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Microvascular Dysfunction in Collateral-Dependent Myocardium

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Objectives. **The aim of this study was to evaluate myocardial blood flow regulation in collateral-dependent myocardium of patients with coronary artery disease.**

Background. **Despite great clinical relevance, perfusion correlates of collateral circulation in humans have rarely been estimated by quantitative methods at rest and during stress.**

Methods. **Nineteen patients with angina and isolated occlusion of the left anterior descending (n = 14) or left circumflex (n = 5) coronary artery were evaluated. Using positron emission tomography and nitrogen-13 ammonia, we obtained flow measurements at baseline, during atrial pacing-induced tachycardia and after intravenous administration of dipyridamole (0.56 mg/kg body weight over 4 min). Flow values in collateral-dependent and remote areas were compared with values in 13 normal subjects.**

Results. **Flow at rest was similar in collateralized and remote myocardium (0.61 ± 0.11 vs. 0.63 ± 0.17 ml/min per g, mean ± 1 SD), and both values were lower than normal (1.00 ± 0.20 ml/min per g, $p < 0.01$). During pacing, blood flow increased to 0.83 ± 0.25 and 1.11 ± 0.39 ml/min per g in collateral-dependent and remote areas, respectively ($p < 0.05$ vs. baseline); both values were lower than normal (1.86 ± 0.61 ml/min per g, $p < 0.01$). Dipyridamole induced a further increase in perfusion in remote areas (1.36 ± 0.57 ml/min per g, $p < 0.01$ vs. pacing) but not in collateral-dependent regions (0.93 ± 0.37 ml/min per g, p = NS vs. pacing); again, both values were lower ($p < 0.01$) than normal (3.46 ± 0.78 ml/min per g). Dipyridamole flow in collateral-dependent myocardium was slightly lower in patients with poorly developed than in those with well developed collateral channels (0.75 ± 0.29 vs. 1.06 ± 0.38 ml/min per g, respectively, $p = 0.06$); however, the former showed higher flow inhomogeneity (collateral/control flow ratio 0.58 ± 0.10 vs. 0.81 ± 0.22, respectively, $p < 0.02$). A linear direct correlation was observed between flow reserve of collateral-dependent and remote regions ($r = 0.83$, $p < 0.01$).**

Conclusions. **Despite rest hypoperfusion, collateral-dependent myocardium maintains a vasodilator reserve that is almost fully utilized during increases in oxygen consumption. A global microvascular disorder might hamper adaptation to chronic coronary occlusion.**

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Despite its great clinical and therapeutic relevance, the exact role of coronary collateral circulation in flow regulation of the myocardium supplied by severely stenotic or occluded coronary arteries is still uncertain (1). Early clinical studies (2–5) provided contradictory conclusions that were shown to be a result of problems in patient selection and limitations of angiography for assessing collateral channels (1). Moreover, the most common clinical method for evaluating myocardial perfusion—myocardial scintigraphy—only delineates perfusion homogeneity without measuring regional blood flow (6,7). Accordingly, insights into the efficacy of collateral channels have been obtained only by relative comparison of collateral-dependent and remote regions that are assumed to be truly normal (7). Recently, several investigators (8–12) demonstrated that, in patients with stable angina and single-vessel disease, a dysfunction of the resistance vessels decreases vasodilator capacity in areas supplied by angiographically normal coronary arteries. This microvascular dysfunction might affect blood flow regulation in the whole heart and smooth perfusion differences between stenotic and remote "control" regions, independently from the resistance offered by the epicardial obstruction (12). Thus, a full comprehension of collateral circulation should imply the measurement of absolute perfusion rate in collateral-dependent areas at rest and during stress.

The introduction of positron emission tomography for measuring regional myocardial blood flow has overcome many of the limitations of the previous methods (13). This technique provides a noninvasive means to measure absolute tracer concentration in the myocardium and, thus, makes possible absolute quantitation of regional myocardial perfusion (9–12,14,15). In the present study, we applied this method to

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patients without myocardial infarction and with single-vessel disease characterized by *chronic occlusion of a major coronary branch*. Our aim was to evaluate flow response to increasing metabolic demand and its relation to coronary reserve in collateral-dependent myocardial regions.

Methods

Study group. *Patients with coronary artery disease.* Nineteen patients (mean age ±SD 59 ± 8 years) were selected for the study on the basis of the following criteria: 1) history of typical angina pectoris; 2) lack of anamnestic or electrocardiographic (ECG) evidence of myocardial infarction; 3) clear-cut signs of myocardial ischemia on exercise stress testing or dipyridamole echocardiography testing or both; 4) isolated complete occlusion of the left anterior descending (14 patients) or left circumflex (5 patients) coronary artery; 5) absence of arterial hypertension or left ventricular hypertrophy (septal or posterior wall ≤11 mm on echocardiography); 6) absence of valvular disease or other detectable cardiac disorders.

Normal subjects. We also studied 13 subjects (mean age 49 ± 8 years) with atypical chest pain who were referred for coronary arteriography to exclude an organic cause of their symptoms. All had normal findings on physical examination, rest ECG, echocardiogram, exercise stress test, coronary angiography and left ventriculography.

