PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY FLOW RESERVE

The effect of coronary angioplasty on coronary flow reserve

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ABSTRACT To determine the effects of coronary angioplasty on coronary flow reserve (CFR), we studied 32 patients before and immediately after single-vessel coronary angioplasty and 31 patients evaluated late after angioplasty (7.5 ± 1.2 months, mean ± SEM). The geometry (percent area stenosis and minimal cross-sectional area) of each lesion was determined by quantitative coronary angiography (Brown/Dodge method) and the integrated optical density was measured by videodensitometry. CFR was measured with a No. 3F coronary Doppler catheter placed immediately proximal to the lesion and a maximally vasodilating dose of intracoronary papaverine. The translesional pressure gradient was obtained in all lesions before and immediately after angioplasty and in 18 of 31 vessels late after angioplasty. CFR immediately after angioplasty returned to normal levels (>3.5 peak/resting velocity ratio) in 14 of 31 patients and was improved, although not normalized, in the remaining 17 patients. CFR immediately after dilation was not significantly correlated with any of the angiographic variables of arterial stenosis nor the resting pressure gradient. Moreover, the pressure gradient and absolute distal coronary pressure at peak hyperemia were not significantly different in vessels with normal and those with abnormal flow reserve immediately after dilation, suggesting that the residual stenosis did not significantly limit hyperemia. Late after angioplasty, however, a significant relationship emerged between CFR and all four indexes of residual arterial stenosis (percent area stenosis r = .70, p < .01; minimum arterial cross-sectional area r = .70, p < .01; integrated optical density r = .60, p < .01; and translesional pressure gradient r = .77, p < .01). Furthermore, in the absence of restenosis, CFR eventually normalized in all patients. These findings demonstrate that in one-half of patients there is a transient reduction in coronary flow reserve immediately after angioplasty. In the absence of restenosis, coronary flow reserve later normalizes. Consequently, measurements of coronary flow reserve immediately after angioplasty may not reflect the eventual success of the procedure in removing physiologic obstruction to coronary blood flow.


ALTHOUGH coronary angioplasty has been shown to increase coronary luminal cross-sectional area, reduce the translesional pressure gradient, ameliorate the symptoms of myocardial ischemia, and normalize previously positive noninvasive studies of provokable myocardial ischemia (e.g., exercise electrocardiographic, thallium-201 scintigraphic, and diastolic ventricular function studies), its efficacy in restoring normal coronary flow reserve has been difficult to assess.

It has been proposed that measurements of coronary flow reserve be used during angioplasty to determine when physiologically significant obstruction to coronary blood flow has been removed. One group of investigators, however, has reported that flow reserve in dilated coronary arteries, although improved, was still depressed compared with that in normal vessels. They attributed this failure of coronary reserve to normalize to the effects of diffuse residual atherosclerosis. Other investigators, however, have found flow reserve to normalize immediately after dilation.

The explanation for these prior inconsistent results might reside in methodologic difficulties in measuring maximal coronary flow reserve, problems in quanti-

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tating the extent of residual arterial stenosis, and the
effects of temporal factors that may transiently alter
coronary hemodynamics immediately after the proce-
dure. Each technique previously used to measure cor-
onary reserve tends to underestimate maximal coronary
hyperemia; consequently, it might have been difficult
to distinguish between normal and mildly to moder-
ately reduced coronary reserve after dilation.12–14
Additionally, flow reserve in previously reported
patients might have failed to normalize because the
procedure was not entirely successful in removing the
obstruction to hyperemic blood flow. We have previ-
ously shown that coronary flow reserve in patients with
limited coronary artery disease (similar to those typ-
cally suitable for angioplasty) is highly dependent on
the degree of arterial stenosis determined by quanti-
tative coronary angiography.15 Finally, temporal fac-
tors that might cause transient alterations in the cor-
onary circulation were not evaluated (e.g., transiently
increased resting coronary blood flow, intraluminal
thrombosis, etc.).

The recent development and validation of a small
subselective coronary Doppler catheter and character-
ization of the dose-response kinetics of intracoronary
papaverine have enabled repeated measurements of
coronary flow reserve in individual vessels of patients
undergoing cardiac catheterization.16, 17 The purpose
of this study was to determine the impact of coronary
angioplasty on coronary flow reserve both immediately
and late after coronary dilation and to relate the changes
in coronary flow reserve to changes in quantitatively
determined arterial stenosis, the translesional pressure
gradient, and time.

Methods

Patient selection. We examined the effect of a coronary
stenosis on coronary flow reserve and hemodynamics in three
settings: immediately before coronary angioplasty (n = 32),
immediately after coronary angioplasty (n = 31), and late after
angioplasty (n = 31). The composition of each group is
described below.

Patients studied before and immediately after angioplasty.
Thirty-two sequential patients (28 men and four women) under-
going single-vessel coronary angioplasty and meeting the cri-
teria outlined below were studied. Each patient had a single
lesion in the coronary vessel under study (10 left anterior
descending, 11 left circumflex, and 11 right coronary arteries)
and no more than three discrete stenoses (>50% diameter ste-
nosis by visual inspection) in all coronary vessels. Twenty-six
patients had single-vessel (single lesion) coronary artery disease
and six had discrete obstructive disease in two coronary arteries.
In each patient with two-vessel disease, the dilated lesion was
judged visually by the operator to have the most severe stenosis.

