Background. In the catheter laboratory there is a need for functional tests validating the hemodynamic significance of coronary artery stenosis.

Objectives. It was the objective of our study to compare the long-term cardiac event rate and the clinical symptoms in patients with reduced coronary flow velocity reserve (CFVR) and standard PTCA with patients with normal CFVR and deferred angioplasty.

Methods. Our study included 70 patients with intermediate coronary artery stenoses (13 f, 57 m; diameter stenosis >50%, <90%) and an indication for PTCA due to stable angina pectoris and/or signs of ischemia in noninvasive stress tests. CFVR was measured distal to the lesion after intracoronary administration of adenosine using 0.014 inch Doppler-tipped guide wires.

Results. In 22 patients (31%), PTCA was deferred due to a CFVR ≥ 2.0 (non-PTCA group). In the remaining 48 patients (69%) mean CFVR of 1.4 ± 0.23 (p < 0.001) was measured (PTCA group). CFVR increased to 2.0 ± 0.51 after angioplasty. During follow-up (average 15 ± 6.0 months), the following major adverse cardiac events (MACE) occurred: in the PTCA group re-PTCA was performed in nine patients (18.8%) because of unstable angina, five patients (10.4%) suffered an acute myocardial infarction (MI) (two infarctions occurred during the angioplasty, three patients suffered an infarction during follow-up), two patients (4.2%) needed blood transfusions due to severe bleedings, two patients (4.2%) underwent bypass surgery and one patient (2.1%) died. In the non-PTCA group, angioplasty was necessary only in two cases (9.1%) during follow-up. We did not observe any MI in the non-PTCA group.

The overall rate of MACE was significantly lower in the non-PTCA group compared to the PTCA group (9.1% vs. 33.3%, p < 0.01). However, only 40% of the patients of the non-PTCA group were free of angina pectoris at stress. In the PTCA group, 63% did not complain of any symptoms at follow-up (p < 0.05).

Conclusions. We conclude that determination of the CFVR is a valuable parameter for stratifying the hemodynamic significance of coronary artery stenosis. PTCA can safely be deferred in patients with significant coronary stenosis but a CFVR ≥ 2.0. The total rate of MACE at follow-up was below 10% among these patients. However, if PTCA was deferred the number of patients who are free of angina is lower compared to those patients who underwent angioplasty.

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define prospectively the group of patients whose coronary vessel flow capacity is sufficient despite a stenosis, and therefore PTCA seems unnecessary. Measurements of translesional pressure-flow velocity measurements and of the fractional flow reserve (FFR) have already been established by clinical studies (5,7). The registration of coronary flow velocity reserve (CFVR) can easily be performed. Recent studies have demonstrated a correlation between CFVR after angioplasty and the clinical outcome (8). However, the value of the CFVR to evaluate the indication for PTCA has not been proven so far in a prospective study. Therefore, we tested the hypothesis that CFVR is able to distinguish those patients who may benefit from an angioplasty procedure from those for whom PTCA seems unnecessary.

**Methods**

**Patient selection.** Between July 1994 and December 1996, 2,760 PTCA were performed in our clinic. In this prospective trial we consecutively included 70 patients who were referred for elective angioplasty during certain terms of this period. All patients met the inclusion criteria as shown in Table 1. They were referred for coronary angioplasty due to a de novo lesion of $>50\%$. In addition, they reported chest pain at stress and/or they showed signs of ischemia in noninvasive stress tests. Precatheterization stress tests were performed by bicycle exercise testing or thallium scintigraphy in a standard manner without antianginal drugs. All patients had to reach at least 85% of their maximum heart rate during exercise. Bicycle stress test was considered positive if ST-segment depression of $\geq 0.2$ mV in two standard leads was measured. Scintigraphy was considered positive if thallium storage was reversibly diminished in at least two regions in the area of interest. Patients were excluded if more than one lesion had to be treated, collateral flow was present, the left main was stenosed, the patient had unstable angina or angina at rest. Further exclusion criteria were previous myocardial infarction or reduced coronary blood flow ($<\text{TIMI III}$) in the vessel of interest.

All patients had given written informed consent to take part in the study. They were well informed about the aim and the strategy of treatment evaluated in the study.

