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Coronary Flow Reserve During Coronary Angioplasty in Patients With a Recent Myocardial Infarction: Relation to Stenosis and Myocardial Viability

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Objectives. **In the present study, we examined post-stenotic coronary flow before and after percutaneous transluminal coronary angioplasty (PTCA) in patients with and without a recent myocardial infarction (MI) and related it to stenosis severity and residual viability.**

Background. **Post-stenotic coronary blood flow velocity reserve (CFVR) has been used with success to estimate functional stenosis severity in patients with stable angina. However, in patients with a recent MI, the impaired coronary vasodilator response of the reperfused myocardium may substantially alter the flow dynamics of the infarct-related artery.**

Methods. **Distal coronary flow velocities were recorded before and after PTCA in 36 patients at day 13 ± 7 (mean ± SD) after acute MI and in 38 patients without MI. The CFVR was assessed by the ratio of distal hyperemic to baseline average peak velocity, using a 0.014-in. Doppler guide wire. Stenosis severity was analyzed by quantitative coronary angiography, and infarct size was assessed scintigraphically.**

Results. **For similar angiographic stenosis severity, pre- and post-PTCA values of CFVR were significantly lower in patients with than without MI: 1.22 ± 0.26 versus 1.50 ± 0.45 before PTCA ($p < 0.05$) and 1.72 ± 0.43 versus 2.21 ± 0.74 after PTCA, respectively ($p < 0.01$). Although CFVR increased significantly ($p < 0.0001$) after angiographically successful PTCA in both study groups, abnormal CFVR (≤2.0) was still observed in 80% of patients with MI and in 44% of those without MI (MI vs. no MI, $p = 0.001$). Patients with an extensive infarction (relative infarct size ≥50%) and those with a small infarction (relative infarct size <50%) had comparable levels of post-PTCA CFVR (1.6 ± 0.3 vs. 1.8 ± 0.5, p = NS). Among a variety of factors, angiographic stenosis severity was the most important determinant of CFVR in both study groups.**

Conclusions. **In patients with a recent MI, CFVR was significantly lower than in those without MI, both before and after PTCA. Besides the presence of this postreperfusion-related impairment of the coronary vasodilating response, CFVR was mainly influenced by stenosis severity and not by residual viability.**

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Coronary angiography is commonly used to assess the severity of coronary artery disease. However, coronary anatomy may not reflect the functional significance of coronary stenosis (1,2). Experimental studies have demonstrated (3,4) that coronary flow reserve is a reliable marker of the physiologic significance of a given coronary obstruction. The recent development of an intracoronary Doppler guide wire has facilitated routine measurement of coronary flow velocity and coronary flow velocity reserve (CFVR) both proximal and distal to coronary artery lesions (5). Recent clinical studies (6,7) in patients with angiographically intermediate coronary artery stenoses have demonstrated good correlation between Doppler-derived post-stenotic intracoronary flow reserve and stress perfusion scintigraphy with either thallium-201 or technetium-99m sestamibi. Furthermore, there is early clinical evidence (8,9) that Doppler flow measurements during percutaneous transluminal coronary angioplasty (PTCA) give important information about the short- and medium-term functional outcome of the early angioplasty result. Most of these studies evaluated patients with stable angina. Less is known with regard to coronary flow dynamics in patients with a myocardial infarction (MI). Experimental work on reperfusion models and recent clinical studies with perfusion imaging techniques have shown (10–12) that the coronary vasodilating response is severely impaired after a transient occlusion of the target vessel. To assess the extent of this impaired flow response of the reperfused myocardium and to study its effect on the coronary flow dynamics of the infarct-related artery during PTCA, flow velocities were recorded before and after PTCA in patients with a recent MI and were compared with flow velocity data from a matched control group of patients with stable angina and no MI. In addition, the relation of coronary

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Abbreviations and Acronyms

ANOVA = analysis of variance
APV = time-averaged peak velocity
CFVR = coronary flow velocity reserve
CSA = cross-sectional area
DS = diameter stenosis
DSVR = diastolic/systolic velocity ratio
MI = myocardial infarction
MLD = minimal lumen diameter
PTCA = percutaneous transluminal coronary angioplasty
SPECT = single-photon emission computed tomography

flow velocity reserve to angiographic stenosis severity and residual viability was examined.

Methods

Study patients. A total of 74 patients (56 men, 19 women; mean [±SD] age 63 ± 9 years, range 37 to 80) undergoing elective PTCA of nonocclusive significant stenosis (>50% diameter stenosis [DS]) in a native coronary artery were prospectively enrolled in the study. The decision to perform elective PTCA was based on angiographic and clinical findings. Patients with valvular disease, congestive heart failure and significant left ventricular hypertrophy, as defined electrocardiographically, were excluded from the study. Angiographic exclusions included collateral supply, bypass graft to the target vessel, ostial narrowing inducing wedging of the catheter, distal lesions with a small perfusion bed and lesions not eligible to be crossed by the Doppler coronary guide wire. In three patients with stable angina pectoris, repeated angioplasty was performed because of restenosis, so that in the total cohort of 74 patients, intracoronary flow velocity measurements were obtained for 77 lesions.

The study group included 36 patients with a recent (<1 month) MI and 38 patients without MI. Twenty-seven (75%) patients with MI received thrombolytic therapy, and 31 developed electrocardiographic evidence of a transmural infarction (Q wave in at least two leads or r/s wave in leads V_1 to V_2 >1). Clinical characteristics of both subgroups are summarized in Table 1. Evaluation of cardiac risk factors was based on the presence or absence of a serum cholesterol level ≥240 mg%, arterial hypertension, current smoking and diabetes mellitus. Cardiovascular medications (nitrates, beta-adrenergic blocking agents, calcium channel antagonists, antiplatelet agents) were continued as clinically indicated. Informed consent was obtained from all patients, and the protocol was approved by the institutional ethical committee of the University Hospital of Antwerp.

