Paradoxical Increase in Microvascular Resistance During Tachycardia Downstream From a Severe Stenosis in Patients With Coronary Artery Disease

Reversal by Angioplasty

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Background—The pathophysiology of microvascular response to a severe coronary stenosis has not been conclusively identified. The aim of this study was to characterize the human vasomotor response to pacing-induced ischemia of both the stenotic arterial segment and the distal microcirculation.

Methods and Results—Sixteen patients with stable angina and single-vessel disease were studied. Blood flow velocity and transstenotic pressure gradient were monitored at baseline, after intracoronary adenosine (2 mg), and during ischemia induced by atrial pacing with and without adenosine. At the end of this protocol, the study was repeated after intracoronary phentolamine in 7 patients and after angioplasty in 9. Stenosis resistance was calculated as the ratio between mean pressure gradient and mean flow, and microvascular resistance as the ratio between mean distal pressure and mean flow; values were expressed as percent of baseline. Adenosine decreased (P<0.05) baseline microvascular resistance to 52±17%, but not stenosis resistance. Pacing increased both stenosis and microvascular resistances (244±96% and 164±60% of baseline, respectively, P<0.05). Addition of adenosine to pacing decreased both stenosis (143±96% of baseline, P<0.05 versus ischemia) and microvascular (51±17% of baseline, P<0.05 versus baseline and ischemia) resistances. Phentolamine did not affect coronary resistance at any step of the protocol. Angioplasty and stenting restored a progressive decline in microvascular resistance during pacing (51±19% of baseline, P<0.05 versus baseline).

Conclusions—In patients with coronary artery disease, tachycardia-induced ischemia was associated with elevated resistance of both the stenotic segment and the microvasculature. Revascularization prevents this paradoxical behavior.

(Circulation. 2001;103:2352-2360.)

Key Words: coronary disease ◼ circulation ◼ blood flow ◼ microcirculation ◼ vasoconstriction

In patients with coronary artery disease, the occurrence of myocardial ischemia during increased oxygen demand is attributed to the inadequate flow increase despite maximal vasodilation of the coronary microvasculature.1 According to this view, maximal flow capacity and coronary flow reserve (ie, the ratio between maximal and baseline flow) have been proposed as the most accurate descriptors of stenosis severity to identify the need for revascularization.2 The clinical correlation between severity of lumen obstruction and coronary reserve is widely scattered,3-7 however, and the correlation between reduction in vasodilating capability and evidence of ischemia is far from convincing.8

These findings suggest that other factors might precipitate myocardial ischemia. The angiographic severity of coronary artery stenosis can increase during exercise or atrial pacing because of increased tone.9 Moreover, an increase in calculated total coronary resistance has also been observed during tachycardia in regions supplied by severely stenotic coronary arteries both in experimental studies10 and in patients.5,9,11,12 Thus, it seems conceivable that in coronary artery disease, the response of the coronary tree to increased oxygen demand might be more complex than a progressive arteriolar vasodilation and that changes at the level of coronary stenosis may modulate the flow response. To investigate the possible role of the microcirculation as well, the present study was designed to measure the resistance of both the stenotic arterial segment and the downstream microvasculature at rest and during pacing-induced ischemia in patients with stable angina. Moreover, to verify the relevance of epicardial stenosis and α-receptor activation, the response to tachycardia was also evaluated after intracoronary phentolamine or coronary angioplasty.
Methods

Study Population
Sixteen patients (mean age 59±11 years) were included according to the following criteria: (1) history of stable angina, (2) evidence of ischemia during exercise ECG, (3) no evidence of previous myocardial infarction, (4) preserved left ventricular function, (5) single-vessel disease of the left anterior descending coronary artery, (6) no evidence of collateral circulation, (7) absence of arterial hypertension and/or left ventricular hypertrophy, and (8) absence of diabetes.

