Coronary microcirculatory vasoconstriction is heterogeneously distributed in acutely ischemic myocardium

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Am J Physiol Heart Circ Physiol 288: H2298–H2305, 2005; doi:10.1152/ajpheart.00870.2004.—The classical model of coronary physiology implies the presence of maximal microcirculatory vasodilatation during myocardial ischemia. However, Doppler monitoring of coronary blood flow (CBF) documented severe microcirculatory vasoconstriction during pacing-induced ischemia in patients with coronary artery disease. This study investigates the mechanisms that underlie this paradoxical behavior in nine patients with stable angina and single-vessel coronary disease who were candidates for stenting. While transmural pressures were continuously monitored, input CBF (in ml/min) to the poststenotic myocardium was calculated as CBF/MBF. Measurements were obtained at baseline, during pacing-induced ischemia, and after stenting. CBF and distal coronary pressure values were also measured during pacing with intracoronary adenosine administration. During pacing, CBF decreased to 64 ± 24% of baseline and increased to 265 ± 100% of ischemic flow after adenosine administration. In contrast, pacing increased MBF to 184 ± 66% of baseline, measured as a function of the increased rate-pressure product (r = 0.69; P < 0.05). Thus, during pacing, perfused myocardial mass drastically decreased from 30 ± 23 to 12 ± 11 g (P < 0.01). Distal coronary pressure remained stable during pacing but decreased after adenosine administration. Stenting increased perfused myocardial mass to 39 ± 23 g (P < 0.05 vs. baseline) as a function of the increase in distal coronary pressure (r = 0.71; P < 0.02). In conclusion, the vasocostructor response to pacing-induced ischemia is heterogeneously distributed and excludes a tissue fraction from perfusion. Within perfused tissue, the metabolic demand still controls the vasomotor tone.

According to the classical model of coronary physiology, ischemia on effort is thought to occur because metabolic microvascular dilatation does not allow a flow increase large enough to meet the increased oxygen consumption of poststenotic myocardium (24). An important contribution to this model was made by pioneering studies with inert gas washout analysis (4, 18, 30), which documented a flow increase, although not large enough to meet the augmented myocardial metabolism, during pacing-induced ischemia in patients with coronary artery disease.

However, the introduction of alternative methods challenged the validity of this model, as flow reduction was documented in the majority of patients during studies using coincidence detection systems (23), positron emission tomography (28), or krypton techniques (31). Similarly, Doppler monitoring of blood flow to the ischemic myocardium consistently documented an increase in microvascular resistance during pacing that could be abolished by intracoronary adenosine administration, which suggests the presence of microvascular constriction during tachycardia (21, 25, 27).

This consideration indicates that methodology strongly affects our understanding of vasomotor tone regulation in ischemic myocardium. The inert gas washout procedure measures the ratio between flow and perfused volume (13), whereas Doppler monitoring provides an index of the total flow entering a territory regardless of its intramyocardial distribution. Thus changes in the fraction of myocardium perfused (or largely heterogeneous flow distribution) might explain the conflicting results given by inert gas and Doppler methods. Actually, myocardial perfusion and metabolism (as well as coronary reserve) have been found largely heterogeneous in both the subendocardial and subepicardial myocardia of animal models of acute ischemia or reduced coronary pressure (1, 5, 19).

Were these data extended to patients, this would indicate that the response of the coronary tree to increased oxygen demand might be more complex than generally assumed, at least downstream from a severely diseased and stenotic coronary branch. Thus the aim of this study was to verify whether an increase in perfusion heterogeneity underlies the observed vasoconstriction in patients with coronary artery disease.

MATERIALS AND METHODS

Study population. Thirteen patients (11 men and 2 women; mean age, 62 ± 4 yr) provided their informed consent for participation in the study, which was approved by the local ethics committee. Patients were included in the study according to the following criteria: 1) history of stable angina; 2) stress ECG indicative of coronary artery disease upon exercise; 3) no previous myocardial infarction; 4) preserved left ventricular function; 5) single-vessel disease of either the left anterior descending (n = 12) or left circumflex coronary artery; 6) left main stem longer than 2 cm; 7) no angiographic evidence of collateral circulation; and 8) no diabetes, hypertension, or...
left ventricular hypertrophy. All patients were studied while being actively treated with oral nitrates, diltiazem, and aspirin.