Catheterization procedure. Cardiac catheterization was performed on day 13 ± 7 (range 4 to 30) after acute MI. Diagnostic coronary arteriography was done with standard catheters and conventional orthogonal views. The left ventriculogram was obtained in the right and left anterior oblique projections with 20° of cranial angulation.

Table 1. Clinical Characteristics of Study Patients

	No MI (n = 38)	MI (n = 36)	p Value
Age (yr)	63 ± 9	62 ± 10	0.8
Male/female	28/10	27/9	0.9
Hypertension	10 (26)	12 (33)	0.5
Cholesterol (mg)	226 ± 43	212 ± 59	0.3
Diabetes mellitus	5 (13)	5 (14)	0.9
Smoker	11 (29)	17 (47)	0.1
No. of risk factors	1.1 ± 1.0	1.2 ± 0.8	0.7
1/2/3 VD	31/7/0	29/7/0	0.9
Ejection fraction (%)	70 ± 6	59 ± 12	< 0.0001
Medications			
Beta-blocker	25 (66)	28 (78)	0.3
Nitrates	22 (58)	21 (58)	0.9
Ca channel blocker	20 (53)	3 (8)	< 0.0001

Data presented are mean value ± SD, number of patients or number (%) of patients. Ca = calcium; MI = myocardial infarction; VD = vessel disease.

The angioplasty procedure was performed after intravenous administration of 10,000 U of heparin. A continuous infusion of intravenous isosorbide dinitrate (0.5 μg/kg body weight per min) and dextran (100 ml/h) was started 30 min before procedure.

Coronary flow velocity measurements were done with a 0.014-in. Doppler angioplasty guide wire (FloWire, Cardiometrics) after intracoronary administration of isosorbide dinitrate (1 mg). Continuous flow velocity data along with simultaneous electrocardiography and aortic pressure waveforms were displayed on the video monitor and recorded continuously on Super-VHS videotape.

Distal flow velocities were obtained at least 2 cm beyond the stenosis at baseline and again during coronary hyperemia induced by administration of intracoronary adenosine (18-μg bolus for the left main and 12-μg for the right coronary artery). The maximal hyperemic response after adenosine injection was automatically detected and reported on the video printer. Systolic, diastolic and mean arterial pressures and heart rate were recorded on a multichannel recorder (Siemens) during baseline conditions and 20 s after intracoronary injection of adenosine. Rate-pressure product (mm Hg × beats per min) was calculated as heart rate multiplied by systolic arterial pressure. After measurement of the hyperemic response, coronary angiography was performed to define the lumen diameter at the site of the Doppler sample volume. Angioplasty was then carried out and completed in accordance with standard clinical and angiographic judgment. Fifteen minutes after angiographically successful PTCA, baseline and hyperemic distal flow velocity data were again obtained as before angioplasty.

Angiographic data analysis. Coronary angiographic films were quantitatively analyzed with a computer-based Cardiovascular Angiography Analysis System (CAAS II, Pie Medical Data, Maastricht, The Netherlands), which has been previously described in detail (13). End-diastolic frames that showed the narrowest stenotic diameter were selected and digitized. The absolute diameter of the lesion (in mm) was determined using the tip of the guiding catheter as a scaling device. Stenosis

severity was calculated from the minimal lumen diameter (MLD) and a computer-estimated reference diameter and expressed as percent diameter stenosis (%DS) and minimal cross-sectional area (CSA). Significant *coronary artery stenosis* was defined as lumen diameter stenosis >50% in a major epicardial coronary artery or branch.

Left ventricular ejection fraction was calculated using end-diastolic and end-systolic frames in the 30° right anterior oblique projection. End-diastolic and end-systolic volumes were derived by the area–length ellipsoid method (14).

Coronary flow velocity data analysis. The Doppler guide wire was connected to the 15-MHz pulsed-Doppler velocimeter (FloMap, Cardiometrics), which analyzed on-line Doppler velocity spectra and calculated the temporal average of the instantaneous peak velocity waveform both during baseline conditions and during maximal hyperemia. Coronary flow velocity reserve was then computed as the ratio of hyperemic to baseline average peak velocity of the distal vessel. Although the Doppler guide wire measures only relative velocity changes and not the absolute volumetric flow, flow velocity measurements can be used as an accurate indicator of coronary flow reserve, provided that the vessel CSA is constant during hyperemia. Intracoronary bolus injection of adenosine does not modify coronary lumen diameter (15); therefore, CFVR should closely reflect volumetric coronary flow reserve. On the basis of previous studies (6,7), a CFVR ≤2.0 was considered abnormal.

A quantitative estimate of coronary flow (ml/min) distal to the lesion was calculated as the arterial CSA (mm^2) at the site of the Doppler sample volume multiplied by 1/2 of the time-averaged peak velocity (APV [cm/s]) times 0.6 (unit conversion factor). In addition, the diastolic/systolic velocity ratio (DSVR) was calculated from the ratio of the diastolic APV to the systolic APV.

Rest technetium-99m sestamibi single-photon emission computed tomography (SPECT). Scintigraphic studies were performed in patients with MI 6 ± 3 days (range 2 to 13) after angioplasty. Tomographic acquisition of the tracer distribution was performed 1 to 3 h after injection of 555 MBq of technetium-99m-labeled sestamibi by means of SPECT with a circular field rotating gamma camera (Sophycamera CF, Sopha Medical, Buc, France).

