Dobutamine Infusion in Conscious Dogs with and without Acute Myocardial Infarction
Effects on Systemic Hemodynamics, Myocardial Blood Flow, and Infarct Size

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SUMMARY We infused dobutamine (20 µg/kg per min) intravenously, once before and once after coronary artery occlusion, in 10 chronically instrumented dogs. Both infusions increased cardiac output and left ventricular dp/dt and dp/dt/P, but divergent effects on heart rate and aortic blood pressure were observed. Dobutamine decreased heart rate and increased mean aortic blood pressure before coronary artery occlusion, whereas after occlusion it increased heart rate while mean aortic blood pressure remained unchanged. A greater decrease in total peripheral vascular resistance occurred during dobutamine infusion after coronary artery occlusion than before. These differences may relate to withdrawal of enhanced sympathetic tone after coronary occlusion. Similar infusions of normal saline (n = 9) produced no systemic hemodynamic changes either before or after coronary artery occlusion. Myocardial blood flow increased to both non-ischemic and ischemic regions of the heart during dobutamine infusion, but the endocardial:epicardial blood flow ratio did not change significantly. In addition, infarct size, measured by nitroblue tetrazolium stain, was smaller in the dobutamine group (10 ± 1 g) than in the normal saline group (15 ± 2 g). Neither left ventricular weight nor risk zone differed between the two groups. These results indicate that dobutamine may be a useful inotropic agent during acute myocardial infarction. CIRC RES 49: 170-180, 1981

DOBUTAMINE is a potent β1 adrenergic agonist with minimal β2 and α adrenergic effects (Tuttle and Mills, 1975; Sonnenblick et al., 1979). Studies in normal conscious dogs (Vatner et al., 1974; Hinds and Hawthorne, 1975; Liang and Hood, 1979) have shown that dobutamine augments cardiac output and myocardial contractility but has little effect on heart rate and aortic blood pressure. Total peripheral vascular resistance decreases during dobutamine infusion. However, when ganglionic blockade is produced by pretreatment with mecamylamine, both heart rate and arterial blood pressure are increased by dobutamine, and peripheral vascular resistance does not change (Liang and Hood, 1979). These results suggest that dobutamine has significant direct chronotropic as well as inotropic effects but only a minimal direct vascular effect. However, in the presence of an intact baroreceptor reflex, the direct chronotropic effect of dobutamine is offset by the reflex slowing of heart rate caused by the increased stroke volume and cardiac output, and reflex vasodilation and a decrease in peripheral vascular resistance also occur.

The hemodynamic effects of dobutamine in the presence of myocardial infarction might differ significantly from those in normal dogs, because autonomic nervous activities are altered by myocardial infarction (Liang and Hood, 1974; Webb et al., 1972). Dobutamine also increases blood flow to the ischemic myocardium and limits infarct size after partial coronary occlusion in dogs (Tuttle et al., 1977). Its effects after complete coronary artery occlusion, however, are less certain. Willerson et al. (1976) reported that, although blood flow was increased to the ischemic myocardium, dobutamine might further the myocardial damage as determined by epicardial ST segment elevation in anesthetized open-chest dogs. On the other hand, Vatner and Baig (1979) showed in conscious dogs that dobutamine increased blood flow and contractile function in moderately ischemic areas of the myocardium, but not in the center of the infarct which was severely ischemic. Infarct size was not measured in any of the studies.

The purpose of the present study was: (1) to study the hemodynamic responses to dobutamine before and after the production of acute myocardial infarction, and (2) to study whether dobutamine...
exerted a salutary effect by reducing infarct size in conscious dogs. Our results show that infarct size was reduced by dobutamine infusion, and that this reduction in infarct size probably was caused at least in part by the increase in blood flow to the ischemic myocardium following dobutamine infusion.

Methods

Surgical Procedure

Adult beagles weighing 7.0 to 15.8 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv) and artificially ventilated with room air using a Harvard respirator (Harvard Apparatus). Through a sterile thoracotomy via the 5th left intercostal space, a Silastic balloon occluder (i.d. 3.5 mm) was implanted around the left anterior descending coronary artery immediately distal to its first diagonal branch. Heparin-filled Tygon catheters (i.d. 1.02 mm) were inserted into the main pulmonary artery, left atrium, and aorta. The occluder tubing and catheters then were tunneled through a left intercostal space and secured externally at the back of the neck. Veterinary procaine penicillin G (400,000 U) and dihydrostreptomycin (500 mg) (Combiotic, Pfizer Inc.) intramuscularly and ferrous sulfate (325 mg, po) were administered daily after the surgery.

Two to 3 weeks after surgery, each dog was given morphine sulfate (0.5 mg/kg) subcutaneously, and a French 7 catheter was placed via an external jugular vein into the coronary sinus under local anesthesia with 0.5% lidocaine (Xylocaine; Astra Pharmaceutical Products, Inc.), and using fluoroscopic guidance. A high-fidelity transducer-tip catheter (Millar Instruments, Inc.) was inserted into the left ventricle via a femoral artery, also using local anesthetics and fluoroscopic guidance. A peripheral vein in a hind leg was cannulated for drug infusion. After the surgical preparation, we administered heparin (500 U/kg, iv) and maintained the dog in a lateral decubitus position with limbs lightly restrained.