All patients and normal subjects gave written consent to participate in the study after being informed of the partially investigative nature of the protocol, which was approved by the local Ethical Committee on Human Studies. The results obtained in 8 of the 19 patients and 9 of the 13 normal subjects have been published previously in a report (12) demonstrating an abnormal vasodilating capability in myocardial regions supplied by nonstenotic coronary arteries.

Coronary angiography and quantitative analysis of angiograms. Standard coronary angiography in multiple views was performed according to the Judkins technique ≤2 weeks before the study. At least five and two projections were acquired for the left and the right coronary artery, respectively. Patients were selected because of complete occlusion of the left anterior descending or the left circumflex coronary artery. Patients with ≥25% area reduction of the remaining coronary arteries were excluded from the study. The score of collateral circulation was based on the injection that best opacified the occluded vessel: 0 = none; 1 = filling of side branches without visualization of the epicardial segment; 2 = partial filling of the epicardial segment by way of collateral vessels; 3 = complete filling of the epicardial segment by way of collateral vessels (16). Biplane left ventriculography was performed in all patients. The 30° right anterior projection was processed by a dedicated computer (Mipron, Kontron, Germany), as previously described (17). Regional ejection fraction values were considered abnormal when they were <2 SD from the mean normal value obtained in the 13 normal subjects.

Study protocol. Quantitation of regional myocardial blood flow at rest, during pacing-induced tachycardia and after dipyridamole infusion was obtained by means of nitrogen-13 (^{13}N)-ammonia (half-life 9.8 min) and positron emission tomography. All patients were studied after an overnight fasting period; caffeine and theophylline were withheld at least 12 h before imaging. Antianginal therapy was interrupted 24 h (for nitrates) or 48 h (for calcium channel blockers) before the study; no patient was receiving beta-adrenergic blocking agents.

A pacing study was not performed in 8 of the 19 patients and in 4 of the 13 normal subjects because of technical difficulties or refusal of right heart catheterization. A bipolar pacing catheter was advanced up to the right atrium through a right antecubital vein under fluoroscopy and continuous ECG monitoring. The patients were then taken to the nearby positron tomography room and positioned on the bed of a two-ring positron tomograph (ECAT III, Siemens, CTI) 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 with the use of a light beam and indelible marks on the subject's torso. Thereafter, 7.4 MBq/kg body weight (0.2 mCi/kg) of ^{13}N-ammonia was infused over 10 to 20 s in the left antecubital vein. Dynamic acquisition was started simultaneously with tracer injection; 28 frames were acquired over 8 min (16 frames × 3 s, 11 × 12 s and 1 × 300 s).

Fifty minutes after the baseline study, the heart rate was increased by using an external pacemaker connected with the bipolar catheter, starting from 10 beats/min over the patient's heart rate, with 20 beats/min 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. At this stage, the heart rate was kept constant for 1 min, ^{13}N-ammonia injected and dynamic acquisition started with the same protocol as for the baseline study; 2 min later the heart rate was decreased and the pacemaker was switched off within 1 min.

Fifty minutes later, dipyridamole (0.56 mg/kg) was infused intravenously over 4 min; ^{13}N-ammonia was injected 2 to 3 min later and dynamic acquisition started. Aminophylline (120 to 240 mg) was always infused intravenously ≥3 min after injection of ^{13}N-ammonia to antagonize the effects of dipyridamole.

A three-lead ECG was continuously monitored, a nine-lead ECG and arterial blood pressure were obtained during ^{13}N-ammonia injection at rest and every minute during both the pacing and dipyridamole tests.

Regional myocardial blood flow analysis. Computation of regional myocardial blood flow was performed according to a method previously validated in our laboratory (14). With this method, positron emission tomographic measurements of regional blood flow showed a close correlation ($r = 0.96$, slope 1.08) with those obtained with the reference technique of radioactive microspheres in a broad range of flow values (from 0.2 to 5 ml/min per g). On the last 300-s frame, seven regions

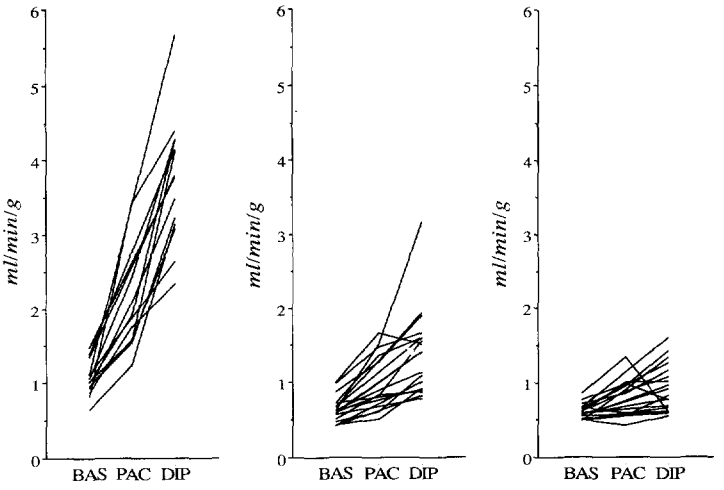


Figure 1. Individual flow values at rest (BAS), during pacing-induced tachycardia (PAC) and after administration of dipyridamole (DIP). **Left,** Normal regions. **Middle,** Control regions; flow values were lower than normal in all conditions of the study protocol. **Right,** Stenotic regions; significant vasodilation was observed despite a marked reduction in rest blood flow.

of interest were drawn (one in the left ventricular cavity and two each in the posterolateral, anterior and septal walls). In each region, the count density (counts/voxel) was obtained after correction for decay and dead time loss, and the values were then averaged to obtain the mean tracer concentration in the septum and the anterior and the posterolateral wall, respectively.

