Long-Term Follow-Up After Deferral of Percutaneous Transluminal Coronary Angioplasty of Intermediate Stenosis on the Basis of Coronary Pressure Measurement

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Objectives. This study sought to determine the safety of deferral of percutaneous transluminal coronary angioplasty (PTCA) of angiographically intermediate but functionally nonsignificant stenosis, as assessed by coronary pressure measurement and myocardial fractional flow reserve (FFR<sub>myo</sub>).

Background. Decision making in patients with chest pain and intermediate coronary stenosis remains difficult. In these cases it is unclear whether the risk of an intervention and the potentially subsequent restenosis outweigh the future risk of an event if the lesion remains untreated. FFR<sub>myo</sub> is a lesion-specific functional index of epicardial stenosis severity that accurately distinguishes stenoses associated with inducible ischemia.

Methods. Retrospective analysis and follow-up was performed in 100 consecutive patients referred to our centers for PTCA of an intermediate stenosis but in whom the planned intervention was deferred on the basis of an FFR<sub>myo</sub> > 0.75.

Results. During a follow-up period of 18 ± 13 months (mean ± SD, range 3 to 42), two patients died of noncardiac causes. Ninety patients remained free of any coronary events, and their average Canadian Cardiovascular Society class decreased from 2.0 ± 1.2 at baseline to 0.7 ± 0.9 at follow-up (p < 0.0001). A coronary event occurred in eight patients and was target-vessel related in four.

Conclusions. In patients with chest pain referred for PTCA of an intermediate stenosis, deferral of the intervention on the basis of an FFR<sub>myo</sub> > 0.75 is safe and is associated with a much lower clinical event rate than if the procedure had been performed as initially planned in these patients.

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Manuscript received July 10, 1997; revised manuscript received December 2, 1997, accepted December 17, 1997.

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safety and long-term outcome of deferring a coronary intervention in patients initially referred for PTCA of an intermediate coronary stenosis, but in whom the intervention was deferred on the basis of a sufficiently high $\text{FFR}_{\text{myo}} \approx 0.75$.

**Methods**

$\text{FFR}_{\text{myo}}$. The $\text{FFR}_{\text{myo}}$ of a coronary artery is defined as the ratio between maximal achievable blood flow to its dependent myocardium and the hypothetically maximal achievable blood flow to that same territory if the supplying artery were completely normal (10). Contrary to absolute coronary flow reserve, $\text{FFR}_{\text{myo}}$ is independent of changes in systemic blood pressure and heart rate and is not affected by conditions known to increase baseline myocardial blood flow (8,11). In addition, $\text{FFR}_{\text{myo}}$ takes into account collateral blood flow to the dependent myocardium (12). $\text{FFR}_{\text{myo}}$ can be easily and rapidly obtained during cardiac catheterization as the ratio between distal hyperemic coronary pressure, measured by a pressure guide wire, and aortic pressure, measured by the guiding catheter (8). The normal value of this index is 1.0 and because there is no need for a control artery, it is also applicable in multivessel disease (8).

**Patients.** Between May 1993 and May 1997 at our centers in Aalst and Eindhoven, guide wire-based coronary pressure measurements to determine $\text{FFR}_{\text{myo}}$ were performed in >600 patients, either at diagnostic or at interventional catheterization. From this patient group all records were reviewed to select the first 100 patients who fulfilled the following inclusion criteria: 1) Patients were referred for intervention of one stenosis in the mid or proximal part of a native coronary artery; 2) the myocardial territory dependent on the stenosed target vessel was normokinetic, as assessed by visual estimation of the ventriculogram; and 3) the planned intervention was deferred on the basis of a pressure-derived $\text{FFR}_{\text{myo}} \approx 0.75$, determined during the control angiogram just before the planned PTCA.

**Coronary catheterization and coronary pressure measurement.** In all patients, at the time of the planned PTCA, a 6F to 8F guiding catheter was introduced into the femoral artery and advanced into the ostium of the target vessel. Intracoronary or sublingual nitroglycerin and 10,000 U of heparin were administered just before control angiograms were made, according to local routine. Thereafter, a pressure monitoring guide wire (Pressure Guide, Radi Medical Systems, Uppsala, Sweden) was zeroed, calibrated and advanced through the catheter into the coronary artery and positioned distal to the stenosis, as previously described (8). Next, maximal myocardial hyperemia was induced by adenosine, either as an intracoronary bolus of 12 to 20 $\mu$g or by intravenous infusion in a femoral vein at an infusion rate of 140 $\mu$g/kg body weight per min for a duration of 2 to 4 min (13–15). Examples of the angiogram and pressure recordings from one study patient are shown in Figures 1 and 2, respectively.

