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, β-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

β-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 positive 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-
Regional 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 (Konigsberg Instruments) were calibrated in vitro and in vivo against a calibrated Statham P23 Db 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 Cleveite-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 (Domenech 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, 85Sr, 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-ray 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 85Sr, 1720 for 141Ce, and 232 ± 6 for 46Sc.
± 8 for $^{46}$Sc, and 2413 ± 6 for $^{114}$Ce in the most ischemic zones. The raw counts then were corrected for background and energy crossover and compared with reference arterial blood samples according to standard techniques to obtain flow for each sample expressed as ml/min per g of tissue, as well as the ratio of endocardial-to-epicardial flows.

The experiments with sympathomimetic amines were divided into several groups. The first group (eight dogs) received isoproterenol in a dose of 0.03 μg/kg per min. Another group (10 dogs) received dopamine and dobutamine in a dose of 4.0 μg/kg per min. These doses were chosen since they elicit an increase of approximately 20% in LV dP/dt. Finally, 20 dogs received dopamine and dobutamine in a dose of 10 μg/kg per min. However, nine of the dogs in the latter group responded with no tachycardia (NT), whereas 11 of the dogs responded with tachycardia (T). Thus, the dogs receiving the 10 μg/kg per min dose were separated according to their heart rate responses. The larger dose was selected, since undesired side effects, e.g., arrhythmias and emesis, are still rare in conscious dogs with acute myocardial ischemia at this dose.

Experiments were conducted 1–4 weeks after operation in the conscious unsedated dogs. LV pressure and its rate of change (dP/dt), mean arterial and left atrial pressures, heart rate, multiple SL’s and velocity of SL shortening (dSL/dt) were recorded continuously throughout the course of the experiment. Velocity data for the severely ischemic zones are not reported, since velocity of shortening does not apply to segments exhibiting paradoxical bulging. Preoclusion control measurements were obtained during a 30- to 60-minute period when variables were stable. After this time, the coronary vessel was occluded. The first microsphere injection was made 10–15 minutes after coronary artery occlusion at a time when overall ventricular function, as well as regional myocardial function, were observed to be stable. At this time, the first sympathomimetic amine infusion (the order of dopamine and dobutamine infusions was randomized throughout) was begun. Seven to 10 minutes after the start of the infusion, at a time when a stable plateau of inotropy had been achieved, the hemodynamic data were assessed, and the second injection of microspheres was made to determine the effects of the intervention on myocardial blood flow distribution. The infusion then was stopped, and a period of 30–40 minutes was allowed for the continuously measured parameters to return to their preinfusion control levels. At this time, the third injection of microspheres was made to determine the second coronary artery occlusion baseline blood flow level. There were no statistical differences in the first and second coronary artery occlusion baselines for measurements of overall cardiac function, regional contractile function, or blood flow (see Tables 1–3 for coronary artery occlusion baseline values prior to dopamine and dobutamine). The second 10-minute infusion was begun with measurements continuously recorded as described above, and the fourth microsphere injection was made 7–10 minutes after starting the infusion. Following a 20- to 30-minute recovery period after the end of this infusion, the

### Table 1: Effects of Dopamine (DP) and Dobutamine (DB) in the Presence of Coronary Artery Occlusion (CAO) on Overall LV Function

<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>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>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>10 (T)</td>
<td>98 ± 4.5</td>
<td>17.5 ± 2.0§</td>
<td></td>
<td>99 ± 4.4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>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>10 (T)</td>
<td>101 ± 3.1</td>
<td>8.4 ± 3.7†</td>
<td></td>
<td>100 ± 2.5</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>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>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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>10 (NT)</td>
<td>11.9 ± 1.0</td>
<td>0.9 ± 1.8</td>
<td>11.3 ± 2.0</td>
<td>0.7 ± 0.7</td>
</tr>
<tr>
<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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3200 ± 390</td>
<td>730 ± 180*</td>
<td>3120 ± 390</td>
<td>730 ± 180*</td>
</tr>
<tr>
<td>10 (NT)</td>
<td>3160 ± 390</td>
<td>2170 ± 220*§</td>
<td></td>
<td>3360 ± 130</td>
</tr>
<tr>
<td>10 (T)</td>
<td>3250 ± 110</td>
<td>1860 ± 330*§</td>
<td></td>
<td>3100 ± 150</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, $P < 0.05$. 

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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 cardiometer, 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 in the normal zone. Vascular 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).

