Importance of Heart Rate in Determining the Effects of Sympathomimetic Amines on Regional Myocardial Function and Blood Flow in Conscious Dogs with Acute Myocardial Ischemia

STEPHEN F. VATNER AND HANK BAIG

SUMMARY We examined the effects of dopamine (DP), dobutamine (DB), and isoproterenol (ISO) in 38 conscious dogs after coronary artery occlusion on measurements of overall left ventricular (LV) function (i.e., LV pressure, dP/dt, mean arterial pressure, and heart rate), while regional myocardial function was assessed, using an ultrasonic gauge to measure segment length (SL) in normal and ischemic areas of myocardium. We measured regional myocardial blood flow, using the radioactive microsphere technique. Coronary occlusion resulted in graded reductions of blood flow and function from the normal to severely ischemic zones. DP and DB, 4.0 µg/kg per min, and ISO, 0.03 µg/kg per min, iv, increased LV dP/dt similarly; i.e., by 20%, and increased blood flow and systolic SL shortening in the normal zone. ISO increased heart rate (29.9 ± 4.6%) and decreased SL shortening and blood flow (32.9 ± 6.1%) in the severely ischemic zone. In contrast, we observed significantly different \( (P < 0.01) \) effects with these doses of DP and DB, which caused no increases in heart rate or decreases in blood flow or contractile function in the ischemic zone. DP and DB, 10 µg/kg per min, iv, increased LV dP/dt 3- to 4-fold more than with the lower dose, but still failed to elicit reductions in contractile function or blood flow in the severely ischemic zone when heart rate did not rise. In contrast, when the same doses of DP and DB increased heart rate in another group of dogs, blood flow and contractile function fell in the ischemic zone. Thus, \( \beta \)-adrenergic agents do not always elicit a "coronary steal" or deleterious effects on ischemic myocardial function, despite coronary dilation in the normal zone. However, when inotropic stimulation is coupled with tachycardia, blood flow falls and contractile function deteriorates in the ischemic myocardium. Circ Res 45: 793-803, 1979

\( \beta \)-ADRENERGIC inotropic agents are generally thought to be deleterious in the presence of myocardial ischemia, since, by increasing myocardial metabolic demands in the face of limited oxygen supply, ischemia can be intensified. This concept is based primarily on the effects of isoproterenol, which has been shown to increase the extent of experimental myocardial infarction (Maroko et al., 1971), as well as to intensify global (Vatner et al., 1974b) and regional ischemia (Cohen et al., 1976; Vatner and Baig, 1978; Kerber et al., 1974). In addition, isoproterenol can induce a "coronary steal" (Cohen et al., 1976); i.e., it reduces blood flow to ischemic tissue as a consequence of the concomitant vasodilation in the normal zone. On the other hand, dopamine and dobutamine are potent posi-

tive inotropic agents, which have potential utility in the treatment of acute myocardial ischemia because of their lack of pronounced pressor and chronotropic effects. Studies conducted in man (Horwitz et al., 1962; Loeb et al., 1975; Meyer et al., 1976; Goldberg, 1972) and in conscious animals (Goldberg, 1972; Vatner et al., 1973; Vatner et al., 1974a; Cobb et al., 1972) without myocardial ischemia consistently have shown increases in cardiac output, stroke volume, LV dP/dt, and coronary perfusion after administration of either dopamine or dobutamine. However, in the presence of myocardial ischemia, the effects of these drugs are controversial; studies have shown that these drugs improve (Tuttle et al., 1977; Lipp et al., 1972; Willerson et al., 1976) and do not change (Gillespie et al., 1977; McClenathan et al., 1977; Ramanthan et al., 1977), or exacerbate (Mueller et al., 1978) the ischemic condition. The disparate effects of dopamine and dobutamine on ischemic myocardial function may be due to differences in dose, the presence of anesthesia and recent surgery in animal experiments, or the lack of directly measured regional myocardial function in conscious animals or man. It is important to note that measurements of overall cardiac function may be misleading in the presence of re-

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gional myocardial ischemia, where diverse actions can occur in zones of myocardium, which may be either normally perfused or exhibit intense regional ischemia.

Accordingly, the first goal of this investigation was to examine the effects of intravenous infusions of dopamine and dobutamine, administered in similar inotropic doses, on simultaneous measurements of regional myocardial function and blood flow in normal, moderately, and severely ischemic zones, in conscious dogs with acute myocardial ischemia. Furthermore, the effects of dopamine and dobutamine were compared with the effects of a similar inotropic dose of isoproterenol, a β-adrenergic inotropic agent which has been shown to exert a deleterious effect on the severely ischemic myocardium (Maroko et al., 1971; Vatner et al., 1974b; Cohen et al., 1976; Vatner and Baig, 1978; Kerber et al., 1974).