$\text{FFR}_{\text{myo}}$ was then calculated at maximal hyperemia from the simultaneously recorded aortic ($P_a$) and distal coronary pressure ($P_d$) by the ratio

$$
\text{FFR}_{\text{myo}} = \frac{P_d}{P_a},
$$

as described previously (8).

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**Abbreviations and Acronyms**

- **CCS** = Canadian Cardiology Society
- **$\text{FFR}_{\text{myo}}$** = myocardial fractional flow reserve
- **$P_a$** = mean aortic pressure
- **$P_d$** = mean distal coronary pressure, measured at maximal coronary hyperemia
- **PTCA** = percutaneous transluminal coronary angioplasty
- **QCA** = quantitative coronary arteriography

**Figure 1.** Coronary angiogram in right anterior oblique projection from a 77-year old woman with persistent chest pain and negative noninvasive stress test results but admitted for PTCA of a 70% stenosis in the proximal left anterior descending coronary artery (arrow). The dilemma was to perform angioplasty or to leave this lesion untreated. The pressure tracings from this patient are shown in Figure 2.

**Figure 2.** Simultaneous phasic and mean pressure recordings of distal coronary pressure ($P_d$) and aortic pressure ($P_a$) in the patient from Figure 1. The pressure wire is positioned across the stenosis, and no gradient is observed at rest (RESTING). After start of intravenous adenosine infusion (140 $\mu$g/kg per min), a pressure gradient gradually develops, and at steady state maximal coronary hyperemia (HYPEREMIA), $\text{FFR}_{\text{myo}}$ is calculated by the $P_d/P_a$ ratio, which equals $82/93 = 0.89$. This value is well above the cutoff point of 0.75 for reversible ischemia; therefore, no intervention was performed.
Quantitative coronary arteriography. Quantitative coronary arteriographic (QCA) analysis of the control cine angiograms, obtained just before the planned intervention in preferably two orthogonal projections by the cardiovascular angiography analysis system (16,17), was performed. Using the guiding catheter as a scaling device, the reference diameter, minimal lumen diameter, percent diameter stenosis and percent area stenosis of the target lesion were assessed. The values presented are the average of the orthogonal projections.

Follow-up and clinical events. Follow-up clinical data were obtained in all patients by patient interview and by written correspondence with the cardiologist who was presently treating or had last treated the patient. Clinical events were mutually exclusive and were defined in the following ranking order as death, myocardial infarction, unstable angina, coronary artery bypass graft surgery and coronary angioplasty. Death was considered cardiac related, unless proved otherwise. Coronary events were subclassified into target vessel related or target vessel unrelated.

The decision not to perform the planned angioplasty required extensive explanation to the patient and the referring cardiologist. In particular, it was explained that the decision to defer the intervention was based on coronary pressure measurements indicating adequate myocardial perfusion and that the operator had concluded that the lesion could not be held responsible for the patient’s chest pain. Decisions regarding medical treatment of the patient after deferral of PTCA were left to the referring physician.

Statistics. Data are reported as number of patients and mean value ± SD. Differences between mean CCS class and mean number of antianginal drugs used at baseline and at follow-up were determined using the Wilcoxon test. Differences between mean percent diameter stenosis and FFR\text{myo}, in the event-free and event group were assessed using the t test. A p value < 0.05 was considered significant, and all tests were two-tailed. Patient curves for freedom from death and coronary events were constructed according to the method of Kaplan and Meier (18).

Results

Baseline characteristics. The clinical characteristics of the study patients are shown in Table 1. At least one noninvasive stress test had been performed in 64 patients, of whom 28 had a positive result for ischemia. Therefore, in a total of 72 patients, noninvasive stress tests for ischemia were negative (n = 30), inconclusive (n = 6) or not available (n = 36). In those patients, the decision to schedule PTCA had been based solely on persistent chest pain and the presence of an angiographically suspect lesion. Ten patients were in CCS class I but were referred for an intervention on the basis of coincident positive stress test results and the presence of an intermediate stenosis.