Regional myocardial blood flow times ^{13}N-ammonia extraction (rMBFe) was calculated as rMBFe = Cm × 60/∫ Cb(t) × dt, where Cm and Cb are ^{13}N activity concentrations (counts/voxel) in the myocardium (as measured in the last frame) and in the arterial blood (at each time t), respectively. The curve Cb(t) was fitted by a gamma variate function for the integration. The final rMBFe, expressed as ml/min per ml, was then converted to ml/min per g by dividing by tissue gravity (1.08 g/ml).

To correct for the loss in linearity between ^{13}N-ammonia uptake and blood flow at high flow rates, rMBFe values were corrected by using an equation obtained in the experimental preparation from the relation between rMBFe and rMBF by radioactive microspheres (14): rMBF = Exp ((rMBFe + 0.04)/1.45) − 1. Regional blood flow values were obtained by using such an algorithm.

Because all patients had a normal dominant right coronary artery supplying the posterior septum, accurate attribution of this myocardial segment to the left or right coronary system could not be accomplished with the present protocol; accordingly, myocardial blood flow in the septal wall was not considered. Therefore, the anterior and posterolateral walls were considered as the distribution territories of the left anterior descending and left circumflex coronary artery, respectively.

Statistics. All values are expressed as mean value ± 1 SD. A paired *t* test was used to compare continuous data between collateral-dependent and remote regions in patients with coronary artery disease. Comparison of patients and normal subjects as well as comparison of blood flow values in different conditions of the study protocol in each group was performed by using analysis of variance (ANOVA) and the Newman-Keuls procedure for multiple comparisons. Chi-square analysis was performed to determine the significance in rate of occurrence. Linear regression analysis was performed by least squares method. Differences in regression lines between patients and normal subjects were tested by using covariance analysis. A p value < 0.05 was considered significant.

Results

Clinical and angiographic findings. At baseline, no patient showed chest pain or ECG abnormalities. ST segment changes were observed in 7 (64%) of 11 and 10 (53%) of 19 patients with coronary artery disease, during atrial pacing and after dipyridamole infusion, respectively. Normal subjects remained asymptomatic and had normal ECG findings during the study.

At the time of tracer injection, the rate-pressure product was similar in patients with coronary artery disease and normal subjects at baseline (8,767 ± 2,256 vs. 8,822 ± 2,498 beats/min·mm Hg, respectively, p = NS) during pacing (16,296 ± 2,093 vs. 16,355 ± 2,169 beats/min·mm Hg, respectively, p = NS) and after dipyridamole (11,198 ± 2,299 vs. 11,656 ± 3,694 beats/min·mm Hg, respectively, p = NS). On angiography, collateral circulation was scored as poorly developed (grade 0 to 1) or well developed (grade 2 to 3) in 8 and 11 of the 19 patients, respectively. The average left ventricular ejection fraction was 0.58 ± 0.12; 6 (32%) of the 19 patients showed wall motion abnormalities in the distribution territory of the occluded artery: 4 and 2 patients showed hypokinesia and akinesia, respectively. Wall motion in remote regions was normal in all.

Myocardial blood flow in normal subjects. The average flow value in normal subjects was 1.00 ± 0.20 ml/min per g at baseline, 1.86 ± 0.61 ml/min per g during pacing-induced tachycardia ($p < 0.01$ vs. baseline) and 3.46 ± 0.78 ml/min per g after dipyridamole infusion ($p < 0.01$ vs. both baseline and pacing) (Fig. 1). No differences were observed between the anterior and posterolateral wall at baseline, during pacing tachycardia or after dipyridamole.

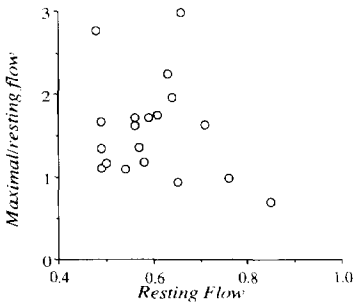


Figure 2. Relation between perfusion at rest (X axis) and vasodilator reserve (Y axis) in collateral-dependent myocardium. These two variables are not correlated, suggesting that a reduction in blood flow at rest does not imply the exhaustion of vasodilating capability.