Sixteen patients had unstable angina pectoris defined as (1)
new-onset angina (less than 4 weeks duration), (2) an increase
in the frequency of previously stable angina by two or more
Canadian Heart Association functional classes, or (3) angina of
new onset at rest. The remaining 16 had Canadian Heart Asso-
ciation functional class 3 or 4 stable angina.

One patient suffered abrupt coronary occlusion during angi-
oplasty that was treated with emergency coronary bypass surgery
and was not restudied immediately after angioplasty.

Patients studied late after coronary angioplasty. Thirty-
one consecutive patients (29 men and two women) meeting the
criteria outlined below and undergoing angiography for the
assessment of coronary restenosis 4 to 49 months (mean 7.4 ±
1.2 months) after angioplasty were selected for study. Each
patient had undergone prior dilation of a single, discrete stenosis
in a major coronary vessel (12 left anterior descending, 10 left
circumflex, and nine right coronary artery) and no more than
three focal stenoses (>50% diameter stenosis, visual inspection)
in all coronary vessels. Seventeen patients had single-vessel
(single lesion) coronary artery disease; 14 patients had two-
vessel (two or three lesions) obstructive coronary disease, but
only one stenosis in the previously dilated artery. Twenty-five
patients developed recurrent chest pain after angioplasty. Sixteen
patients had an abnormal noninvasive study suggesting the
presence of provokable myocardial ischemia (exercise electro-
cardiography or 201TI scintigraphy).

Twelve of the 31 patients had been previously studied before
and immediately after coronary angioplasty. In these patients,
repeat angiography was performed for the assessment of resten-
osis. Seven patients had developed recurrent chest pain and five
were asymptomatic.

Entry criteria. Before measurement of coronary flow re-
serve, each patient underwent M mode and cross-sectional eco-
cardiographic examinations to exclude ventricular hypertrophy
and valvular heart disease. Left ventricular function was shown
to be normal in each patient by contrast or equilibrium radio-
nuclide ventriculography (left ventricular ejection fraction
>50%; normal regional wall motion).

Patients with abnormalities that might affect the vasodilator
capacity of the arteriolar vasculature were excluded from the study.
These included: (1) historical or electrocardiographic evidence of
myocardial infarction, (2) left ventricular hypertrophy (septal or
posterior wall thickness >1.1 cm by echocardiography or left
ventricular mass >130 g/m2 by cine computed tomography [Ima-
tron, Inc.]),18 (3) left ventricular dysfunction (left ventricular
ejection fraction <50% or focal wall motion abnormality), (4)
valvular heart disease, (5) angiographic findings suggestive of
intraluminal thrombus or filling defect,19 (6) left main coronary
stenosis or severe proximal lesions precluding safe intracorony
catheterization, (7) angiographically apparent collateral circulation
from the vessel under study to an adjacent perfusion field, and (8)
lesions in the distal vasculature not accessible to Doppler catheter
catheterization (usually the right coronary artery beyond the posterior
descending origin or the left anterior descending beyond the sec-
ond diagonal branch). Additionally, arteries in which a branch
vessel of greater than 12% of the cross-sectional area of the parent
vessel arose immediately proximal to the coronary lesion were not
studied.

Measurements obtained from patients with coronary arterial
stenoses were compared with flow reserve measurements
obtained in 14 patients with normal coronary arteries meeting the
criteria described above. Data from these patients have been
previously reported.17

All studies were approved by the Institutional Review Boards
of the University of Iowa and the University of Minnesota
and informed consent was obtained from each patient studied.

Catheterization protocol. Patients were brought to the car-
diac catheterization laboratory in a fasting state. A variety of
premedications were given, but no patient received atropine.
Nitroglycerin (200 to 400 μg sublingually, 10 to 20 μg/min iv,
or 100 to 400 μg ic) was administered before diagnostic angi-
PATHOPHYSIOLOGY AND NATURAL HISTORY–CORONARY FLOW RESERVE

graphy. Angiograms of each lesion were obtained in orthogonal projections (e.g., 60° degree left anterior oblique and 30° degree right anterior oblique). In patients studied after angioplasty (immediate or late), we obtained angiograms in the same projections used before the angioplasty.

A No. 3F 20 MHz coronary Doppler catheter (Nu Vel, Nu Med Inc., or Cardiovascular Bioengineering, University of Iowa) was advanced through a No. 8F coronary guiding catheter (USCI, Bard, Inc.) into the coronary vessel and positioned immediately proximal to the coronary lesion. The catheter position and the Doppler range gate were adjusted to obtain an adequate tracing of phasic coronary blood flow velocity within the artery. The technique has been previously reported.16 Care was taken to minimize the distance between the Doppler crystal and the coronary lesion, but the catheter did not enter the stenosis in any patient.

Mean and phasic signals of coronary blood flow velocity (kHz shift), arterial pressure obtained via the guiding catheter, heart rate, and the electrocardiogram were continuously recorded on a multichannel direct-writing recorder. The arterial pressure waveform obtained from the guiding catheter was damped by the presence of the coronary Doppler catheter; consequently, only mean arterial pressure could be accurately monitored.

