Global Alteration in Perfusion Response to Increasing Oxygen Consumption in Patients With Single-Vessel Coronary Artery Disease

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Background Recent evidence suggests that, in coronary artery disease (CAD), myocardial blood flow (MBF) regulation is abnormal in regions supplied by apparently normal coronary arteries. However, the relation between this alteration and MBF response to increasing metabolic demand has not been fully elucidated.

Methods and Results MBF was assessed at baseline, during atrial pacing tachycardia, and after dipyridamole (0.56 mg/kg IV over 4 minutes) in 9 normal subjects and in 24 patients with ischemia on effort, no myocardial infarction, and isolated left anterior descending (n=19) or left circumflex (n=5) coronary artery stenosis (≥50% diameter narrowing). Perfusion of both poststenotic (S) and normally supplied (N) areas was measured off therapy by positron emission tomography and [13N]ammonia. Normal subjects and CAD patients showed similar rate-pressure products at baseline, during pacing, and after dipyridamole. In CAD patients, MBF was lower in S than in N territories at rest (0.68±0.14 versus 0.74±0.18 mL·min⁻¹·g⁻¹, respectively, P<.05), during pacing (0.92±0.29 versus 1.16±0.40 mL·min⁻¹·g⁻¹, respectively, P<.01), and after dipyridamole (1.18±0.34 versus 1.77±0.71 mL·min⁻¹·g⁻¹, respectively, P<.01). However, normal subjects showed significantly higher values of MBF both at rest (0.92±0.13 mL·min⁻¹·g⁻¹, P<.05 versus both S and N areas), during pacing tachycardia (1.95±0.64 mL·min⁻¹·g⁻¹, P<.01 versus both S and N areas), and after dipyridamole (3.59±0.71 mL·min⁻¹·g⁻¹, P<.01 versus both S and N areas). The percent change in flow was strictly correlated with the corresponding change in rate-pressure product in normal subjects (r=0.85, P<.01) but not in either S (r=.04, P=NS) or N regions (r=.08, P=NS) of CAD patients.

Conclusions Besides epicardial stenosis, further factors may affect flow response to increasing metabolic demand and coronary reserve in patients with CAD. (Circulation. 1994;90:1696-1705.)

Key Words • coronary disease • microcirculation • blood flow • tomography

The issue of myocardial blood flow (MBF) regulation in patients with coronary artery disease (CAD) has long been a matter of controversy. In fact, although the majority of experimental and clinical literature has been focused on the striking effects of epicardial stenosis, several recent studies report an abnormal microvascular response to endothelium-mediated vasodilators,1 while others document a mild reduction in microvascular response to papaverine2 or dipyridamole.3 Unfortunately, despite its great clinical relevance, the overall effect of this microcirculatory abnormality on the myocardial oxygen demand-supply balance has not been clearly defined4-7; similarly, the MBF response to increased oxygen consumption has not been fully characterized in patients with CAD, mainly because of the limitations of the available methods (such as thermodilution or inert gas washout analysis) in the presence of perfusion heterogeneity.8

The introduction of positron emission tomography for measuring regional MBF has helped to overcome many of the limitations of the previous methods. This technique provides a noninvasive reconstruction of absolute tracer concentrations in the myocardium and thereby absolute measurements of regional MBF.9 Moreover, because of the short half-life of radioisotopes, this technique allows repeated measurements under different conditions during the same session. In the present study, we applied this method to patients with single-vessel disease and without myocardial infarction, aiming to evaluate MBF response to increased metabolic demand (by atrial pacing) and its relation with maximal coronary vasodilatation (elicited by dipyridamole) in myocardial regions supplied by both stenotic and nonstenotic coronary arteries. We used [13N]ammonia as a flow tracer, since its use has been validated in a broad range of flow conditions in both clinical and experimental studies.3-9-12

Methods

Study Population

Patients With CAD

Twenty-four patients (mean age, 56±10 years) were included according to the following criteria: (1) history of angina pectoris; (2) evidence of ischemia either during exercise stress test (ST-segment depression, ≥1.5 mm) (n=7) or during dipyridamole echocardiography test according to the conventional criteria (n=5) or both (n=12); (3) absence of clinical or ECG evidence of previous myocardial infarction; (4) angiographic documentation of single-vessel disease; and (5) absence of arterial hypertension and/or left ventricular hypertrophy (septal and posterior wall thickness ≤11 mm at two-dimensional echocardiography).
Normal Subjects

Nine subjects (mean age, 47±6 years) with atypical chest pain were referred for coronary arteriography to exclude an organic cause of their symptoms. All had normal physical examination, resting ECG, chest radiograph, two-dimensional echocardiogram, and negative exercise stress test. All had normal coronary angiograms and left ventriculograms.