Blood flow in collateral-dependent myocardium. Collateral-dependent regions showed abnormally low flow values at rest (0.61 ± 0.11 ml/min per g, $p < 0.01$ vs. values in normal subjects); an obvious reduction in regional perfusion (>2 SD from the mean normal value, i.e., <0.60 ml/min per g) was observed in 11 (58%) of the 19 patients. All six patients with a wall motion abnormality showed flow values >2 SD below normal values.

During pacing, mean blood flow increased to 0.83 ± 0.25 ml/min per g ($p < 0.05$ vs. baseline); this value was reduced with respect to normal subjects ($p < 0.01$). After dipyridamole, mean blood flow increased to 0.93 ± 0.37 ml/min per g ($p < 0.05$ vs. baseline, p = NS vs. pacing); this value was lower ($p < 0.01$) than that in normal subjects (Fig. 1). A residual vasodilating capability was maintained even in severely hypoperfused regions, and no correlation was observed between rest blood flow and coronary reserve (Fig. 2). Maximal flow capacity was slightly though not significantly lower in the 6 patients with than in the 13 patients without a wall motion abnormality in the collateral-dependent regions (0.73 ± 0.18 vs. 1.02 ± 0.40 ml/min per g, respectively, p = 0.11).

Blood flow in remote regions supplied by nonstenotic vessels. Regions supplied by angiographically normal coronary arteries showed reduced flow values at rest (0.63 ± 0.17 ml/min per g, $p < 0.01$ vs. normal subjects); this value was similar to that observed in collateral-dependent areas; an obvious reduction (>2 SD from the mean normal value) was observed in 7 (37%) of the 19 patients.

During pacing tachycardia, average myocardial blood flow increased to 1.11 ± 0.39 ml/min per g ($p < 0.05$ vs. baseline). This value was higher ($p < 0.01$) than pacing flow in collateral-dependent regions; however, it was lower than normal ($p < 0.01$). After dipyridamole, mean flow increased to 1.36 ± 0.57 ml/min per g ($p < 0.01$ vs. both pacing and baseline). Again, this value was higher ($p < 0.01$) than flow after dipyridamole in collateral-dependent regions; however, it was markedly ($p < 0.01$) lower than that in normal subjects (Fig. 1).

Relation between angiographic appearance of collateral circulation and myocardial blood flow. The angiographic score of collateral circulation was not associated with differences in baseline myocardial perfusion or function. In fact, blood flow was similar in the 11 patients with well visualized and in the 8 patients with poorly visualized collateral circulation (0.63 ± 0.09 vs. 0.58 ± 0.13 ml/min per g, respectively, p = 0.34). Abnormal wall motion was observed in 3 of 11 and 3 of 8 patients in the respective groups. During pacing, myocardial blood flow was similar in the six patients with well visualized and in the five patients with poorly visualized collateral circulation (0.84 ± 0.17 vs. 0.82 ± 0.34 ml/min per g, respectively, p = NS). A slight though not significant difference was observed in maximal (dipyridamole) blood flow (1.06 ± 0.38 vs. 0.75 ± 0.29 ml/min per g, respectively, p = 0.06) and coronary reserve (1.68 ± 0.42 vs. 1.36 ± 0.65, respectively, p = 0.21) (Fig. 3 and 4).

The angiographic score of collateral circulation was associated with differences in the degree of flow inhomogeneity; in fact, the ratio between flow in collateral-dependent regions and in remote "control" areas was lower in patients with poorly developed collateral vessels both during pacing (0.64 ± 0.11 vs. 0.92 ± 0.26, respectively, $p < 0.05$) and after dipyridamole (0.58 ± 0.10 vs. 0.81 ± 0.22, respectively, $p < 0.02$) (Fig. 3 and 4).

Reduction in myocardial blood flow during coronary vasodilation. During pacing, an absolute flow decrease in one or more myocardial regions was observed in six patients, all of whom showed ST segment depression. In four of six areas, a significant vasodilator reserve (i.e., an absolute increase in blood flow) was observed after dipyridamole. The flow reduction during pacing was not associated with higher flows in remote areas or with differences in rate-pressure products or in angiographic score of collateral vessels with respect to values in the remaining patients.

After dipyridamole, a decrease in regional perfusion in one or more regions occurred in six patients, all of whom had ST segment changes. Interestingly, five of nine areas with decreased perfusion had shown significant vasodilation during pacing. None of the six patients had an absolute decrease of myocardial perfusion in regions supplied by nonstenotic vessels. With respect to the remaining 13 patients, those with dipyridamole-induced reductions in collateral-dependent myocardial perfusion showed lower maximal flow (1.06 ± 0.39 vs. 1.55 ± 0.69 ml/min per g, respectively, $p < 0.05$) and coronary reserve (1.71 ± 0.4 vs. 2.54 ± 1.1, respectively, $p < 0.01$) in remote areas as well (Fig. 5). This behavior was not associated with a different angiographic collateral vessel score or with differences in baseline wall motion.