After measurements of resting coronary blood flow velocity, 6 to 12 mg of papaverine hydrochloride (2 mg/ml 0.9% saline) was injected through the guiding catheter into the coronary ostium. The resultant increase in coronary blood flow velocity was recorded. To confirm that any dose of papaverine produced maximal hyperemia, an additional larger dose (2 to 4 mg larger than the prior dose) was administered and the resultant hyperemic response was recorded. Flow velocity was allowed to return to baseline levels between doses of papaverine. After the final dose, the guide catheter was withdrawn from the coronary ostium to ensure that it did not obstruct maximal hyperemic blood flow.

The translesional pressure gradient was measured with a coronary angioplasty catheter (USCI, Bard, Inc.; 1.4 mm outer diameter, 1.5 mm² cross-sectional area) in all vessels undergoing angioplasty and in 18 of 31 vessels studied late after angioplasty. The pressure gradient was determined as the difference between the mean arterial pressure measured via the guiding catheter and the mean arterial pressure distal to the lesion measured with the angioplasty catheter (computerized waveform analysis, SIECOR, Siemens).

Coronary angioplasty. In the 32 patients undergoing angioplasty, coronary dilation was performed with a steerable angioplasty balloon catheter system (USCI, Bard, Inc.) with inflation pressures and balloon sizes thought appropriate by the operator. The distal coronary pressure during balloon inflation (the coronary “wedge” pressure) was measured with the angioplasty catheter in nine patients. The decision to terminate further dilation was at the discretion of the operator.

After angioplasty, a final resting translesional pressure gradient was measured with the dilating catheter in the fashion described above. Additionally, in 20 patients the peak mean translesional pressure gradient and mean arterial pressure distal to the dilated lesion were measured after intracorony administration of papaverine (6 to 8 mg into the right coronary or 10 to 12 mg into the left coronary artery). We have previously shown that these doses of papaverine produce maximal coronary hyperemia 15 to 30 sec after intracoronary injection.17

The coronary Doppler catheter was advanced proximal to the dilated lesion and placed in a position similar to that in the preangioplasty study. Coronary flow reserve was measured in an identical fashion to that used before angioplasty. After withdrawal of the intracoronary guidewire and Doppler catheter, orthogonal angiograms were obtained in the same projections as before the dilation.

Creatine kinase (total and MB fraction) was measured imme-

diately and every 6 hr for 18 hr after angioplasty. No patient had elevation of total creatine kinase or MB fraction above the normal values.

Coronary flow reserve analysis. Coronary flow reserve was calculated as the quotient of the peak blood flow velocity (maximal mean kHz shift after administration of papaverine) and mean resting blood flow velocity.

Quantitative angiographic analysis. Angiograms of each dilated lesion were analyzed by the Brown/Dodge method of quantitative coronary angiography. The technique has been described in detail elsewhere.15, 20

Late restenosis was defined as 50% decrease in the minimum arterial cross-sectional area of the dilated stenosis, compared with that measured immediately after dilation.

 Videodensitometric analysis. Videodensitometric analysis of each dilated lesion was performed by a method we have previously described.21 Nine stenoses could not be analyzed because of poor film quality (n = 5) or unavailability of the angiogram (n = 5). Two patients had angiographic evidence of a perivascular dissection immediately after angioplasty. Their angiograms also were not analyzed by videodensitometry because radiographic contrast material within the dissection might have increased the optical density of the stenotic area.

Statistical analysis. Differences between group means were analyzed by analysis of variance (ANOVA, Clininfo) unless stated otherwise. Curvilinear correlation coefficients were obtained by use of a quadratic regression model (SAS; Cary, NC). Non-parametric analysis was performed with Fisher’s exact test. A p value of .05 was used to define statistical significance. All values are expressed as mean ± SEM.

Results

Hemodynamics. The mean arterial pressure and heart rate rate for each group are displayed in table 1. These two important determinants of resting myocardial blood flow and coronary flow reserve were not significantly different in the study groups. Additionally, the hemodynamic variables were similar in vessels with abnormally low coronary flow reserve (<3.5 peak/resting velocity ratio) and in vessels with normal coronary flow reserve (≥3.5 peak/resting velocity ratio).

Immediate effects of angioplasty

Coronary flow reserve. Coronary flow reserve was

<p>| TABLE 1 |
| Systemic hemodynamics during measurement of coronary flow reserve |</p>
<table>
<thead>
<tr>
<th>Coronary flow reserve (peak/resting velocity ratio)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (bpm)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels studied before angioplasty</td>
<td>&lt;3.5</td>
<td>89 ± 3</td>
<td>66 ± 2</td>
</tr>
<tr>
<td>Vessels studied immediately after angioplasty</td>
<td>&lt;3.5</td>
<td>84 ± 3</td>
<td>69 ± 2</td>
</tr>
<tr>
<td>Vessels studied late after angioplasty</td>
<td>≥3.5</td>
<td>90 ± 4</td>
<td>63 ± 2</td>
</tr>
<tr>
<td>None of the values are significantly different (ANOVA).</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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TABLE 2