Finally, higher doses of dopamine and dobutamine were divided into two groups, those in which heart rate rose and those in which heart rate did not change appreciably, since under these two circumstances the effects of the drugs could be quite different. Thus, the specific goals were to ascertain whether (1) β-adrenergic inotropic stimulation is always deleterious in the presence of acute regional myocardial ischemia; (2) function in the severely ischemic zones improved or deteriorated with dopamine and dobutamine in comparison with a similar inotropic dose of isoproterenol; (3) these observed changes were associated with a rise or fall in regional myocardial blood flow; (4) reductions in normal zone resistance induced by sympathomimetic amines always correlated with decreases in severely ischemic zone flow; i.e., whether coronary dilation in the normal zone always elicited a "coronary steal;" and (5) any adverse effects of these agents could be attributed to changes in arterial pressure, heart rate, or myocardial contractility.

**Methods**

Mongrel dogs, weighing between 22 and 30 kg, were anesthetized with sodium pentobarbital, 30 mg/kg, iv. Through a thoracotomy in the 5th left intercostal space, a miniature pressure gauge was implanted within the left ventricle through a stab wound in the apex. A hydraulic occluder was implanted on either the left anterior descending (24 dogs) or circumflex coronary artery (14 dogs), 2–3 cm from the bifurcation of these vessels, to produce regional myocardial ischemia. Heparin-filled Tygon catheters were implanted in the left atrium and aorta. Up to six pairs of miniature ultrasonic transducers were implanted intramyocardially, parallel to the muscle fibers, 1–2 cm apart and varying in depth from 4 to 15 mm, in potentially normal and moderately and severely ischemic zones. These zones were confirmed after completion of the experiment. The severely ischemic zone was located in the central distribution of the occluded vessel and showed reductions in blood flow of greater than 70% and in systolic segment shortening of greater than 90%. The moderately ischemic zone was characterized by smaller reductions in blood flow and contractile function. The normal zone was located on the opposite side of the heart in the central distribution of the nonoccluded coronary vessel and did not exhibit reduction in blood flow or loss of contractile function.

The miniature left ventricular (LV) pressure gauges (Königsberg Instruments) were calibrated in vitro and in vivo against a calibrated Statham P23Db strain gauge manometer (Statham Instruments) connected to the implanted left atrial and aortic catheters. At autopsy, the position of the gauge within the ventricular cavity was confirmed.

An improved ultrasonic transit-time dimension gauge was used to measure continuously instantaneous regional myocardial segment length (SL). The operation of this instrument in our laboratory has been described previously (Vatner et al., 1978a; Vatner et al., 1978b; Pagani et al., 1978; Heyndrickx et al., 1975). The instrument used in this study was modified further to provide continuous measurements of the regional electrographic potential at each crystal site. Each crystal was connected sequentially to a Cleveit-Brush ECG recording preamplifier. A Wilson central terminal was used as a reference. The electrograms verified the absence of cardiac arrhythmias.

Regional myocardial blood flows were measured by the radioactive microsphere technique (Dome- nech et al., 1969). The microspheres (3M Company) were suspended in 0.01% Tween solution (10% dextran) and placed in an ultrasonic bath. Subsequently, they were agitated by direct application of an ultrasonic probe to ensure dispersion of the spheres just prior to injection. Absence of microsphere aggregation was verified by microscopic examination. Prior to injection of microspheres, 0.7 ml of the Tween-dextran solution (without microspheres) was injected to determine if the diluent for the microsphere suspension was to have an adverse effect on cardiac dynamics (Millard et al., 1977). One to two million microspheres (15 ± 3 μm) labeled with 51Cr, 86Sr, 141Ce, and 46Sc were injected through the catheter implanted in the left atrium for four separate determinations of blood flow. The radioisotope sequence was randomized throughout. A reference sample of arterial blood was withdrawn beginning 10 seconds before microsphere injection and continuing for 40 seconds after the injection was completed. After the dog had been killed, myocardial tissue samples were obtained from the sites where function was measured. These were dissected into endocardial, midwall, and epicardial layers. All samples were weighed, placed in a multichannel γ well counter (Searle Analytic) and counted with appropriately selected energy windows. The samples averaged 1.21 ± 0.08 g in weight, while counts averaged 1866 ± 5 for 51Cr, 3977 ± 8 for 86Sr, 1720
TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Dose (µg/kg per min)</th>
<th>CAO baseline</th>
<th>Δ with DP</th>
<th>CAO baseline</th>
<th>Δ with DB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>4</td>
<td>111 ± 6.4</td>
<td>2.6 ± 2.7</td>
<td>117 ± 6.1</td>
<td>3.5 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>112 ± 4.1</td>
<td>-4.7 ± 2.7</td>
<td>112 ± 5.2</td>
<td>-0.6 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>98 ± 4.5</td>
<td>17.5 ± 2.0* $</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>4</td>
<td>102 ± 3.4</td>
<td>1.6 ± 2.3</td>
<td>101 ± 3.3</td>
<td>4.5 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>102 ± 3.7</td>
<td>12.4 ± 3.5*</td>
<td>104 ± 4.0</td>
<td>7.5 ± 2.2*</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>101 ± 3.1</td>
<td>8.4 ± 3.7*</td>
<td>100 ± 2.5</td>
<td>10.8 ± 3.3*</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>4</td>
<td>120 ± 3.6</td>
<td>2.5 ± 3.5</td>
<td>125 ± 4.5</td>
<td>1.5 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>123 ± 5.7</td>
<td>19.7 ± 5.0* $</td>
<td>134 ± 4.8</td>
<td>8.9 ± 2.4*</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>128 ± 5.0</td>
<td>14.2 ± 5.3*</td>
<td>129 ± 3.6</td>
<td>15.1 ± 3.5*</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>4</td>
<td>9.8 ± 0.8</td>
<td>0.2 ± 0.4</td>
<td>11.0 ± 1.1</td>
<td>0.1 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>11.9 ± 1.0</td>
<td>0.9 ± 1.8</td>
<td>11.2 ± 2.0</td>
<td>0.7 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>10.6 ± 3.1</td>
<td>1.4 ± 2.5</td>
<td>9.0 ± 1.3</td>
<td>2.8 ± 1.4</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>4</td>
<td>3200 ± 350</td>
<td>730 ± 150*</td>
<td>3120 ± 390</td>
<td>730 ± 180*</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>3160 ± 250</td>
<td>2170 ± 230* $</td>
<td>3380 ± 130</td>
<td>2040 ± 220* $</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>3250 ± 110</td>
<td>1860 ± 330* $</td>
<td>3100 ± 150</td>
<td>1950 ± 200* $</td>
</tr>
</tbody>
</table>