**Study protocols.** After patients were catheterized in standard fashion, a 5-Fr bipolar pacing catheter was advanced into the right atrium, and an 8.0-Fr guiding catheter was positioned into the left main coronary artery. Patients received an intracoronary bolus of isosorbide dinitrate (0.6 mg) before a 0.014-in., manometer-tip guide wire (Radi Medical; Uppsala, Sweden) was positioned distally to the stenosis, and a 2.5-Fr Doppler-tip catheter (Millar Instruments; Houston, TX) was advanced proximally to the obstruction.

A mobile gamma camera (Elscint F1; Haifa, Israel) equipped with a low-energy, high-sensitivity collimator was oriented on the patient’s chest according to a 70° left anterior oblique projection.

Patients were then assigned to one of two protocols as shown in Fig. 1. In the nine patients of **protocol 1**, ischemic threshold was tested by progressive pacing until the occurrence of angina or ST segment depression or a maximum of 150 beats/min for 1 min. After we checked for hemodynamic stability, a dynamic acquisition (1-s frames for 195 s) was started 15 s before a bolus injection of 2–4 mCi of $^{133}$Xe was administered through the guiding catheter. Fifteen minutes later, patients were randomized as follows: in five patients, heart rate was suddenly increased to ischemic threshold within 15 s before $^{133}$Xe injection and was then maintained at a constant rate for 180 s. In the remaining patients, tachycardia was induced immediately after tracer injection. After a 20-min recovery, a second study was performed with the reverse sequence of the first protocol. This second protocol was selected to avoid the possible interference of preconditioning during the second run of pacing. At the end of the second acquisition, while pacing and ischemia were kept constant, a bolus of 2 mg of adenosine was given through the Doppler catheter, and, 30 s later, the pacing rate was progressively decreased.

The four patients of **protocol 2** were studied under baseline conditions as in **protocol 1**. Thereafter, adenosine was infused at a rate of 1 mg/min through the Doppler catheter into the diseased vessel for 5 min. At 1 min of infusion, $^{131}$Xe was injected through the guiding catheter while flow velocity and distal pressure were continuously monitored. The Doppler catheter was then removed for performance of transluminal coronary angioplasty (PTCA) and stenting. At the end of the procedure, the Doppler catheter was readvanced as in the pre-PTCA study, a new angiography was performed, and measurements of flow velocity, pressures, and $^{131}$Xe washout were repeated with all patients under resting conditions. Finally, flow and pressure responses to adenosine administration were investigated in **protocol 1**, and, in **protocol 2**, $^{131}$Xe washout was evaluated during adenosine administration and after stenting.

**Data analysis.** ECGs that registered soon before and 30 s after adenosine administration were scanned at high resolution. ST segment shift was manually measured using an electronic caliper at 0.08 s after the J point by an observer unaware of other protocol data.

The stenosis severity (percent lumen area reduction) and cross-sectional area at the Doppler catheter tip were automatically measured by quantitative coronary angiography; the latter was multiplied per flow velocity to obtain total coronary blood flow (CBF; Ref. 25). Total microvascular resistance was estimated by the ratio of distal coronary pressure and CBF.

To compute $^{131}$Xe mean transit time (MTT), the original images were grouped into 20-s frames to yield a better definition of ventricular walls. Two regions of interest of equal size were drawn, one each on the anterior and posterolateral walls. Frames displayed in cine mode verified stability of geometry. Thereafter, time-activity curves in the two regions were generated using the original frames.

MTT was computed as the ratio of the area under the curve to the dose entering the region using a mathematical model to extrapolate the curve to infinity and estimate the dose as previously described (26).

The inverse of MTT is the ratio of flow through a tissue region to the tracer distribution volume in that region. To refer blood flow to the myocardial perfused tissue mass [myocardial blood flow (MBF), in $\text{ml}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$] the following conversion was used:

$$\text{MBF} = \frac{\text{flow}}{\text{distribution volume}}$$

Fig. 1. Schematic representation of the study protocol. Heart rate changes are indicated (dotted line). PTCA, percutaneous transluminal coronary angioplasty.
CORONARY MICROCIRCULATION AND ISCHEMIA IN CAD

MBF = \frac{0.72}{1.08 \times MTT} \tag{1}

where 0.72 is the $^{131}\text{Xe}$ partition coefficient (18) and 1.08 is the myocardial tissue density (in g/ml).

