels, MD; H. Rolf Michels, MD; Hans J.R.M. Bonnier, MD, PhD; Jacques J. Koolen, MD, PhD

Background—After regular coronary balloon angioplasty, it would be helpful to identify those patients who have a low cardiac event rate. Coronary angiography alone is not sensitive enough for that purpose, but it has been suggested that the combination of optimal angiographic and optimal functional results indicates a low restenosis chance. Pressure-derived myocardial fractional flow reserve (FFR) is an index of the functional severity of the residual epicardial lesion and could be useful for that purpose.

Methods and Results—In 60 consecutive patients with single-vessel disease, balloon angioplasty was performed by use of a pressure instead of a regular guide wire. Both quantitative coronary angiography (QCA) and measurement of FFR were performed 15 minutes after the procedure. A successful angioplasty result, defined as a residual diameter stenosis (DS) $\leq 50\%$, was achieved in 58 patients. In these patients, DS and FFR, measured 15 minutes after PTCA, were analyzed in relation to clinical outcome. In those 26 patients with both optimal angiographic (residual DS by QCA $\leq 35\%$) and optimal functional (FFR $\geq 0.90$) results, event-free survival rates at 6, 12, and 24 months were 92±6%, 92±6%, and 88±6%, respectively, versus 72±8%, 69±8%, and 59±9%, respectively, in the remaining 32 patients in whom the angiographic or functional result or both were suboptimal ($P=0.047$, $P=0.028$, and $P=0.014$, respectively).

Conclusions—In patients with a residual DS $\leq 35\%$ and FFR $\geq 0.90$, clinical outcome up to 2 years is excellent. Therefore, there is a complementary value of coronary angiography and coronary pressure measurement in the evaluation of PTCA result. (Circulation. 1999;99:883-888.)

Key Words: pressure ■ balloon ■ angioplasty ■ blood flow ■ prognosis

Since the introduction of PTCA 20 years ago, the high incidence of restenosis has remained the major limitation of this technique. Although coronary stenting has reduced the restenosis rate in some patients, there is increasing evidence that it may not be beneficial in others. In addition, in-stent restenosis appears to be more difficult to treat than restenosis after regular balloon angioplasty. Therefore, it is important to identify patients in whom clinical outcome after regular PTCA will be favorable and in whom no further benefit can be expected by additional interventional techniques.

How do we identify such patients? Both visual angiography and quantitative coronary angiography (QCA) before and after PTCA are poor predictors of clinical outcome. Therefore, alternative approaches to assess lumen enlargement, such as intracoronary ultrasound or Doppler flow velocity measurement, have been advocated to better identify patients in whom restenosis is less likely.

Recently, pressure-derived myocardial fractional flow reserve (FFR) has been introduced as a functional index of stenosis severity. FFR is defined as maximum achievable blood flow to the dependent myocardium of a coronary artery in the presence of a stenosis divided by normal maximum flow, ie, maximum flow to that same distribution if the coronary artery had been normal. FFR is easily obtained at maximum coronary hyperemia by the ratio of mean distal coronary pressure to mean aortic pressure. The concept of FFR and its characteristics have been described and validated extensively.

Until now, the best indication to measure FFR was during diagnostic catheterization or just before PTCA to determine whether a particular stenosis could be held responsible for inducible ischemia and, if it was subsequently dilated, to evaluate the functional improvement immediately after PTCA. The predictive value of FFR after PTCA in relation to long-term outcome has not yet been investigated. Therefore, the purpose of the present study was to investigate the correlation—if any—between FFR after plain balloon angioplasty and long-term clinical outcome and hence to identify a threshold value of FFR above which long-term clinical outcome might be particularly favorable.
Methods

Study Population
Because the threshold to place a stent after PTCA is currently very low, considerable bias would be introduced in the study of an unstented patient cohort today. Such a group of patients would probably represent an extremely positive selection bias and would have a better prognosis anyway. Therefore, to investigate the relation between FFR after plain balloon angioplasty and clinical outcome, we studied a patient cohort that underwent PTCA in 1994, when stenting in our laboratory was performed only as bailout procedure and not as additional treatment after suboptimal PTCA. This patient cohort was part of an earlier study aimed at defining ranges of FFR, whether associated with inducible ischemia or not.13 The study population consisted of 60 consecutive patients with single-vessel disease and normal left ventricular function who underwent plain balloon angioplasty of a single lesion. In all patients, a positive exercise test was available ≤24 hours before PTCA. In these patients, a pressure guide wire was used to record distal coronary pressure (Pd) and to calculate FFR before, during, and after the procedure. After successful PTCA, all medication was stopped except nifedipine 20 mg BID, which was stopped 48 hours later, and aspirin 80 mg/d, which was continued. In those 58 patients with successful PTCA, the exercise test was repeated 5 to 7 days later. If the second exercise test was completely normal, from Bayesian considerations, it was claimed that no inducible ischemia was present at that moment and that a positive exercise test later at follow-up would again indicate inducible ischemia.19,20