Study Protocol
Patients were studied under active treatment with oral diltiazem, isosorbide mononitrate, and aspirin. An 8F guiding catheter was advanced into the left main coronary artery and a 5F bipolar pacing catheter into the right atrium. Heparin (10 000 IU) was injected intravenously, and isosorbide dinitrate (0.6 mg) intracoronarily. A 0.014-in guidewire was advanced distally to the stenosis, and a 0.014-in fiberoptics pressure-monitoring guidewire (Radi Medical) was calibrated and positioned distal to the stenosis.13 Finally, a 2.5F Doppler-tip catheter (Millar Instruments Inc) was placed into the prestenotic segment, and a coronary angiography was obtained to measure cross-sectional area at the catheter tip. Care was taken not to have side branching between the catheter tip and the stenosis and to maintain the catheter in the center of the lumen to obtain a stable flow velocity signal.

The following signals were continuously monitored: (1) 4 ECG leads (D1, D2, D3, and V4), (2) phasic and mean aortic pressure, (3) phasic and mean distal coronary pressure, and (4) phasic and mean coronary blood flow velocity.

Stable blood flow and hemodynamics were verified for ≥5 minutes before baseline recordings. A bolus of adenosine (2 mg) was injected into the left anterior descending coronary artery through the Doppler catheter. After the restoration of a steady baseline condition, atrial pacing was started, with 20-bpm increments every 30 seconds. The heart rate was increased until angina or ST-segment shift was produced or to a maximum of 150 bpm. At maximum pacing, heart rate was kept constant for 30 seconds, and a new bolus of adenosine was given. Forty-five seconds later, the heart rate was decreased, and the pacemaker was switched off within 2 minutes.

After completion of this protocol, 7 patients received phentolamine (2 mg) through the Doppler catheter, and a new angiogram was obtained. The pacing protocol was repeated at the same heart rates. Thereafter, the Doppler catheter was removed, and coronary angioplasty was performed according to the standard technique. At the end of the procedure, in the remaining 9 patients, the Doppler catheter was readvanced into the proximal left anterior descending coronary artery. All measurements were repeated at the same heart rates as in the preangioplasty study. In all patients, distal coronary pressure was also obtained during balloon coronary occlusion.

Data Analysis
Paper recordings (2.5 cm/s) were obtained at the following times: (1) baseline, (2) 30 seconds after intracoronary adenosine, (3) at maximal heart rate, and (4) at maximal heart rate 30 seconds after intracoronary adenosine. Systolic time index was calculated as QT interval times heart rate. Diastolic time per minute (s/min) was calculated as 60 minus systolic time index.

Stenosis severity (percent lumen area reduction) and vessel diameter at the tip of the Doppler catheter were measured with an automated edge-detection system (Mipron; Kontron). Coronary blood flow index was obtained by mean flow velocity times cross-sectional area at the site of the Doppler transducer as previously described.14 Stenosis resistance index was calculated as the ratio between mean transstenotic pressure gradient and blood flow index. Coronary microvascular resistance index was calculated as the ratio between distal coronary pressure and flow index. Both resistance indices were expressed as percent of baseline. Phasic coronary flow velocities were also analyzed for timing of peak in diastole or in systole.

Statistical Analysis
All data are expressed as mean±SD. ANOVA, followed by the Newman-Keuls procedure for multiple comparisons and repeated measures, was used in each population to test changes in blood flow and resistance indices at the various stages of the protocol before and after either phenolamine or angioplasty. Comparison between pretreatment and posttreatment values in each step of the protocol was performed by Student’s t test for paired data. Linear regression analysis was performed by the least-squares method. A probability value of P<0.05 was considered significant.

Results
Clinical and Hemodynamic Effects of Tachycardia and Adenosine
No serious side effects occurred during the study. Left ventriculography showed mild to moderate anterior dysynchrony in 4 of 16 patients; left ventricular ejection fraction was 0.59±0.04. Coronary angioplasty was successful in all patients and was optimized by stent deployment in 14 of 16 patients. Stenosis severity evaluated by percent area reduction decreased from 91±11% to 8±7% (P<0.01); percent diameter reduction decreased from 74±13% to 6±6%.