Specific microvascular resistance (resistance per gram of perfused tissue) was estimated by the ratio of distal coronary pressure to MBF in poststenotic myocardium and of aortic pressure to MBF in control myocardium.

By knowing both the input CBF (by Doppler catheter, in ml/min) and the MBF (by $^{131}\text{Xe}$ washout, in ml.min$^{-1}$.g$^{-1}$), we could calculate perfused myocardial mass (in g) as the ratio of

\[
\text{perfused myocardial mass} = \frac{\text{CBF}}{\text{MBF}} \tag{2}
\]

Input blood flow in the remote region, which was not measured by Doppler monitoring, was calculated according to the Sapirstein principle (29) as

\[
\text{CBF}_{\text{remote}} = \frac{D_{\text{remote}}}{D_{\text{poststenotic}}} \times \text{CBF}_{\text{poststenotic}} \tag{3}
\]

where \(D\) denotes the $^{131}\text{Xe}$ dose entering the region (remote or poststenotic).

The perfused myocardial mass in the remote region was calculated according to Eqs. 1 and 2 using a CBF estimate as given by Eq. 3.

Statistical analysis. All data are expressed as means \(\pm\) SD. ANOVA and subsequent Newman-Keuls procedure for multiple comparisons and repeated measures were used to identify significant changes in flow and resistance indices at the various stages of the protocol. Comparison between poststenotic and remote myocardium was performed using Student’s t-test for paired data. Linear regression analysis was performed using the least-squares method. A \(P\) value of <0.05 was considered significant.

RESULTS

Left ventricular function was normal, and resting ejection fraction and end-diastolic pressure measured during standard catheterization study were 0.57 \(\pm\) 0.05 and 10 \(\pm\) 3 mmHg, respectively. The exercise stress test was positive for ischemia with a rate-pressure product of 23,512 \(\pm\) 1,098 mmHg\cdot\text{beats/min}.

No serious side effects occurred during the study. Stenting virtually abolished the pressure gradient in all patients (Table 1) and improved lumen reduction from 97 \(\pm\) 4 to 9 \(\pm\) 7% \(P < 0.01\).

Aortic pressure did not change throughout the study (Table 1). Distal coronary pressure did not change during pacing, but it decreased after adenosine administration. The average ST segment depression was similar during the two runs of pacing (0.19 \(\pm\) 0.05 vs. 0.17 \(\pm\) 0.06 mV, respectively; \(P =\) not significant) and decreased to 0.07 \(\pm\) 0.04 mV after adenosine administration during pacing \((P < 0.05; \text{Fig. 2})\).

Balloon inflation induced angina and ST segment elevation in all patients and caused an abrupt decrease in coronary pressure to 21 \(\pm\) 10 mmHg, although values \(>20\) mmHg occurred in two patients.

Total microvascular resistance in poststenotic myocardium. Total microvascular resistance of poststenotic myocardium increased to a similar extent during both runs of pacing in all nine patients of protocol 1 (Table 2 and Fig. 3). Nevertheless, adenosine injected during pacing documented a preserved vasodilating capability by decreasing microvascular resistance to 33 \(\pm\) 9% of values observed during ischemia; moreover, it reduced ST segment depression in five of six patients. Percentage changes in rate-pressure product and total microvascular resistance were not correlated (Fig. 4).

As shown in Table 2, adenosine infusion increased CBF and decreased distal coronary pressure in all patients of protocol 2.

MBF and microvascular resistance in perfused fraction of poststenotic myocardium and in remote region. The behavior of specific myocardial resistance during ischemia is reported in Table 3. During pacing, in contrast with Doppler monitoring, tracer injection documented a similar decrease in specific microvascular resistance through poststenotic and remote myocardium. This finding was not reproduced when the tissue was presaturated with tracer immediately before pacing as higher resistance values were measured in the poststenotic vs. the remote regions. Tracer injection during ischemia documented a significant correlation between the percentage increase in the rate-pressure product and percentage decrease in specific myocardial resistance (Fig. 4). Doppler monitoring and $^{131}\text{Xe}$ tracer estimates of flow changes induced either by tachycardia or stenting did not correlate under any condition except when tracer was injected immediately before pacing \((r = 0.61; P < 0.05)\).