All patients and normal subjects agreed to participate in the study after being informed of the partially investigative nature of the protocol, which was approved by the local Ethics Committee on Human Studies.

Coronary Angiography and Left Ventriculography

Standard coronary angiography in multiple views was performed ≤2 weeks before the study. All angiograms were evaluated by two independent observers who identified the stenotic segments and scored control arteries as either smooth or irregular. Thereafter, all angiograms were evaluated by an automated edge detection system (Mipron; Kontron) providing the percent cross-sectional area reduction of coronary obstruction. Coronary arterial stenosis was located at the left anterior descending (19 patients; mean cross-sectional area reduction, 91±9%) and in the left circumflex coronary artery (5 patients; mean cross-sectional area reduction, 87±12%). Patients with >25% diameter reduction on the remaining coronary arteries were excluded. All patients had a dominant right coronary artery. Biplane left ventriculography was performed in all patients. The 30° right anterior projection was processed by a dedicated computer (Mipron; Kontron). The end-diastolic and end-systolic borders were manually outlined by visual inspection and contrast enhancement. Ectopic and postectopic beats were excluded. Six radial grids and areas were generated from the center of gravity of the ventricular silhouette to the endocardial borders. Regional ejection fraction values obtained in each patient were compared with those obtained in 13 subjects with normal ventricular function and normal coronary arteries: values below 2 SD from the mean ejection fraction of the corresponding region of normal subjects were considered abnormal. Akinesis was defined by the absence of systolic excursion of the left ventricular wall. Mild to moderate dyskinesy was observed in 8 of 24 patients (33%) and was always located in the territory supplied by the stenotic artery (Table 1).

Study Protocol

None of the patients were under β-blocking therapy; calcium-channel blockers and long-acting nitrates were discontinued at least 5 plasma half-lives before the study. All patients were studied after an overnight fasting period; caffeine, theophylline, and theophylline derivatives were withheld for 12 hours before imaging.

A right antecubital vein was cannulated, and a bipolar pacing catheter (Cordis Catheters) was advanced up to the right atrium under fluoroscopy and continuous ECG monitoring. The patients were then brought to the nearby positron tomography room and positioned on the bed of a two-ring ECAT III positron tomograph (ECAT III, CTI Inc) providing three simultaneous cross-sectional planes. Transmission images were acquired up to the collection of 60 million counts and subsequently used to generate attenuation correction factors. Correct positioning was maintained throughout the study by use of a light beam and indelible marks on the subject's torso. Thereafter, 7.4 MBq/kg body wt (0.2 mCi/kg) of [15N]ammonia was infused over a 10- to 20-second period in the left antecubital vein. Dynamic acquisition was started simultaneously with tracer injection; 28 frames were acquired over 8 minutes (16 frames×3 seconds, 11×12 seconds, and 1×200 seconds).

Fifty minutes after the baseline study, the heart rate was increased by external pacemaker connected with the bipolar catheter, starting from 10 beats per minute (bpm) above the patient's heart rate, with 20-bpm steps every minute. The heart rate was increased up to twice the baseline heart rate until angina or ST-segment depression was produced or Wenckebach block developed. Atioventricular Wenckebach block was not treated with intravenous atropine so as not to influence coronary blood flow. At this stage, the heart rate was kept constant for 1 minute, [15N]ammonia was injected, and dynamic acquisition was started with the same protocol as for the baseline study; 2 minutes later, the heart rate was lowered, and the pacemaker was switched off within 1 minute.

Fifty minutes later, dipyridamole (0.56 mg/kg body wt) was infused intravenously over 4 minutes; [15N]ammonia was injected 2 to 3 minutes later, and dynamic acquisition was started with the same protocol as for the baseline study. Aminophylline (120 to 240 mg) was always injected intravenously ≥3 minutes after [15N]ammonia injection to antagonize the effects of dipyridamole.

A three-lead ECG was continuously monitored, while a nine-lead ECG and arterial blood pressure were obtained during [15N]ammonia injection at rest as well as every minute during both pacing and dipyridamole test.

Blood Flow Analysis

Computation of regional MBF was performed according to a previously validated method. Briefly, a small region of interest was drawn within the left ventricular cavity in the last 300-second image to obtain, from serial acquisition, the time-activity curve of [15N]ammonia in the arterial blood. In the last “equilibrium” frame, six circular regions of interest (size 13 to 22 pixels) were drawn (two in the posteroextrasal wall, two in the anterior wall, and two in the septal wall). The values in each myocardial region were then averaged to obtain the mean count density (counts per voxel) in the three walls. Since all the patients had a dominant right coronary artery, the septal wall could not be accurately attributed to either the right or the left coronary system; accordingly, flow values in this region were not considered in patients with stenosis of the left anterior descending coronary artery, while they were attributed to the control region in patients with left circumflex disease.