Relation between rest blood flow and perfusion reserve in collateral-dependent and remote regions. In normal subjects, dipyridamole flow values in the anterior and posterolateral walls were significantly correlated ($r = 0.81$, $p < 0.01$); the slope of the regression line was 0.99. In patients with coronary occlusion, blood flows in collateral-dependent regions were closely correlated with corresponding values in remote areas ($r = 0.83$, $p < 0.01$); this regression line was not statistically different from the line of identity; however, its slope (0.38) was significantly ($p < 0.05$) lower than that observed in normal

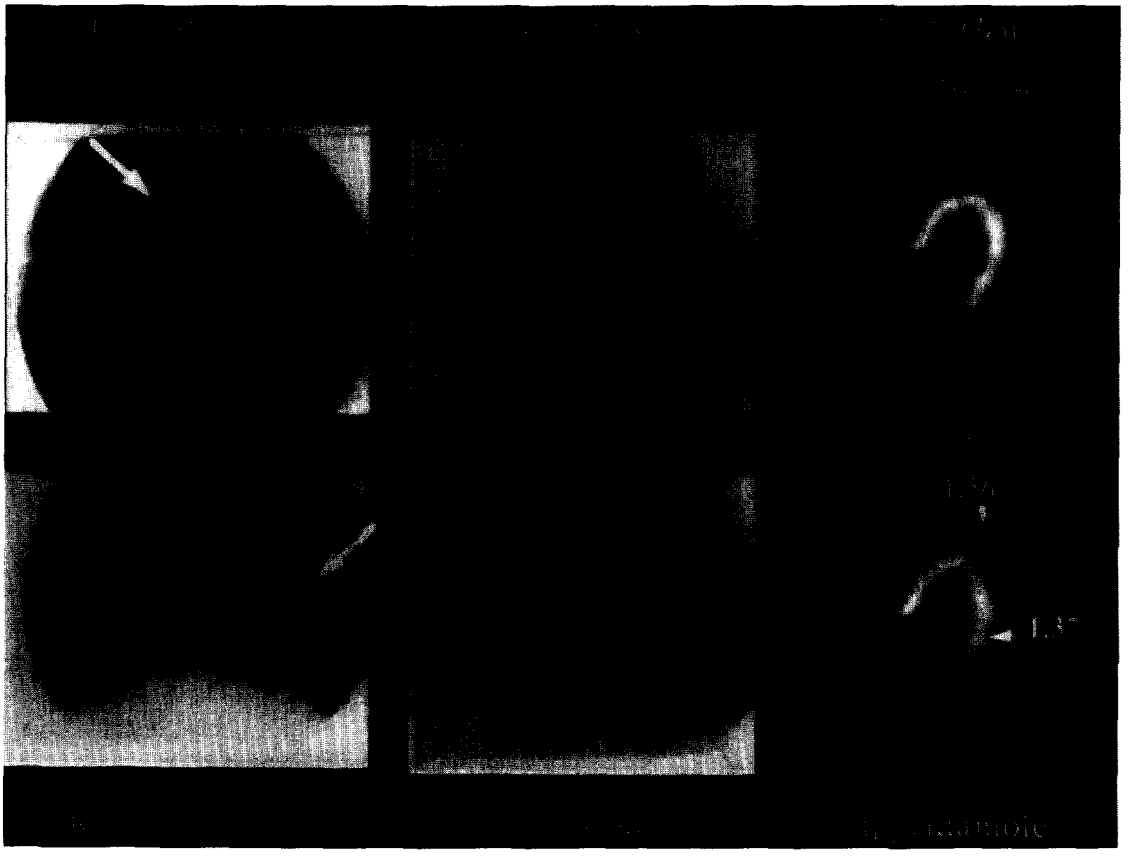


Figure 3. Coronary angiograms (**left panels**), contrast ventriculograms (**center panels**) and positron emission tomographic (PET) images of blood flow distribution (**right panels**). This patient had chronic occlusion of the left anterior descending coronary artery and well developed collateral circulation to the distal portion of the vessel (**arrows**); despite the occlusion, dipyridamole perfusion imaging was quite homogeneous, mainly because of a large reduction in vasodilating capability of the remote regions (**arrowheads, right bottom panel**). LM and RCA injection = injection of contrast medium into the left main and the right coronary artery, respectively.

subjects. Similarly, perfusion reserve values in the anterior and posterolateral walls were correlated in normal subjects ($r = 0.93$, $p < 0.01$; slope 0.91). In patients with coronary occlusion, perfusion reserve in collateral-dependent regions closely correlated with that in remote areas ($r = 0.83$, $p < 0.01$); this regression line was not statistically different from the line of identity, whereas its slope (0.46) was slightly though not significantly ($p = 0.15$) lower than that observed in normal subjects (Fig. 6).

Indexes of myocardial viability in collateral-dependent dyssynergic areas. Although no patient selected for the study had had a previous myocardial infarction and no abnormal Q waves were observed on standard ECG, the possibility of a myocardial scar in dyssynergic regions downstream from the coronary occlusion was also considered. However, a functional recovery was observed in the four patients who underwent revascularization, whereas a normal uptake of fluorine-18–deoxyglucose was observed in the two patients in whom coronary angioplasty was not successful.