Coronary flow reserve, arterial stenosis, and hemodynamics before and immediately after angioplasty

<table>
<thead>
<tr>
<th></th>
<th>Before angioplasty (all patients)</th>
<th>Immediately after angioplasty</th>
<th>Coronary flow reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>&lt;3.5</td>
<td>≥3.5</td>
</tr>
<tr>
<td>Coronary flow reserve (peak/</td>
<td>2.3 ± 0.1</td>
<td>3.6 ± 0.3 ^A</td>
<td></td>
</tr>
<tr>
<td>resting velocity ratio)</td>
<td>All patients</td>
<td>63 ± 3</td>
<td>59 ± 3</td>
</tr>
<tr>
<td>Area stenosis (%)</td>
<td>90 ± 1</td>
<td>61 ± 2 ^A</td>
<td></td>
</tr>
<tr>
<td>Minimal cross-sectional area</td>
<td>0.7 ± 0.1</td>
<td>2.5 ± 0.1 ^A</td>
<td></td>
</tr>
<tr>
<td>(mm²)</td>
<td>2.2 ± 0.3</td>
<td>6.9 ± 0.7 ^A</td>
<td></td>
</tr>
<tr>
<td>Translesional gradient (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At basal flow</td>
<td>56 ± 2</td>
<td>12 ± 1 ^A</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>At peak hyperemia</td>
<td>—</td>
<td>26 ± 3</td>
<td>27 ± 3</td>
</tr>
<tr>
<td>Distal coronary pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At basal flow</td>
<td>32 ± 2</td>
<td>74 ± 3 ^A</td>
<td>79 ± 5</td>
</tr>
<tr>
<td>At peak hyperemia</td>
<td>—</td>
<td>59 ± 5</td>
<td>61 ± 7</td>
</tr>
<tr>
<td>n</td>
<td>32</td>
<td>31</td>
<td>17</td>
</tr>
</tbody>
</table>

^p < .01 vs before angioplasty.

impaired in all vessels before angioplasty (2.3 ± 0.1; table 2, figure 1). Immediately after angioplasty, coronary flow reserve increased in each vessel (mean increase 110%, range 8% to 650%). In 14 patients, coronary flow reserve returned to normal levels (≥3.5 peak/resting velocity ratio; figures 1 and 2). In the remaining 17 patients, flow reserve (range 1.9 to 3.3 peak/resting velocity ratio), although increased, remained below that measured in patients with normal coronary arteries.

There was no significant relationship between coronary flow reserve measured immediately after angioplasty to the flow reserve measured before angioplasty (r = .24).

Arterial stenosis. Before angioplasty, all vessels were severely stenosed (table 2, figures 3 and 4). After angioplasty, percent area stenosis fell, and the minimum arterial cross-sectional area and integrated optical density increased in all arteries.

None of the angiographic variables of luminal

FIGURE 1. Left, The change in coronary blood flow velocity (ΔCBFV) after intracoronary administration of a maximally vasodilating dose of intracoronary papaverine in 14 patients with normal coronary vessels. Right, The change in coronary blood flow velocity (i.e., coronary flow reserve) in each vessel before, immediately after, and late after coronary angioplasty. Before angioplasty, coronary flow reserve was significantly reduced (2.3 ± 0.1 peak/resting velocity ratio). Immediately after angioplasty coronary flow reserve increased to 3.6 ± 0.3. In the seven vessels without restenosis studied late after angioplasty, flow reserve increased further to 4.7 ± 0.4.
FIGURE 2. A record obtained from a patient undergoing right coronary artery angioplasty. The top tracing shows phasic coronary blood flow velocity (CBFV), the second tracing mean coronary blood flow velocity, and the bottom two panels the arterial pressure and electrocardiogram. Before angioplasty (left), the lesion produced 95% area stenosis with an associated translesional pressure gradient of 52 mmHg. Six milligrams of intracoronary papaverine produced only a 1.5-fold increase in blood flow velocity. After angioplasty (right) the percent area stenosis was decreased to 68% and the translesional pressure gradient was reduced to 12 mmHg. Six milligrams of intracoronary papaverine resulted in a 5.0-fold increase in blood flow velocity, demonstrating that physiologically significant obstruction to coronary blood flow had been removed.

obstruction after dilation appeared to predict the flow reserve immediately after dilation. There was no significant relationship between coronary flow reserve measured immediately after angioplasty and the residual percent area stenosis (r = .30; figure 5), minimum arterial cross-sectional area (r = .19; figure 6), or integrated optical density (r = .24; figure 7). Moreover, the degree of arterial stenosis after angioplasty was similar in vessels with coronary reserve in the lowest quartile (area stenosis 63 ± 4%, minimum arterial cross-sectional area 72 ± 9%, integrated optical density 81 ± 10%).

FIGURE 3. The area stenosis of each vessel studied before, immediately after, and late after coronary angioplasty. Immediately after angioplasty, area stenosis fell from 90 ± 1 to 61 ± 2. Late after angioplasty five patients developed restenosis (solid dots) and seven had continued patency of the dilated vessel.
cross-sectional area 2.2 ± 0.4 mm², integrated optical density 7.3 ± 1.6) and in the highest quartile (area stenosis 70% ± 3%, minimum cross-sectional area 2.5 ± 0.2 mm², integrated optical density 5.8 ± 1.1) of all vessels. Importantly, 14 of 25 arteries with less than 70% residual area stenosis and six of 13 vessels with a residual minimum cross-sectional area of 2.5 mm² or more had a flow reserve of less than 3.5 peak/resting velocity ratio.