Atrial pacing increased heart rate from 64±11 to 124±17 bpm (P<0.01) and decreased diastolic time from 20±7 s/min (P<0.01). During pacing, angina occurred in 14 patients, ST-segment depression in 9, and elevation in 1. There were no significant changes in systolic or diastolic aortic pressure (Figure 1). Adenosine affected neither aortic pressure nor heart rate (Figure 1); however, it reduced ST-segment depression in 5 of 9 patients (Figure 2). Distal coronary pressure during balloon coronary occlusion was 14±8 mm Hg.

Effects of Tachycardia and Adenosine on Coronary Hemodynamics
Flow
Baseline blood flow index was 14.8±10.2 mL/min and increased in all patients to 161±34% (P<0.01) after adenosine (Figure 1). At maximum pacing, blood flow index decreased in all patients below resting values (61±20% of baseline, P<0.01 versus baseline and adenosine) (Figure 1). Under the same conditions, however, adenosine markedly increased blood flow in all patients to 153±63% of baseline (P<0.01 versus pacing, 0.05 versus baseline, 0.05 versus adenosine at sinus rhythm).

Thus, tachycardia markedly decreased blood flow when vasomotor tone was intact but not when vasomotor tone was abolished (Figure 2). Phasic flow analysis showed that velocity peaked during diastole in 11 patients under baseline conditions but in only 3 during maximum pacing (P<0.05).

Distal Pressure
As shown in Figure 1, mean distal pressure was 56±19 mm Hg at baseline and decreased to 43±13 mm Hg after adenosine (P<0.05 versus baseline). At maximum heart rate, it showed only a slight but not significant decrease (54±20 mm Hg, P=NS versus baseline, P<0.01 versus adenosine). Under these conditions, adenosine once again decreased distal coronary pressure to 43±16 mm Hg.
Figure 1. Behavior of heart rate (top left), % baseline flow (top right), mean aortic (second row left) and distal coronary (second row right) pressure, and % of baseline stenosis (third row left) and distal (third row right) resistances. Thicker lines indicate average values, vertical lines SDs. Bottom, Behavior of stenosis, distal, and global resistances as % global baseline resistance. ADO indicates intracoronary adenosine; P max, maximum pacing; and ADO P max, adenosine at maximum pacing. A progressive increase in global, stenosis, and distal resistances can be observed during pacing. Adenosine had a marked vasodilator effect on distal microcirculation and a lower efficacy on stenotic arterial segment. *P<0.05 vs baseline, †P<0.05 vs adenosine at sinus rhythm, §P<0.05 vs maximum pacing.
(P<0.05 versus baseline and maximal heart rate, P=NS versus adenosine at sinus rhythm).

**Resistance**
Stenosis resistance did not change after adenosine (109±47%), whereas it increased during pacing to 246±115% of baseline (P<0.05 versus baseline and adenosine) (Figure 1). Under these conditions, adenosine reduced stenosis resistance to 146±99% of baseline (P<0.05 versus pacing, P=NS versus baseline and adenosine at sinus rhythm). Resistance of the coronary microvasculature decreased to 52±14% of basal (P<0.01) after adenosine (Figure 1). By contrast, it increased during pacing to 179±81% of baseline (P<0.01 versus baseline and adenosine). Under these conditions, adenosine restored minimal resistance (69±22% of baseline, P<0.01 versus maximum pacing, P<0.05 versus baseline, P=NS versus adenosine at sinus rhythm).

**a-Receptor Blockade and Vasomotor Tone Control**
Intracoronary phentolamine slightly but significantly decreased aortic and distal coronary pressure at all steps of the protocol (Figure 3, Table 1). Phentolamine did not affect distal resistance and had only a minimal effect on stenosis coronary resistance, which slightly increased only at baseline. Thus, phentolamine did not affect the response of stenosis and microvascular resistance to either tachycardia or adenosine.

