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**Conditions for Vasodilator-induced Coronary Steal in Experimental Myocardial Ischemia**

**LEWIS C. BECKER, M.D.**

**SUMMARY** The conditions for coronary steal were determined using the two vasodilators — dipyridamole and nitroglycerin — in anesthetized dogs after ligation of the left anterior descending coron-
ary artery (LAD). Previous studies have shown that when the non-
ligated coronary arteries are normal, collateral flow increases after dipyridamole. This study utilized a model in which the distal LAD
was ligated and the proximal LAD and left circumflex (LC) arteries
were stenosed. Heart rate and blood pressure were kept constant.
In 20 dogs, 1-1.5 mg/kg dipyridamole caused a decrease in flow to the
ischemic region as measured by radioactive microspheres (0.19 to
0.14 ml/min/g, P = 0.05) while flow increased four-fold to surround-
ing nonischemic myocardium. The decrease in collateral flow was
confined to the epicardial half of the ischemic region (0.26 to 0.14
ml/min/g, P < 0.001) and was associated with an increase in ZST
from 30.9 to 44.7mV (P < 0.01). In five dogs nitroglycerin, 5
µg/kg/min, produced no significant changes in collateral flow or flow
to other parts of the LV, and ZST was unchanged. Vasodilator-
induced coronary steal therefore appears to require 1) an arteriolar-
type dilator like dipyridamole and 2) stenoses of the arteries supply-
ing collateral flow to the ischemic region. The steal phenomenon is
probably caused by a decrease in pressure distal to the stenoses in
these vessels, resulting in reduced driving pressure for collateral flow.

**VASODILATOR DRUGS** are gaining increasing use in the treatment of acute myocardial infarction. Vasodilators have been
found to improve left ventricular function in patients with congestive heart failure or low cardiac output states resulting from myocardial infarction. In addition, there is evidence to suggest that vasodilators may limit myocardial ischemia in the early stages of acute myocardial infarction. At least part of the beneficial effect on ischemia has been attributed to the decreases in myocardial oxygen demands which result from reductions in blood pressure and left ventricular filling. However, experimental studies in animals support the concept that vasodilators may also reduce ischemia by increasing collateral blood flow to ischemic myocardium. Both direct and indirect effects on the heart could theoretically account for improved collateral flow. Direct dilatation of collateral channels has been demonstrated in several studies but reduction in left ventricular filling could also improve collateral flow indirectly by decreasing compressive forces on collateral vessels. Under certain conditions, however, vasodilators may have adverse effects on collateral flow. Vasodilator-induced hypotension is generally beneficial because of the associated decrease in left ventricular wall tension, but an excessive reduction in perfusion pressure may be harmful. When the decrease in pressure is disproportionately more than the reduction in collateral vessel resistance, collateral flow diminishes. Furthermore, vasodilators may decrease flow to an ischemic region by markedly increasing flow to surrounding nonischemic areas. This diversion of flow from ischemic to nonischemic tissue has been termed a myocardial steal or coronary steal. The steal is believed to be related to a selective dilatation of resistance vessels in nonischemic areas; since vessels within ischemic regions are

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already maximally dilated, they are incapable of further vasodilator response.

The conditions required for the steal phenomenon have not been clearly defined. In a recent report, the potent coronary arteriolar dilator dipyridamole was given during myocardial ischemia. Flow increased markedly to nonischemic tissue surrounding the ischemic region, but collateral flow to the ischemic region increased rather than decreased. As in most previous studies, one major coronary artery was ligated while the other arteries were normal. We felt that the presence of stenosis in the nonligated vessels, which provide the source of collateral flow to the ischemic region, might be important for the occurrence of a steal. We therefore studied dipyridamole-induced changes in flow to ischemic and nonischemic areas of the left ventricle in anesthetized dogs in which one coronary artery was ligated and the nonligated vessels providing collateral flow were stenosed.

**Methods**

Experiments were performed on a total of 28 mongrel dogs weighing 20 to 30 kg. Anesthesia was induced by thiopental sodium, 1 mg/kg, and maintained with alphachloralose in polyethylene glycol 200 (0.08 g/ml, initial dose = 20 mg/kg). Respiration was maintained with room air through a cuffed endotracheal tube by Harvard pump. The heart was exposed through a left thoracotomy and a pericardial cradle was formed. Polyethylene catheters (PE 160) were placed in the left atrium, brachial and femoral arteries, and femoral vein for pressure monitoring and blood sampling. The electrocardiogram was monitored continuously. Hemodynamic parameters were recorded on a Brush 200 direct writing recorder (Gould Inc.).