T = tachycardia; NT = no tachycardia.
* Significant change from CAO baseline, P < 0.01.
† Significant change from CAO baseline, P < 0.05.
$ Response to either high dose group significantly different from low dose, P < 0.05.
§ Response to high dose (T) group significantly different from high dose (NT) group, P < 0.05.
dogs were anesthetized with sodium pentobarbital, 30 mg/kg, and killed to confirm the placement of intramyocardial transducers and to obtain myocardial tissue samples.

Data were recorded continuously on a multichannel tape recorder and played back on three multichannel direct-writing oscillographs. A cardiocapnometer, triggered by the pressure pulse signal, provided an instantaneous and continuous record of heart rate. Continuous records of dP/dt and dSL/dt were derived from the signals of LV pressure and SL with Philbrick operational amplifiers (Teledyne Philbrick) connected as differentiators and having frequency responses of 700 and 140 Hz, respectively. A triangular wave signal with known rate of change was substituted for the appropriate input signals to calibrate the differentiators directly. Vascular resistance per gram of tissue was calculated for the normal zone of the heart as the quotient of mean arterial pressure and measured blood flow. Overall, resistance was not calculated for ischemic zones, since perfusion pressure was not measured in ischemic vessels.

Results are expressed as mean ± SEM. The significance of the changes produced by a given drug from the occlusion baseline level was determined using the t-test for paired data. Comparisons of the effects of dopamine, dobutamine, and isoproterenol, as well as differences between the high and low doses of dopamine and dobutamine, were determined using the analysis of variance and the method of least significant differences (Armitage, 1973).

**Effects of Coronary Artery Occlusion**

**Overall LV Function**

Coronary artery occlusion increased significantly (P < 0.01) mean arterial pressure by 5.8 ± 1.7 mm Hg, LV end-diastolic pressure by 2.2 ± 0.6 mm Hg, and heart rate by 21 ± 2.7 beats/min. LV systolic pressure and dP/dt did not change significantly.

**Regional Myocardial Effects**

Coronary artery occlusion did not change regional systolic SL shortening or velocity in the normal zone. In contrast, in the severely ischemic zone, coronary artery occlusion reduced systolic SL shortening by 118 ± 3.4% (i.e., systolic bulging appeared) and velocity by 97 ± 1.4% (P < 0.01). Intermediate, but significant (P < 0.01), reductions in contractile function were observed in the moderately ischemic zone.
TABLE 3  Effects of DP and DB in the Presence of CAO on Regional Myocardial Blood Flow