Changes in perfused myocardial mass. In the poststenotic myocardium, perfused mass markedly decreased during pacing.

Table 1. Clinical variables

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate, beats/min</th>
<th>Rate-Pressure Product, mmHg \times \text{beats/min}</th>
<th>Mean Aortic Pressure, mmHg</th>
<th>Distal Coronary Pressure, mmHg</th>
<th>Angina/ST Shift, no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>70 (\pm) 10</td>
<td>7,728 (\pm) 1,830</td>
<td>97 (\pm) 15</td>
<td>68 (\pm) 9</td>
<td>4/6</td>
</tr>
<tr>
<td>Pacing (\rightarrow) Xe</td>
<td>109 (\pm) 15*</td>
<td>12,715 (\pm) 1,852*</td>
<td>103 (\pm) 37</td>
<td>72 (\pm) 19</td>
<td></td>
</tr>
<tr>
<td>Postpacing</td>
<td>69 (\pm) 12</td>
<td>7,642 (\pm) 1,715</td>
<td>98 (\pm) 16</td>
<td>63 (\pm) 17</td>
<td></td>
</tr>
<tr>
<td>Xe (\rightarrow) pacing</td>
<td>110 (\pm) 15*</td>
<td>12,922 (\pm) 2,170*</td>
<td>105 (\pm) 37</td>
<td>74 (\pm) 21</td>
<td>5/6</td>
</tr>
<tr>
<td>Adenosine + pacing</td>
<td>108 (\pm) 16*</td>
<td>12,541 (\pm) 2,337*</td>
<td>102 (\pm) 36</td>
<td>58 (\pm) 12*</td>
<td>6/1</td>
</tr>
<tr>
<td>Post-PTCA</td>
<td>70 (\pm) 8</td>
<td>7,877 (\pm) 1,131</td>
<td>100 (\pm) 35</td>
<td>99 (\pm) 8*</td>
<td></td>
</tr>
<tr>
<td>Adenosine after stenting</td>
<td>72 (\pm) 8</td>
<td>8,384 (\pm) 1,191</td>
<td>104 (\pm) 37</td>
<td>99 (\pm) 10*</td>
<td></td>
</tr>
<tr>
<td><strong>Protocol 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>69 (\pm) 6</td>
<td>9,812 (\pm) 1,058</td>
<td>108 (\pm) 7</td>
<td>60 (\pm) 13</td>
<td></td>
</tr>
<tr>
<td>Adenosine (1 mg/min)</td>
<td>69 (\pm) 5</td>
<td>9,838 (\pm) 689</td>
<td>109 (\pm) 8</td>
<td>45 (\pm) 13*</td>
<td></td>
</tr>
<tr>
<td>Baseline post-PTCA</td>
<td>68 (\pm) 5</td>
<td>9,865 (\pm) 1,434</td>
<td>94 (\pm) 8</td>
<td>89 (\pm) 8*</td>
<td></td>
</tr>
<tr>
<td>Adenosine (1 mg/min) after stenting</td>
<td>71 (\pm) 5</td>
<td>9,522 (\pm) 1,466</td>
<td>106 (\pm) 16</td>
<td>92 (\pm) 14*</td>
<td></td>
</tr>
</tbody>
</table>

Values are means \(\pm\) SD; \(n = 9\) patients in protocol 1 and \(4\) patients in protocol 2. PTCA, percutaneous transluminal coronary angioplasty. *\(P < 0.01\) vs. baseline.
when the tracer was injected during ischemia but not when the tracer was injected immediately before tachycardia (Table 3). PTCA increased perfused myocardial mass as a function of the increase in coronary pressure \((P < 0.01; \text{Fig. 5})\). Perfused mass in the remote region was less variable, although slightly decreased, during pacing.