Discussion

The major findings of the present study in patients with chronic coronary occlusion are that: 1) despite marked reduction in blood flow at rest, collateral-dependent myocardium maintains a residual vascular tone and vasodilator capacity that can be almost fully utilized to meet moderate increases in oxygen demand; 2) in a small but measurable proportion of patients, coronary vasodilation decreases collateral-dependent perfusion; and 3) in addition to correlation with the angiographic appearance of collateral branches, coronary reserve in collateral-dependent regions is directly correlated with vasodilator capacity in areas supplied by nonstenotic vessels. These observations suggest a global impairment in blood flow regulation that may affect the microvascular adaptation to chronic coronary artery occlusion in coronary artery disease.

Vasodilating capability despite rest hypoperfusion in collateral-dependent myocardium. In agreement with previous work (18,19), the present study shows reduced blood flow at rest in collateral-dependent myocardium; in addition, it documents a residual vasodilator reserve in 16 of 19 patients, suggesting the persistence of a residual vascular tone and vasodilator capacity despite rest hypoperfusion (Fig. 1 and 2)

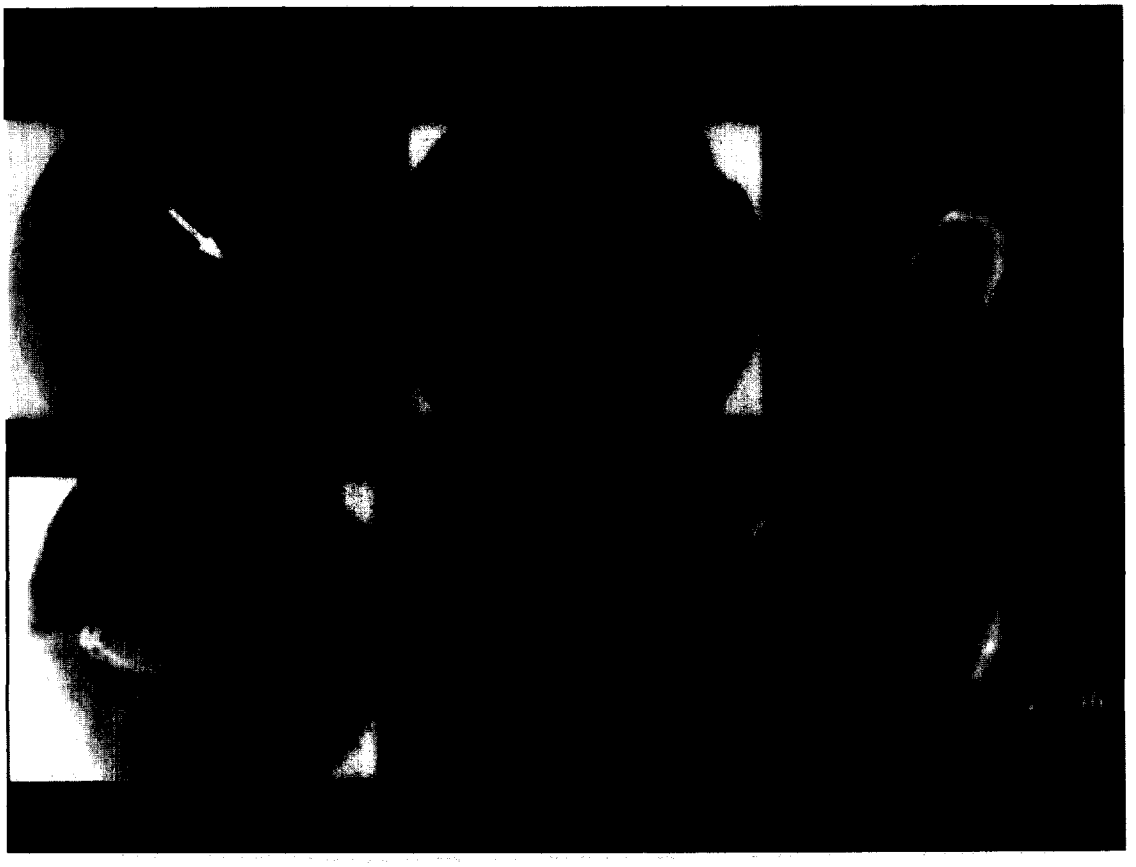
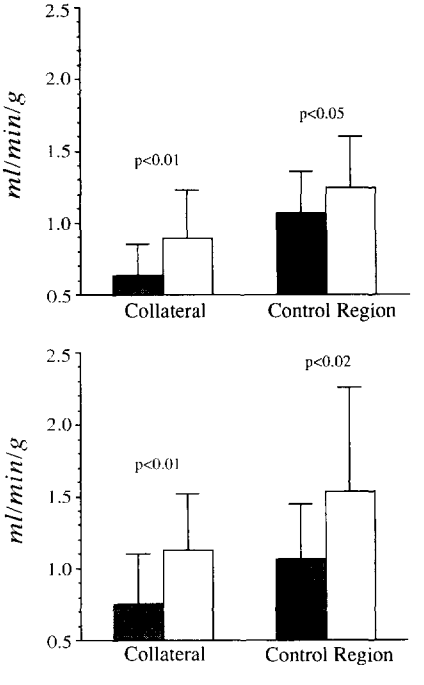


Figure 4. Coronary angiograms (**left panels**), contrast ventriculograms (**center panels**) and positron emission tomographic images of blood flow distribution (**right panels**). This patient had chronic occlusion of the left anterior descending coronary artery (**left arrow**) and poorly developed collateral circulation to the distal portion of the vessel; the anterior wall showed normal regional function and homogeneous perfusion at rest. However, after dipyridamole infusion (**right bottom panel**), a large perfusion defect was observed in collateral-dependent myocardium. The perfusion inhomogeneity was mainly caused by a maintained vasodilating capability of the remote regions (**arrowheads, right bottom panel**). Abbreviations as in Figure 3.