Angiographic characteristics and FFR\text{myo}. The lesion characteristics, as well as the results of the pressure measurements, are shown in Table 2. The target lesion was located in the proximal or midsection of the left anterior descending coronary artery in 64 patients, the left circumflex coronary artery in 10 and the right coronary artery in 26. Quantitative coronary angiographic analysis of the reference diameter of the adjacent normal segment, minimal stenosis lumen diameter, percent diameter stenosis and percent area stenosis resulted in average values of 3.17 ± 0.67 mm, 1.68 ± 0.45 mm, 46.9 ± 9.4% and 68.5 ± 10.5%, respectively (Table 2). In 40 patients, the percent diameter stenosis was >50%. In 35 patients, the minimal lumen diameter was <1.5 mm. The average FFR\text{myo} was 0.87 ± 0.07 (range 0.75 to 1.00). The average peak hyperemic transstenotic pressure gradient was 12 ± 6 mm Hg (range 0 to 24).

Procedural safety and follow-up. There were no procedural complications related to catheterization or coronary pressure measurements. Complete clinical follow-up was obtained in all patients. The average follow-up period was 18 ±
Table 2. Angiographic Characteristics and Myocardial Fractional Flow Reserve in 100 Study Patients

| Coronary artery involved | LAD | LCx | RCA | QCA
|--------------------------|-----|-----|-----|-----
| Ref diam (mm)            | 3.17 ± 0.67 | 1.86 ± 0.45 | 46.9 ± 9.4 | 68.5 ± 10.5
| MLD (mm)                 | 1.68 ± 0.45 | 6
| %DS                      | 0.374 | 6
| % area stenosis          | 0.45 | 7

Data presented are mean value ± SD, range or number of patients. DS = diameter stenosis; FFR_{myo} = myocardial fractional flow reserve; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MLD = minimal lumen diameter; QCA = quantitative coronary arteriography; RCA = right coronary artery; Ref diam = reference diameter.

13 months (range 3 to 42) and was >6 months in 79 patients. During the follow-up period (Table 3), two patients died of noncardiac causes after 3 and 10 months, respectively. The first was a 49-year-old man with atypical complaints and a mild aortic stenosis (mean gradient 12 mm Hg), who committed suicide 3 months after catheterization. The second was a 77-year-old man who died of a gastric cancer. In this patient with chest pain and known coronary disease, gastrectomy was considered. Intracoronary pressure measurements were performed to evaluate the need for preoperative PTCA of the stenosis. PTCA was deferred on the basis of an FFR_{myo} of 0.87. No cardiac-related deaths occurred.

In eight patients coronary events occurred, four of which were target vessel related (Table 3). The characteristics of these patients are shown in Table 4. The average interval to a target vessel-related incident was 27 months, whereas the average interval to incidents not related to the target vessel was 11 months. Only two coronary events occurred within 6 months after deferral, and both were unrelated to the target vessel. There was no difference in QCA variables (p = 0.909) or in FFR_{myo} (p = 0.374) at the initial assessment between patients with an event at follow-up and the remaining group.

The average CCS class in the event-free group (90 patients) decreased from 2.0 ± 1.2 at baseline to 0.7 ± 0.9 at follow-up (p < 0.0001). The average number of antianginal drugs used in these 90 patients decreased from 2.4 ± 1.2 at baseline to 1.9 ± 1.2 at follow-up (p = 0.0022). At follow-up, 81 patients were in CCS class I or had no chest pain.

Survival and event-free survival. As analyzed by the Kaplan-Meier method, at 42 months the percent estimated survival (±SEM) after deferral of PTCA was 97 ± 2%; survival free from death or target vessel-related events was 84 ± 7%; and survival free from death or any coronary event was 78 ± 7% (Fig. 3).

**Discussion**

Favorable outcome without intervention. The present study indicates that it is safe to defer angioplasty of an intermediate stenosis if that stenosis has no physiologic importance, as assessed by pressure-derived FFR_{myo} ≥ 0.75.

No cardiac-related deaths occurred in our deferred group, and during an average follow-up period of 18 months, a target vessel-related event occurred only in 4 of 100 patients. Only one patient experienced a myocardial infarction after 26 months because of disease progression in the target vessel. The average reference diameter of the coronary arteries in the present study was >3 mm, indicating that these were all large vessels and that the favorable outcome was not due to inclusion of smaller vessels that would have had a good outcome in any case.