Regional MBF times [15N]ammonia extraction (MBFE) was then calculated as

$$\text{regional MBF} = \sum_{0}^{C_{m}(t)} C_{m}(t) dt$$

where $C_{m}$ and $C_{a}$ are [15N]ammonia activity concentrations (counts per voxel) in the myocardium (in the last frame) and in the arterial blood (at each time $t$), respectively. The $C_{m}(t)$ curve was fitted by a gamma variate function for the integration. The $rMBF_{e}$ values were then divided by tissue density (1.08 g/mL) to obtain the values in mL·min⁻¹·g⁻¹. Actual MBF values were calculated from $rMBF_{e}$ by use of the experimental relation between ammonia uptake and microsphere-determined MBF observed in animal preparations:

$$\text{regional MBF} = \exp(rMBF_{e} + 0.04)/1.45 - 1.$$

Statistical Analysis

All data are expressed as mean±SD. ANOVA, followed by Sheffé’s test, was used to compare flow values at baseline, during pacing, and after dipyridamole within each group. Paired Student’s $t$ test was also used to compare values between stenotic and remote regions of individual patients; unpaired Student’s $t$ test was used to compare values between groups. Linear regression analysis was performed by the least-squares method. A value of $P<.05$ was considered significant.

Results

Clinical and Hemodynamic Findings

At baseline, no patient showed chest pain or ECG abnormalities. ST-segment depression was observed in
1. Atrial fibrillation showed a normal ECG after 24 and Hypo, hypokinesis.

2. Patients with normal ECG and LAD showed smooth and normal Wall motion and deviation; AK, akinesis; and Hypo, hypokinesis.

3. ST indicates ST segment deviation; LAD, left anterior descending coronary artery; LC, left circumflex coronary artery; Irreg, irregular; AK, akinesis; and Hypo, hypokinesis.

4. *Angina.

5. Of 24 (62%) and 8 of 24 (33%) patients with CAD during atrial pacing and after dipyridamole, respectively. Normal subjects remained asymptomatic and showed a normal ECG during the study.

6. At the time of ammonia injection, rate-pressure product and heart rate were similar in patients with CAD and in normal subjects at baseline (8791 ± 1708 versus 8196 ± 1957 bpm · mm Hg, respectively, P=NS), during atrial pacing.

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<th>Rate-Pressure Product</th>
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Mean 47

SD 6

10 LAD 53 M 94 Smooth Normal 9375 14 850 16 940 No No
11 LAD 62 M 92 Irreg AK 7540 14 700 10 875 No* No
12 LAD 61 M 91 Irreg Normal 6720 21 250 7975 Yes No
13 LAD 60 F 76 Irreg Normal 8840 15 680 10 400 Yes* Yes*
14 LAD 64 M 100 Irreg Hypo 7200 15 600 11 200 No No
15 LAD 70 F 76 Irreg Normal 10 075 17 400 10 800 Yes* No*
16 LAD 58 M 94 Smooth Hypo 9760 19 520 12 000 Yes No
17 LAD 48 M 100 Irreg Hypo 7475 14 300 9750 Yes* Yes*
18 LAD 45 M 93 Irreg Normal 7280 15 600 11 050 Yes No
19 LAD 38 M 76 Smooth Normal 7200 21 000 15 600 No No
20 LAD 61 F 75 Smooth Normal 10 125 18 750 15 750 Yes* Yes*
21 LAD 38 M 85 Smooth Hypo 7350 20 300 11 250 No No
22 LAD 60 M 100 Irreg Normal 8550 16 800 12 800 No No
23 LAD 67 M 92 Smooth Normal 9490 17 250 11 700 Yes Yes
24 LAD 61 M 100 Smooth Normal 6825 13 260 7700 Yes No
25 LAD 61 M 100 Smooth Normal 8120 18 600 12 750 No No
26 LAD 67 M 100 Smooth Normal 8960 17 250 14 100 Yes* Yes*
27 LAD 42 M 93 Smooth Normal 8450 14 560 11 760 No Yes
28 LAD 61 M 93 Smooth Normal 7980 22 500 15 000 Yes No