A 2 cm segment of the left circumflex (LC) and anterior descending (LAD) coronary arteries was dissected free, as proximal as possible without interference from side branches. A cuff-type electromagnetic flow transducer, small adjustable plastic screw occluder and snare were placed around each artery (fig. 1). The snare was used to produce temporary myocardial ischemia and obtain mechanical flow zeros. Flow was measured in arbitrary units with a Biotronix BL-610 sine-wave flowmeter. After a 10 minute period of stabilization, the screw occluder was adjusted to limit the peak reactive hyperemic response following a 15 second period of coronary occlusion to approximately 50% of the control peak reactive hyperemia value. Resting coronary blood flow was not reduced.

The mid-LAD was then ligated to produce myocardial ischemia. The site of ligation was chosen so that at least one large LAD diagonal branch was present between the screw occluder and ligature. One hour later, control measurements of regional myocardial blood flow were made using radioactive tracer microspheres. Spheres of 8–10 μm diameter labelled with one of the gamma-emitting nuclides, 47Sc, 47Nb, or 47Sc, were injected into the left atrium. They were obtained as 1mCi of nuclide in 10 ml of 10% dextran with 1 drop of polysorbate 80 added to minimize clumping (3M Co). Microsphere vials were vigorously agitated on a mechanical mixer for 2–3 minutes before injection. Starting just before injection and continuing for three minutes afterwards, reference blood samples were withdrawn by Harvard pump from brachial and femoral arteries at 2.1 ml/min for use in quantitating flow.

After control blood flow measurements 23 dogs received dipyridamole, 1–1.5 mg/kg i.v. bolus (obtained in ampules of 2 ml containing 10 mg dipyridamole, 4 mg tartaric acid, and 100 mg polyethylene glycol 600; Boehringer Ingelheim). Given in this way, the onset of action of dipyridamole is about 2–3 minutes, peak effect 5–10 minutes, and duration of action 20–40 minutes. About five minutes after injection, left atrial pacing was begun at the control heart rate to prevent the fall in rate that is generally seen after dipyridamole. An i.v. infusion of phenylephrine hydrochloride (20 mg in 1000 ml 5% dextrose in water) was titrated to return mean aortic pressure to control. Blood pressure was usually stabilized within 5–10 minutes. After 5–15 minutes at the controlled blood pressure, blood flow was remeasured using a microsphere with a different nuclide label. Blood flow distribution has been shown to be stable within the time period of 60 to 90 minutes after coronary artery ligation if no intervention is performed.

In seven of these dogs mean pressures were measured in the LC coronary artery distal to the stenosis and in the LAD distal to the ligature. Before control flow measurements, a Becton Dickinson fine vinyl catheter (ID = 0.02 in., OD = 0.036 in.) was inserted through the vessel wall with the aid of a sharpened guide wire. The end of the catheter was tapered slightly to allow easier penetration of the vessel. A suture placed in the perivascular fat secured the catheter which was cut to a length of about 12 inches and connected to a pressure transducer through a 25 gauge needle. Aortic pressure was maintained constant by distal aortic constriction in three of the seven dogs and by i.v. phenylephrine in the other four.

In five other dogs nitroglycerin was administered instead of dipyridamole. Four of the dogs had circumflex plus

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**Figure 1.** Experimental preparation. I, LC, LAD, NI represent four regions of LV sampled for blood flow: LC and LAD regions are perfused by stenosed vessels. NI region by normal vessels.
anterior descending stenoses, and the remaining dog had circumflex stenosis alone. A continuous infusion of 4.5–5.5 mg/kg/min nitroglycerin was used (0.5–0.6 ml/min of a solution of concentrated alcoholy nitroglycerin diluted with 5% dextrose/water, prepared sterile and pyrogen-free by the Johns Hopkins Hospital Pharmacy). Again, blood pressure was maintained constant by phenylrhine and a fall in heart rate prevented by left atrial pacing. Heart rate increased above baseline level in only one dog during drug infusion.