Rationale of coronary pressure measurement. FFR_{myo} is a functional index of epicardial stenosis severity, and it has been well demonstrated (7,8) that the cutoff value of 0.75 discriminates between functionally significant and nonsignificant stenoses. The diagnostic accuracy of FFR_{myo} for this purpose is 93% and is higher than any other single noninvasive stress test if performed alone (7). Therefore, in our catheterization laboratories, it is standard practice to determine the FFR_{myo} if there is reasonable doubt that the culprit lesion scheduled for PTCA is actually causing the complaints. Such is often the case when the lesion is moderate and the exercise test not clearly positive or when the complaints are atypical. FFR_{myo} is easily obtained just before PTCA by using a pressure guide wire instead of a regular guide wire and by measuring distal coronary pressure and aortic pressure simultaneously at maximal hyperemia.

In patients with persistent chest pain, coronary angiography is often performed despite the absence of objective proof of ischemia (7,19). It has been shown (20) that in a randomly selected group of asymptomatic 60-year-old men, the preva-
lence of apparently significant coronary stenoses is 20%. Therefore, one must assume that in a number of such patients, the presence of a lesion may be coincidental and that a direct relation between the angiographic lesion and the chest pain is unclear. Nevertheless, in clinical practice, PTCA of the intermediate lesion is often performed despite the absence of objective proof of ischemia (19). This practice has been defended in that even if that lesion is not related to the patient’s chest pain, PTCA would be justified by the “plaque-sealing” concept (21). However, this concept is unproved, and in so performing PTCA, a previously stable (and functionally not significant) lesion might be activated and a deleterious “restenosis” process triggered. In fact, it is expected that in 20% to 30% of such patients, a clinically relevant restenosis will occur within 6 months. It is therefore unclear whether the risk of dilating a functionally nonsignificant but angiographically intermediate stenosis outweighs the risk of leaving such a lesion untreated.

**Evidence of reversible ischemia as a prerequisite for performing PTCA.** In the present study, 72 patients had been scheduled for angioplasty only on the basis of clinical and visual angiographic criteria. Stress testing in these patients was either negative, inconclusive or not performed. Although our study cohort was restricted to patients with intermediate stenoses, their data are comparable to those of a general PTCA population, as reported by Topol et al. (19), indicating that in the United States, 60% of coronary interventions are performed without objective proof of reversible ischemia.

By QCA, 40 of 100 stenoses in the present study group appeared to be >50% in diameter stenosis, the anatomic cutoff value generally accepted for discriminating between “significant” and “nonsignificant” lesions. Such lesions would have been routinely dilated had only angiographic criteria been applied (22, 23). However, by our measuring FFR$_{myo}$ a number of unnecessary PTCA were avoided in this group.

**Figure 3.** Estimated survival and event-free survival curves (Kaplan-Meier) of all patients in whom the planned PTCA of an intermediate coronary stenosis was deferred on the basis of a pressure-derived FFR$_{myo} < 0.75$. Numbers below the x-axis represent patients at risk at 0, 6, 12, 18, 24, 30, 36 and 42 months after deferral of angioplasty for survival; survival or target vessel-related event; and survival or any coronary event, respectively.

### Table 4. Coronary Events in Eight Study Patients

<table>
<thead>
<tr>
<th>Pt No./Gender</th>
<th>Target Vessel</th>
<th>Initial FFR$_{myo}$</th>
<th>%DS</th>
<th>Interval to Event (mo)</th>
<th>Incident</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients With Coronary Event Related to Target Vessel (n = 4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M</td>
<td>LAD</td>
<td>0.89</td>
<td>28%</td>
<td>21</td>
<td>UA, followed by PTCA</td>
</tr>
<tr>
<td>2/M</td>
<td>RCA</td>
<td>0.85</td>
<td>58%</td>
<td>26</td>
<td>Acute MI</td>
</tr>
<tr>
<td>3/M</td>
<td>RCA</td>
<td>0.94</td>
<td>61%</td>
<td>30</td>
<td>UA, followed by PTCA</td>
</tr>
<tr>
<td>4/M</td>
<td>RCA</td>
<td>0.85</td>
<td>40%</td>
<td>32</td>
<td>CABG, including target vessel</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.89</td>
<td>47%</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>±SD</td>
<td></td>
<td>±0.04</td>
<td>±16%</td>
<td>±5</td>
<td></td>
</tr>
<tr>
<td><strong>Patients With Coronary Event Not Related to Target Vessel (n = 4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/M</td>
<td>RCA</td>
<td>0.94</td>
<td>49%</td>
<td>5</td>
<td>UA, followed by PTCA</td>
</tr>
<tr>
<td>6/M</td>
<td>LCx</td>
<td>0.85</td>
<td>52%</td>
<td>6</td>
<td>Disease progression, elective PTCA</td>
</tr>
<tr>
<td>7/F</td>
<td>LCx</td>
<td>0.91</td>
<td>48%</td>
<td>8</td>
<td>Disease progression, elective PTCA</td>
</tr>
<tr>
<td>8/F</td>
<td>LAD</td>
<td>0.94</td>
<td>42%</td>
<td>26</td>
<td>UA, followed by PTCA</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.90</td>
<td>48%</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>±SD</td>
<td></td>
<td>±0.04</td>
<td>±4%</td>
<td>±10</td>
<td></td>
</tr>
</tbody>
</table>