<table>
<thead>
<tr>
<th>Dose (µg/kg per min)</th>
<th>CAO baseline</th>
<th>Δ with DP</th>
<th>CAO baseline</th>
<th>Δ with DB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmural flow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal zone</td>
<td>4</td>
<td>1.54 ± 0.06</td>
<td>0.30 ± 0.05*</td>
<td>1.75 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>1.62 ± 0.07</td>
<td>0.63 ± 0.07§</td>
<td>1.59 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>1.47 ± 0.06</td>
<td>0.47 ± 0.05§</td>
<td>1.59 ± 0.08</td>
</tr>
<tr>
<td>Moderately ischemic</td>
<td>4</td>
<td>0.77 ± 0.04</td>
<td>0.10 ± 0.04‡</td>
<td>0.73 ± 0.05</td>
</tr>
<tr>
<td>zone</td>
<td>10 (NT)</td>
<td>0.70 ± 0.04</td>
<td>0.14 ± 0.04*</td>
<td>0.84 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>0.96 ± 0.04</td>
<td>0.11 ± 0.06</td>
<td>0.92 ± 0.04</td>
</tr>
<tr>
<td>Severely ischemic</td>
<td>4</td>
<td>0.22 ± 0.02</td>
<td>0.00 ± 0.01</td>
<td>0.22 ± 0.03</td>
</tr>
<tr>
<td>zone</td>
<td>10 (NT)</td>
<td>0.20 ± 0.02</td>
<td>0.07 ± 0.02‡</td>
<td>0.24 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>0.30 ± 0.03</td>
<td>-0.08 ± 0.02§</td>
<td>0.30 ± 0.04</td>
</tr>
<tr>
<td>Endo flowepi flow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal zone</td>
<td>4</td>
<td>1.34 ± 0.04</td>
<td>-0.06 ± 0.03§</td>
<td>1.34 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>1.50 ± 0.08</td>
<td>-0.08 ± 0.06</td>
<td>1.50 ± 0.09</td>
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<tr>
<td></td>
<td>10 (T)</td>
<td>1.38 ± 0.07</td>
<td>-0.18 ± 0.04*</td>
<td>1.44 ± 0.06</td>
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<tr>
<td>Moderately ischemic</td>
<td>4</td>
<td>0.91 ± 0.09</td>
<td>-0.09 ± 0.06</td>
<td>0.73 ± 0.09</td>
</tr>
<tr>
<td>zone</td>
<td>10 (NT)</td>
<td>0.82 ± 0.12</td>
<td>0.03 ± 0.04</td>
<td>0.58 ± 0.08</td>
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<tr>
<td></td>
<td>10 (T)</td>
<td>0.69 ± 0.11</td>
<td>-0.07 ± 0.08</td>
<td>0.75 ± 0.13</td>
</tr>
<tr>
<td>Severely ischemic</td>
<td>4</td>
<td>0.26 ± 0.03</td>
<td>0.02 ± 0.03</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td>zone</td>
<td>10 (NT)</td>
<td>0.20 ± 0.03</td>
<td>0.00 ± 0.02</td>
<td>0.26 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>10 (T)</td>
<td>0.36 ± 0.05</td>
<td>-0.08 ± 0.04§</td>
<td>0.37 ± 0.07</td>
</tr>
</tbody>
</table>

* Significant change from CAO baseline, P < 0.01.
† Significant change from CAO baseline, P < 0.05.
§ Response to either high dose group significantly different from low dose, P < 0.05.
|| Response to high dose (T) group significantly different from high dose (NT) group, P < 0.05.
▲ Response to dobutamine significantly different from dopamine, P < 0.05.

Effects of Dopamine, 4.0 µg/kg per min, Dobutamine, 4.0 µg/kg per min, and Isoproterenol, 0.03 µg/kg per min, in the Presence of Coronary Artery Occlusion

Overall LV Function (Fig. 1)

Isoproterenol decreased mean arterial pressure (7.0 ± 1.2%) and LV end-diastolic pressure (11.0 ± 3.3%) and increased heart rate (29.9 ± 4.6%). These changes were significant (P < 0.01). In contrast, these variables did not change significantly from occlusion baseline with dopamine and dobutamine. LV systolic pressure did not change significantly with any of the drugs, whereas LV dP/dt rose (P < 0.01) similarly, i.e., by 20-22%, with all three drugs.

Regional Myocardial Function

In the normal zone, the three drugs increased systolic SL shortening significantly (P < 0.01) and by similar amounts, ranging from 0.35 to 0.40 mm (Fig. 2). End-diastolic length, which is not shown in Figure 2, fell with isoproterenol and this change was significantly different (P < 0.05) from the response to dobutamine, but not dopamine.

In the moderately ischemic zone, systolic SL shortening increased (P < 0.05) by 0.18 ± 0.08 mm with dopamine and by 0.13 ± 0.04 mm with dobutamine, but did not change with isoproterenol. The increases in systolic SL shortening with dopamine and dobutamine as well as velocity of shortening, which increased similarly with all three drugs, were less than observed in the normal zone. Changes in end-diastolic SL were not significantly different for the three drugs.

In the severely ischemic zone, isoproterenol increased the extent of paradoxical bulging, i.e., systolic SL shortening became more negative by 0.27%.