Figure 5. Myocardial blood flow values in patients with (**solid columns**) or without (**open columns**) absolute flow reduction in collateral-dependent areas (Collateral) during pacing (**top panel**) and after dipyridamole infusion (**bottom panel**). Patients with evidence of absolute decreases in blood flow to collateralized areas did not have larger flows in the remote (Control) regions, suggesting that this phenomenon might be related to factors other than "horizontal" coronary steal.



or dysfunction. Although this paradox has been previously reported in experimental (20) and clinical studies (21,22), its nature and mechanisms are not well known. An incomplete microvascular response to a severe stenosis might be hypothesized on the basis of a microvascular constriction in response to reduced lumen pressure (23). Alternatively, an active depression of contractility below actual flow availability might also occur as, in animal models of sustained myocardial hypoperfusion, initial ischemia subsides and both metabolic pattern and energy stores progressively normalize despite the persistence of contractile dysfunction (24,25). In these models, pacing tachycardia did not increase flow despite a vasodilator capability elicited by adenosine during increases in heart rate (25,26). In the present study, collateralized areas almost fully utilized their own vasodilator reserve during pacing, up to near maximal (dipyridamole) flow, emphasizing the differences be-

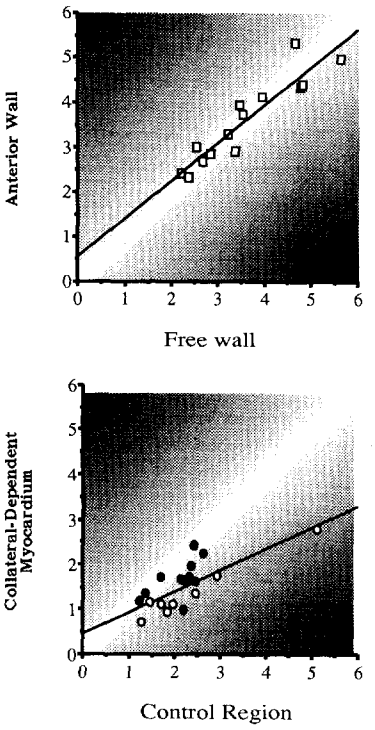


Figure 6. Scatterplot of coronary reserve in collateral-dependent myocardium (Y axis) and in remote "control" regions supplied by angiographically normal vessels (X axis). The **top panel** shows the results obtained in the 13 normal subjects. The **white area** indicates the line of identity; the **shaded areas** indicate the severity of perfusion defects (i.e., the degree of inhomogeneity). Values from patients with well developed collateral circulation (**bottom panel, solid circles**) are close to the line of identity; those from patients with poor collateral circulation (**bottom panel, open circles**) are more scattered. However, a direct correlation ($r = 0.83$, slope = 0.46, $p < 0.01$) can be observed between the flow reserve of these two regions with completely different coronary artery anatomy (one patent, the other occluded). The correlation remained significant when the outlying point on the right edge was deleted ($r = 0.68$, slope = 0.66, $p < 0.01$).

tween coronary artery disease and animal models of moderate ischemia (27).

Whatever the mechanism, the present data suggest that, in coronary artery disease, rest myocardial blood flow may be reduced by factors in addition to the intrinsic resistance of collateral vessels. The residual vasodilation in response to increasing oxygen demand (or dipyridamole) might explain the tolerance to intermediate degrees of effort that is frequently observed (and not fully explained) in patients with coronary occlusion, regardless of baseline myocardial hypoperfusion and dysfunction.

Absolute reduction in regional blood flow during coronary vasodilation. It is well recognized that pharmacologic vasodilation can induce ischemia downstream from a coronary stenosis even without increases in oxygen demand, when vasodilation lowers post-stenotic pressure, thus reducing subendocardial perfusion ("transmural steal") (5,28,29). Alternatively, when a large part of rest perfusion in jeopardized areas is provided by collateral channels, the vasodilation in the donor artery decreases the perfusion pressure at the origin of these channels, leading to a decrease in collateral flow ("horizontal steal") (5,6).