F = female; M = male; Pt = patient; other abbreviations as in Tables 1 to 3.
and only in 10% of this study group did events occur after an average follow-up of 18 months. This event rate is only slightly above the coronary event rate found in an asymptomatic 60-year old population of ~2% to 3%/year and is in accordance with previous studies (7,25–27) in similar patient groups where intervention was deferred on the basis of physiologic measurements of either coronary blood flow velocity or coronary pressure.

In 28 patients the pre-PTCA exercise test was positive despite a FFR\textsubscript{myo} >0.75. Exercise-induced spasm may have played a role in some patients, and the exercise test could have been false positive in others. It is well known that the accuracy of exercise testing in patients with moderate stenosis is low and that false positive results may occur in up to 20% of these patients (7). Moreover, as described earlier, in 10 of these 28 patients no complaints were present, and the indication for angiography, which revealed the intermediate stenosis, had been the positive exercise test itself. In those patients the rate of false positive exercise tests must have been higher than usual (27). Two of these 28 patients experienced a coronary event, respectively, at 20 and 24 months, both target vessel related. This long event-free interval suggests that these events may have been related to the natural progression of atherosclerotic disease rather than to incorrect initial diagnosis.

In the 90 event-free patients, anginal class improved significantly at follow-up despite a decrease in the average number of antianginal medications taken by these patients. This improvement is possibly related to patient reassurance by our explaining that the lesion was not clinically important and that the chest pain could very well be of other than cardiac origin (7,25). This decrease in symptoms after reassurance supports the idea that in many of these patients the chest pain was not caused by the coronary lesion, underlining that deferral of the planned PTCA had been the correct decision.

**Indications for coronary pressure measurement before PTCA.** As stated earlier, in our catheterization laboratories coronary pressure measurement and determination of FFR\textsubscript{myo} are routinely performed in patients in whom reasonable doubt exists about the significance of coronary lesions, either at diagnostic angiography or just before planned PTCA. This is the case in ~10% of our patients and relates to intermediate stenosis, equivocal noninvasive stress test results or atypical complaints. Other indications are facilitating the decision to perform either PTCA of one or two vessels or bypass surgery of three or more vessels, depending on the significance of the respective lesions, or to decide whether minimal invasive surgery of a left anterior descending coronary artery stenosis is a reasonable option for multivessel disease (28). The technique of coronary pressure measurement is easily applicable during a routine procedure, and additional costs are U.S.$500 for the pressure wire in cases of PTCA and an additional U.S.$150 in a diagnostic case for the Y-connector and a (generally 6F or 7F) guiding catheter. If FFR\textsubscript{myo} >0.75, intervention of the respective lesion is always deferred. Therefore, selection bias was unlikely in the present study.

**Conclusions.** Because this study is retrospective and non-randomized and does not provide comparative data from a control group of patients in whom angioplasty was actually performed, it is impossible to establish the clinical event rate that would have occurred had angioplasty actually been performed. Nevertheless, it can be concluded that in patients with chest pain who are scheduled for PTCA of an intermediate coronary stenosis, deferral of PTCA on the basis of an FFR\textsubscript{myo} >0.75 is safe, irrespective of the noninvasive stress test result, and is associated with a very low coronary event rate of ~5%/year, much lower than expected had PTCA been performed in all patients. To confirm these observations, a large randomized, prospective study is currently underway.

We are grateful to the referring cardiologists of the study patients for their contribution during follow-up and to Bert Jan Arends, BSc for expert statistical assistance.

**References**