**Figure 1** The effects of isoproterenol (ISO), 0.03 µg/kg per min (shaded bars), dopamine (DP), 4 µg/kg per min (open bars), and dobutamine (DB), 4 µg/kg per min (filled bars), in the presence of coronary artery occlusion are shown on left ventricular systolic pressure (LVSP), mean arterial pressure (AP), left ventricular end-diastolic pressure (LVEDP), dP/dt, and heart rate. Pre-drug coronary artery occlusion baseline values are shown below the bars, and significant changes are indicated by the symbols. Note that dP/dt rose by a similar amount with all three drugs. ISO induced significantly different effects from DP and DB, in that it increased heart rate and decreased mean arterial pressure.
NORMAL ZONE  

SEVERELY ISCHEMIC ZONE

0.50

T

E	co

CO

••ft.

2.93 2 14 2 24

-0.15

-0.20 -0.21

yp<0.01

0.22

0 22 0.22

p<0.01

0.03

DP 4.0

DB 4.0

p<0.01

0.07 mm (P < 0.01). In contrast, dobutamine reduced the extent of paradoxical bulging by 0.16 ± 0.04 mm (P < 0.01), whereas it was not significantly affected by dopamine (Fig. 2). Changes in end-diastolic SL were not significantly different for the three drugs.

Regional Myocardial Blood Flow

In the normal zone, blood flow increased (P < 0.01) by 43.1 ± 7.1% with isoproterenol, by 20.6 ± 3.2% with dopamine, and by 34.8 ± 4.3% with dobutamine (Fig. 2), whereas resistance fell (P < 0.01) by 29.9 ± 5.9% with isoproterenol, 11.9 ± 2.7% with dopamine, and 21.7 ± 2.4% with dobutamine.

In the moderately ischemic zone, blood flow increased by 14.7 ± 4.8% with dopamine (P < 0.01) and by 48.8 ± 9.3% (P < 0.01) with dobutamine. Isoproterenol did not change blood flow significantly in this zone.

In the severely ischemic zone, isoproterenol reduced blood flow by 32.9 ± 6.1% (P < 0.01). Dopamine and dobutamine did not change blood flow significantly. The endo:epi blood flow ratio fell significantly (P < 0.05) with isoproterenol, from 0.24 ± 0.05 to 0.15 ± 0.03, but did not change significantly with dopamine or dobutamine.

Comparison of the Three Sympathomimetic Amines which Increased LV dP/dt by 20% The increase in heart rate and decrease in mean arterial pressure observed with isoproterenol were significantly different from responses with dopamine and dobutamine (Fig. 1). None of the other responses for overall LV function were significantly different for the drugs. The only significant difference for regional myocardial function occurred in the severely ischemic zone, where the extent of paradoxical motion increased with isoproterenol, but not with dopamine or dobutamine. Similarly, the fall in blood flow to the severely ischemic zone with isoproterenol was a significantly different response from those observed with dopamine and dobutamine (Fig. 2).

Effects of Dopamine, 10 µg/kg per min, and Dobutamine, 10 µg/kg per min, in the Presence of Coronary Artery Occlusion

Overall LV Function (Table 1)

Both with dopamine and dobutamine, two types of responses were observed. In one group, no appreciable tachycardia (NT) occurred, whereas in the other group (T) heart rate rose (P < 0.01) by 18.5 ± 2.5% with dopamine and by 25.5 ± 3.4% with dobutamine. In both the T and NT groups, dopamine and dobutamine induced similar increases in mean arterial pressure, LV systolic pressure, and dP/dt. In the NT group, dopamine and dobutamine increased LV dP/dt by 70.6 ± 8.3% and 60.2 ± 5.0%, respectively. In the T group, dopamine and dobutamine increased LV dP/dt by 58.6 ± 10.9% and 63.9 ± 7.9%, respectively (Fig. 3).

Regional Myocardial Function (Table 2)

In the normal zone, both the NT and T groups responded with significant increases in systolic SL shortening and velocity.

In the moderately ischemic zone, significant increases occurred in velocity of shortening with all groups. The only significant increase in systolic SL shortening occurred in the dobutamine (NT) group.

In the severely ischemic zone, there were no significant changes in systolic SL shortening with dopamine or dobutamine in the NT group, whereas, in the T group, both drugs reduced contractile function significantly (P < 0.02), i.e., dopamine and dobutamine increased paradoxical bulging by 0.16 ± 0.05 and 0.07 ± 0.03 mm, respectively (Fig. 4).
Regional Myocardial Blood Flow (Table 3)

In the normal zone, blood flow increased and resistance decreased with all doses. The endo:epi ratio fell slightly ($P < 0.05$) with both drugs in the T group.