Mean 57 91

SD 10 9

10 1116 2670 2376
29 LC 65 M 100 Irreg Normal 11 600 19 575 11 475 Yes* No
30 LC 69 M 79 Smooth AK 13 440 21 000 17 000 Yes No
31 LC 55 M 100 Smooth AK 11 625 14 175 13 920 Yes* Yes*
32 LC 52 F 77 Irreg Normal 9520 20 300 13 440 Yes* Yes*
33 LC 57 M 79 Smooth Hypo 7500 14 400 9200 No* No*

Mean 60 87

SD 7 12

2280 3328 2907

ST indicates ST segment deviation; LAD, left anterior descending coronary artery; LC, left circumflex coronary artery; Irreg, irregular; AK, akinesis; and Hypo, hypokinesis.
(17 442±2749 versus 16 355±2169 bpm · mm Hg, respectively, P=NS), and after dipyridamole (12 342±2452 versus 10 888±2586 bpm · mm Hg, respectively, P=NS). Clinical and hemodynamic findings are shown in Table 1.

**Myocardial Perfusion in Stenosis-Related Areas**

MBF in the stenosis-related areas was 0.68±0.14 mL · min⁻¹ · g⁻¹ at rest, 0.92±0.29 mL · min⁻¹ · g⁻¹ during pacing (P<.01 versus baseline), and 1.18±0.34 mL · min⁻¹ · g⁻¹ after dipyridamole (P<.01 versus both baseline and pacing) (Fig 1). Flow values were significantly lower than those of both contralateral areas and normal subjects (Table 2).

A significant inverse relation was observed between severity of epicardial stenosis (percent area reduction) and dipyridamole MBF (r=–.5, P<.03); by contrast, the degree of epicardial obstruction did not correlate with either baseline or pacing MBF (Fig 2).

**TABLE 2. Flow Data in 9 Normal Subjects and 21 Patients With Single-Vessel CAD**

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<tr>
<th>Normal Subjects</th>
<th>Control Regions</th>
<th>Stenotic Regions</th>
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<td>Baseline</td>
<td>0.92±0.13*</td>
<td>0.74±0.18†</td>
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<tr>
<td>Pacing</td>
<td>1.95±0.64§</td>
<td>1.16±0.40§</td>
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<tr>
<td>Pacing/baseline</td>
<td>2.17±0.81†</td>
<td>1.57±0.38†</td>
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<tr>
<td>Dipyridamole</td>
<td>3.59±0.71§</td>
<td>1.77±0.71§</td>
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</table>

Coronary reserve (dipyridamole/resting MBF) = 3.97±0.85‡/ 2.36±0.91‡ | 1.72±0.44‡ |

CAD indicates coronary artery disease. Flow values are expressed in mL · min⁻¹ · g⁻¹.

Resting wall motion abnormalities in stenotic regions were shown by 8 of 24 patients (33%), while 16 showed normal regional function. Rate-pressure products and heart rates were similar in the two subgroups in all study conditions; no differences were observed in the severity of coronary artery stenosis (88±10% versus 89±10%, respectively, P=NS). Abnormal wall motion was not associated with lower MBF values in stenotic regions either at baseline (0.66±0.12 versus 0.69±0.15 mL · min⁻¹ · g⁻¹, respectively, P=NS) or during pacing tachycardia (0.87±0.25 versus 0.95±0.31 mL · min⁻¹ · g⁻¹, respectively, P=NS); however, a larger reduction in dipyridamole MBF (0.94±0.24 versus 1.30±0.33 mL · min⁻¹ · g⁻¹, respectively, P<.02) and, consequently, in coronary reserve (dipyridamole/resting MBF) (1.4±0.33 versus 1.9±0.38, respectively, P<.01) was observed in patients with regional dysfunction (Fig 3).

During pacing tachycardia, the occurrence of ST-segment depression was not associated with a more severe reduction in MBF; however, the 15 patients with ischemic ECG abnormalities showed an incomplete utilization of actual vasodilating capability, while the remaining 9 patients showed a near maximal vasodilation: in fact, pacing MBF was significantly lower than maximal flow capacity, elicited by dipyridamole in the former (0.89±0.23 versus 1.22±0.36 mL · min⁻¹ · g⁻¹, respectively, P<.05) but not in the latter (0.98±0.38 versus 1.14±0.32 mL · min⁻¹ · g⁻¹, respectively, P=NS). During pacing, rate-pressure products (17 854±2848 versus 16 757±2587 bpm · mm Hg, respectively, P=NS) and heart rates (125±14 versus 120±13 bpm, respectively, P=NS) were similar in both subgroups. An absolute decrease in MBF during increased oxygen consumption was observed in 4 of 24 patients, all of whom had ST-segment depression.