**Study protocol.** Coronary angiography was performed in standard manner by femoral approach with 7F Judkins guiding catheter. After intracoronary injection of 0.2 mg of nitroglycerin, quantitative coronary angiography (QCA) of the target lesion was obtained. QCA was performed by Philips DCI automated coronary analysis using the 7F guiding catheter as reference standard (9). The lesion severity was determined by percent diameter stenosis relative to angiographically normal diameter.

A 0.014” Doppler guide wire (FlowWire™, Cardiometrics, Mountain View, California) was placed 1-2 cm distal to the stenosis after intravenous administration of 10,000 IU of heparin. The 175 cm long wire has an integrated piezoelectric ultrasound transducer in the tip. The signal of the 12 MHz pulsed Doppler was analyzed by a computer system (FlowMap™, Cardiometrics, Mountain View, California) using fast Fourier transformation. The validity of these Doppler wire measurements has been demonstrated in various settings (10,11). The mechanical and electrical characteristics of this Doppler guide wire are reported in detail elsewhere (12). The average peak velocity (APV) 4 mm distal of the tip of the Doppler wire was obtained from the spectral signals averaged over two cardiac cycles. After registration of APV at rest, adenosine was injected through the guiding catheter to induce coronary hyperemia. We used 12 µg for the right and 18 µg for the left coronary artery. The coronary flow velocity reserve (CFVR) was computed as the ratio of hyperemic to basal APV. In those patients who had CFVR $\geq 2$, PTCA was deferred and they were allotted to the non-PTCA group. In the remaining patients with CFVR $<2$, balloon angioplasty was performed in standard manner (PTCA group) after administration of an additional 5,000 IU of heparin. Balloon inflation or stent implantation was performed until an angiographically satisfying result was achieved in all patients of the PTCA group (degree of stenosis $<30\%$).

In addition, all 70 patients received optimal medication consisting of aspirin, nitrates, beta-adrenergic blocking agents, ACE-inhibitors and lipid lowering drugs as appropriate to each individual. Patients with stents received ticlopidine 250 mg bid for four weeks.

### Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Written informed consent</td>
<td>Acute myocardial infarction or unstable angina</td>
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<tr>
<td>Age $\geq 18$ years</td>
<td>Stenosis of the left main</td>
</tr>
<tr>
<td>Positive stress test and/or stable angina during exercise</td>
<td>CCS class IV</td>
</tr>
<tr>
<td>De novo lesion</td>
<td>NYHA class IV</td>
</tr>
<tr>
<td>Only one lesion to be treated</td>
<td>Pregnancy (in women)</td>
</tr>
<tr>
<td>Degree of stenosis $&gt;50%$ &amp; $&lt;90%$</td>
<td>Previous Q-wave infarction/hypokinesia in the region of interest</td>
</tr>
<tr>
<td>TIMI flow III</td>
<td>Known malignancy which would interfere follow-up</td>
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<tr>
<td>Vessel suitable for angioplasty</td>
<td>Relevant collateral flow</td>
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</table>
Clinical follow-up. We defined as major adverse cardiac event (MACE) the occurrence of severe bleeding requiring blood transfusion, repeated PTCA or primary PTCA in the non-PTCA group, acute myocardial infarction, coronary bypass surgery, cardiac death during angioplasty or during follow-up period. A myocardial infarction was considered if an increase of creatine kinase to more than twice the normal value was measured and a Q-wave developed in at least two leads of standard ECG recordings. Severe bleeding was defined as blood loss requiring transfusion of blood or surgical intervention. Follow-up period was at least six months. All patients underwent physical examination and noninvasive stress tests (bicycle exercise testing or thallium scintigraphy) in our clinic. The same stress test protocol was used at follow-up examination as at the beginning of the study. All patients had to cycle until at least ≥85% of their maximum heart rate was reached. In those patients who reported new onset or aggravation of angina or showed pathological results in noninvasive stress test at follow-up, reangiography was performed.