None of the specific descriptors of luminal stenosis obtained before angioplasty were related to flow reserve immediately after angioplasty (percent area stenosis r = .07; minimum arterial cross-sectional area r = .06; integrated optical density r = .15; table 3).

**Translesional pressure gradient.** The mean translesional pressure gradient was 56 ± 2 mm Hg before angioplasty and decreased to 12 ± 1 mm Hg (range 2 to 24 mm Hg, p < .01) after dilation (table 2). The mean arterial pressure distal to the dilated lesion rose from 32 ± 2 to 74 ± 3 mm Hg. There was no significant

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**FIGURE 4.** The minimum cross-sectional area of each vessel studied before, immediately after, and late after coronary angioplasty. Minimal cross-sectional area increased from 0.7 ± 0.1 to 2.5 ± 0.1 mm² immediately after angioplasty. Late after angioplasty, five patients developed restenosis (>50% reduction in minimal cross-sectional area; solid dots). The remaining seven patients had no significant change in vessel caliber.

**FIGURE 5.** The relationship between area stenosis and coronary flow reserve (∆CBFV) in vessels studied immediately and late after coronary angioplasty. The bar in the upper left corner of each panel displays the mean and range of coronary flow reserve measured in normal coronary vessels. **Left,** Immediately after angioplasty coronary flow reserve (∆CBFV) was unrelated to area stenosis. **Right,** Late after angioplasty there was a significant curvilinear relationship of area stenosis to flow reserve. In contrast to vessels studied immediately after dilation, coronary flow reserve in all vessels studied late after angioplasty was normal if the lesion produced less than 70% area stenosis (the area delineated by the box in the lower left corner of each panel).
the relationship between the translesional pressure gradient and coronary flow reserve immediately after angioplasty ($r = .20$; figure 8).

The mean translesional pressure gradient and absolute mean distal coronary pressure at rest or at peak hyperemia were not significantly different immediately after angioplasty in vessels with normal flow reserve and in those with low flow reserve (figure 9, table 2). Thus, at rest and at peak flow, the driving pressure distal to the dilated stenosis was similar in vessels with normalized coronary reserve and vessels with persistently depressed coronary reserve.

**Relationship of coronary flow reserve immediately after angioplasty to technical factors, clinical syndrome, and drug treatment.** The flow reserve measured in patients receiving calcium-channel antagonists, β-adrenergic receptor antagonists, nitrates, or with angiographically visible collateral blood supply to the dilated vessel before angioplasty was not significantly different from flow reserve in patients without those descriptors (table 3). The incidence of unstable angina was also not significantly different between groups. Moreover, the quantity of radiographic contrast material injected into the vessel, the time from the first or last dilation to the measurement of flow reserve, the duration of the longest balloon inflation, the total duration of all balloon inflations, and the total duration of the procedure were not significantly different in patients with normal and those with abnormal flow reserve immediately after dilation. Additionally, when all of the variables in table

**FIGURE 6.** The relationship between minimal arterial cross-sectional area and coronary flow reserve ($\Delta$CBFV) in vessels studied immediately and late after coronary angioplasty. The bar in the upper right corner of each panel displays the mean and range of coronary flow reserve measured in normal coronary vessels. **Left,** Immediately after angioplasty, coronary flow reserve was unrelated to minimal cross-sectional area. **Right,** Late after angioplasty there was a significant curvilinear relationship between flow reserve and minimal arterial cross-sectional area. Importantly, coronary flow reserve was normal in all vessels studied late after angioplasty if the lesion had 2.5 mm$^2$ or more minimal cross-sectional area (the area delineated by the box in the lower right corner of each panel).

**FIGURE 7.** The relationship between integrated optical density of stenosis and coronary flow reserve ($\Delta$CBFV) in vessels studied immediately and late after angioplasty. The bar in the upper left corner of each panel displays the mean and range of coronary flow reserve measured in normal coronary arteries. **Left,** Immediately after angioplasty, coronary flow reserve was unrelated in integrated optical density of stenosis. **Right,** Late after angioplasty there was a significant curvilinear relationship between flow reserve and integrated optical density of stenosis.
TABLE 3
Relationship of coronary flow reserve after angioplasty to lesion severity before angioplasty: clinical syndrome, technical factors, and drug therapy

| Coronary flow reserve immediately after angioplasty |
|---------------------------------|----------|
| <3.5                            | >3.5     |