The 8 patients with and the 16 patients without ECG changes during dipyridamole infusion showed similar...
values of both maximal MBF (1.19±0.27 versus 1.18±0.49 mL·min\(^{-1}\)·g\(^{-1}\), respectively, \(P=NS\)) and coronary reserve (1.65±0.43 versus 1.79±0.42, respectively, \(P=NS\)). Two patients showed an absolute decrease in MBF associated with ST-segment elevation during pharmacological vasodilatation.

**Myocardial Perfusion in Areas Remote From the Stenotic Coronary Artery**

MBF in areas remote from the stenosis was 0.74±0.18 mL·min\(^{-1}\)·g\(^{-1}\) at rest, 1.16±0.40 mL·min\(^{-1}\)·g\(^{-1}\) during pacing (\(P<.01\) versus baseline), and 1.77±0.71 mL·min\(^{-1}\)·g\(^{-1}\) after dipyridamole (\(P<.01\) versus both baseline and pacing) (Fig 1). Flow values were significantly lower than those in normal subjects under all conditions of the study protocol (Table 2).

No differences in MBF values were observed between 10 vessels scored as irregular (<25% area reduction) and 14 scored as smooth in the three flow conditions.

Wall motion in areas supplied by normal coronary arteries was normal in all patients. Compared with the 16 patients with normal regional function, the 8 patients with resting wall motion abnormalities in poststenotic regions also showed a greater impairment in coronary reserve in these remote areas (1.89±0.50 versus 2.66±0.90, respectively, \(P<.05\)), although the differences in absolute MBF values did not achieve statistical significance (Fig 3).

Patients with and without ST-segment depression during pacing showed similar MBF values in contralateral regions. Both these groups showed significantly (\(P<.02\)) lower MBF values compared with the normal population. Also in these contralateral areas, the 15 patients with ST-segment depression during pacing showed an incomplete utilization of actual vasodilating capability, while the remaining 9 patients showed a near-maximal vasodilation. In fact, pacing MBF was significantly lower than maximal flow capacity, elicited by dipyridamole, in the former (1.11±0.34 versus 1.90±0.82 mL·min\(^{-1}\)·g\(^{-1}\), respectively, \(P<.05\)) but not in the latter (1.24±0.49 versus 1.55±0.43 mL·min\(^{-1}\)·g\(^{-1}\), respectively, \(P=NS\)).

The 8 patients with and the 16 patients without ECG changes during dipyridamole infusion showed similar values of maximal MBF (1.86±0.70 versus 1.72±0.73 mL·min\(^{-1}\)·g\(^{-1}\), respectively, \(P=NS\)). Both these values were significantly (\(P<.01\)) reduced with respect to normal subjects.

**Relation Between Rate-Pressure Product and Myocardial Perfusion**

In normal subjects, percent increase in rate-pressure product during pacing showed a significant correlation with the corresponding percent increase in MBF (\(r=.85, P<.01\)) (Fig 4).

By contrast, in patients with single-vessel CAD, this correlation was completely absent, not only in myocardial regions supplied by stenotic coronary arteries (\(r=.08, P=NS\)) but also in remote contralateral areas (\(r=.04, P=NS\) (Fig 4).

As expected, in normal subjects as well as in stenotic and remote regions of patients with single-vessel CAD, percent changes in rate-pressure product after dipyridamole did not correlate with percent changes in MBF.

**Perfusion Inhomogeneities During Pacing Tachycardia and After Dipyridamole**

In normal subjects, anterior/posterolateral wall flow ratio was 1.02±0.11 and 1.04±0.12 during pacing and after dipyridamole, respectively. Accordingly, stenotic/control area MBF ratios <0.8 (mean, 2 SD) were considered to reflect perfusion inhomogeneity. According to this arbitrary cutoff, 13 of 24 patients (52%) showed a perfusion defect during pacing. Compared with those with homogeneous perfusion, these patients showed a significantly lower flow in stenotic regions during pacing (0.77±0.18 versus 1.10±0.30 mL·min\(^{-1}\)·g\(^{-1}\), respectively, \(P<.01\)) despite the presence of similar values of coronary reserve (dipyridamole/resting
flow, 1.78±0.51 versus 1.70±0.29, respectively, P=NS). Regional MBF in contralateral regions was similar in these two subgroups (1.13±0.33 versus 1.2±0.49 mL min⁻¹ g⁻¹, respectively, P=NS) (Fig 5). ST-segment depression was observed in 9 of 13 and in 6 of 11 patients with and without perfusion defects, respectively (P=NS).