Regional Tc-99m sestamibi activity was visually analyzed on a 17-segment left ventricular model by consensus of two expert observers (B.K., M.C.) who had no knowledge of the angiographic and coronary flow data. For the purpose of the present study, a binary scintigraphic uptake score was used to assess viability. Segments showing normal or moderately reduced tracer activity (>50% of maximal activity) were considered *viable*. Segments with severe reduction of tracer activity (≤50% of maximal activity) were considered *necrotic*. Technetium-99m sestamibi has been shown (16,17) to be a good viability tracer at least in regions supplied by a vessel without severe residual stenosis. To avoid the effect of hypoperfusion due to severe residual stenosis on the total tracer activity within the infarct region, the scintigraphic study was performed after PTCA. Because no patient showed clinical evidence of an early restenotic process (recurrent angina or infarction) after PTCA, the infarct-related artery was assumed not to be severely stenotic at the time of the rest scintigraphic study.

Absolute infarct size was defined as the number of necrotic segments within the infarct risk area. The infarct risk area corresponded to the vascular territory distal to the infarct-related vessel stenosis and was assigned by carefully taking into account the localization of the lesion (proximal or mid) and the presence of major branches (diagonal, marginal, inferolateral, posterior descending), as previously described (18). *Relative infarct size* was expressed as the ratio of absolute infarct size to infarct risk area and was used as a marker of residual viability. Patients with a relative infarct size <50% were considered to have a *small infarction*, whereas a relative infarct size ≥50% indicated an *extensive infarction*.

Statistical analysis. Results are expressed as mean value ± SD. Demographic, angiographic and coronary flow variables for the two study groups were compared by chi-square analysis for categoric variables and by analysis of variance (ANOVA) for continuous variables. Comparison between both study groups of pre-PTCA and post-PTCA data was done by two-way repeated measures ANOVA with a post hoc Student-Newman-Keuls test to evaluate differences. To identify the determinants of CFVR, the relation between CFVR and angiographic, scintigraphic and clinical variables was examined by forward stepwise linear regression analysis, with $F_{enter} = 4$ and $F_{remove} = 3.9$. The relation between CFVR and stenosis severity was further assessed by polynomial regression analysis. A p value <0.05 was considered significant.

Results

Clinical data. There were no significant differences with regard to cardiovascular risk factors and extent of coronary artery disease (Table 1). Patients without MI had a higher ejection fraction (70 ± 6 vs. 59 ± 12, $p < 0.0001$) and were treated more frequently with calcium channel blockers (53% vs. 8%, $p < 0.0001$) than those with MI.

Hemodynamic data. Systolic blood pressure during PTCA was higher in patients without than in those with MI (129 ± 23 vs. 116 ± 23 mm Hg, $p < 0.01$), whereas heart rate was significantly higher in patients with MI (72 ± 12 vs. 66 ± 12, $p < 0.05$). Rate-pressure product did not differ significantly between study groups (MI: 8.6 ± 2.3 × 10^3 mm Hg/beats per min; no MI: 8.3 ± 2.2 × 10^3 mm Hg/beats per min). Systolic blood pressure, heart rate and rate-pressure product did not change significantly during adenosine-induced hyperemia (baseline: 126 ± 26 mm Hg, 70 ± 14 beats/min, 8.8 ± 2.4 × 10^3 mm Hg/beats per min; maximal hyperemia: 124 ± 24 mm Hg, 68 ± 14 beats/min, 8.4 ± 2.3 × 10^3 mm Hg/beats per min).

There were no complications related to intracoronary flow velocity measurements in any patient studied, except for transient total atrioventricular block during intracoronary adenosine administration in four patients (infarct-related ar-

Table 2. Angiographic and Hemodynamic Data for Target Lesions

	No MI (n = 41)	MI (n = 36)	p Value
Target vessel: RCA/LAD/LCx	10/24/7	12/16/8	0.5
Ref diam (mm)			
Pre-PTCA	2.8 ± 0.5	2.9 ± 0.6	0.4
Post-PTCA	2.8 ± 0.5	2.9 ± 0.6	
MLD (mm)			
Pre-PTCA	0.9 ± 0.3	1.0 ± 0.3	0.1
Post-PTCA	1.7 ± 0.4*	1.9 ± 0.5*	
%DS			
Pre-PTCA	65.8 ± 9.5	65.2 ± 10.1	0.2
Post-PTCA	38.2 ± 11.0*	34.6 ± 11.5*	
CSA (mm^2)			
Pre-PTCA	0.8 ± 0.5	0.9 ± 0.6	0.07
Post-PTCA	2.5 ± 1.2*	3.1 ± 1.7*	
Diam at Doppler site (mm)			
Pre-PTCA	2.3 ± 0.4	2.3 ± 0.6	0.05
Post-PTCA	2.3 ± 0.4	2.4 ± 0.7	
SBP (mm Hg)			
Pre-PTCA	127 ± 20	113 ± 24	< 0.05
Post-PTCA	132 ± 26	118 ± 23	< 0.05
DBP (mm Hg)			
Pre-PTCA	67 ± 10	64 ± 13	0.1
Post-PTCA	70 ± 12	65 ± 13	
MAP (mm Hg)			
Pre-PTCA	90 ± 16	85 ± 16	NS
Post-PTCA	95 ± 16†	87 ± 15	NS
HR (beats/min)			
Pre-PTCA	65 ± 10	69 ± 12	NS
Post-PTCA	66 ± 13	74 ± 13†	< 0.01
RPP × 10^3			
Pre-PTCA	8.5 ± 2.0	7.9 ± 2.0	0.5
Post-PTCA	8.7 ± 2.5	8.8 ± 2.3	

*$p < 0.0001$, †$p < 0.05$, post-PTCA versus pre-PTCA. Data presented are mean value ± SD or number of lesions. CSA = cross-sectional area; DBP = diastolic blood pressure; diam = diameter; %DS = percent diameter stenosis; HR = heart rate; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MAP = mean arterial pressure; MI = myocardial infarction; MLD = minimal lumen diameter; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; RPP = rate-pressure product; SBP = systolic blood pressure.