At the completion of each experiment the edges of cyanosis of the ischemic region were outlined on the epicardial surface with a marking pen. The dogs were then killed with potassium chloride and the hearts removed. The left ventricular (LV) free wall was isolated and gross epicardial fat and vessels discarded. Full-thickness myocardial samples were taken from four areas of the LV (fig. 1). A total of 2–6 g of tissue were obtained from 1) the posterior LV wall in the territory of the stenosed left circumflex coronary artery (LC-restricted), 2) the anterior LV wall in the distribution of the stenosed anterior descending artery (LAD-restricted), and 3) an area at the base of the heart fed by normal vessels (nonischemic). These large pieces were divided into 1–2 g samples, which were then subdivided into inner and outer halves, weighed to the nearest 0.01 g and placed in plastic tubes for counting of radioactivity. The territory of the ligated LAD was excised, traced on a plastic sheet, and divided into 0.5–2.0 g samples. The position of each piece was recorded on the tracing. Each sample was counted for radioactivity at energy levels corresponding to the nuclides injected using a Packard 5986 scintillation spectrometer with a multichannel analyzer. Blood samples drawn during microsphere injection were counted similarly in aliquots. Geometrical differences between tissue and blood samples in the counting chamber were found to be unimportant. The activities of nuclides in each sample were separated by standard techniques and the counts per gram of tissue computed. Myocardial blood flow, in ml/min/g, was calculated for each nuclide by the formula: MBF = Cm × RBF/Cr, where MBF = myocardial blood flow, Cm = counts per gram in myocardial samples, RBF = reference blood flow (Harvard pump withdrawal rate), and Cr = counts in reference blood samples (average of total counts of simultaneous brachial and femoral samples). This relationship is based on the fact that microspheres mixed in the left atrium distribute to myocardium and peripheral artery in proportion to the blood flow to each.19

Maps of blood flow to the left ventricular free wall were constructed.20 The ischemic region consisted of all samples in the distribution of the ligated anterior descending artery with initial flow less than 50% of nonischemic flow. Inner and outer wall samples were pooled separately to determine mean flows in each of the four LV regions before and after the vasodilator. Flow was also determined in peripheral and central parts of the ischemic region by pooling ischemic samples geographically located at the edge of the LAD territory separately from the other ischemic samples.

Myocardial ischemia was estimated from ST-segment elevation in epicardial electrocardiograms.21 These were recorded from 10–15 sites on the LV surface at vessel bifurcations to allow easy relocation, using a 0.01 in. diameter, insulated braided stainless steel wire attached to the V lead of a standard electrocardiograph. A 1 mm loop in the end was held gently against the epicardial surface. Elevation of the ST segment was measured from the T-P baseline to the midpoint of the ST segment (generally 0.10 sec after the onset of ventricular activation) at a standardization of 1 mV/mm. Recordings were made at each site before coronary ligation and just after each microsphere injection. The ST-segment deviation present before ligation was subtracted from that present afterwards to determine the change due to ischemia. Sites with more than 2 mV ST-segment elevation before coronary occlusion were seen occasionally; they were felt to be related to coronary artery manipulation and were excluded. Indices of ischemia corresponding to each blood flow measurement were obtained by summing the significant ST elevations (> 2 mV) present in each dog (2ST), and by dividing the summed ST elevations by the number of sites showing elevation (ST).

The statistical significance of differences in results was determined by Student's t-test for paired data. Results were expressed as the mean ± 1 sem.

Results

Dipyridamole

The stenoses applied to the LC and LAD coronary arteries were relatively mild. Peak reactive hyperemia following a 15 second arterial occlusion was reduced to 54.1 ± 2.7% and 52.9 ± 2.6% of control in the LC and LAD arteries, respectively. Resting flow was unaffected. Control reactive hyperemic responses were 380 ± 25% for the LC artery and 391 ± 25% for the LAD, measured as a percentage of resting flow.

Hemodynamic changes after dipyridamole during phenylephrine infusion are shown in table 1. Heart rate and mean aortic pressure were held constant. Aortic systolic pressure increased slightly as pulse pressure widened, and mean left atrial pressure increased. Aortic diastolic pressure did not change significantly. The left ventricle and left atrium were observed to dilate in most animals during dipyridamole-phenylephrine administration. Three dogs demonstrated severe left ventricular failure after dipyridamole while phenylephrine was being infused. Two of the animals developed ventricular fibrillation and the third developed atrial fibrillation with an increase in left atrial pressure from 3 to 26 mm Hg. These three animals were not included in the data analysis because of the absence of flow measurements after dipyridamole.