After dipyridamole, 18 of 24 patients (75%) showed a perfusion defect. With respect to those with homogeneous myocardial perfusion, these patients did not show a greater reduction in maximal flow in stenotic regions (1.16±0.38 versus 1.24±0.20 mL min⁻¹ g⁻¹, respectively, P=NS); rather, they showed higher MBF values in contralateral areas (1.95±0.72 versus 1.22±0.28 mL min⁻¹ g⁻¹, P<0.03) (Fig 5). All 8 patients with ischemic ECG changes after dipyridamole showed perfusion defects.

**Discussion**

The major finding of the present study is that flow response to increased oxygen consumption is reduced in the whole myocardium of patients with single-vessel CAD. As a matter of fact, a reduced MBF response to pacing tachycardia and to dipyridamole infusions was observed not only in myocardial regions supplied by stenotic vessels but also in remote "control" regions supplied by nonstenotic arteries. Furthermore, the occurrence of ECG ischemia during increased oxygen consumption did not appear to be related to a greater reduction in maximal flow capacity in areas subtended by severely stenotic coronary arteries but rather to an incomplete utilization of coronary reserve during pacing in both stenotic and contralateral areas. Finally, a physiological relation between increase in rate-pressure product and increase in MBF was observed in normal subjects during pacing, while it was absent in both stenotic and contralateral regions of patients with single-vessel CAD.

**Comparison With Previous Studies**

The hydraulic effects of coronary stenosis have been elegantly defined both in animal models and in patients with CAD; however, it has not been fully established whether, in the latter, coronary atherosclerosis might affect the oxygen demand-supply balance by further factors besides epicardial obstruction. Using washout technique, several authors have reported a global alteration in perfusion response to increased heart rate in patients with CAD, independently of the presence of stenosis and/or ischemia. Others have reported a normal behavior of MBF up to the onset of ST-segment depression and/or angina. A similar degree of discrepancy has been reported when great cardiac vein thermodilution is used. More recently, Nabel and colleagues have observed, with Doppler catheter and quantitative angiography, a reduced flow response to pacing tachycardia in five vessels with "insignificant" atherosclerosis. Several factors may explain these disappointing discordancies. On one hand, the limitations of xenon and thermodilution techniques in measuring regional MBF under conditions of perfusion heterogeneity might have hampered the precise identification of stenotic and control beds. On the other hand, the high prevalence of patients with dilated cardiomyopathy, coronary atherosclerosis, and hypertension and of patients treated with β-blockers in both subjects with normal coronary arteries and patients with CAD might have hampered the precise definition of normal MBF response.

Positron emission tomography overcomes many of the limitations related to perfusion regionality, and when applied to patients with single-vessel disease, it allows an accurate identification of vascular territories. Moreover, because of its noninvasive nature, it can be easily applied in a truly normal control population. Using this technique, previous studies reported a difference in coronary reserve between collateral-dependent and control territories in patients with CAD or between stenotic or remote regions of CAD patients and normal subjects. Very concordant findings have already been reported by our group, despite differences in absolute flow values probably related to the use of different tracers or to the different kinetic model adopted for MBF calculation. Similarly, in the present study, the greatest impairment in myocardial perfusion was ob-
Microvascular Dysfunction in the “Control” Myocardium of Patients With CAD

The major finding of the present study is a reduced flow response to atrial pacing in the myocardium supplied by angiographically normal coronary arteries of patients with CAD. This observation expands the physiological relevance of the impaired vasodilating capability in these “control” regions, which has already been reported in the literature and attributed to the endothelial dysfunction caused by atherosclerosis.

In contrast to dipyridamole infusion, which directly dilates coronary microvessels without modifying metabolic demand, pacing tachycardia increases myocardial oxygen consumption, which, in turn, causes coronary vasodilation. Normal subjects and patients showed similar increases in rate-pressure product during pacing, thus ruling out differences in the main hemodynamic determinants of oxygen consumption. Therefore, the present data would suggest a role for microvascular dysfunction in the abnormal MBF response to pacing. In agreement with this hypothesis, several authors have observed a close correlation between the extent of endothelial dysfunction associated with atherosclerosis and the failure of coronary flow to increase during either cold pressor test or atrial pacing tachycardia.

However, a reduced flow response in the face of a normal increase in metabolic demand should have been associated with myocardial ischemic dysfunction: this phenomenon has never been described in myocardial regions supplied by normal vessels in patients with CAD. Thus, the microvascular dysfunction should be paralleled by unknown metabolic changes leading to lower flow requirements for a similar rate-pressure product. 
product. In this regard, Przyklenk and colleagues demonstrated that the occurrence of ischemia in one myocardial area also increases the endurance against coronary occlusion in the contralateral "virgin myocardium." Similarly, Uren and coworkers observed a reduced flow response to pacing tachycardia, in regions remote from coronary stenosis, associated with an abnormally increased glucose and alanine extraction.