Table 3. Intracoronary Flow Velocity Measurements in Target Lesions

	No MI (n = 41)	MI (n = 36)	p Value
Basal APV (cm/s)			
Pre-PTCA	17.3 ± 6.6	15.5 ± 6.5	0.6
Post-PTCA	22.0 ± 8.9*	22.3 ± 8.0*	
Hyperemic APV (cm/s)			
Pre-PTCA	26.4 ± 13.0	19.0 ± 8.5	< 0.05
Post-PTCA	45.4 ± 16.0†	37.2 ± 11.7†	< 0.01
Basal DSVR			
Pre-PTCA	1.6 ± 0.8	1.6 ± 1.3	0.8
Post-PTCA	1.8 ± 0.9	1.4 ± 0.4	
Hyperemic DSVR			
Pre-PTCA	1.3 ± 0.7	1.5 ± 1.6	0.6
Post-PTCA	1.4 ± 0.3	1.4 ± 0.4	
Basal flow (ml/min)			
Pre-PTCA	21.7 ± 11.0	20.9 ± 14.0	0.5
Post-PTCA	26.7 ± 13.6‡	31.4 ± 18.4*	
Hyperemic flow (ml/min)			
Pre-PTCA	34.0 ± 22.8	25.7 ± 17.6	0.3
Post-PTCA	56.2 ± 29.1*	53.0 ± 30.7†	
CFVR			
Pre-PTCA	1.50 ± 0.45	1.22 ± 0.22	< 0.05
Post-PTCA	2.21 ± 0.74†	1.72 ± 0.43*	< 0.01
%DS			
<35	2.21 ± 0.66 (n = 17)	1.84 ± 0.52 (n = 19)	NS
35–50	2.24 ± 0.81 (n = 23)	1.60 ± 0.27 (n = 18)	< 0.01
51–65	1.81 ± 0.45 (n = 20)	1.33 ± 0.33 (n = 16)	< 0.01
>65	1.23 ± 0.19 (n = 22)	1.11 ± 0.08 (n = 19)	< 0.05

*$p < 0.001$, †$p < 0.0001$, ‡$p < 0.05$, post-PTCA versus pre-PTCA. Data presented are mean value ± SD or number of lesions. APV = average peak velocity; CFVR = coronary flow velocity reserve; DSVR = diastolic/systolic velocity ratio; other abbreviations as in Table 2.

tery in three), which lasted a maximum of 3 s, with no hemodynamic compromise.

Angiographic data (Table 2). The distribution of target arteries studied was similar, as was the reference diameter of the target lesion and the diameter at the Doppler site, in each group. Angiographic severity of the lesions before and after PTCA (expressed as %DS), CSA and MLD did not differ significantly between study groups. In both groups, the mean %DS of the lesions decreased significantly as a result of successful balloon angioplasty (65.8 ± 9.5% and 65.2 ± 10.1% before PTCA; 38.2 ± 11% and 34.6 ± 11.5% after PTCA) in the noninfarct-related and infarct-related vessels, respectively ($p < 0.001$).

Intracoronary Doppler flow velocity data (Table 3). After PTCA, APV values, coronary volumetric flow (particularly during hyperemia) and CFVR increased significantly in both study groups: CFVR increased from 1.50 ± 0.45 to 2.21 ± 0.74 in patients without MI and from 1.22 ± 0.26 to 1.73 ± 0.43 in those with MI ($p < 0.0001$ for both).

Comparison of coronary flow velocity characteristics between study groups revealed no significant differences in infarct-related and noninfarct-related vessels for rest APV values. However, hyperemic APV values were significantly lower in patients with than in those without MI, both before PTCA (19.0 ± 8.5 vs. 26.4 ± 13.0 cm/s, $p < 0.05$) and after PTCA (37.2 ± 11.7 vs. 45.4 ± 16.0 cm/s, $p < 0.01$).

Furthermore, a significantly different CFVR value was observed in patients with versus without MI both before (1.22 ± 0.26 vs. 1.50 ± 0.45, $p < 0.05$) and after PTCA (1.72 ± 0.43 vs. 2.21 ± 0.74, $p < 0.01$) (Fig. 1). Further data analysis after categorizing the study groups according to different classes of stenosis severity (%DS <35, 35 to 50, 51 to 65 and >65) revealed that CFVR remained consistently lower in patients with MI, independent of stenosis severity (Table 3).

The majority of patients (>90%) had abnormal CFVR values (≤2.0) before PTCA. After angiographically successful

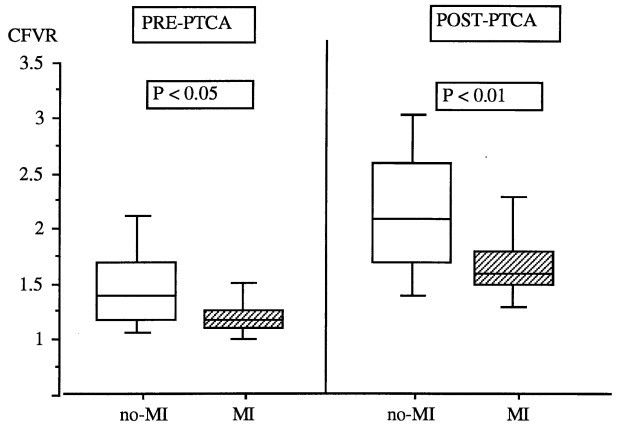

Figure 1. Boxplot showing distribution (10th, 25th, 50th, 75th, 90th percentiles) of CFVR obtained before and after PTCA in patients with (**hatched boxes**) and without MI (**open boxes**). A significantly lower CFVR value was observed in patients with a recent MI both before and after PTCA.

PTCA, CFVR values remained abnormal in 29 patients with MI (80%) and in 18 without MI (44%) ($p = 0.001$, MI vs. no MI).

The phasic velocity pattern (Table 3, DSVR values) did not differ between study groups. The right coronary artery tended to have less diastolic predominance than the left anterior descending coronary artery, particularly after PTCA, although the difference did not reach significance (post-PTCA DSVR: 1.3 ± 0.3 vs. 1.8 ± 0.4 for no MI; 1.3 ± 0.3 vs. 1.9 ± 0.9 for MI, respectively).