**Effect of Coronary Angioplasty**
Angioplasty virtually abolished transstenotic pressure gradient and increased blood flow index at all steps of the protocol except baseline (Table 2, Figure 4). Thus, removal of epicardial obstruction abolished the paradoxical microvascular response to tachycardia; in fact, distal coronary resistance decreased in all patients at maximal heart rate, although a further reduction could still be induced by adenosine.

The angiographic estimate of stenosis severity correlated significantly with both fractional flow reserve, defined as the ratio between distal coronary and aortic pressure under maximal vasodilation13 (r=−0.86, P<0.01), and coronary flow reserve (r=0.62, P<0.01).

**Discussion**
The major finding of the present study is that coronary resistance distal to a severe stenosis increased during tachycardia up to a maximum at the development of angina and ischemia. This phenomenon was abolished by intracoronary adenosine, was not prevented by a-receptor blockade, and disappeared after angioplasty.

**Comparison With Previous Studies**
To our best knowledge, this is the first study to measure both stenosis and microvascular resistance in response to pacing in...
Figure 3. Effect of phentolamine (PHE) on heart rate (top left), blood flow (top right), and aortic and distal coronary pressure (second row) as well as on stenosis and distal resistances (third row) at various steps of protocol as in Figure 1. Values obtained before and after phentolamine are displayed as solid and dashed lines, respectively. Bottom, Behavior of stenosis, distal, and global resistances as % of global baseline resistance before and after phentolamine (+PHE). Phentolamine decreased aortic and distal coronary pressure but did not affect coronary resistances at any step of study protocol. *P<0.05 vs corresponding step before treatment. Abbreviations as in Figure 1.
patients with stable angina. Previous clinical studies have either assessed changes in stenosis lumen or calculated total coronary resistance by measuring aortic pressure and coronary flow by Doppler technology, coronary sinus thermodilution, inert gas washout analysis, or PET.

Several angiographic studies showed an increase in stenosis severity during exercise or pacing.\textsuperscript{9,15} The present data closely agree with these observations by documenting an increase in stenosis resistance during tachycardia. Previous findings on coronary blood flow response to pacing are controversial. Some studies have documented a decrease in flow\textsuperscript{9,11,12,16}; others have not. The majority of studies using Doppler technology reported an increase in blood flow during atrial pacing in coronary arteries with mild to moderate stenoses.\textsuperscript{17,18} Nabel and coworkers,\textsuperscript{9} however, reported a flow reduction in severely stenotic arteries, as opposed to a flow increase in mildly obstructed vessels. Similarly, we reported a flow reduction in patients with severe stenosis and pacing-induced ischemia.\textsuperscript{12}

Almost all venous outflow measurements reported an increase in flow during atrial pacing in patients with coronary artery disease.\textsuperscript{19,20} Because venous outflow measurement is affected by contamination of flow from regions supplied at high perfusion pressure,\textsuperscript{21} however, the flow increase occurring in nonstenotic arteries might have strongly affected the measurement. Studies using an \textsuperscript{81}Kr technique frequently reported a flow reduction during pacing in a large number of patients.\textsuperscript{11,16} In contrast, the great majority of studies based on residue detection after bolus injection of radioactive diffusible tracers (such as \textsuperscript{133}Xe) reported a flow increase during atrial pacing in the myocardium supplied by stenotic coronary arteries.\textsuperscript{22,23} The interpretation of these results needs caution, because the tracer washout is particularly sensitive to flow heterogeneity, a condition widely documented in ischemic areas, with largest flow impairment in the subendocardium\textsuperscript{24,25} and a mixture of ischemic and nonischemic islands throughout the left ventricular wall.\textsuperscript{26} Under these circumstances, the tracer is delivered according to flow distribution, and thus, its washout mainly reflects blood flow in the better-perfused areas and systematically overestimates blood flow in the presence of acute coronary occlusion.\textsuperscript{27} Accordingly, when xenon was injected just before rather than during pacing, so that the myocardium was traced according to its perfusion at rest, a decrease in the washout rate and thus in flow was frequently observed.\textsuperscript{22} Similarly, studies using PET and \textsuperscript{15}NH\textsubscript{3} also demonstrated a reduction of specific flow during pacing in some patients,\textsuperscript{9} although these studies could not elucidate the underlying mechanism because of the limited number of measurements and the low temporal resolution.