Unfortunately, the present study does not assess whether abnormal MBF behavior is the cause or the effect of an altered metabolism; however, it demonstrates that, whatever the mechanism, coronary atherosclerosis is associated with abnormalities of coronary microcirculation other than the effects of epicardial stenosis.

Flow Regulation in Dysynergic Myocardium

Baseline wall motion abnormalities were observed in 8 of 24 patients, always in the regions supplied by a stenotic coronary artery. Although patients with either a history of prolonged chest pain or ECG markers of previous myocardial infarction were carefully excluded, it cannot be ruled out that small foci of fibrosis were present in some cases. However, myocardial ischemia was induced by exercise and/or dipyridamole, thus identifying the presence of myocardial viability in all patients.

Despite its great clinical relevance, the pathogenesis of chronic contractile impairment in regions supplied by a severely stenotic coronary artery has not been conclusively clarified. A downregulation in myocardial function may parallel the decrease in coronary blood flow, so that a restoration of the energetic balance may occur, avoiding maintenance of ischemia. This phenomenon might represent a primary myocardial adaptation to the reduction in MBF, as well as the consequence of frequent ischemic episodes. On one hand, persistent wall motion abnormalities have been demonstrated after repetitive ischemic episodes. On the other hand, depression of contractile performance has been extensively demonstrated during sustained low-flow perfusion in animal models: initial ischemia subsides and both metabolic pattern and energy stores progressively normalize, while reduced contractility persists.

Interestingly, a residual vasodilating capability was observed in dysynergic segments. The persistence of a coronary reserve in the face of reduced resting perfusion and function has been already reported by experimental and clinical studies; this paradox has been attributed to the capability of the myocardium to actively downregulate its own oxygen demand below the actual flow availability, thus restoring coronary tone. In agreement with these previous studies, the finding of a residual vasodilating capability—elicited by dipyridamole and by pacing—might indicate that, in patients with CAD, chronic dysfunction is caused not only by the flow restriction due to epicardial obstruction but also by a chronic metabolic alteration.

Microvascular Response to Myocardial Ischemia

Demand-induced ischemia occurs when the increase in oxygen consumption exceeds oxygen delivery; other authors have hypothesized that, under this condition, the coronary microvasculature is vasodilated to the maximum possible extent, although a direct and conclusive demonstration of this hypothesis has not been obtained in patients with CAD. The data of the present study do not support the assumption of a maximal vasodilation in the ischemic myocardium. In fact, the 15 patients with ST-segment depression during pacing showed an incomplete utilization of actual vasodilator reserve elicited by dipyridamole; this phenomenon was especially evident in two patients who showed an absolute flow reduction during pacing (to 88% of baseline) despite a substantial coronary reserve (1.8). By contrast, the nine patients without ischemic response to atrial pacing showed a near maximal vasodilation in stenosis-related areas despite similar increases in rate-pressure product. Interestingly, a similar behavior was also observed in contralateral areas supplied by angiographically normal vessels. Possible explanations for this phenomenon may be the hemodynamic sequelae of ischemic left ventricular dysfunction, an abnormal microvascular response to signals of increased metabolic demand, or the occurrence of generalized vasocostriction during ischemia. The present study does not allow understanding of the mechanism of this abnormal behavior but suggests that regional ischemia may also affect MBF regulation in addition to epicardial stenosis and atherosclerotic microvascular dysfunction. The occurrence of ST-segment depression after dipyridamole did not identify the patients with largest reductions in coronary reserve. However, similar values of MBF may have been associated with different transmural flow distributions and with an absolute reduction in MBF of the subendocardium leading to ECG evidence of ischemia. Because of the limited spatial resolution of positron emission tomography, this issue cannot be solved. In two patients, an absolute MBF reduction in ischemic regions associated with transmural ischemia (ST-segment elevation) occurred after dipyridamole; both cases showed a coronary occlusion at baseline angiography. It is conceivable that, in these patients, a coronary steal occurred, leading to the disappearance of collateral perfusion, as hypothesized on the basis of previous data.