Figure 2 shows the changes that occurred in regional myocardial blood flow. Prevasodilator mean flows in nonischemic, LC, and LAD-flow restricted regions were 1.00–1.11 ml/min/g, while flow in the ischemic region was

<table>
<thead>
<tr>
<th>Table 1. Hemodynamic Measurements</th>
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<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>SAP = 133 ± 4</td>
</tr>
<tr>
<td>DAP = 107 ± 4</td>
</tr>
<tr>
<td>MAP = 116 ± 4</td>
</tr>
<tr>
<td>HR = 176 ± 8</td>
</tr>
<tr>
<td>LAP = 3.7 ± 0.8</td>
</tr>
</tbody>
</table>

*p <0.001 vs control.

Abbreviations: SAP = systolic arterial pressure (mm Hg); DAP = diastolic arterial pressure (mm Hg); MAP = mean arterial pressure (mm Hg); HR = heart rate (beats/min); LAP = mean left atrial pressure (mm Hg).

Values are mean ± SEM.
about 20% of this value. Dipyridamole given with phenylephrine resulted in an average four-fold increase in flow to the nonischemic region. Smaller increases were seen in the two flow restricted regions. Flow in the ischemic region decreased from 0.19 to 0.14 ml/min/g (P = 0.05) despite maintenance of aortic pressure.

The changes in flow to inner and outer layers of the ventricular wall are shown in table 2. In the nonischemic region the increase in flow after dipyridamole was essentially uniform across the wall. In the LAD-restricted region flow was increased to both inner and outer halves, but the increase to the outer half was greater. Consequently, the mean ratio of inner/outer wall (I/O) flow decreased from 0.85 to 0.72 (P < 0.01). In the LC-restricted region, outer wall flow doubled but inner wall flow did not change significantly; the I/O ratio decreased from 1.06 to 0.51 (P < 0.001). In the ischemic region, flow to the outer half of the wall decreased but flow to the inner half was unchanged, resulting in an increase in I/O ratio from 0.55 to 1.05 (P < 0.01).

In table 3, the ischemic region is analyzed in terms of peripheral and central ischemic samples. The flow changes were similar in both areas: outer wall flow was decreased and inner wall flow did not change significantly.

The effect of dipyridamole with phenylephrine on the epicardial ST-segment height is shown in figure 3. SST from sites overlying the ischemic region increased from 30.9 ± 6.2 mV to 44.7 ± 7.4 mV (P < 0.01) and mean ST-segment elevation, ST, increased from 6.27 ± 0.97 mV to 9.33 ± 1.14 mV (P < 0.005). Sites overlying the nonischemic, LC-restricted, and LAD-restricted regions all showed ST-segment depression before dipyridamole. After dipyridamole-phenylephrine administration, the ST-segment depressions became deeper over the nonischemic region (−0.86 ± 0.31 mV to −1.66 ± 0.33 mV, P < 0.02) and the LAD-restricted region (−1.88 ± 0.46 mV to −3.47 ± 0.55 mV, P < 0.01). There was no significant change over the LC-restricted region.

### Distal Coronary Pressure
In seven dogs given dipyridamole, distal coronary pressures were measured in both LC and LAD arteries. Before LC stenosis the mean distal LC pressure was almost identical to mean aortic pressure. After stenosis, but before dipyridamole, a gradient of 15 ± 4 mm Hg appeared between aortic and distal LC pressures (table 4). Despite this gradient both total resting flow and I/O flow ratios stayed normal as measured by microspheres. After administration of dipyridamole with the mean aortic pressure held constant, the gradient increased in every animal. Mean distal LC pressure fell from 110 ± 9 to 81 ± 10 mm Hg and mean LAD pressure in the ischemic region also decreased from 32 ± 4 to 26 ± 3 mm Hg. The difference between the distal LC pressure and the coronary pressure within the ischemic region, which can be considered to represent the driving

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**Table 2. Dipyridamole Effect on Regional Myocardial Blood Flow**

<table>
<thead>
<tr>
<th>Region Type</th>
<th>Condition</th>
<th>Control</th>
<th>Dipyridamole &amp; phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic region</td>
<td>In</td>
<td>0.12 ± 0.02</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>Out</td>
<td>0.26 ± 0.04</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>In</td>
<td>0.97 ± 0.07</td>
<td>3.98 ± 0.38</td>
</tr>
<tr>
<td>region</td>
<td>Out</td>
<td>1.03 ± 0.06</td>
<td>4.06 ± 0.41</td>
</tr>
<tr>
<td>LAD restricted</td>
<td>In</td>
<td>0.94 ± 0.06</td>
<td>2.30 ± 0.33</td>
</tr>
<tr>
<td>region</td>
<td>Out</td>
<td>1.12 ± 0.06</td>
<td>3.24 ± 0.38</td>
</tr>
<tr>
<td>LC restricted</td>
<td>In</td>
<td>1.12 ± 0.05</td>
<td>1.15 ± 0.15</td>
</tr>
<tr>
<td>region</td>
<td>Out</td>
<td>1.09 ± 0.06</td>
<td>2.35 ± 0.21</td>
</tr>
</tbody>
</table>

*P < 0.001 vs control.