Determinants of CFVR. In both study groups, CFVR was related to a variety of factors, including clinical, hemodynamic and angiographic factors and residual viability, expressed as relative infarct size. From all studied factors, forward stepwise linear regression analysis selected angiographic stenosis severity as the most important independent determinant of CFVR both in patients with and without MI (Table 4). Besides angiographic stenosis severity, heart rate was the only other independent factor that significantly affected CFVR in both study groups.

Table 4. Determinants of Coronary Flow Velocity Reserve: Stepwise Regression Analysis

Variable	No MI (F to enter)	MI (F to enter)
%DS	34.3	35.2
HR (beats/min)	15.0	4.6
Relative infarct size (%)	—	0.5
Time delay: MI to PTCA (days)	—	0.7
SBP (mm Hg)	1.1	1.7
RPP (mm Hg × beats/min)	0.4	1.5
Ejection fraction (%)	0.7	0.3
Cholesterol (mg%)	3.8	0.7
Risk factors	0.005	2.0
Age	0.6	0.2
Intake of Ca channel blocker	1.3	0.2

Abbreviations as in Table 2; — = not applicable.

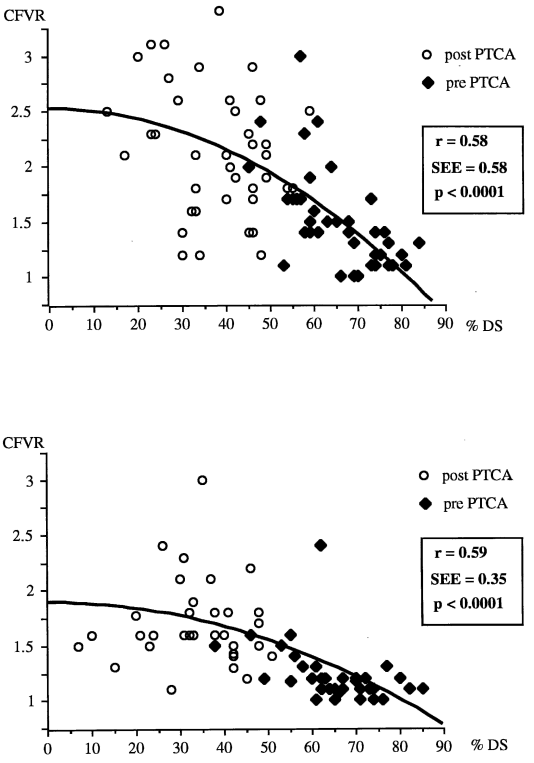

Figure 2. Scatterplots showing relation of CFVR to stenosis severity (%DS) for all measured lesions before and after PTCA. A significant but moderate nonlinear correlation was found both in patients without (**top**) and with MI (**bottom**): $y = a - bx^2$, where $a = 2.5$, and $b = 2.3 \times 10^{-4}$ for patients without MI, and $a = 1.8$ and $b = 1.4 \times 10^{-4}$ for patients with MI.

Nonlinear regression analysis showed a significant but moderate correlation between CFVR and stenosis severity (%DS) for all lesions measured (before and after PTCA: $r = 0.59$, $p < 0.0001$ for MI; $r = 0.58$, $p < 0.0001$ for no MI) (Fig. 2). Further analysis revealed that the relation between CFVR and %DS is mainly determined by pre-PTCA measurements because no significant correlation was found between CFVR and stenosis severity after PTCA in both study groups ($r = 0.05$ and $r = 0.15$ for patients with and without MI, respectively).

In the present study, relative infarct size, which was used as a scintigraphic marker of residual viability, averaged $49 \pm 34\%$ (range 0% to 100%). In the lesions studied after PTCA, CFVR was not correlated with the amount of residual viability ($r = 0.07$, p = NS) (Fig. 3). Patients with an extensive infarct (relative infarct size ≥50%) and those with a small infarct relative infarct size <50%) had comparable levels of post-PTCA CFVR (1.6 ± 0.3 vs. 1.8 ± 0.5, p = NS). In addition, APV values and coronary flow variables during baseline conditions and during maximal hyperemia showed a poor nonsignificant correlation with residual viability. The time delay between acute MI and coronary flow measurements during angioplasty did not significantly affect CFVR ($r = 0.12$ both before and after PTCA).

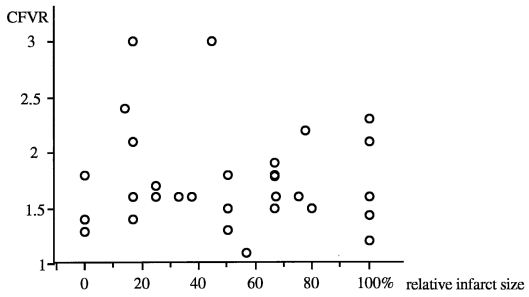

Figure 3. Scatterplot showing the relation of CFVR after PTCA to relative infarct size, as assessed scintigraphically. No significant correlation was found (r = 0.07, p = NS).

Discussion

In the present study we investigated the post-stenotic flow velocity characteristics of the infarct-related vessel before and after PTCA. We demonstrated that CFVR values were significantly lower in patients with a recent MI than in those without MI and that CFVR remained severely impaired even after angiographically successful PTCA. Despite the presence of this postreperfusion impairment of the coronary vasodilating response, CFVR was mainly related to stenosis severity, not to the amount of residual viability.

Postreperfusion-related impairment of coronary vasodilating response. In the present study, CFVR values were much lower in infarct-related than in noninfarct-related vessels over a wide range of stenosis severity. Baseline characteristics did not differ significantly between study groups, except for heart rate and systolic blood pressure. It has been shown (19) that major hemodynamic changes may induce a substantial decrease in CFVR, mainly through an increase in baseline coronary flow blood flow. Because differences in heart rate and systolic blood pressure were small, and since baseline APV did not differ between both groups, it is unlikely that the observed differences in CFVR were due to differences in hemodynamic status between both study groups.