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>17</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of stenosis before angioplasty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area stenosis (%)</td>
<td>91 ± 1</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>Minimal cross-sectional area (mm²)</td>
<td>0.6 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Integrated optical density (units)</td>
<td>1.9 ± 0.4</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>Translesional pressure gradient (mm Hg)</td>
<td>52 ± 3</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>Pressure distal to stenosis (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon deflated</td>
<td>33 ± 2</td>
<td>31 ± 3</td>
</tr>
<tr>
<td>Balloon inflated (n = 9)</td>
<td>32 ± 12</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Collateral filling of dilated vessels (% of patients)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Technical factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographic contrast material (ml)</td>
<td>60 ± 8</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>Duration of longest balloon inflations (sec)</td>
<td>43 ± 3</td>
<td>43 ± 1</td>
</tr>
<tr>
<td>Duration of all balloon inflation (sec)</td>
<td>133 ± 12</td>
<td>106 ± 10</td>
</tr>
<tr>
<td>Time from insertion of arterial cannula (min)</td>
<td>106 ± 8</td>
<td>119 ± 9</td>
</tr>
<tr>
<td>Time from first balloon inflation (min)</td>
<td>46 ± 5</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>Time from last balloon inflation (min)</td>
<td>29 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Drug therapy (% of patients receiving)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel antagonist</td>
<td>82</td>
<td>79</td>
</tr>
<tr>
<td>β-Adrenergic antagonist</td>
<td>47</td>
<td>57</td>
</tr>
<tr>
<td>Nitrates</td>
<td>47</td>
<td>57</td>
</tr>
<tr>
<td>Unstable angina (% with)</td>
<td>65</td>
<td>43</td>
</tr>
</tbody>
</table>

None of the values are significantly different.

3 were considered together (stepwise forward regression analysis, BMDP), no significant relationship emerged.

Hence, although coronary flow reserve improved in all patients immediately after angioplasty, normalization of flow reserve could not be predicted by geometric or nongeometric angiographic measurements of arterial stenosis, the translesional pressure gradient at rest or at maximal hyperemia, drug therapy, clinical syndrome, or a variety of technical factors related to balloon dilation.

Late effects of angioplasty. Late after angioplasty, a clear relationship emerged between coronary flow reserve and the residual lesion percent area stenosis (r = .70, p < .01; figure 5), minimum arterial cross-sectional area (r = .70, p < .01; figure 6), integrated optical density (r = .60, p < .01; figure 7), and the translesional pressure gradient (r = .77, p < .01). In contrast to arteries studied immediately after angioplasty, all vessels with less than 70% area stenosis (n = 14) or 2.5 mm² or more minimal cross-sectional area (n = 12) had normal flow reserve (≥ 3.5 peak/resting velocity).

Sequential studies in individual patients. Twelve patients were studied before, immediately after, and late after coronary angioplasty (table 4, figure 10). Late after angioplasty, five patients had angiographic evidence of restenosis.

Of the remaining seven patients without restenosis, the minimum arterial cross-sectional area immediately after dilation (2.5 ± 0.2 mm²) was not significantly
coronary flow reserve (mean 2.7 peak/resting velocity ratio, range 2.0–3.1) at the time of the follow-up study. Importantly, coronary flow reserve immediately after angioplasty was normal in two of the five vessels that later developed restenosis.

**Discussion**

There are three principle findings of this study. First, in nearly one-half of patients, coronary flow reserve normalizes immediately after angioplasty. Immediately after dilation, however, there is a transient dissociation between coronary flow reserve and quantitative angiographic, videodensitometric, and hemodynamic variables of luminal obstruction, suggesting that the flow reserve capacity of recently dilated vessels is reduced disproportionately to the degree of residual stenosis. Finally, late after angioplasty, coronary flow reserve, corrected for the degree of residual stenosis, returns to normal levels. These results suggest that measurements of coronary flow reserve obtained immediately after angioplasty may not reflect the success of the procedure in removing physiologically significant obstruction to coronary blood flow.

**Potential methodologic limitations.** There are several potential problems inherent in measurement of coronary flow reserve with a coronary Doppler catheter and intracoronary papaverine. These potential limitations (obstruction to maximal coronary blood flow, alterations in vascular cross-sectional area after intracoronary administration of papaverine, blood flow obstruction produced by the coronary guiding catheter, and alterations in flow velocity profiles) have been discussed in detail elsewhere.15–17

Measurements of translesional pressure gradients with fluid-filled long thin catheters that have a cross-

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**TABLE 4**

Comparison of the immediate and late results of angioplasty

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th></th>
<th>Sequentially studied patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immed. after</td>
<td>Late after</td>
<td></td>
</tr>
<tr>
<td></td>
<td>angioplasty</td>
<td>angioplasty</td>
<td>(without restenosis)</td>
</tr>
<tr>
<td>n</td>
<td>31</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Coronary flow reserve (peak/resting velocity)</td>
<td>3.6±0.3</td>
<td>5.1±0.3a</td>
<td>3.6±0.6</td>
</tr>
<tr>
<td>Area stenosis (%)</td>
<td>61±2</td>
<td>62±2</td>
<td>58±4</td>
</tr>
<tr>
<td>Minimal cross-sectional area (mm²)</td>
<td>2.5±0.1</td>
<td>2.9±0.2</td>
<td>2.5±0.2</td>
</tr>
<tr>
<td>Integrated optical density (units)</td>
<td>6.9±0.7</td>
<td>7.7±0.8</td>
<td>6.7±0.9</td>
</tr>
<tr>
<td>Drug therapy (% receiving)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel antagonists</td>
<td>81</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>β-receptor antagonists</td>
<td>52</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Nitrates</td>
<td>55</td>
<td>30</td>
<td>57</td>
</tr>
</tbody>
</table>

a*p < .05 vs immediately after angioplasty; b*p = .05 vs immediately after angioplasty (paired t test).
Before Angioplasty  

Immediately after Angioplasty  

Late after Angioplasty  

Restenosis n=5  

No Restenosis n=7

FIGURE 10. Angiographic variables of arterial stenosis and coronary flow reserve in sequentially studied vessels. Late after angioplasty coronary flow reserve increased in vessels without restenosis.