### Results

#### 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 (ml/min per g)</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 zone</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></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 zone</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></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 flow:epi 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>
</tr>
<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>
</tr>
<tr>
<td>Moderately ischemic zone</td>
<td>4</td>
<td>0.91 ± 0.09</td>
<td>-0.09 ± 0.06</td>
<td>1.44 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>10 (NT)</td>
<td>0.82 ± 0.12</td>
<td>0.03 ± 0.04</td>
<td>0.58 ± 0.08</td>
</tr>
<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 zone</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></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

\[ \Delta SL \text{ Shortening (mm)} \]

\[ \begin{array}{c|c|c|c}
   & 2.93 & 2.14 & 2.24 \\
   ISO & * & * & * \\
   DP & * & * & * \\
   DB & * & * & * \\
   \end{array} \]

\[ \Delta Flow \text{ (ml/min/g)} \]

\[ \begin{array}{c|c|c|c|c}
   & 1.44 & 1.54 & 1.75 \\
   ISO 0.03 & * & * & * \\
   DP 4.0 & * & * & * \\
   DB 4.0 & * & * & * \\
   \end{array} \]

**Figure 2** The effects of ISO, 0.03 μg/kg per min (shaded bars), DP, 4 μg/kg per min (open bars), and DB, 4 μg/kg per min (filled bars), in the presence of coronary artery occlusion are shown on regional systolic SL shortening and regional myocardial blood flow 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 from eight dogs receiving ISO and 10 dogs receiving DP and DB. ISO induced significantly different effects from DP and DB in the severely ischemic zone, in that it reduced function and blood flow.

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 increased 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 62.0 ± 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

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.
SYMPATHOMIMETIC AMINES IN MYOCARDIAL ISCHEMIA/Vatner and Baig

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.

**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.
Relationship 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 $\mu$g/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).

Discussion

Dopamine, dobutamine, and isoproterenol are sympathomimetic amines, all of which augment myocardial contractility through $\beta$-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-
ied. The doses were matched to increase LV dP/dt by similar amounts in conscious dogs with acute myocardial ischemia. It is recognized that LV dP/dt yields only a rough indication of the inotropic state. However, it was felt that this would be a sufficiently accurate measurement for means of comparison. It is also important to note that the velocity of myocardial fiber shortening in the normal zone rose by similar amounts with the three inotropic agents (Fig. 2), further supporting the contention that isoproterenol, dopamine, and dobutamine were compared at similar inotropic doses. Although at the lower dose studied, dopamine and dobutamine had relatively little effect on arterial and LV pressures and heart rate, this was in direct contrast to isoproterenol, which reduced mean arterial pressure slightly and produced a significant tachycardia.

In the normal zone, all three drugs enhanced mechanical function by similar amounts, as indicated by increases in the extent and rate of myocardial fiber shortening. In contrast, in the severely ischemic zone, dopamine and dobutamine had little effect on contractile function, whereas isoproterenol caused an increase in the extent of paradoxical bulging.

All three drugs increased blood flow to the normal myocardium. However, isoproterenol caused a significant fall in blood flow to the ischemic myocardium, in direct contrast to the effects of dopamine and dobutamine, which did not change blood flow. The decrease in blood flow produced by isoproterenol was accompanied by significant underperfusion of the subendocardium, as the endo:epi blood flow ratio fell. Although the decrease in blood flow to ischemic myocardium was relatively small, it was significant statistically. Moreover, these data must be analyzed in combination with the simultaneous data for regional myocardial function at the same sites, which also deteriorated when blood flow fell with isoproterenol.

The finding in this study that dobutamine does not improve blood flow to the ischemic zone is apparently in contrast to the results of Willerson et al. (1976), who concluded that dobutamine significantly increased regional myocardial blood flow to all areas of the heart, both in anesthetized dogs with acute myocardial ischemia and conscious dogs with myocardial infarction. It should be pointed out, however, that the degree of ischemia in that study (Willerson et al., 1976) was quite different from that of the present investigation, in that the occlusion values for ischemic zone blood flow were on the order of 3 times greater than those for the severely ischemic zone of the present study and were actually similar to the values found in the moderately ischemic zone in this study. The data for the moderately ischemic zone from the present study, where blood flow rose with dobutamine, compare favorably with the ischemic zone data of Willerson et al. (1976).

Another study in anesthetized dogs has shown that with both dobutamine (Tuttle et al., 1977) and dopamine (McLennathan 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, where 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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