Pressure Measurements
During the PTCA, both aortic pressure (P a) and distal (transstenotic) coronary pressure (P d) were measured continuously by the guiding catheter and the pressure-monitoring guide wire (Radi Medical Systems), respectively. FFR was calculated 15 minutes after a satisfactory angiographic result had been obtained by FFR = P d/P a, where P d and P a were recorded simultaneously at maximum coronary vasodilation, induced by infusion of adenosine (140 μg kg⁻¹ min⁻¹) into a femoral vein for 2 to 4 minutes.13,15 The method of coronary pressure measurement has been described previously.13–16

Quantitative Coronary Angiography
QCA analysis was performed on the pre-PTCA angiograms and on the post-PTCA angiograms 15 minutes after the final balloon inflation, preferably in 2 orthogonal projections, with the Cardiovascular Angiography Analysis System.21 With the guiding catheter as a scaling device, reference diameter, minimal lumen diameter (MLD), and percentage diameter stenosis (DS) of the target lesion were calculated as the average value of both projections.

Follow-Up and Adverse Cardiac Events
Exercise testing was repeated after 5 to 7 days in all patients with successful PTCA. Follow-up visits were performed at 6, 12, and 24 months. Adverse cardiac events were defined in a hierarchic ranking order as death, myocardial infarction, unstable angina, coronary bypass surgery, repeated PTCA, and the recurrence of anginal complaints accompanied by a positive exercise test, which was always performed in case of recurrent chest pain. No repeated angiography was performed, except in patients with a reintervention, for reasons to be discussed later.

Statistical Analysis
Continuous data are reported as mean±SD. Differences between subgroups were tested by use of paired or unpaired Student’s t test when appropriate. Categorical differences between subgroups were tested by use of Fisher’s exact test.

Univariate and multivariate logistic regression analyses were performed to determine independent predictors of an adverse cardiac event within 24 months of follow-up.

Results
Baseline Data and Procedural Results
In 2 patients, no immediate satisfactory PTCA result could be achieved. Both patients underwent bypass surgery. Therefore, successful PTCA was performed in 58 patients, who were eligible for further follow-up.

The baseline clinical data and procedural results of these patients are summarized in Tables 1 and 2. In all 58 patients,
TABLE 2. Angiographic and Pressure Data Before and After PTCA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before</th>
<th>After</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>0.56±0.14</td>
<td>0.88±0.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$P_w$ mm Hg</td>
<td>94±16</td>
<td>90±16</td>
<td>&lt;0.0060</td>
</tr>
<tr>
<td>$P_a$ mm Hg</td>
<td>53±17</td>
<td>79±15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$\Delta P_{max}$ mm Hg</td>
<td>41±15</td>
<td>11±7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$P_{min}$ mm Hg (during PTCA)</td>
<td>26±11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>2.99±0.58</td>
<td>2.96±0.52</td>
<td>0.7294</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>1.30±0.42</td>
<td>2.19±0.38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DS, %</td>
<td>57±12</td>
<td>26±9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

$P_w$ indicates coronary wedge pressure. n=58.

DS immediately after PTCA was <50%; in 52 patients, DS was ≥50%. FFR increased from 0.56±0.14 before PTCA to 0.88±0.07 after the procedure (P<0.0001). In all 58 patients, FFR immediately after PTCA was ≥0.75; in 29 patients, FFR was ≥0.90. In 56 of these 58 patients, the exercise test 5 to 7 days after PTCA reverted to negative.

Follow-Up and Predictive Value of FFR and DS for Adverse Cardiac Events

A 24-month follow-up was obtained in all patients. During follow-up, 16 adverse cardiac events occurred, which are specified in Table 3. FFR and mean hyperemic transstenotic pressure gradient ($\Delta P_{max}$) in patients with or without an event at follow-up were significantly different. DS in this respect was not different between groups (Table 4).

Multivariate logistic regression analysis of clinical, angiographic, and pressure variables demonstrated that post-PTCA FFR was the most significant independent predictor for adverse cardiac events (Table 5). By ROC analysis, the best discriminating value of FFR with the highest sum of sensitivity and specificity was 0.89 (Figure 1; ROC area, 68%; P=0.0103). Therefore, FFR ≥0.90 was defined as indicating an optimal functional PTCA result, whereas 0.75≤

TABLE 3. Adverse Cardiac Events at 6, 12, and 24 Months of Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AMI</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Repeated PTCA</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent ischemia*</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction. A indicates the 26 patients in whom both optimal angiographic (residual DS ≥35%) and optimal functional (FFR ≥0.90) results were obtained. B indicates the remaining 32 patients in whom either the angiographic or functional result or both were suboptimal.