In conclusion, studies dealing with blood flow response to tachycardia often reported a flow increase when patients with normal or mildly stenotic coronary arteries were studied. By contrast, in patients with more severe stenosis, studies with

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### TABLE 1. Effect of Intracoronary Phentolamine on Coronary and Systemic Hemodynamics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heart Rate, bpm</th>
<th>Mean Aortic Pressure, mm Hg</th>
<th>Mean Distal Coronary Pressure, mm Hg</th>
<th>Coronary Blood Flow, %</th>
<th>Distal Coronary Resistance, %</th>
<th>Stenosis Coronary Resistance, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>60±6</td>
<td>82±6</td>
<td>57±8</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>PHE</td>
<td>60±2</td>
<td>72±6</td>
<td>48±14*</td>
<td>78±15*</td>
<td>105±15</td>
<td>127±31</td>
</tr>
<tr>
<td>ADO</td>
<td>60±5</td>
<td>81±6</td>
<td>43±6</td>
<td>151±34</td>
<td>52±12</td>
<td>112±30</td>
</tr>
<tr>
<td>ADO+PHE</td>
<td>62±4</td>
<td>75±6</td>
<td>37±6*</td>
<td>145±64</td>
<td>51±17</td>
<td>126±41</td>
</tr>
<tr>
<td>P max</td>
<td>112±18</td>
<td>88±5</td>
<td>58±13</td>
<td>61±23</td>
<td>201±123</td>
<td>235±99</td>
</tr>
<tr>
<td>P max+PHE</td>
<td>112±18</td>
<td>79±6*</td>
<td>49±15*</td>
<td>68±28</td>
<td>181±81</td>
<td>261±146</td>
</tr>
<tr>
<td>ADO P max</td>
<td>112±18</td>
<td>87±6</td>
<td>45±11</td>
<td>154±66</td>
<td>57±15</td>
<td>132±57</td>
</tr>
<tr>
<td>ADO P max+PHE</td>
<td>112±18</td>
<td>79±6*</td>
<td>43±11</td>
<td>144±67</td>
<td>59±17</td>
<td>134±66</td>
</tr>
</tbody>
</table>

ADO indicates adenosine; P max, maximal paced heart rate; PHE, intracoronary administration of phentolamine (2 mg).

\*P<0.05 vs pre-PHE data.

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### TABLE 2. Effect of Coronary Angioplasty on Coronary and Systemic Hemodynamics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heart Rate, bpm</th>
<th>Mean Aortic Pressure, mm Hg</th>
<th>Mean Distal Coronary Pressure, mm Hg</th>
<th>Coronary Blood Flow, %</th>
<th>Distal Coronary Resistance, %</th>
<th>Stenosis Coronary Resistance, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>65±13</td>
<td>88±8</td>
<td>60±26</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>PTCA</td>
<td>67±12</td>
<td>87±11</td>
<td>87±8†</td>
<td>130±64</td>
<td>242±320</td>
<td>4±4†</td>
</tr>
<tr>
<td>ADO</td>
<td>66±15</td>
<td>91±9</td>
<td>48±18</td>
<td>168±35</td>
<td>52±17</td>
<td>100±150</td>
</tr>
<tr>
<td>ADO+PTCA</td>
<td>67±13</td>
<td>94±10</td>
<td>86±9†</td>
<td>526±315†</td>
<td>75±118</td>
<td>2±5†</td>
</tr>
<tr>
<td>P max</td>
<td>133±10</td>
<td>95±12</td>
<td>56±25</td>
<td>66±26</td>
<td>160±55</td>
<td>312±537</td>
</tr>
<tr>
<td>P max+PTCA</td>
<td>131±12</td>
<td>98±10</td>
<td>87±11†</td>
<td>481±263*</td>
<td>103±165*</td>
<td>8±5†</td>
</tr>
<tr>
<td>P max+PTCA</td>
<td>131±12</td>
<td>98±10</td>
<td>87±11†</td>
<td>481±263*</td>
<td>103±165*</td>
<td>8±5†</td>
</tr>
<tr>
<td>ADO P max+PTCA</td>
<td>132±10</td>
<td>97±12</td>
<td>48±20</td>
<td>127±38</td>
<td>54±17</td>
<td>134±191</td>
</tr>
<tr>
<td>ADO P max+PTCA</td>
<td>131±12</td>
<td>103±9</td>
<td>83±12†</td>
<td>291±247*</td>
<td>78±90</td>
<td>10±9†</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