Abbreviations: In = inner half; Out = outer half. Values are flows (mean ± SEM) in ml/min/g.

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**Table 3. Dipyridamole Effect on Flow in Central and Peripheral Portions of Ischemic Region**

<table>
<thead>
<tr>
<th>Region</th>
<th>Condition</th>
<th>Control</th>
<th>Dipyridamole &amp; phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>In</td>
<td>0.09 ± 0.02</td>
<td>0.07 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>Out</td>
<td>0.23 ± 0.05</td>
<td>0.11 ± 0.03</td>
</tr>
<tr>
<td>Peripheral</td>
<td>In</td>
<td>0.14 ± 0.02</td>
<td>0.14 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>Out</td>
<td>0.29 ± 0.04</td>
<td>0.20 ± 0.04</td>
</tr>
</tbody>
</table>

*P < 0.01 vs control.
pressure for collateral flow from the LC coronary artery, fell from 73 ± 10 to 47 ± 7 mm Hg (P < 0.01).

Nitroglycerin

In five dogs, 5 μg/kg/min i.v. nitroglycerin was given instead of dipyridamole. After nitroglycerin was started, mean aortic pressure fell 16.1% (P < 0.005); phenylephrine was then added to return the blood pressure to control levels. As seen in table 5, mean, systolic, and diastolic aortic pressures, heart rate, and left atrial pressure were unchanged from baseline during the combined administration of nitroglycerin and phenylephrine. In addition, blood flow to inner and outer layers of the ventricular wall did not change significantly in any of the regions examined, and ΣST and ST both remained unchanged.

Discussion

Coronary Steal

In the present study, mild stenoses were placed on the major coronary arteries providing collateral flow to an ischemic myocardial region. Administration of dipyridamole caused an augmentation of ischemia, shown by a decrease in collateral flow and an increase in epicardial ST-segment elevation. The decrease in flow occurred even though blood pressure was maintained constant and flow was markedly increased to surrounding nonischemic myocardium. The effect of dipyridamole in this experiment could justifiably be called a coronary steal, since blood flow appeared to be stolen from the ischemic region to surrounding nonischemic myocardium. The results of this study contrast with an earlier report in which dipyridamole was given under similar conditions except that the arteries supplying collateral flow were normal. In that study dipyridamole caused an increase in collateral flow and a decrease in epicardial ST-segment elevation. The production of a steal by dipyridamole therefore seems to depend on stenoses being present in the major arteries supplying collateral flow to the ischemic region.

A hypothetical framework for understanding coronary steal is presented in figure 4. Stenoses in the nonligated arteries provide sites for pressure gradient development. Under resting conditions there may be no pressure drop or only a small gradient across a stenosis, but after dipyridamole a pressure gradient may appear or become accentuated. Even if aortic pressure is maintained, coronary pressure may decrease markedly distal to the stenosis. Reduction in downstream pressure in turn causes a decrease in driving pressure for collateral flow; i.e., there is a narrowing of the pressure difference between the bed originating collateral flow and the bed receiving it. Decreased driving pressure causes a diminution in collateral flow and an augmentation of ischemia. In contrast, when the arteries providing collateral flow are normal, dipyridamole does not produce a significant fall in downstream pressure. Distal coronary pressure remains within a few mm Hg of the aortic pressure, and as long as aortic pressure is maintained, collateral driving pressure is also maintained. In this setting, collateral flow may increase if collateral resistance (either the vascular or extravascular components) is reduced sufficiently.