In the moderately ischemic zone, blood flow increased ($P < 0.01$) with dopamine (22.4 ± 5.9%) and dobutamine (30.5 ± 7.3%) in the NT group, but did not change significantly in the T group. The endo:epi blood flow ratio did not change significantly in any of these groups.

In the severely ischemic zone, in the NT group, blood flow rose ($P < 0.01$) by 32.5 ± 6.5% with dopamine and did not change with dobutamine. The endo:epi blood flow ratio did not change significantly with either drug. In contrast, in the T group, dopamine and dobutamine produced significant decreases ($P < 0.01$) in blood flow of 26.2 ± 3.8% and 27.0 ± 3.8%, respectively (Fig. 4). The endo:epi blood flow ratio fell significantly ($P < 0.01$) with dopamine from 0.36 ± 0.05 to 0.28 ± 0.04 and with dobutamine from 0.37 ± 0.07 to 0.24 ± 0.04.

Differences between Responses for Dopamine and Dobutamine

For both the T and NT groups, the only significant difference was in the response of blood flow in the severely ischemic zone in the NT group, which rose with dopamine, but not with dobutamine.

Figure 3. The effects of DP, 10 μg/kg per min, and DB, 10 μg/kg per min, in the presence of coronary artery occlusion are shown on LV systolic pressure (SP), mean arterial pressure (AP), LV dP/dt, LV end-diastolic pressure (EDP), and heart rate (HR). The results for the groups with no tachycardia are shown by the open bars, and the results for the groups with tachycardia are shown by the shaded bars. Pre-drug coronary artery occlusion baseline values are shown below the bars. Significant changes are indicated by the symbols.

Figure 4. The effects of DP, 10 μg/kg per min, and DB, 10 μg/kg per min, in the presence of coronary artery occlusion, on regional systolic SL shortening and regional myocardial blood flow are shown for the normal zone, on the left, and the severely ischemic zone, on the right. Pre-drug coronary artery occlusion baseline values are shown below the bars, and significant changes are indicated by the symbols. Multiple samples were averaged for the groups with no tachycardia as indicated by the open bars (nine dogs) and for the groups with tachycardia as indicated by the shaded bars (11 dogs). Both DP and DB elicited significantly different responses for ischemic zone contractile function and blood flow in the groups with tachycardia when compared to the responses in the groups without tachycardia.

Figure 5. The relationship between increases in heart rate (ordinate) and decreases in segment shortening (abscissa) in severely ischemic segments is shown. The linear regression was significant, $P < 0.01$, $r = 0.79$. 
FIGURE 6  The changes from coronary artery occlusion baseline control for severely ischemic zone (SIZ) flow (ml/min per g) (top) are shown with corresponding reductions in normal zone (NZ) resistance (mm Hg/ml per min per g) (bottom) for ISO, 0.03 μg/kg per min, DP, and DB, 4.0 and 10.0 μg/kg per min, in experiments where tachycardia (T) and no tachycardia (NT) occurred. Pre-drug coronary artery occlusion control values are shown below the bars, and significant changes from control are denoted by the asterisks. There was no consistent relationship between changes in NZ resistance and SIZ blood flow.

Differences between NT and T Groups

In addition to the differences for the response of heart rate (by definition), the major differences occurred in the ischemic zone, where the responses for both systolic SL shortening and blood flow were significantly different (P < 0.01) in the NT and T groups. Both dopamine and dobutamine induced reductions in blood flow and increases in paradoxical bulging in the presence of tachycardia, which were not observed in the absence of tachycardia (Fig. 4).

Relationships between Increases in Heart Rate and Reduction in Ischemic Zone Function (Fig. 5)

The changes in regional segment shortening in the ischemic zone were plotted against increases in heart rate for the experiments in which the sympathomimetic amines caused tachycardia, using standard least-squares linear regression (Armitage, 1973). This relationship, shown in Figure 5, was significant (r = 0.79, P < 0.01).

Relationships between the Decrease in Normal Zone Resistance and in Blood Flow to Severely Ischemic Myocardium for All Sympathomimetic Amines Studied (Fig. 6)

Although all sympathomimetic amines studied reduced normal zone resistance significantly, only dopamine and dobutamine at the higher tachycardia-producing dose, and isoproterenol, which also produced tachycardia, induced significant reductions in blood flow to the severely ischemic zone. There was no consistent relationship between the decreases in normal zone resistance and severely ischemic zone blood flow. For instance, dopamine, 10 μg/kg per min, induced a significantly greater decrease in normal zone resistance in the T group, in which blood flow to the severely ischemic zone fell.

The one hemodynamic factor that consistently correlated with a reduction in blood flow to the severely ischemic zone was the presence of tachycardia. When tachycardia was coupled with inotropic stimulation, blood flow to the severely ischemic zone fell; when tachycardia did not occur, blood flow to the ischemic myocardium was either maintained or rose (Table 4).