FIGURE 11. A record obtained from a patient undergoing right coronary angioplasty demonstrating the late return of normal flow reserve. Left, Immediately after angioplasty. The top tracing displays Phasic coronary blood flow velocity (CBFV). The second tracing shows mean coronary blood flow velocity, and the bottom three panels the arterial pressure, heart rate, and the electrocardiogram. Immediately after angioplasty intracoronary papaverine produced only 2.1-fold increase in blood flow velocity, despite the presence of 3.1 mm² minimal arterial cross-sectional area and 69% area stenosis. Right, A record obtained from the same patient studied 5 months after angioplasty. Late after angioplasty, intracoronary papaverine increased blood flow velocity to 5.6-fold resting velocity, demonstrating normal coronary flow reserve.

sectional area of 1.5 mm² are associated with some problems. The fidelity of the pressure measurements is limited, the catheter produces superimposed obstruction, and the gradient measured is related to blood flow velocity in an exponential manner.22 Because translesional gradients are often used to determine the success
of angioplasty procedures, we correlated these measurements with the other more sophisticated variables we assessed. Despite the limitation of these measurements, we found that the relationship between flow reserve and lesion gradient late after angioplasty was similar to that previously reported in vessels with undilated stenoses. Immediately after dilation, however, flow reserve was unrelated to the translesional pressure gradient.\textsuperscript{15} In fact, 11 of 22 lesions with a resting translesional gradient of less than 15 mm Hg had depressed coronary reserve. This contrasts sharply with our findings in vessels with undilated lesions and vessels studied late after dilation. In those settings, all lesions with less than 20 mm Hg translesional pressure gradient had normal coronary reserve.

Quantitative angiographic and videodensitometric measurements of luminal stenosis are subject to intraobserver and interobserver variability. Prior studies by Brown et al.\textsuperscript{20} and from our laboratory,\textsuperscript{23} however, suggest that interobserver variability with the Brown/Dodge technique of quantitative angiography is low (SEE $\pm 1.9\%$ area stenosis and $\pm 0.11$ mm\textsuperscript{2} minimal arterial cross-sectional area in our laboratory). Similarly, videodensitometric measurements of arterial stenosis in our laboratory vary by only 0.8 density units ($\pm$ SEE, interobserver variability).\textsuperscript{21} Similar interstudy variability has been reported by Riebers et al.\textsuperscript{24} using another quantitative angiographic technique.

Quantitation of the extent of residual arterial stenosis after angioplasty can be problematic and might have interfered with our analysis. Identification of arterial borders immediately after angioplasty may not be accurate because the luminal outline is sometimes indistinct.\textsuperscript{25} Our findings that both geometric and nongeometric determinants of lesion severity failed to correlate with coronary flow reserve immediately after angioplasty suggest that failure to ascertain accurately the luminal borders was not responsible for the dissociation between luminal stenosis and coronary reserve.

In this study we artificially separated patients into those with normal (>3.5 peak/resting velocity) and abnormal (<3.5) coronary flow reserve immediately after angioplasty. These two groups had remarkably similar characteristics with regard to a host of angiographic hemodynamic, clinical, and procedural variables (tables 2 and 3). To determine whether the point of arbitrary separation (flow reserve of less than 3.5) prevented us from identifying characteristics of these patient groups that might be significantly different, we also compared these characteristics in a subgroup of patients with flow reserve measurements immediately after angioplasty in the highest and lowest quartiles. Because no differences were observed, it is unlikely that the artificial separation influenced our conclusion.

**Comparison with previous studies.** Several of our results confirm previous reports by other groups of investigators.\textsuperscript{25–28} Additionally, our finding that coronary flow reserve late after angioplasty is correlated with angiographic measurements of the residual luminal stenosis (area stenosis, minimum cross-sectional area, and integrated optical density) is consistent with a recent study from our laboratory demonstrating a close relationship between luminal stenosis and flow reserve in undilated coronary vessels.\textsuperscript{15} In both studies, lesions producing less than 70% area stenosis or with more than 2.5 mm\textsuperscript{2} minimal cross-sectional area had normal coronary reserve. In contrast, immediately after angioplasty one-half of vessels with these angiographic variables had diminished flow reserve.