The lower coronary flow reserve values in patients with MI were related to lower hyperemic APV values, suggesting impaired vessel resistance in the reperfused myocardium. Differences in calculated hyperemic blood flow values between the two study groups were less prominent, probably due to the high variation induced by individual disparity of the vessel size at the Doppler site.

Impairment of coronary flow reserve in patients with a recent MI has been recognized by previous investigators using positron emission tomography or videodensitometry (12,20) and may reflect the impaired myocardial vasodilating response from postreperfusion-related microvascular injury (10,21). Prolonged ischemia, resulting in cellular injury, may initiate local inflammatory responses, including accumulation of neutrophils and production of leukotrienes, thereby increasing vascular permeability (10,22,23). Increasing vascular permeability completes a vicious circle by exacerbating interstitial edema and extravascular resistance to blood flow. Beyond the microvascular injury, patients with a recent MI may also show an abnormal vasomotor response with inappropriate constriction of the small resistance vessels as a result of the release by platelets of vasoactive substances (thromboxane A_2, serotonin, thrombin) (10,24). Thus, the reduced CFVR in patients with a recent MI may reflect severe impairment of the functional integrity of the microcirculation resulting from microvascular damage or abnormal vasomotor response of the small resistance vessels.

It has recently been shown (12,25,26) that the coronary vasodilatory reserve after acute MI is most severely impaired early after reperfusion and improves gradually over 6 months without reaching normal values, suggesting that the impaired CFVR is mediated by a process of microvascular stunning that is partially reversible over time. In the present study, no significant correlation was found between CFVR and the time delay between MI and flow velocity measurements, suggesting that no great spontaneous changes had occurred in the study patients during the subacute phase (day 4 to 30) of an acute MI.

Determinants of CFVR. Coronary blood flow and the coronary flow reserve depend on many factors, including variable coronary stenosis geometry, hemodynamic factors, left ventricular hypertrophy, MI, resistive vessel dysfunction resulting from atherosclerosis and extent of collateral circulation (19,27–31). Among a variety of factors evaluated in the present study, angiographic stenosis severity was the most important determinant of CFVR both in patients with and without MI with a correlation coefficient of r = 0.59 and r = 0.58, respectively. Lack of close correlation between angiographic stenosis severity and CFVR is consistent with previous studies performed in patients without a previous MI (13) and may indicate that quantitative angiographic analysis of stenosis severity does not always reflect the functional significance of the target stenosis. This finding was recently demonstrated by Miller et al. (6) and Joye et al. (7), who reported intracoronary Doppler flow velocity measurements in noninfarct-related arteries with intermediate stenosis severity and found that the Doppler-derived post-stenotic flow reserve correlated better with stress perfusion scintigraphy than with angiographic stenosis severity. Furthermore, CFVR measurement reflects both epicardial and myocardial flow capacity, and alterations in the microcirculation will interfere with the relation between CFVR and angiographic stenosis severity and may thus account for the data scatter.

In the present study the relation between CFVR and angiographic stenosis severity was determined mainly by pre-PTCA measurements, which is in agreement with other angioplasty studies performed in noninfarct-related arteries (32–34). Furthermore, a substantial proportion of patients had abnormal CFVR values (≤2.0) after successful angioplasty (44% for no MI, 80% for MI). Reasons for the high rate of abnormal post-PTCA CFVR levels, even in patients without MI, include inadequate lumen expansion (35), abnormalities in autoregulation resulting from long-standing ischemia with release of local factors that affect coronary vasomotor tone (24,36) and an increase in baseline flow that would obscure significant

changes in the hyperemic/baseline flow ratio (33,37). We attempted to prevent changes in vasomotor tone by inducing constant maximal epicardial coronary vasodilation by means of intracoronary and intravenous administration of isosorbide dinitrate. Furthermore, CFVR measurement after PTCA were obtained 15 min after the last inflation, allowing the return of baseline APV values to the steady state.

Stepwise linear regression analysis indicated heart rate as second independent determinant of CFVR in both study groups. The heart rate dependency of CFVR has been shown in studies assessing the variability and reproducibility of flow velocity measurements (19,31,38).

In the present study, coronary flow measurements, both during baseline conditions and maximal hyperemia, were not related to the amount of residual viability as assessed scintigraphically and could not discriminate patients with an extensive infarction from those with a small infarction. These data suggest that the coronary vasodilating capacity was not affected by the amount of microvascular necrosis and support the idea that impaired CFVR is instead related to the degree of injury of the remaining microvascular circulation. Until now, only few data are available that related intracoronary Doppler flow measurements with viability. A recent study by Kim et al. (39) in small number of post-MI patients suggested that CFR measurements during diagnostic catheterization might be useful to predict functional recovery. However, functional recovery does not always equate residual viability because the process of functional recovery is also dependent on other factors, including severity of the residual infarct-related stenosis (40). Furthermore, most of these patients had significant infarct-related stenosis, which might generate some uncertainty, especially in small series, as to whether disparities in coronary flow reserve corresponded to the presence or absence of functional recovery and not to differences in epicardial vessel resistance. To avoid the confounding effect of residual stenosis on the relation between coronary flow reserve and viability, only post-PTCA coronary flow reserve values were analyzed for that purpose in the present study.

The relation between flow and viability has mainly been investigated in studies using positron emission tomography with nitrogen-13 ammonia as the flow tracer and fluorine-18 fluoredoxyglucose as the viability tracer (41–44). In those studies, regional blood flow was lower in nonviable than viable regions. However, these studies focused on regional flow, whereas in the present study, flow variables were measured within the infarct-related artery, which reflects a weighted average of the flow characteristics of different areas (viable and nonviable) within the region supplied by the target vessel. An additional explanation for the lack of correlation between flow and viability in the present study is the presence of high data scatter due to variations in hemodynamic status and vessel size in the study patients.