An alternative explanation for the steal should also be considered, namely that it is caused by an increase in left ventricular filling pressure (LVFP), with compression of collateral vessels or subendocardial vessels within the ischemic region. Although we found an increase in LVFP, it seems more likely that the rise in LVFP was the result rather than the cause of increased ischemia. The decrease in collateral flow we observed did not correlate with the increase in left atrial pressure, and reduced flow occurred as

| Table 4. Effect of Dipyridamole on Distal Coronary Artery Pressures |
|-----------------|-----------------|-----------------|
| Dog             | MAP             | LCCP            | ICP             |
| Before stenosis | After stenosis  |                 |                 |
| Dog             | MAP             | LCCP            | ICP             |
| 1               | 104             | 104             | 78              |
| 2               | 98              | 98              | 78              |
| 3               | 98              | 98              | 78              |
| 4               | 98              | 98              | 78              |
| 5               | 98              | 98              | 78              |
| 6               | 98              | 98              | 78              |
| 7               | 98              | 98              | 78              |
| Mean            | 124             | 122             | 125             |
| SEM             | NS              | NS              | NS              |

Abbreviations: MAP = mean aortic pressure; LCCP = left circumflex coronary pressure; ICP = ischemic zone intracoronary pressure; C = control; D & F = dipyridamole and phenylephrine.

| Table 5. Nitroglycerin Effect on Hemodynamics, Flow, and ST Segments |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | MAP (mm Hg)     | HR (min⁻¹)      | LAP (mm Hg)     | ΣST (mV)        | ΔST (mV)        |
| Control         | 137 ± 5         | 178 ± 8         | 3.2 ± 1.3       | 37.7 ± 10.5     | 7.6 ± 1.1       |
| Nitroglycerin   |                 |                 |                 |                 |                 |
| + phenylephrine | 137 ± 5         | 181 ± 9         | 4.7 ± 1.8       | 36.8 ± 8.9      | 7.9 ± 1.1       |
| + pacing        |                 |                 |                 |                 |                 |

Abbreviations: I = ischemic region; NI = nonischemic region; LC-Rest = circumflex-restricted region; LAD-Rest = anterior descending-restricted region.
Figure 4. Schematic diagram of coronary circulation showing proposed mechanism for dipyridamole-induced coronary steal. Coronary artery divides into two branches, one completely occluded, the other stenosed but providing collaterals to the first. In the control situation on the left, distal pressure is low in the occluded arterial bed and there is a small gradient in mean pressure across the stenosis. Flow in the ischemic region (dotted area) is 20 ml/min/100 g and is determined by the collateral driving pressure, or the difference between distal pressures in the bed supplying collaterals (80 mm Hg) and the ischemic bed (20 mm Hg). Flow in the distribution of the stenotic vessel is normal at 70 ml/min/100 g and is evenly distributed between subendocardium (lower value in bracket) and subepicardium (upper value). During dipyridamole, with blood pressure maintained constant by phenylephrine, flow increases in the nonischemic bed to 200 ml/min/100 g but becomes maldistributed between subendocardium and subepicardium. In addition, pressure distal to the stenosis falls to 50 mm Hg, causing a reduction in collateral driving pressure. As a result, flow to the ischemic region decreases to 10 ml/min/100 g, interpreted as a coronary steal.

The possibility should also be considered that the steal was caused by the phenylephrine utilized for blood pressure support. The decrease in flow we observed in ischemic subepicardium could have been related to constriction of epicardial vessels induced by alpha-adrenergic stimulation. However, several factors make this explanation unlikely. First, the results were similar in three dogs in which mechanical constriction of the descending aorta rather than phenylephrine was used to control blood pressure. Second, constriction of epicardial vessels in nonischemic areas might also have been expected, but none was found. Third, although alpha receptors exist in the larger conductive arteries on the surface of the heart, they have not been shown to be present in the smaller vessels located within the myocardium. The resistance of the small rather than the large vessels should be the determinant of blood flow. Finally, the results of this study are opposite to those of the previously cited study in which the arteries providing collateral flow were normal. In those experiments flow to the ischemic region increased rather than decreased, even though a similar alpha-adrenergic agonist, methoxamine, was used to control blood pressure.

Schemes similar to the one presented in Figure 4 have been suggested by Gorlin, Schaper and colleagues, and Maseri. Viewed in this framework, coronary steal is really a misnomer. In reality, there is simply a decrease in effective perfusion pressure resulting in a decrease in flow. When inflow to nonischemic beds is restricted, the perfusion pressure for collateral flow is no longer directly related to the aortic pressure, but rather to the distal coronary artery pressure in the beds giving rise to collaterals.