*Patients with a negative exercise test 5–7 days after the intervention and recurrent ischemia confirmed by a positive exercise test at follow-up.

FFR<0.90 was defined as indicating an initially successful but suboptimal PTCA result.

According to these cutoff values of 0.90 for FFR and 35% for DS, patients were then stratified into 4 subsets according to optimal versus suboptimal post-PTCA FFR and optimal versus suboptimal percentage DS. The result of this stratification in relation to the occurrence of cardiac adverse events is presented in Figure 2. Points in the right upper quadrant of Figure 2 represent the 26 favorable patients with optimal results by both angiography and pressure measurements, defined as group A. The points in the remaining 3 quadrants represent the patients in whom either the angiographic or functional result or both were suboptimal and who were defined as group B.

As shown in Figure 3, event-free survival rates at 6, 12, and 24 months in patients with optimal functional and anatomic results were 92±5%, 92±5%, and 88±6%, respectively, versus 72±8%, 69±8%, and 59±9%, respectively, in the remaining patients (P=0.047, P=0.028, and P=0.014, respectively). If the criterion of FFR ≥0.90 was used alone, an almost similar event-free survival was observed.

Discussion

This retrospective study with 2 years of follow-up confirms the complementary value of anatomic and physiological

TABLE 4. Post-PTCA Pressure and Angiographic Variables in Patients With and Without Adverse Cardiac Event

<table>
<thead>
<tr>
<th>Adverse Cardiac Event at Follow-Up</th>
<th>Yes (n=16)</th>
<th>No (n=42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_w$ mm Hg</td>
<td>92±16</td>
<td>89±15</td>
<td>0.5432</td>
</tr>
<tr>
<td>$P_a$ mm Hg</td>
<td>78±15</td>
<td>79±15</td>
<td>0.6907</td>
</tr>
<tr>
<td>$P_{min}$ mm Hg</td>
<td>23±9</td>
<td>27±12</td>
<td>0.1958</td>
</tr>
<tr>
<td>$\Delta P_{max}$ mm Hg</td>
<td>14±7</td>
<td>10±7</td>
<td>0.0273</td>
</tr>
<tr>
<td>FFR</td>
<td>0.84±0.07</td>
<td>0.89±0.07</td>
<td>0.0299</td>
</tr>
<tr>
<td>DS, %</td>
<td>28±9</td>
<td>29±8</td>
<td>0.6256</td>
</tr>
</tbody>
</table>

FRR<0.90 was defined as indicating an initially successful but suboptimal PTCA result.

According to these cutoff values of 0.90 for FFR and 35% for DS, patients were then stratified into 4 subsets according to optimal versus suboptimal post-PTCA FFR and optimal versus suboptimal percentage DS. The result of this stratification in relation to the occurrence of cardiac adverse events is presented in Figure 2. Points in the right upper quadrant of Figure 2 represent the 26 favorable patients with optimal results by both angiography and pressure measurements, defined as group A. The points in the remaining 3 quadrants represent the patients in whom either the angiographic or functional result or both were suboptimal and who were defined as group B.

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Discussion

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TABLE 5. Results of Univariate and Multivariate Logistic Regression Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.0749</td>
<td>0.0454</td>
</tr>
<tr>
<td>Age</td>
<td>0.1866</td>
<td>0.0721</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.1283</td>
<td>0.4969</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.3580</td>
<td>0.2575</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.3580</td>
<td>0.4811</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.7004</td>
<td>0.6508</td>
</tr>
<tr>
<td>Family history</td>
<td>0.7004</td>
<td>0.1836</td>
</tr>
<tr>
<td>Vessel</td>
<td>&gt;0.8</td>
<td>0.2801</td>
</tr>
<tr>
<td>DS</td>
<td>0.6192</td>
<td>0.6314</td>
</tr>
<tr>
<td>$P_w$</td>
<td>0.8388</td>
<td>0.1914</td>
</tr>
<tr>
<td>FFR</td>
<td>0.0342</td>
<td>0.0084</td>
</tr>
</tbody>
</table>

Reported probability values indicate whether the related variable has significant predictive power by logistic regression analysis.
approaches in the evaluation of the PTCA result and indicates that a subgroup of patients (45% in this study) can be discriminated in whom an excellent long-term outcome with a low event rate can be obtained by regular balloon angioplasty. This study also confirms earlier results that the coronary angiogram alone is not able to predict clinical outcome. The present data also show that 50% of the patients with an angiographically optimal result (DS ≤ 35%) still have an FFR, 0.90.