Limitations of the study. Several limitations of the present study deserve further consideration. Coronary flow velocity measurements of the infarct region were compared with flow velocity measurements of normal myocardial regions by comparing data from patients with MI with those from patients without MI. Flow velocity measurements during PTCA of a noninfarct-related vessel stenosis in the same patients might have allowed more accurate comparison but was not feasible because most patients with MI had single-vessel disease or noninfarct-related lesions not suitable for PTCA. Inaccuracies in data interpretation, related to a nonpaired comparative study design, could be restricted to a minimum because both study groups were well matched with regard to clinical, hemodynamic and angiographic variables.

The technical limitations of obtaining satisfactory flow velocity signals have been described in detail elsewhere (7,33,45). We tried to avoid these limitations by careful patient selection (e.g., patients with a narrow ostium, tortuous target vessel or multiple serial distal lesions were excluded) and by appropriate positioning of the Doppler guide wire away from regions of nonlaminar flow (e.g., no Doppler sampling at the site of a great branch or directed to the vessel wall).

Estimation of residual viability was based on a semiquantitative assessment of infarct size and infarct risk area. Although quantitative analysis allows more accurate distinction between viable and necrotic areas, it is unlikely that the use of more sophisticated image analysis techniques would have altered the finding that CFVR was unrelated to myocardial viability.

Finally, CFVR measurements were performed 4 to 30 days after acute MI. In view of a possible time-dependent change in CFVR after MI, our data cannot be extrapolated to CFVR measurements carried out very early (<48 h) or late (>1 month) after the acute MI.

Clinical implications. Identification of myocardial viability and residual ischemia after MI is highly relevant to avoid inappropriate mechanical interventions in patients who have angiographically significant coronary artery stenosis. The present study demonstrated that intracoronary flow velocity measurements were not able to assess post-MI residual viability. With regard to detection of ischemia within the infarct region, our data emphasized that the commonly used coronary flow reserve criteria for ischemia, based on studies in patients with stable angina, cannot be applied to patients with MI because of the impaired vasodilating capacity of the reperfused myocardium. Other, probably lower, reference values of coronary flow reserve remain to be determined in patients with a recent MI before its use can be recommended for the functional assessment of infarct-related vessel stenosis.

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References

1. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;310:819–24.
2. Marcus M, Skorton D, Johnson M, et al. Visual estimates of percent

diameter coronary stenosis: a battered gold standard. J Am Coll Cardiol 1988;11:882–5.

3. Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation. I. Physiologic basis and experimental validation. Am J Cardiol 1978;41:267–78.
4. Gould K, Kirkeeide R, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. J Am Coll Cardiol 1990;15:459–74.
5. Doucette J, Corl P, Payne H, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. Circulation 1992;85:1899–911.
6. Miller D, Donohue T, Younis L, et al. Correlation of pharmacological Tc-99m sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. Circulation 1994;89:2150–60.
7. Joye J, Schulman D, Lasorda D, Farah T, Donohue B, Reichek N. Intracoronary Doppler guide wire versus stress single-photon emission computed tomographic thallium-201 imaging in assessment of intermediate coronary stenosis. J Am Coll Cardiol 1994;24:940–7.
8. Serruys P, Di Mario C, Meneveau N, et al. Intracoronary pressure and flow velocity from sensor tip guidewires: a new methodological comprehensive approach for the assessment of coronary hemodynamics before and after interventions. Am J Cardiol 1993;71:41D–53D.
9. Di Mario C, Piek J, Vrints C, et al. Are flow velocity measurements after percutaneous transluminal coronary angioplasty predictive of recurrence of angina or of positive exercise stress test early after balloon angioplasty? [abstract]. Eur Heart J 1995;16 Suppl:216.
10. Kloner R, Giacomelli F, Alker K, Hale S, Matthews R, Bellows B. Influx of neutrophils into the walls of large epicardial coronary arteries in response to ischemia/reperfusion. Circulation 1991;84:1758–72.
11. Bolli R, Triana J, Jeroudi M. Prolonged impairment of coronary vasodilation after reversible ischemia: evidence for microvascular "stunning." Circ Res 1990;67:332–43.
12. Uren N, Crake T, Lefroy D, De Silva R, Davies G, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. N Engl J Med 1994;331:222–7.
13. Serruys W, Zijlstra F, Laarman G, Reiber H, Beatt K, Roelandt J. A comparison of two methods to measure coronary flow reserve in the setting of coronary angioplasty: intracoronary blood flow velocity measurements with a Doppler catheter, and digital subtraction cineangiography. Eur Heart J 1989;10:725–36.
14. Fifer FA, Grossman W. Measurement of ventricular volumes, ejection fraction, mass, wall stress, and regional wall motion. In: Grossman WBD, ed. Cardiac Catheterization, Angiography and Intervention. London: Lea & Febiger, 1991:300–7.
15. Kern M, Deligonul U, Tatineni S, Serota H, Aguirre F, Hilton T. Intravenous adenosine: continuous infusion and low dose bolus administration for determination of coronary vasodilator reserve in patients with and without coronary artery disease. J Am Coll Cardiol 1991;18:718–29.
16. Dilsizian V, Rocco T, Strauss H, Boucher C. Technetium-99m isonitrile myocardial uptake at rest: relation to severity of coronary artery stenosis. J Am Coll Cardiol 1989;14:1673–7.
17. Claeys M, Rademakers F, Vrints C, et al. Comparative study of rest technetium-99m sestamibi SPECT and low dose dobutamine stress echocardiography for the early assessment of myocardial viability after acute myocardial infarction: importance of the severity of the infarct related stenosis. Eur J Nucl Med 1996;23:748–55.
18. Claeys M, Vrints C, Krug B, et al. Adenosine technetium-99m sestamibi SPECT for the early assessment of jeopardized myocardium after acute myocardial infarction. Eur Heart J 1995;16:1186–94.
19. Hongo M, Nakatsuka T, Watanabe N, et al. Effects of heart rate on phasic coronary blood flow pattern and flow reserve in patients with normal coronary arteries: a study with an intravascular Doppler catheter and spectral analysis. Am Heart J 1994;127:545–51.
20. Suryapranata H, Zijlstra F, MacLeod D, Van den Brand M, De Feyter P, Serruys P. Predictive value of reactive hyperemic response on reperfusion on recovery of regional myocardial function after coronary angioplasty in acute myocardial infarction. Circulation 1994;89:1109–17.
21. Kloner R, Ganote C, Jennings R. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496–508.
22. Cobb F, McHale P, Rembert J. Effects of acute cellular injury on coronary vascular reactivity in awake dogs. Circulation 1978;57:962–8.
23. Engler R. Free radical and granulocyte-mediated injury during myocardial ischemia and reperfusion. Am J Cardiol 1989;63:19E–23E.
24. Willerson J, Golino P, Eidt J, Campbell W, Buja L. Specific platelet mediators and unstable coronary artery lesions: experimental evidence and potential clinical implications. Circulation 1989;80:198–205.
25. Ishihara M, Sato H, Tateishi H, et al. Time course of impaired coronary vasodilatory reserve after reperfusion in acute myocardial infarction [abstract]. J Am Coll Cardiol 1995;25:208A.
26. Yamaguchi H, Atsuchi Y, Arima S, Nakao S, Tanaka H. Effect of direct angioplasty on coronary flow reserve in acute myocardial infarction [abstract]. J Am Coll Cardiol 1995;25:207A.
27. Uren N, Marraccini P, Gistri R, DeSilva R, Camici P. Altered coronary vasodilator reserve and metabolism in myocardium subtended by normal arteries in patients with coronary artery disease. J Am Coll Cardiol 1993;22:650–8.
28. Pichard A, Gorlin R, Smith H, Ambrose J, Meller J. Coronary flow studies in patients with left ventricular hypertrophy of the hypertensive type. Am J Cardiol 1981;47:547–54.
29. Cleary R, Ayon D, Moore N, DeBoe S, Mancini G. Tachycardia, contractility and volume loading alter conventional indexes of coronary flow reserve, but not the instantaneous hyperemic flow versus pressure slope index. J Am Coll Cardiol 1992;20:1261–9.
30. Zeiher A, Drexler H, Wollschläger H, Just H. Endothelial dysfunction of the coronary microvasculature is associated with impaired coronary blood flow regulation in patients with early atherosclerosis. Circulation 1991;84:1984–92.
31. McGinn A, White C, Wilson R. Interstudy variability of coronary flow reserve: influence of heart rate, arterial pressure, and ventricular preload. Circulation 1990;81:1319–30.
32. Sunamura M, Vrints C, Probst P, et al. Do angiographic measurements of stenosis severity correlate with Doppler flow reserve? Effect of balloon angioplasty [abstract]. J Am Coll Cardiol 1995;25:153A.
33. Segal J, Kern M, Scott N, et al. Alterations of phasic coronary artery flow velocity in humans during percutaneous coronary angioplasty. J Am Coll Cardiol 1992;20:276–86.
34. Wilson F, Laughlin D, Ackell P, et al. Subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 1985;72:82–92.
35. Ge J, Erbel R, Zamorano J, Kearney P, Görge G, Meyer J. Improvement of coronary morphology and blood flow after stenting: assessment by intravascular ultrasound and intracoronary Doppler. Int J Card Imaging 1995;11:81–7.
36. Vanhoutte P, Houston D. Platelets, endothelium, and vasospasm. Circulation 1985;72:728–34.
37. Uren N, Crake T, Lefroy D, de Silva R, Davies G, Maseri A. Delayed recovery of coronary resistive vessel function after coronary angioplasty. J Am Coll Cardiol 1993;21:612–21.
38. Di Mario C, Gil R, Serruys P. Long-term reproducibility of coronary flow velocity measurements in patients with coronary artery disease. Am J Cardiol 1995;75:1177–80.
39. Kim H, Tahk S, Shin J, et al. Coronary flow reserve in infarct related artery and myocardial viability in patients with recent myocardial infarction [abstract]. Circulation 1995;92 Suppl:2870.
40. Sheehan F, Mathey D, Schofer J, Dodge H, Bolson E. Factors that determine recovery of left ventricular function after thrombolysis in patients with acute myocardial infarction. Circulation 1985;71:1121–8.
41. Gewirtz H, Fischman A, Abhraham S, Gilson M, Strauss H, Alpert N. Positron emission tomographic measurements of absolute regional myocardial blood flow permits identification of nonviable myocardium in patients with chronic myocardial infarction. J Am Coll Cardiol 1994;23:851–9.
42. Maes A, Van de Werf F, Nuyts J, Bormans G, Desmet W, Mortelmans L. Impaired myocardial tissue perfusion early after successful thrombolysis: impact on myocardial flow, metabolism, and function at late follow-up. Circulation 1995;92:2072–8.
43. Vanoverschelde J, Melin J, Bol A, et al. Regional oxidative metabolism in patients after recovery from reperfused anterior myocardial infarction: relation to regional blood flow and glucose uptake. Circulation 1992;85:9–21.
44. Marzullo P, Parodi O, Sambuceti G, et al. Residual coronary reserve identifies segmental viability in patients with wall motion abnormalities. J Am Coll Cardiol 1995;26:342–50.
45. Torn C, Donohue T, Kern M. Normal coronary flow velocity patterns: considerations of artifacts, arrhythmias, and anomalies. Cathet Cardiovasc Diagn 1995;34:337–46.