In previous reports of vasodilator-induced coronary steal stenoses have not been present in the nonligated vessels. However, inflow to these arteries may nonetheless have been inadvertently restricted. Schaper and colleagues found that lidoflazine and carbochromen, two potent vasodilators similar in action to dipyridamole, caused a steal in dogs with chronic amerdoid occlusion of the circumflex coronary artery. The authors speculated that because the LAD artery was carrying flow for the entire left ventricle, there may have been a relative flow restriction under resting conditions. Cohen et al. demonstrated that intracoronary adenosine or isoproterenol produced a steal from regions of acute ischemia in dogs in which the main left coronary artery was perfused at constant pressure. However, distal coronary pressure was not measured and may have fallen during vasodilator administration due to the relative restriction of inflow by the perfusion cannula. Chiarwelli et al. recently showed that nitroprusside reduced collateral blood flow in anesthetized dogs after coronary artery ligation. However, their experiment did not really demonstrate steal because the decrease in collateral flow was accompanied by a proportional decrease in blood pressure; flow also decreased rather than increased to surrounding nonischemic myocardium.

The present study did not address the question of how much stenosis must be present in the nonoccluded arteries for a vasodilator-induced steal to occur. We used relatively mild stenoses which limited peak reactive hyperemia by only 50% and were associated with small resting pressure gradients. However, Schaper's experiments suggest that if the volume flow carried by an artery is significantly increased because of occlusions in the other major vessels, even less stenosis, or possibly no stenosis at all, would be needed. Another consideration relates to the potency of the vasodilator used. When vasodilatation is mild, either because of the intrinsic properties of the vasodilator or the responsiveness of the distal vessels, a relatively severe stenosis probably would be required to produce a fall in distal coronary pressure. When vasodilatation is marked, a

Table 6. Relation between Change in Flow to Ischemic Region and Change in Left Atrial Pressure after Dipyridamole and Phenylephrine

<table>
<thead>
<tr>
<th>ΔLAP &lt;4 mm Hg (N = 10)</th>
<th>ΔLAP &gt;4 mm Hg (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Dipyridamole &amp; phenylephrine</td>
</tr>
<tr>
<td>In</td>
<td>0.16 ± 0.02</td>
</tr>
<tr>
<td>Out</td>
<td>0.30 ± 0.07</td>
</tr>
</tbody>
</table>

*0.05 < P < 0.10.
**P < 0.05 vs control.
ΔLAP = change in mean left atrial pressure.

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mild stenosis probably would suffice. The important concept is that inflow to the artery must be restricted sufficiently to allow a pressure gradient to develop.

The results from this and other studies suggest that an arteriolar type of vasodilator is required for a coronary steal. Dipyridamole, which potentiates the effects of adenosine, is a dilator of this type, as are adenosine itself, lidoflazine, and carbochromen. These drugs exert their primary effect on small resistance vessels and cause a marked increase in coronary blood flow. Nitrates, in contrast, have a major effect on large conductive vessels and only transient effects on arterioles. Nitroglycerin has been shown in most previous studies to increase collateral flow to ischemic myocardium rather than cause a steal.5-7, 11-12 In the present study nitroglycerin did not produce a steal but did not increase collateral flow either. The lack of improvement of collateral flow in this model suggests that the stenoses may have pre-empted nitroglycerin's effect, possibly by causing dilatation of the coronary vessels normally affected by nitroglycerin and rendering them unresponsive.

Transmural Flow

The reduction in collateral flow after dipyridamole was found only in the epicardial half of the ischemic region. Subendocardial flow, which was very low before dipyridamole, did not decrease further. Although there is no ready explanation for this transmural difference, the epicardial location of most of the collaterals in the dog may play a role. The pressure gradients discussed previously for epicardial vessels may not occur in vessels located deep in the ventricular wall and subendocardial flow may therefore not be affected. Alternatively, the subendocardium may receive significant perfusion directly from the left ventricular cavity, particularly under ischemic conditions.27 This direct portion of its blood supply would probably not be subject to the harmful effects of dipyridamole. Finally, dipyridamole may cause a selective reduction in resistance to subendocardial perfusion by dilating the intramural perforating arteries, thereby altering the distribution of flow in the ischemic region toward the subendocardium.5

Despite maintenance of aortic pressure with phenylephrine, dipyridamole caused a striking maldistribution of flow across the left ventricular wall in regions perfused by stenosed coronary arteries, but not in areas fed by normal vessels. Mean flow to the inner half of the wall in these regions either increased moderately (LAD region) or remained unchanged (LC region) while outer wall flow increased very substantially. The more striking changes seen in the LC-restricted region were probably related to the somewhat greater overall restriction of flow in this area. In addition, although inner wall flow did not change significantly in the LC region for the group as a whole, flow actually decreased in 10 of the 20 dogs, and in six the decrease was more than 50%. Dipyridamole therefore caused true ischemia as well as relative ischemia of the subendocardium in a significant number of the animals.