Statistical analysis. Data are reported for 70 patients. They were divided into two groups after measurement of coronary flow velocity reserve. All values are expressed as mean ± SD and the percentage in each group. P values were calculated using paired Student t tests for statistical analysis of continuous variables within a group. Associations between the two groups were tested for, using two-tailed unpaired Student t tests for continuous data after F-test determination of standard distribution or chi-square ($x^2$) test without continuity adjustment for categorical data. A p value < 0.05 was considered statistically significant.

Results

The clinical data of the 70 patients are shown in Table 2. Angiographic characteristics are summarized in Table 3. Age, gender, NYHA class, CCS class, extent of coronary artery disease, results of stress tests and incidence of angina pectoris were comparable between the two groups at the time of inclusion (Fig. 1).

The degree of coronary artery stenosis was significantly lower in those patients who had a CFR ≥ 2 compared with the PTCA group (66.1% ± 8.52 vs. 76.5% ± 8.35%, p < 0.05). However, for all patients the indication for PTCA was made by independent cardiologists.

Acute results. In 22 patients angioplasty was deferred due to a CFVR ≥ 2 (non-PTCA group). No acute complication was observed among this group. New York Heart Association (NYHA) and angina pectoris status have been improved by optimization of medical therapy.

In the PTCA group, the CFVR increased from 1.4 to 2.0 after angiographically successful angioplasty (p < 0.001). The degree of stenosis was reduced from 76.5% to 16.5% (p < 0.001). The incidence of angina pectoris was reduced nearly one class according to CCS (Canadian Cardiac Society). Among those who underwent PTCA, two patients (4.2%) suffered an acute myocardial infarction. Another patient (2.1%) underwent emergency coronary bypass surgery after dissection into the left main. In two patients (4.2%) bleeding occurred at the femoral puncture site requiring blood transfusion; surgical intervention was necessary in one of these cases. In total, we noticed major adverse cardiac events (MACE) related to the initial PTCA in five patients in the PTCA group (10.4%).

Follow-up results. The follow-up period was 15 ± 6.0 months (range: 6 to 30 months). At follow-up, there was no difference in medical treatment between the PTCA and the non-PTCA group (data not presented). In the non-PTCA group, we found progression of CAD with an aggravation of angina in two patients (9.1%). In these two patients, PTCA was
performed after 11 and 12 months, respectively, both in an outside institutions while measuring the CFVR.

Among those with an initially normal CFVR in the target vessel, three other patients (13.6%) underwent angiography during follow-up. They showed abnormalities during stress ECG in different leads as before angiography. However, they did not require PTCA. The degree of coronary diameter narrowing remained unchanged in those five patients of the non-PTCA group who were restudied by coronary angiography. Neither an acute myocardial infarction nor cardiac death was observed in this group. Thirteen patients of the non-PTCA group (59.1%) reported chest pain at follow-up examination. Eight patients (36.4%), including those two who were dilated, showed signs of ischemia in noninvasive stress tests. Considering PTCA, MACE occurred in two patients of the non-PTCA group (9.1%) during follow-up.

In the PTCA group, three patients (6.3%) suffered myocardial infarction during follow-up. Two of them underwent re-PTCA, one patient had emergency coronary bypass surgery two years after initial angioplasty due to occlusion. Other than the two emergency PTCA, an additional seven patients (14.6%) underwent re-PTCA for relevant restenosis. Another 15 patients (31.25%) underwent angiography during follow-up because of new onset or aggravation of angina or suspect results in noninvasive stress tests. They did not require re-intervention. Eighteen patients (37.5%), including the seven patients who had re-PTCA, reported angina at stress at follow-up. Eight of them, plus 10 other patients who were free of angina showed signs of ischemia in noninvasive stress tests among the PTCA group (37.5%).

In summary, 11 patients of the PTCA group (22.9%) had MACE during the follow-up period. The total MACE rate in the PTCA group at follow-up was approximately 30%.