Table 4  Effects of Heart Rate on Resistance and Flow

<table>
<thead>
<tr>
<th></th>
<th>ISO (0.03)</th>
<th>DP (10)</th>
<th>DP (10)</th>
<th>DB (10)</th>
<th>DB (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(T)</td>
<td>(T)</td>
<td>(NT)</td>
<td>(T)</td>
<td>(NT)</td>
</tr>
<tr>
<td>LV dP/dt</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>–</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Normal zone</td>
<td>––</td>
<td>––</td>
<td>––</td>
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<td>––</td>
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<tr>
<td>resistance</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ischemic zone</td>
<td>–</td>
<td>0</td>
<td>–</td>
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<tr>
<td>blood flow</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

+= increase, -= decrease, 0 = no significant change.

Discussion

Dopamine, dobutamine, and isoproterenol are sympathomimetic amines, all of which augment myocardial contractility through β-adrenergic receptor stimulation but exert differing actions on arterial pressure and heart rate (Goldberg, 1972, Vatner et al., 1974a, Tuttle and Mills, 1975). In the present investigation, similar inotropic doses of isoproterenol, dopamine, and dobutamine were stud-
Sympathomimetic Amines in Myocardial Ischemia

Vatner and Baig

Other studies in anesthetized dogs have shown that with both dobutamine (Tuttle et al., 1977) and dopamine (McLennan et al., 1977) blood flow to the area of myocardium supplied by a narrowed coronary vessel increased after drug infusion. Two important differences between these studies and the present one are the use of an anesthetized animal preparation and the fact that the coronary vessel was merely constricted, and not completely occluded. Thus, not only are reflex effects likely to be different in the conscious and anesthetized state (Vatner and Braunwald, 1975), but also the intensity of the ischemia is markedly dissimilar. In a study by Meyer et al. (1976), in patients with coronary artery disease, myocardial blood flow was measured by the xenon-133 washout technique. In that study, it was found that, although total myocardial blood flow increased after dobutamine was administered, the pattern of perfusion was heterogeneous. This is consistent with our findings with that drug, where, by direct measurement of regional myocardial blood flow, we observed a substantial increase in blood flow to the normal zone, a smaller increase to the moderately ischemic zone, and no significant effect in the severely ischemic zone. Thus, in similar inotropic doses, dopamine and dobutamine have markedly dissimilar effects from isoproterenol on ischemic zone mechanical function and blood flow. Isoproterenol was also different in its ability to raise heart rate and lower mean arterial pressure.

To determine if the deleterious effects on the ischemic zone produced by isoproterenol could be observed with higher inotropic doses of dopamine and dobutamine, additional experiments were conducted with these drugs given in a dose of 10 μg/kg per min. Two different responses to the higher dose of dopamine and dobutamine were discerned, one in which no tachycardia occurred, and the other, which was associated with tachycardia. In both groups and with both drugs, contractile function and blood flow increased in the normal zone. With both drugs in the experiments in which heart rate rose, in contrast to what was observed with the corresponding lower doses, there was a significant fall in blood flow, and contractile function deteriorated in the severely ischemic zone. Moreover, the endo/epi blood flow ratio fell, indicating more intense ischemia in endocardial layers. Thus, with higher inotropic doses when heart rate rose, dopamine and dobutamine exerted deleterious effects on ischemic myocardium as occurred with isoproterenol. This is in agreement with the findings of Mueller et al. (1978), who found that dopamine, administered to patients with shock associated with myocardial infarction, caused an increase in myocardial oxygen demand which exceeded availability. It is important to note that in the study by Mueller et al. (1978) dopamine was found to exert a deleterious effect, and heart rate rose significantly in those patients.

However, in the experiments in the present in-
investigation with the higher doses of dopamine and dobutamine, but in which heart rate did not rise, the deleterious effects on regional mechanical function and blood flow in the severely ischemic zone were not observed. Even though LV dP/dt rose 3-fold more than with the low dose of these drugs, as well as isoproterenol (i.e., by 71% with dopamine and by 60% with dobutamine), blood flow did not fall and contractile function did not deteriorate in the severely ischemic zone. In fact, with dopamine, blood flow actually rose significantly in the severely ischemic zone. The results of these experiments suggest that β-adrenergic inotropic stimulation does not necessarily exert a deleterious effect on regional mechanical function and blood flow in the presence of regional myocardial ischemia. It was not determined precisely why the relatively large inotropic doses of sympathomimetic amines did not elicit a deleterious effect. One possible explanation is that increasing myocardial contractility in the intact conscious animal is not associated with a high oxygen cost. Another possible explanation is that these agents elicited an improvement in regional blood flow to the ischemic zone through stimulation of autonomic reflexes. In contrast, the favorable action of an improvement in blood flow might have been overridden by the deleterious effect of tachycardia in those experiments in which heart rate rose.