As shown in Table 3 and Fig. 6, adenosine administration increasedperfused myocardial mass to values close to those

**Table 2. Coronary blood flow and resistance in ischemic vascular bed as measured by Doppler technology**

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Coronary Blood Flow, ml/min</th>
<th>Total Coronary Resistance, mmHg·min·ml⁻¹</th>
<th>Microvascular Resistance, mmHg·min·ml⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>13.0±9.2</td>
<td>12.0±9.5</td>
<td>9.1±9.0</td>
</tr>
<tr>
<td>Pacing→Xe</td>
<td>9.4±9.0</td>
<td>26.3±25.5b</td>
<td>18.7±19.1b</td>
</tr>
<tr>
<td>Postpacing</td>
<td>19.1±17.4bc</td>
<td>9.6±6.5c</td>
<td>6.4±4.6c</td>
</tr>
<tr>
<td>Xe→pacing</td>
<td>8.9±8.7md</td>
<td>26.1±25.8bd</td>
<td>18.1±17.0bd</td>
</tr>
<tr>
<td>Adenosine + pacing</td>
<td>19.8±16.1bkee</td>
<td>9.0±6.8ce</td>
<td>5.1±4.2bdec</td>
</tr>
<tr>
<td>Baseline after stenting</td>
<td>22.7±10.7ace</td>
<td>5.3±1.9bdec</td>
<td>5.3±2.4c</td>
</tr>
<tr>
<td>Adenosine after stenting</td>
<td>48.4±26.6wdef</td>
<td>3.0±1.9wdef</td>
<td>2.9±1.9wdef</td>
</tr>
</tbody>
</table>

**Protocol 2**

| Baseline   | 15.4±7.9                    | 10.32±6.2                                | 6.5±4.8                                |
| Adenosine (1 mg/min) | 31.4±7.6b                  | 6.7±3.21b                               | 3.8±2.0b                               |
| Baseline after stenting | 29.1±8.1b                  | 5.5±2.2b                                | 5.4±3.1b                               |
| Adenosine (1 mg/min) after stenting | 53.3±9.8bc                 | 2.51±1.14ad                              | 2.24±1.12ad                             |

Values are means ± SD; \(n = 9\) patients in protocol 1 and 4 patients in protocol 2. \(^aP < 0.01\) vs. baseline; \(^bP < 0.05\) vs. baseline; \(^cP < 0.05\) vs. pacing→Xe; \(^dP < 0.01\) vs. postpacing; \(^eP < 0.01\) vs. Xe→pacing; \(^fP < 0.01\) vs. baseline after stenting.

![Fig. 2. ECGs in the five patients (Pt, noted by number and initials) who showed ST segment depression during pacing (left) and its improvement after adenosine administration (right).](http://ajpheart.physiology.org/)

AJP-Heart Circ Physiol • VOL 288 • MAY 2005 • www.ajpheart.org
observed after stenting in all four patients of protocol 2. In contrast, after revascularization, perfused tissue mass was not affected by adenosine administration. Collateral flow. In both patients with a high wedge coronary pressure, balloon inflation interrupted the washout of 131Xe (which had been injected immediately beforehand), thereby indicating the virtual absence of tissue perfusion and thus of collateral flow (Fig. 7).

DISCUSSION

The major finding in the present study is that the increase in microvascular resistance observed during pacing is associated with a large perfusion heterogeneity within the ischemic myocardium, with flow measurements close to normal in some vascular units but almost absent in others. Intracoronary adenosine administration markedly increased flow and decreased distal pressure. Despite this latter effect, adenosine injection improved the ECG signs of ischemia during pacing and increased perfused mass under sinus rhythm. These observations strongly suggest that this vascular derecruitment reflects (at least partially) an apparently paradoxical active vasoconstriction that contributes to ischemia.

CBF vs. MBF. The reduction in CBF during pacing contrasted with the increase in MBF and exactly duplicated, in the same patient, the conflict of data reported in the literature. The simultaneous observation of two opposite responses of blood flow in all patients implies that this discordance cannot be ascribed to the limited accuracy of the single technique.