Relation Between Rate-Pressure Product and Myocardial Perfusion

Several authors have reported that increases in rate-pressure product are strictly paralleled by increases in MBF in single individuals. In the present study, this relation could not be investigated owing to the limitations of our method, which does not allow a continuous monitoring of MBF during periods of increased metabolic demand. However, in the whole of our population of normal subjects, a close correlation between percent increases in rate-pressure product (r = .85) and corresponding percent increases in MBF was observed. By contrast, in agreement with data obtained by Zeiher and colleagues during cold pressor test, this relation was lost in patients with single-vessel CAD. In stenotic regions, this phenomenon might have been caused by interpatient differences in the severity of epicardial obstructions; however, its presence in remote "virgin" myocardium suggests an uncoupling of coronary blood flow from rate-pressure product. If this phenomenon exists in the control regions of patients with single-vessel CAD, it might also occur in stenotic myocardial areas. According to this hypothesis,
the analysis of ischemic threshold by maximal rate-pressure product during exercise might not be a marker of the severity of epicardial stenosis.

**Perfusion Defects During Pacing and After Dipyridamole**

Atrial pacing and dipyridamole appeared to induce regional perfusion defects with different pathophysiological mechanisms. In fact, in agreement with previous observations, perfusion defects during increased oxygen consumption identified those patients with lower flow increase in the stenosis-related regions. By contrast, perfusion defects after dipyridamole mostly reflected significant increases in flow in control areas compared with poststenotic territories. In fact, after pharmacological vasodilation, patients with or without perfusion defects showed similar MBF values in poststenotic regions, while the latter showed a more severe “global” reduction in perfusion.

This observation might explain the paradoxical reduction in sensitivity of perfusion scintigraphy in patients with single-vessel CAD: theoretically, these patients should represent the ideal model to amplify perfusion differences between regions supplied by the stenotic artery and the remaining normal myocardium; nevertheless, the reported values of sensitivity are consistently lower in these patients than in those with multivessel disease. It is conceivable that the abnormal microvascular adaptation to exercise or dipyridamole may blunt perfusion differences related to the stenosis. Although this phenomenon might also operate in multivessel disease, the relatively higher incidence of myocardial ischemia in this condition might allow the detection of a larger number of perfusion defects and of patients with CAD as well.

**Limitations**

This study provides insight into the pathophysiology of MBF regulation in CAD. However, it is not possible from our data to say whether, besides the hydraulic effects of coronary stenosis, the flow abnormalities of CAD patients are caused by a global microvascular dysfunction, by the occurrence of regional myocardial ischemia, or by a primary myocardial alteration. Probably, the measurement of regional oxygen consumption, which is now feasible with [11C]acetate and positron emission tomography, might have provided a more detailed understanding of the mechanism underlying this phenomenon. Unfortunately, this possibility was not present in our laboratory at the moment of study planning.

Because of the limited spatial resolution of positron emission tomography, transmural differences in regional MBF could not be investigated in the present study. Actually, this point might be of crucial relevance in the areas supplied by the stenotic coronary artery, in which the driving pressure is markedly affected by the pressure gradient caused by the stenosis. However, in the regions remote from the stenosis, an abnormal transmural distribution of flow would also imply the presence of a microvascular dysfunction as hypothesized on the basis of these data.

The apparent reduction in vasodilating capability in “control” regions might have been caused by the hemodynamic sequelae of ischemia. However, MBF values were markedly abnormal regardless of the presence of ST-segment depression during either pacing tachycardia or dipyridamole infusion, suggesting that the ischemic dysfunction cannot be considered to be totally responsible for flow impairment alone.

Caffeine and theophylline derivatives were withheld for at least 12 hours. Although significant levels of these compounds might have been present in the vascular compartment at this time, no patient was under treatment with these drugs, and therefore the very small residual concentration due to dietary intake should not induce a marked limitation of the effects of dipyridamole. Moreover, this limitation should also affect results obtained in normal subjects.

The factor used in correcting for variable ammonia extraction was derived from experiments in dogs, which may have led to some degree of uncertainty. However, any possible underestimation of MBF at high flow rates would imply an underestimation of the actual impairment of coronary reserve in CAD patients as a result of the relatively greater underrating of maximal flow in normal subjects.

**Conclusions**

The data of the present study demonstrate that vasodilating capability as well as the relation between rate-pressure product and MBF is altered in the whole myocardium of patients with single-vessel CAD. This alteration might occur at any point in the chain linking myocardial oxygen demand to MBF (ie, from the myocardium to the vascular cells).

These findings need further confirmation by similar or different methods able to provide absolute quantitative measurements of regional MBF; however, they add to the recently growing evidence that coronary atherosclerosis affects MBF regulation by mechanisms more complex than the simple epicardial artery obstruction. The impact of these observations is such as to modify our current understanding of the pathophysiology of coronary circulation in CAD. The proper use of positron emission tomography, in this field, allows the detection of phenomena that are absent in the experimental situation. These phenomena are characteristic of human cardiac disorders and are barely detectable by other clinical diagnostic tools.

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