Selective subendocardial ischemia has been reported in other animal studies in which inflow to a region of myocardium was restricted during generalized coronary vasodilation. In some of these studies, a coronary arterial stenosis was present28-29 while in others the inflow restriction was related to the fact that the region of myocardium was entirely dependent on collateral vessels for flow.12-14, 50 Drugs,12-14 ischemia,29 angiographic contrast material,51 and tachycardia29, 30 have been used to elicit coronary vasodilation. Although methods do not currently exist for measuring subendocardial flow in man, a similar maldistribution of flow may occur distal to coronary artery stenoses or in collateral-dependent regions during exercise-induced angina. Exercise would be expected to provide a potent stimulus for coronary vasodilation by increasing myocardial oxygen demands similar to the effects of pacing-induced tachycardia.

Several explanations should be considered for the endocardial/epicardial maldistribution of flow in regions with inflow restriction. First, the fall in coronary artery pressure which occurs distal to a partial obstruction during vasodilation may cause more severe subendocardial ischemia because of the greater dependence of subendocardial flow on perfusion pressure.22 Second, vasodilation may lead to a larger increase in subepicardial than subendocardial flow because of the greater vasodilatory reserve in the superficial layers.32 The difference in reserve stems from the fact that systole preferentially inhibits flow to the subendocardium, requiring greater dilation of subendocardial vessels to maintain normal resting flow.22, 32 Third, changes in systemic hemodynamics may affect the distribution of coronary flow, particularly in regions perfused at reduced pressure. For example, an elevation of LVFP may cause compression of subendocardial vessels and selectively impair subendocardial flow.33 Similarly, an increase in heart rate might reduce subendocardial perfusion by reducing diastolic time per minute.32

Clinical Implications

As in most animal studies, one must extrapolate cautiously to the clinical situation. The dogs in this study had rapid heart rates, high sympathetic tone, and poorly developed collaterals. It is therefore uncertain to what extent the results pertain to patients with well developed muscular collateral connections. Nevertheless, accepting these limitations, the data suggest that in patients, adenosine-type coronary vasodilators may markedly increase total coronary flow but at the same time cause striking abnormalities of flow distribution. In areas of restricted inflow — those areas perfused by stenotic vessels or dependent on collaterals — subendocardial ischemia may develop or become accentuated by these vasodilators. In collateral-dependent regions more severe transmural ischemia may develop if pressure falls in the beds supplying collateral flow. By analogy with the animal studies, coronary anatomy may have important bearing on whether these vasodilators are beneficial or harmful in an individual patient. Benefit might be anticipated in patients with a specific anatomy, i.e., single vessel disease where one coronary artery is completely occluded, the other arteries are normal or have only insignificant disease, and large collaterals perfuse the myocardium in the distribution of the occluded vessel. However, in most other anatomic situations, these vasodilators would be expected to provoke new ischemia or augment pre-existing
ischemia. This would include single vessel disease in which the coronary artery is stenotic rather than totally occluded, and double or triple vessel disease, the usual situation in patients with clinically evident ischemic heart disease. Furthermore, any fall in blood pressure related to these vasodilators would be expected to produce further adverse effects on flow to compromised myocardium.

Large vessel dilators like nitroglycerin should be much less likely to produce harmful effects than the adenosine-type agents. Nitrates are said to be weak arteriolar dilators, although if sufficient drug is administered rapidly enough, significant small vessel effects may occur. Several reports have recently appeared concerning the use of nitroglycerin and nitroprusside to improve left ventricular function in patients with acute myocardial infarction. One study suggests that nitroprusside may sometimes increase myocardial ischemia whereas nitroglycerin consistently improves ischemia. The harmful effects of nitroprusside could be related to a more potent action on myocardial arterioles.

In summary, this study suggests that if vasodilators are to be used in acute myocardial infarction, they should be used cautiously. Nitrates, with a predominantly large vessel dilating effect, may generally produce benefit by increasing collateral blood flow, but other vasodilators with strong arteriolar effects may augment ischemia by causing flow maldistribution and coronary steal despite an increase in total coronary blood flow. A given vasodilator may have opposite effects depending on the particular hemodynamic and coronary anatomical situation.

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