**Table 3.** Angiographic Characteristics and Follow-up Results of 70 Patients

<table>
<thead>
<tr>
<th></th>
<th>Non-PTCA Group CFVR ≥2 (n = 22)</th>
<th>PTCA Group CFVR &lt;2 (n = 48)</th>
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<tbody>
<tr>
<td>Vessel of interest</td>
<td>Left anterior descending</td>
<td>13 (59.1%)</td>
</tr>
<tr>
<td></td>
<td>Circumflex</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td></td>
<td>Right coronary artery</td>
<td>6 (27.3%)</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>pre PTCA</td>
<td>66.1 ± 8.52%</td>
</tr>
<tr>
<td></td>
<td>post PTCA</td>
<td>16.5 ± 20.3%</td>
</tr>
<tr>
<td>At follow-up</td>
<td>65.0 ± 18.03% (5 pts)</td>
<td>49.2 ± 31.41% (25 pts)</td>
</tr>
<tr>
<td>CAD (number of vessels)</td>
<td>1.8 ± 0.73</td>
<td>1.9 ± 0.76</td>
</tr>
<tr>
<td>CFVR pre PTCA</td>
<td>2.7 ± 0.75</td>
<td>1.4 ± 0.23</td>
</tr>
<tr>
<td>post PTCA</td>
<td>2.0 ± 0.51</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction:</td>
<td>Acute</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0</td>
</tr>
<tr>
<td>Other complications:</td>
<td>Severe bleeding</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Coronary bypass surgery</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(Re-) PTCA</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td></td>
<td>Sudden cardiac death</td>
<td>0</td>
</tr>
<tr>
<td>MACE</td>
<td>Acute</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td></td>
<td>Σ</td>
<td>2 (9.1%)</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CFVR = coronary flow velocity reserve; MACE = major adverse cardiac event; t test or χ²-test: n.s. = not significant; * = p < 0.05; ** = p < 0.01; *** = p < 0.001.

Figure 1. Severity of angina pectoris (according to Canadian Cardiac Society) of patients who reported angina at stress before angioplasty, at discharge and after follow-up of 15 months. (n.s.: t test not significant).

In the PTCA group, three patients (6.3%) suffered myocardial infarction during follow-up. Two of them underwent re-PTCA, one patient had emergency coronary bypass surgery two years after initial angioplasty due to occlusion. Other than the two emergency PTCA, an additional seven patients (14.6%) underwent re-PTCA for relevant restenosis. Another 15 patients (31.25%) underwent angiography during follow-up because of new onset or aggravation of angina or suspect results in noninvasive stress tests. They did not require re-intervention. Eighteen patients (37.5%), including the seven patients who had re-PTCA, reported angina at stress at follow-up. Eight of them, plus 10 other patients who were free of angina showed signs of ischemia in noninvasive stress tests among the PTCA group (37.5%).

One patient (2.1%) died of ventricular fibrillation four months after initial angioplasty. Since autopsy was denied, it was unclear whether he had an acute myocardial infarction in the vessel of interest. In summary, 11 patients of the PTCA group (22.9%) had MACE during the follow-up period. The total MACE rate in the PTCA group at follow-up was approximately 30%.

**Discussion**

In this prospective study, we tested the method of deferring PTCA in patients with significant coronary stenosis yet sufficient CFVR. Deferring angioplasty was safe and had a favorable outcome in 22 patients with CFVR ≥2. The rate of MACE was significantly elevated in those patients who had CFVR <2 and underwent PTCA compared to the patients with normal CFVR and deferred angioplasty (Fig. 2). Despite
was safe to defer angioplasty.

measurements of CFVR identified those patients in whom it
between single and multivessel disease. Multicenter trials with
relatively small cohort, we are not able to show any difference
adaptation in the daily catheter laboratory routine. Due to the
of CFVR offer the opportunity to validate the indication for
the hemodynamic significance of coronary artery stenosis, 2.0
time a need to distinguish the relevant stenosis from those
since reangiography was not performed in all patients, we
not able to quantify the degree of progression of CAD. On
one hand there might be some nonsymptomatic restenosis in
patients who underwent PTCA, but on the other hand the
myocardium even if the CFVR is reduced. Since visible
collateral flow in the vessel of interest was an exclusion criteria,
the collateral flow was of minor importance for the flow
velocity measurements in this study. Measurements of the
(FFR) by intracoronary pressure wire may be superior in accurate
determination of functional severity of coronary artery stenoses in
vessels with relevant collateral flow (7,23–25).