Theoretically, an increased collateral feeding of stenotic myocardium might have increased MBF independently from CBF entering the native artery. However, in seven of nine patients, wedge coronary pressure was remarkably low, which suggests insufficient collateral filling of the ischemic vascular bed (22), and in the remaining two patients, 131Xe washout stopped during balloon occlusion, which virtually indicates the lack of perfusion in the ischemic myocardium. Accordingly, all patients showed ST segment elevation and complained of chest pain during balloon inflation. A limited relevance of collaterals is also documented by protocol 2. In these patients, a well-developed collateral circulation should have increased the tracer washout rate from the poststenotic myocardium during adenosine infusion to a greater extent with respect to the increase in native artery flow because of a greater pressure gradient between the donor and the target vascular bed. In contrast, pharmacological vasodilation increased much more in CBF than in MBF.

Finally, a major role for collateral circulation is ruled out by the analysis of tracer washout when 131Xe was injected immediately before pacing. Although this procedure did not satisfy the basic principle of tracer dilution theory (diffusible tracer washout can measure blood flow only under steady-state conditions; Refs. 4, 13, 33), it was not used to accurately compute MBF. Rather, it simply confirmed a limited role for collaterals, as a large portion of preinjected tracer remained trapped in the myocardium (18).

Alternatively, it should be considered that tracer dilution theory (13) dictates that washout rate is a function of the ratio

Fig. 3. Total microvascular resistance increased during atrial pacing but decreased during pacing with adenosine administration (Ado+Pacing) and after stenting. Specific microvascular resistance showed the opposite behavior both when the tracer was injected during pacing (Pacing → Xenon) and after stenting but not when the tracer was injected immediately before tachycardia (Xenon → Pacing). Values are expressed as percentages of baseline.

Fig. 4. Relationship between changes in myocardial oxygen consumption (estimated by rate-pressure product, x-axis) and changes either in total microvascular resistance (top) or specific microvascular resistance (bottom) of perfused tissue. Total microvascular resistance did not decrease as rate-pressure product increased; in contrast, this occurred within perfused tissue and was virtually identical in poststenotic and remote myocardia.
The relevance of extravascular compression has been carefully considered in studies of myocardial ischemia, but its clinical relevance has not been frequently considered, previous experimental and clinical studies (15) documented a progressive decrease in perfused tissue volume during the progressive reduction of coronary pressure below aortic pressure. In addition, that study showed that pharmacological vasodilation with dipyridamole was able to elicit an increase in both flow and perfused myocardial mass in the low range of coronary pressure.

Accordingly, changes in perfused myocardial mass (or changes in flow distribution) might explain the discordant results provided by the two methods. Actually, the perfused tissue mass within poststenotic myocardium was 77% of that measured after revascularization and further decreased to only 32% during ischemia. In contrast, it did not change during pharmacological vasodilation after stenting. This observation strongly suggests that stenosis causes a heterogeneous blood flow distribution. This phenomenon is even more evident during ischemia and disappears when a normal driving pressure is restored.

**Mechanisms underlying flow heterogeneity during ischemia.**

The mechanisms that underlie the heterogeneous flow distribution in ischemic myocardium might be schematically subdivided into two categories: passive vascular collapse due to extravascular compression and active vasoconstriction. The relevance of extravascular compression has been carefully documented in animal models of ischemia and reduced coronary driving pressure (5, 6). This passive mechanism might actually explain the increase of resistance during pacing, the reduction in perfused mass, the persistence of a flow reserve despite ischemia and, finally, the decrease in distal coronary pressure caused by adenosine administration. However, it does not explain the improvement of ST segment depression observed in five of six patients (see Fig. 2) after adenosine administration, which should have further worsened ischemia through the induction of transmural steal. In contrast, the benefit induced by adenosine administration on ECG signs of ischemia suggests that pharmacological vasodilation improved the perfusion of ischemic myocardium, probably by abolishing an active vasoconstriction. Although paradoxical and not considered in the classical models of myocardial ischemia, this hypothesis agrees with several experimental studies of the past (7, 11). Actually, a residual vasodilator reserve has been observed downstream of a stenosis that was severe enough to impair resting perfusion (9). Canty and Klocke (5) documented that the endocardium maintains a residual vasodilator reserve despite hypoperfusion and coronary pressure markedly lower (35 mmHg) than that observed in this study (74 ± 21 mmHg). Laxson et al. (17) documented a subendocardial vasodilator response to adenosine administration during exercise-induced ischemia.
ischemia despite a perfusion pressure of 42 ± 5 mmHg. Altogether, these considerations challenge the interpretation of heterogeneity of ischemia as a result of the heterogeneous distribution of extravascular compression and support the hypothesis of a vasomotor reaction to the reduced coronary pressure leading to a vascular derecruitment during ischemia.