Transmural steal might have occurred in the four patients with ST segment depression during dipyridamole administration, and no reduction in flow; unfortunately, because of the limited spatial resolution of positron emission tomography, this possibility cannot be determined. However, the present data do not confirm the hypothesis that, in patients with coronary artery disease, the horizontal steal is caused only by a decrease in pressure at the origin of collateral vessels; in fact, flow reduction was associated neither with a different degree of collateral circulation on angiography nor with larger maximal flows in remote areas. Assuming a fixed resistance proximal to the input of collateral vessels, the decrease in pressure along the vascular tree is a direct function of flow: Decreased flows in the angiographically normal donor vessels should have been associated with higher pressures at the origin of collateral channels, thus preventing the horizontal steal. Moreover, after dipyridamole, vasodilation occurred in regions with flow reduction during pacing to an extent similar to that in the other collateral-dependent areas. Thus, it is conceivable that, in addition to the hydraulic steal, factors such as an ischemic hemodynamic impairment (increasing extravascular resistances) (30) or an active ischemic vasoconstriction (31,32) may cause absolute flow reductions during vasodilation.

Relation between flow regulation in "control" and collateralized myocardium. The present data confirm previous observations (8–12) that, in patients with single-vessel disease, myocardial blood flow regulation is abnormal in regions supplied by nonstenotic vessels. The mechanism underlying this puzzling finding has not been fully elucidated: several investigators (8) hypothesized a microvascular disorder caused by atherosclerosis; others suggested that regional ischemia (33) or dysfunction (34) may impair metabolism and flow regulation in the whole heart. Whatever the mechanism, this alteration in flow regulation should be paralleled by unknown metabolic changes leading to a lower flow requirement for a similar rate-pressure product. The actual relevance of this abnormality in patients with coronary artery disease remains elusive; although it is well known that the relief from epicardial obstruction is associated with amelioration of symptoms and clinical condition (35), pathologic studies (36) have challenged the close relation between severity or extension of epicardial obstructions and clinical manifestation of coronary artery disease.

As a hypothesis, this abnormality might hamper microvascular adaptation to epicardial obstruction, thus worsening its effects and contributing to the development of myocardial ischemia (37,38). In patients with isolated occlusion of a major coronary artery and no infarction, a uniform severity of epicardial obstruction can be assumed (11). In these patients, perfusion reserve was higher in regions supplied by an unobstructed coronary artery than in collateral-dependent myocardium; however, despite obvious differences in the anatomy of the relative coronary arteries (one occluded, the other angio-

graphically normal), the vasodilating capabilities of these two regions were strictly correlated (Fig. 6). According to these findings, one might hypothesize that in patients with coronary artery disease, a global impairment in myocardial blood flow regulation might actually hamper the microvascular adaptation to chronic coronary occlusion.

Limitations of the study. The present study protocol has some limitations that need further discussion. Although patients with a history or ECG evidence of myocardial infarction were carefully excluded, we cannot rule out that, at least in some of these patients, the presence of subendocardial infarction or patchy fibrosis might have impaired baseline myocardial blood flow. However, all patients had direct or indirect evidence of preserved viability in collateral-dependent regions.

The angiographic score of collateral circulation was not correlated with the presence of wall motion abnormalities. Previous studies (39) reported that a well developed collateral circulation was associated with a lower prevalence of dyssynergy in the areas supplied by the occluded artery. However, that finding was obtained in patients with myocardial infarction, a condition we excluded in our patient group because it strikingly affects both myocardial function and perfusion. Moreover, the limited number of patients selected for our study does not permit any conclusion about the relation between collateral vessels and regional function in patients without infarction.

Clinical implications. Previous studies (4,5) reported that the presence of collateral vessels was associated with a higher incidence of perfusion defects during vasodilation on myocardial scintigraphy, whereas others (2,3) suggested that a well developed collateral circulation may maintain normal perfusion at rest and during exercise. Our present results might partially explain the reason for these highly conflicting findings. The angiographic degree of collateral circulation correlated better with the perfusion homogeneity (Fig. 3 and 4), than with the absolute value of coronary reserve of maximal flow; after dipyridamole administration, patients with well developed collateral channels had more homogeneous perfusion than did those with poor collateral circulation. This finding might suggest that vasodilating capability is affected not only by the degree of epicardial obstruction but by a microvascular dysfunction that is homogeneously distributed in the left ventricle; by contrast, the caliper of collateral vessel is inversely correlated with the pressure decrease upstream to the resistive vessels, and thus with the difference in maximal flow capacity between jeopardized and "control" regions. These observations confirm the limits of conventional scintigraphy, which provides only an index of flow distribution, and they warrant caution in that a negative or a positive result on perfusion scintigraphy is a marker, respectively, of adequate or inadequate perfusion in collateralized areas in patients with symptomatic coronary artery disease.

Conclusions. Symptomatic coronary artery disease in living patients shows "in essence" the failure of collateral vessels to adapt to the worsening of arterial lesions (40). As a consequence, our results cannot be expanded to the function of collateral circulation itself or provide insight into a possible protective role of collateral vessels against the manifestations of coronary artery disease. These data suggest that, in patients with angina on effort, a global derangement in blood flow regulation—not related to the severity of epicardial obstruction—hampers microvascular adaptation to the effects of chronic coronary occlusion. These results need confirmation by other techniques; however, they indicate that the measurement of regional myocardial blood flow can be extremely useful for studying the pathophysiology of coronary artery disease and, ultimately, for correctly interpreting the signals obtained by conventional diagnostic techniques.

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