Since reangiography was not performed in all patients, we
are not able to quantify the degree of progression of CAD. On
one hand there might be some nonsymptomatic restenosis in
the patients who underwent PTCA, but on the other hand the
CFVR may have decreased in some patients with deferred
PTCA, but on the other hand the

Ideal coronary flow velocity reserve. We took the cutoff
value of 2.0 for “normal” CFVR due to findings in single-
photon emission computed tomography (SPECT) (20,21).
Although SPECT is an imperfect method for determination of
the hemodynamic significance of coronary artery stenosis, 2.0
is a clear-cut value for decision making in daily clinical practice. The FACTS Study Group found a cut point for
optimal sensitivity and specificity of CFVR at 1.7 in comparison
with SPECT and Doppler flow velocity measurements in
patients with moderate CAD (22). The DEBATE Study
showed a cutoff of 2.5 for CFVR immediately after PTCA to
predict the incidence of MACE in a retrospective analysis (8).
Thus, optimization of PTCA results according to a
CFVR ≥ 2.5 might reduce the rate of MACE during follow-up,
but this was not the aim of our study. However, the DEBATE
Study also indicates that decision making by angiographic
criteria is insufficient.

Safety and cost. Our data demonstrate the safety, feasibility
and clinical outcome of deferring angioplasty of coronary
artery stenosis associated with “normal” CFVR. The risk of an
adverse outcome was significantly lower among the 22 cases in
whom PTCA was deferred due to normal CFVR compared
with the patients who underwent angioplasty. The costs of
Doppler guide wire compared with the resources which can be
saved by deferring angioplasty in 30% of patients are much
lower especially if the higher incidence of re-PTCA are taken
into account.

Further trials should prove and establish this method for
adaptation in the daily catheter laboratory routine. Due to the
relatively small cohort, we are not able to show any difference
between single and multivessel disease. Multicenter trials with
greater numbers of patients could be a valid basis for replacing
other functional tests with CFVR-detection. In our study
measurements of CFVR identified those patients in whom it
was safe to defer angioplasty.

Other functional tests. Noninvasive tests for detecting
myocardial ischemia are associated with a great number of
false positive or negative results (6,13). There are several
factors influencing the predictive value of noninvasive stress
tests or reported angina pectoris at stress (14–16). Even
invasive examination by quantitative coronary angiography
remains an imperfect method to determine the impact of
coronary artery stenosis (17,18). Measurements of transles-
ional pressure gradient can also be used for analyzing the
hemodynamic significance of coronary artery stenosis (19).
In combination with analysis of flow velocity proximal to distal of
the stenosis, it is a valid parameter for clinical decision making
(5). Kern et al. showed the feasibility and safety of deferring
angioplasty in patients with normal translesional pressure-flow
velocity measurements in a study design similar to the one used
in our investigation. The average CFVR in the patients with
coronary artery stenosis of intermediate severity in whom
PTCA was deferred due to the translesional pressure-flow
velocity measurements was 2.0 ± 0.64. Although nearly half of
their patients had CFVR below two, they did not observe any
adverse outcome in patients with deferred PTCA.

Figure 2. The slopes reflect the relation between risk of major adverse
cardiac event (MACE: severe bleeding, re-PTCA, acute myocardial
infarction, coronary bypass surgery, sudden cardiac death) and benefit
(number of patients who are free of angina pectoris) in the PTCA
subgroup (n = 48) and the non-PTCA subgroup (n = 22).

Moreover, the DEBATE Study revealed that patients
with moderate CAD (22). The DEBATE Study
also indicates that decision making by angiographic
criteria is insufficient.
from functional testing of stenosis severity before elective PTCA. Measurements of CFVR can also be used to improve the result of PTCA beyond angiography (29). Physiologically guided angioplasty can help to reduce the incidence of major adverse cardiac events and the costs.

Conclusion. We conclude that determination of the CFVR is a valuable parameter for stratifying the hemodynamic significance of coronary artery stenosis. A "normal" CFVR can be found in about 30% of patients with angiographically significant stenoses who show an indication for PTCA due to stable angina pectoris or positive noninvasive stress test. PTCA can safely be deferred in patients with significant coronary stenosis but CFVR ≥ 2.0.

References