*P<0.05 vs pre-PTCA; †P<0.01 vs pre-PTCA.
Figure 4. Effect of coronary angioplasty (PTCA) on average heart rate (top left), blood flow (top right), and aortic and distal coronary pressure (second row) as well as on stenosis and distal resistances (third row) at various steps of protocol as in Figure 1. Values obtained before and after PTCA are displayed as solid and dashed lines, respectively. Bottom, Behavior of stenosis, distal, and global resistances as % of global baseline resistance before and after PTCA (\(P_{\text{PTCA}}\)). Revascularization markedly increased distal coronary pressure and markedly decreased stenosis resistance. PTCA did not affect baseline or minimal (adenosine) coronary resistance; however, it prevented microcirculatory vasoconstriction that occurred during pacing in presence of stenosis. \(^*P\leq 0.05\) vs corresponding step before PTCA. Abbreviations as in Figure 1.
Doppler technology, krypton technique, and PET documented that flow can be reduced during rapid atrial pacing. The present study included only patients with coronary stenosis so severe as to cause a baseline transstenotic pressure drop. Thus, the observed decrease in flow caused by atrial pacing agrees with previous studies by our and other laboratories.

Under these circumstances, the high resistance offered by the epicardial obstruction implies that even small changes in flow are paralleled by marked variations in coronary pressure that might per se interfere with the normal microcirculatory response to increased oxygen demand. In fact, severe coronary stenoses able to cause a large pressure drop have been found to be associated with a paradoxical constriction of relatively larger microvessels, compared with either distal dilation or microvascular response to moderate stenoses. Moreover, severe obstruction could favor transstenosis platelet activation and release of vasoconstrictors.

**Mechanisms of Increased Microvascular Resistance During Tachycardia**

Several mechanisms might be proposed to explain the increase of microvascular resistance during tachycardia. They could be schematically subdivided into 2 categories: passive and active mechanisms. Passive mechanisms include vascular collapse caused by an increase in extravascular compression and reduction in diastolic time due to tachycardia. Both mechanisms increase coronary resistance, overriding the ischemic vasodilation, particularly in the subendocardium and when driving pressure is reduced by a severe stenosis. The compression and passive exclusion of a part of the myocardial vasculature will increase local resistance, whereas the adjacent, well-perfused myocardium may actually maintain a residual tone. This passive mechanism might thus explain the increase of resistance during pacing, the persistence of a flow reserve despite ischemia, the occurrence of a systolic peak flow during tachycardia, and the increase in flow and the decrease in distal coronary pressure after adenosine. This hypothesis, however, contrasts with both the reduction of ST-segment depression in 5 of 9 patients and the lack of increase in resistance of maximally dilated vascular bed during pacing. The decrease in coronary pressure should have further worsened ischemia through the induction of transmural steal. Moreover, if a portion of the microcirculation collapsed during pacing, the increase in flow after adenosine should be referred to the myocardium with preserved perfusion only, thus being lower than the one observed at rest when the entire vasculature participate in the vasodilating response. This actually occurred in some patients; however, the overall values of minimal resistance before and during pacing were not statistically different.