Our finding that coronary flow reserve often does not normalize immediately after angioplasty contrasts sharply with studies by Lassar et al.\textsuperscript{10} but is in agreement with a study by Hodgson and Williams.\textsuperscript{11} Both groups of investigators reported that coronary flow reserve measured in dilated vessels immediately after angioplasty approximates that measured in normal coronary arteries. Each group of investigators, however, used measurement techniques that tend to underestimate maximal coronary hyperemia (xenon-133 scintigraphy and digital-subtraction angiographic measurements of contrast transit times).\textsuperscript{12–14} Also, the stimulus for coronary vasodilation (iodinated contrast media or small doses of papaverine) may have been submaximal, and consequently, may have prevented separation of normal from depressed maximal coronary flow reserve.\textsuperscript{17}

Bates et al.\textsuperscript{9} reported that coronary flow reserve measured late after angioplasty remains persistently depressed compared with that in normal vessels. In addition to problems in the measurement of maximal flow reserve, the residual arterial stenosis was not quantified. Consequently, if flow reserve was truly depressed late after angioplasty, it is unclear whether the reduction was commensurate with the residual arterial stenosis.

**Potential mechanisms for reduced coronary flow reserve immediately after angioplasty.** Why is coronary flow reserve immediately after angioplasty sometimes depressed despite a good anatomic result? Three explanations deserve consideration: an increase in resting coronary blood flow, a reduction in the capacity of the arteriolar bed to normally vasodilate, and persistent, yet angiographically inapparent, resistance to hyperemic blood flow through the dilated stenosis.
In a fraction of patients, coronary dilation may have failed to remove physiologically significant obstruction to blood flow (e.g., translesional resting pressure gradient >20 mm Hg or area stenosis >70%). Without absolute measurements of phasic coronary blood flow and pressure, however, it is difficult to directly assess the contribution of stenosis resistance to reduced flow reserve after angioplasty. The data suggest, however, that the residual stenosis may not have been the major factor limiting coronary reserve immediately after angioplasty. The angiographic variables of arterial stenosis and the resting pressure gradient were nearly identical in vessels with flow reserve in the highest and lowest quartiles. Also, the distal coronary pressure at peak hyperemia was similar in vessels with normal and abnormal reserve.

Several organs, including the heart, autoregulate arteriolar resistance in response to alterations of perfusion pressure.\textsuperscript{29-31} Prolonged hypertension can cause a change in autoregulation of the cerebral circulation such that a sudden fall in arterial pressure results in a transient, inappropriate fall in organ perfusion.\textsuperscript{30} While the effects of prolonged hypertension (resulting from an epicardial coronary stenosis) on coronary autoregulation have not been well studied, it is possible that prolonged arteriolar vasodilation resulting from low perfusion pressure distal to the stenosis might cause a transient inability of the arteriolar vasculature to autoregulate in response to a sudden restoration of normal perfusion pressure. If the arteriolar bed failed to vasoconstrict appropriately, the increase in distal coronary pressure produced by coronary angioplasty might result in an increase in resting blood flow and a fall in the peak/resting coronary blood flow velocity ratio. Prior studies suggest that resting coronary blood flow (measured by\textsuperscript{133}Xe scintigraphy and great cardiac vein flow) often increases after angioplasty.\textsuperscript{10, 32} It is not clear whether blood flow is increased above that required for metabolic needs.

Other factors might also transiently change coronary hemodynamics. Release of vasoconstrictor substances by platelets activated by and adherent to the site of dilation might limit maximal vasodilation. A recent study in animals showed that angioplasty can reduce the vasodilator capacity of the resistance vessels if the balloon dilation causes injury of the arterial media.\textsuperscript{33} Embolization of the coronary circulation with platelet aggregates or larger fragments of thrombus, known to occur in patients with unstable angina, might also result in transient alterations in coronary blood flow that later regress.\textsuperscript{34} A previous study in animals has shown that embolization of the coronary circulation with 50 to 300 \(\mu\)m diameter spores can increase resting coronary blood flow and decrease maximal hyperemic coronary blood flow.\textsuperscript{35} Other factors related to the presence of a severe stenosis, such as recurrent ischemia before angioplasty, might have produced transient changes in vasodilator capacity. Additionally, drug therapy might have altered resting coronary blood flow or vasodilator reserve. Several prior studies have demonstrated that short-term administration of calcium-channel antagonists can reduce arteriolar vasodilator capacity.\textsuperscript{36} We found, however, that coronary reserve in patients treated with \(\beta\)-receptor antagonists, nitrates, or calcium-channel antagonists was not significantly different from that in patients not receiving these drugs.

**Clinical implications.** There are two major clinical implications of this study. First, in many patients, measurement of coronary flow reserve immediately after coronary angioplasty cannot by itself be used to assess the adequacy of coronary dilation. If flow reserve returns to normal levels, then one may conclude that the physiologically significant obstruction to coronary blood flow has been removed. If, however, flow reserve fails to immediately return to normal levels, then the reserve ratio is not helpful in determining whether physiologically significant obstruction to blood flow has been removed. Since coronary reserve eventually returns to normal, however, quantitative angiographic measurements of lesion geometry (percent stenosis, minimal cross-sectional area) may better reflect the eventual results of the procedure (in the absence of restenosis).

The second implication is that variables measured in noninvasive studies of provokable myocardial ischemia (e.g., exercise electrocardiography, \textsuperscript{201}TI scintigraphy, exercise ventriculography) might require a period of time after angioplasty to normalize if maximal hyperemic flow is impaired immediately after coronary dilation.

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