The reduction of blood flow in the ischemic zone with isoproterenol has been attributed to a "coronary steal" in response to dilation of vessels in the normal zone (Cohen et al., 1976). This concept is consistent with our findings with isoproterenol, but not entirely compatible with the current observations on the effects of the other sympathomimetic amines, dopamine, and dobutamine. As is shown in Figure 6, there is no consistent correlation between the reduction in normal zone resistance and reduction in blood flow in the ischemic zone. Thus, in the intact conscious animal, inducing vasodilation in the normal zone of the ischemic heart does not necessarily result in a "coronary steal" with reduction of blood flow to the ischemic zone.

The deleterious effects of isoproterenol on ischemic zone blood flow and mechanical function could be attributed to the drug's action to increase myocardial contractility or heart rate or to its hypotensive effect. The results of the present experiments indicate that the increase in myocardial contractility is not the essential mechanism responsible for the reduction in blood flow and contractile function in the ischemic zone, since these deleterious effects did not occur with doses of dopamine and dobutamine sufficient to increase LV dP/dt 3-fold more than that induced by isoproterenol. Most likely, the hypotensive effect of isoproterenol was a contributing factor, yet similar unfavorable effects were observed in the ischemic zone with dopamine and dobutamine, where arterial pressure rose slightly. The one hemodynamic factor that was common to all experiments in which blood flow and function fell in the ischemic zone was the presence of tachycardia (Table 4). The good correlation found between decreases in ischemic zone function and increases in heart rate are shown in Figure 5, which further supports the thesis that the tachycardia associated with administration of sympathomimetic amines is the primary deleterious factor.

Tachycardia is detrimental for several reasons. First, it increases myocardial metabolic demands, which cannot be met by appropriate increases in oxygen supply to the ischemic myocardium. In addition, tachycardia reduces diastolic time, which is not important for coronary inflow in the nonischemic myocardium, since blood flow rate can rise commensurately, but may be critical in the ischemic myocardium, where blood flow rate is limited. In this connection, it is of interest to note the recent study of Bache and Cobb (1977), which showed that increasing heart rate in the nonischemic but vasodilated heart reduced the endo:epi blood flow ratio. Furthermore, preliminary data from our laboratory indicate that increasing heart rate by only 20% in the presence of acute regional myocardial ischemia induces a deleterious effect, i.e., blood flow falls and function deteriorates in the ischemic myocardium (Baig et al., in press).

Myocardial function is determined by the balance between myocardial oxygen supply and myocardial metabolic demand. When oxygen supply is diminished without a change in demand, or when demand is augmented in the absence of an appropriate increase in oxygen supply, myocardial function deteriorates. This was observed clearly in the present study, where coronary artery occlusion reduced oxygen supply modestly in the moderately ischemic zone and by a greater amount in the severely ischemic zone, even myocardial function fell in the moderately ischemic zone and by an appropriately greater amount in the severely ischemic zone. Isoproterenol reduced oxygen supply to the ischemic myocardium and may or may not have increased myocardial metabolic demand. However, it is clear that the balance between supply and demand was unfavorable and regional function deteriorated. This deterioration in regional function, coupled with a reduction in blood flow to the ischemic myocardium, was not observed with dopamine and dobutamine as long as heart rate did not rise. For this reason, it is felt that these agents may not necessarily affect ischemic myocardial mechanical function or blood flow adversely. Whether they induce a salutary effect remains to be demonstrated.

In summary, the results of the present investigation indicate that β-adrenergic inotropic agents that increase myocardial contractility do not always elicit a "coronary steal" or exert a deleterious effect on ischemic myocardial mechanical function or blood flow. These adverse effects may not occur if arterial pressure is maintained and heart rate does
not rise. Indeed, when dopamine and dobutamine increased LV dP/dt by 60-70% in the absence of tachycardia, blood flow to the ischemic zone did not fall. However, when inotropic stimulation is coupled with tachycardia, blood flow falls and contractile function deteriorates in the ischemic myocardium. These findings are also consistent with other recent studies from our laboratory on the effects of ouabain, a positive inotropic agent, which does not elicit tachycardia but exerts a salutary effect on ischemic myocardial mechanical function and blood flow when administered either alone (Vatner et al., 1978b), or in combination with propranolol (Vatner et al., 1978a).

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References

Baig H, Manders T, Vatner S (in press) Differing actions of specific inotropic vs chronotropic stimulation on ischemic myocardium in conscious dogs (abstr). Circulation
Vatner SF, Baig H, Manders WT, Murray PA (1978b) Effects of a cardiac glycoside on regional function, blood flow and electrolygrams in conscious dogs with myocardial ischemia. Circ Res 43: 413-423
Importance of heart rate in determining the effects of sympathomimetic amines on regional myocardial function and blood flow in conscious dogs with acute myocardial ischemia.

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