On the basis of these considerations, we tend to believe that extramural forces and reduction in diastolic time alone could not explain the entire picture. Vasomotor tone regulation could have actively participated in the increase in microvascular resistance through a blunted vasodilation or an active vasoconstriction. Although several studies reported a role for \( \alpha \)-mediated vasoconstriction, particularly in patients with acute coronary syndromes, the response to pacing was not modified by phenolamine. Moreover, the results obtained after coronary angioplasty indicate that the interaction between stenosis, ischemia, and microcirculation should participate in the paradoxical behavior of coronary microvascular tone. Downey et al and Bellamy et al demonstrated a delayed reactive hyperemia in the subendocardium. Moreover, Gould and coworkers documented that a severe stenosis able to reduce resting flow is not associated with maximal distal vasodilation. Finally, Canty and Klocke documented a residual subendocardial vasodilating capability despite hypoperfusion at coronary pressure lower than that observed in the present study (ie, 35 mm Hg).

The behavior of vasomotor tone might reflect the intrinsic control mechanisms of the coronary circulation finalized to the maintenance of the driving pressure in a range of values high enough to perfuse vessels with high opening pressure and low enough to prevent capillary damage. Such a control could be as powerful as the metabolic one, although the two may go in opposite directions in some pathological conditions. In this line, the response of coronary microcirculation to excessively low perfusion pressure could be a heterogeneous vasoconstriction, able to maintain pressure even to the exclusion of some vascular units. Although somewhat paradoxical and apparently not finalized to avoid or reduce ischemia, this hypothesis agrees with the evidence of both flow heterogeneity during hypoperfusion and heterogeneous distribution of the metabolic fingerprints of ischemia in both the subendocardial and subepicardial layers of the left ventricular myocardium. This would explain the apparently contrary findings obtained in different studies or in different patients in the same study, the severity of stenosis and in particular the value of poststenosis coronary pressure being the major candidate to explain differences.

**Limitations of the Study**

Several limitations of the present study deserve further discussion. Active treatment with aspirin, diltiazem, nitrates, and heparin might have altered flow response to tachycardia. An opposite behavior of coronary resistance was observed, however, before and after revascularization. Accordingly, the present data point out that coronary vasoconstrictor response to tachycardia is not fully prevented by these vasodilator drugs.

To avoid the effect of flow turbulence and to allow superselective drug administration, flow velocity was measured by a catheter rather than by a flow wire. In no case did distal coronary pressure decrease during catheter placement, indicating a minor effect of the device on coronary resistance. It is well known that Doppler wire technology allows a better alignment of the ultrasonic beam with the flow vector, a more accurate estimation of absolute flow values, and a more detailed physiological characterization of the epicardial stenosis. These limitations, however, should not apply to the monitoring of relative changes in flow.

Because collateral function was not directly assessed, the reduction in coronary blood flow velocity during pacing might not reflect a parallel reduction in myocardial perfusion. The very low values of coronary pressure during balloon occlusion, however, suggest the lack of significant collateral circulation. Moreover, the finding of decreased coronary...
pressure associated with increased flow after adenosine strongly suggests a decrease in coronary resistance independent of collateral circulation.

Finally, because atrial pacing was used, the data obtained cannot be directly extended to flow regulation during exercise. In this setting, several other variables, such as an increase in both arterial pressure and adrenergic drive, can affect vasomotor tone with different mechanisms whose interaction needs careful evaluation.

Clinical Implications and Conclusions

In conclusion, the present study documents that in the ischemic myocardium, an abnormal regulation of coronary vasomotor tone at the level of both large arteries and microcirculation prevents the utilization of the actual flow availability. Such a phenomenon seems to be triggered at least in part by low coronary pressure downstream from epicardial stenosis. Coronary angioplasty prevents this microvascular response in addition to its beneficial effect on the increase in maximal flow capacity and coronary flow reserve.

References

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Circulation. 2001;103:2352-2360
doi: 10.1161/01.CIR.103.19.2352

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