Although the mismatch between myocardial metabolism and total microvascular resistance appears paradoxical, the microcirculatory vasomotor tone response might have been precipitated by other factors. Several authors (2, 10) proposed an increase in α-adrenergic receptor activation. However, intracoronary administration of phentolamine did not affect the vasoconstriction induced by atrial pacing in a previous study performed in our laboratory (25). On the other hand, increased cardiac release of endothelin has been described during pacing-induced myocardial ischemia (14). Although this phenomenon might be attributed to the atherosclerotic endothelial dysfunction (12), it might also represent a physiological response to the reduction in arterial pressure (20). According to this hypothesis, the putative vasodilation required to match oxygen demand during pacing would have increased the transstenotic pressure drop (8). Because resting aortic pressure was stable, this effect would have caused an excessively low capillary pressure and thus hinder the Starling forces (16) and trigger the release of vasoconstrictor signals. From a theoretical point of view, this task might be achieved by either venous constriction (leading to a homogeneous hypoperfusion) or arteriolar constriction excluding units from perfusion in a parallel circuit model. The dynamic changes observed in the perfused myocardial mass strongly suggest the latter mechanism.

Study limitations. The major limitations of the present study are that it evaluated a limited number of patients (due to its complex nature) and did not directly evaluate the transmural distribution of myocardial perfusion (due to the limited spatial resolution of nuclear imaging methods available for clinical utilization).

Another possible limitation was the short duration of pacing, which might have prevented a complete vasomotor tone adaptation to the myocardial oxygen consumption and thus justified the effects of adenosine administration. However, coronary resistance response to a step increase in heart rate has been found to be complete within 1 min (3); moreover, changes in perfused myocardial mass were also documented under resting sinus rhythm during adenosine administration or after stenting. These findings strongly suggest that adenosine at these large

Fig. 7. Original records obtained from the patient with stenotic left circumflex artery (top) and 131Xe washout curves from the poststenotic myocardium (bottom) are shown. Coronary blood flow decreased during both runs of pacing. With respect to baseline (thick line), tracer washout rate increased when the injection was performed during tachycardia (thin line) and decreased when the tracer was injected immediately before tachycardia (dotted line). Adenosine administration increased coronary blood flow and reduced distal coronary pressure and ST segment depression in D2 lead. A high distal coronary pressure was present during balloon inflation; however, that interrupted 131Xe washout (dashed line, double arrow), which indicates the virtual absence of collaterals.
doses actually reached and re-recruited hyperperfused vascular segments by counteracting a local vasconstriction.

Moreover, the present data do not elucidate whether the heterogeneous vasconstriction observed in the ischemic vascular bed represents a “physiological” reaction to the reduced pressure or is partially caused by a primary microvascular dysfunction. Endothelial function has been documented (32) to play an important role in the autoregulatory response to hypotension in animal models. Similarly, in animal experiments (15), vasodilation increases the number of perfused vascular units, whereas in our patients, a mild reduction in perfused mass was estimated in the remote region during pacing. This finding seems to agree with the abnormal flow response to tachycardia observed in the remote region by PET studies in patients with coronary artery disease (28). To accurately identify the role of atherosclerotic endothelial dysfunction in the precipitation of ischemia, a comparison with “normal” subjects should have been performed, which was prevented by ethical concerns.

Conclusions. This study documents that the increase in coronary microvascular resistance observed in patients with coronary artery disease during ischemia is due to the exclusion of a tissue fraction from perfusion. This phenomenon might reflect either vascular collapse due to compression of endocardial layers by endocavitary pressure or by active vasoconstriction. The benefit induced by intracoronary adenosine administration on pacing-induced ST segment depression strongly supports the latter hypothesis. This heterogeneously distributed vasconstriction might actually reflect intrinsic vascular control of vasomotor tone tuned to preserve stable values of microvascular pressure in a selected number of vascular units.

REFERENCES