The threshold value of 0.90, found in this study to correspond with favorable long-term outcome, needs further explanation. In diagnostic coronary catheterization, it has been established that an FFR of 0.75 reliably identifies lesions associated with reversible ischemia. Therefore, immediately after PTCA, a value of FFR ≥ 0.75 will be sufficient to prevent inducible ischemia and can be called an initially successful functional result. However, when searching for a value of FFR indicating a sufficient long-term PTCA result, it can be expected that such a value must be >0.75, because in the first days, weeks, and months after PTCA, considerable changes in stenosis morphology with some loss of the initial luminal gain may occur. Dynamic processes like recoil, intimal hyperplasia, and smooth muscle cell proliferation may affect part of the initial gain and result in a decrease in FFR to values <0.75 in a number of initially successfully dilated patients. Therefore, although reversible ischemia was absent shortly after PTCA (as indicated by the reversal of the exercise test from positive to negative) in all patients with FFR ≥ 0.75, in a number of patients, some decrease in FFR probably occurred during follow-up because of the dynamic processes described above. For this reason, it is conceivable that although FFR ≥ 0.75 is sufficient to prevent ischemia immediately after PTCA (as was the case in this study), an initially higher value is necessary in a dynamic situation to compensate for the anticipated changes in morphology and function and to minimize the chance of restenosis in the long run. In fact, such differences with respect to threshold values to be used either at diagnostic procedures or after coronary intervention have been established for most other anatomic and functional parameters, including QCA and Doppler flow velocity measurement.

The purpose of the present study was to investigate whether a particular predictive value of FFR, somewhere between 0.75 and 1.00, can be identified above which clinical events become less likely. Our results suggest that such a value exists. The observed differences were significant and maintained over a follow-up of 2 years. In those patients with optimal anatomic and functional results, event rate was low and comparable to event rates in stent studies like BENESTENT and STRESS.

Favorable outcome after PTCA in the presence of a small residual transstenotic gradient was already suggested by Leimgruber et al. However, in those early days, transstenotic gradients were measured only by relatively large balloon catheters under resting conditions, and the concept of FFR, relating distal coronary pressure to blood flow, was not yet available. Recently, it was demonstrated that the combination of optimal angiographic and functional results by coronary flow velocity measurements could identify a subset of patients in whom clinical event rate at 6 months was low and comparable to results after coronary stenting. Our results extend...
these observations to another functional index, coronary pressure–derived FFR.

The reasons why such a strong correlation is present between a high value of FFR and favorable outcome are still speculative. From intracoronary ultrasound studies, it is known that even an almost normal angiographic lumina after PTCA can be accompanied by considerable residual stenosis. Therefore, confounding by differences in collateral significance differs between both groups (Tables 4 and 5).28

Study Limitations
This study was retrospective and rather small. Nevertheless, the results are significant and were maintained over a follow-up of 2 years, longer than in most other restenosis studies. Follow-up angiography was not performed, except in those patients who experienced an event. The reason for this strategy was to avoid repeated PTCA based only on an angiographic stenosis at follow-up angiography (oculostenotic reflex). In clinical practice, the indication to perform repeated angiography should be based on the presence of symptoms, and it has been well demonstrated that routine angiographic follow-up may induce a sharp increase in reinterventions, resulting in considerable bias.29 Because exercise testing, which could be compared with both the positive exercise test obtained shortly before and the negative exercise test obtained immediately after the PTCA, was performed in all patients with recurrent chest pain during follow-up, we believe that no clinically relevant restenosis has been missed. Stated another way, recurrent chest pain during late follow-up in patients after PTCA of single-vessel disease, accompanied by a positive exercise test that had been negative immediately after the PTCA, can be considered hard evidence of restenosis. Therefore, the clinical usefulness of our results is not affected by the lack of follow-up angiography in all patients.

One might speculate whether the better outcome in 1 subset of patients (group A) could be related to a better developed collateral circulation and whether the higher FFR after dilation might reflect this. However, maximum recruitable collateral blood flow during the initial PTCA reflected by the coronary wedge pressure (Pw) during balloon inflation in relation to aortic pressure, was not significantly different between both groups (Tables 4 and 5).30 Therefore, confounding by differences in collateral circulation was unlikely.

Conclusions
This study indicates that long-term clinical outcome after plain balloon angioplasty in patients with both FFR ≥0.90 and residual DS ≤35% is excellent and is comparable to the outcome observed after coronary stenting in patients with similar characteristics.3–5 This suggests that in patients with an optimal functional and angiographic PTCA result, no further improvement in clinical outcome is expected from coronary stenting. Conversely, given the high event rate in this study in patients with a suboptimal functional PTCA result reflected by FFR <0.90, further action to improve the result seems most appropriate.

Acknowledgment
We express our gratitude to Peter Brands, MSc, for his expert statistical assistance.

References


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Circulation. 1999;99:883-888
doi: 10.1161/01.CIR.99.7.883

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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