Measurements and Calculations

The intravascular catheters were connected to Statham P23Db pressure transducers (Statham Instruments, Inc.) and a Brush 480 multichannel recorder (Gould, Inc., Instrument Systems Division). The Millar transducer-tip catheter was also connected to the Brush 480 recorder for measuring left ventricular pressure, and the maximum rate of left ventricular pressure rise (dP/dt) was measured by an electronic differentiator. The ratio of left ventricular dP/dt to a developed left ventricular pressure of 50 mm Hg during isovolumic systole was calculated, for 10 consecutive cardiac cycles during each measurement period, using a PDP 11/10 minicomputer (Digital Equipment Corporation). This ratio is referred to as left ventricular dP/dt/P (Davidson et al., 1974).

Cardiac output was measured using indocyanine green (Cardio-Green; Hynson, Westcott and Dunning, Inc.) injected into the pulmonary artery with sampling from the aorta through a Gilford model 140 cardiac output system (Gilford Instrument Laboratories, Inc.). Organ blood flows were measured by the radioactive microsphere method (Heymann et al., 1977), as we recently described (Liang, 1977). Microspheres, 15 ± 3 μm in diameter and labeled with cerium-141, tin-113, rubidium-103, or scandium-46 at a specific activity of 10 mCi/g, were suspended in a 10% dextran solution containing 0.01% Tween-80. After adequate sonication and mixing, the microspheres were injected into the left atrium, followed immediately by a flush of 10 ml of normal saline over a 30-second period. Arterial reference blood was collected at a rate of 7.75 ml/min with a Harvard pump beginning 10 seconds before microsphere injection and continuing for 80 seconds. A total of 500,000 to 750,000 microspheres was injected for each flow determination prior to coronary artery occlusion, whereas 1 to 1.5 million microspheres were injected after coronary artery occlusion.

Heart rate was measured from the electrocardiogram. Cardiac output was divided by heart rate to give the stroke volume. Cardiac output was also divided into mean aortic blood pressure to yield total peripheral vascular resistance, using the conventional formula. Blood samples were taken from the aorta, pulmonary artery, and coronary sinus for measuring oxygen content and oxygen capacity on a Lex-O2-Con analyzer (Lexington Instruments). Blood pH, PO2, and PCO2 were measured with a Radiometer PHM71 Acid and Base Analyzer (Rainin Instrument Company).

At the end of the experiment on the second day, the animal was treated with heparin (500 units/kg, iv) and killed with a lethal dose of pentobarbital. The heart was removed, and a polyethylene catheter was placed into the left anterior descending coronary artery at the site of the balloon occluder. The left main coronary artery and right coronary artery were cannulated via their respective ostia. Simultaneous perfusions under a constant pressure of 100 mm Hg then were begun with a 1% Monastral Red (E.I. du Pont de Nemours & Co., Inc.) solution into the left anterior descending coronary artery and an 0.5% Monastral Blue solution into the other two catheters. Both kinds of Monastral pigments were suspended in a dextran 70 in normal saline solution (Macrodex; Pharmacia Laboratories, Inc.) and mixed well before use. After 15 minutes of perfusion, the left ventricle was separated from the rest of the heart, weighed, and cut into 6- to 7-mm thick slices. The areas stained red are known as the "risk zones" because they represent the flow distribution of left anterior descending coronary artery, regions that are at risk when the coronary artery is occluded (Lowe et al., 1978). The slices were then weighed, photographed, and immersed for 15 min-
utes in a nitroblue tetrazolium solution (Derias and Adams, 1978; Roberts et al., 1978). The dye stains viable tissues blue, whereas infarcted tissues devoid of dehydrogenases are unstained. As a result, a discrete outline of the infarction can be identified. The tissues were rephotographed. The percent of tissue that was either at risk or infarcted in each slice was determined by planimetry of the zones on the photographs. This was done by an investigator who was unaware of the assignment of the animals to different experimental groups. Values for the apical and basal views of the slice were averaged. The average value then was multiplied by the slice weight to give the mass of myocardium at risk or infarcted for that slice. The total risk zone and infarct size of the heart were obtained by adding up their respective weights for all slices.

Left ventricular slices finally were cut into multiple transmural segments, each of which was divided further into an endocardial and epicardial segment weighing approximately 0.8 g, for radioactivity counting. This resulted in an average of 75 segments (range 52 to 96) for each left ventricle. In addition to the myocardium, lungs, brain, kidneys, liver, stomach, small intestine, large intestine, spleen, pancreas, urinary bladder, adrenal glands, femoral muscle, femur, and skin were removed, cleaned, and weighed. All blood and tissue samples were counted using a Packard Gamma Spectrometer (Packard Instrument Co., Inc.) at window settings corresponding to the peak energies of the nuclides used. The activity of each isotope was corrected for background and cross-over activity from other isotopes. Organ blood flow and vascular resistance were calculated on the PDP-11/10 minicomputer as follows (Liang, 1977):

\[
\text{Blood flow (ml/100 g per min) = } \frac{[\text{arterial reference flow (ml/min) \times \text{organ nuclide radioactivity} \times 100]}{[\text{arterial reference nuclide radioactivity} \times \text{organ weight (g)}].}
\]

Vascular resistance (mm Hg/ml/min) = \(\frac{[\text{mean aortic blood pressure (mm Hg) \times 100}]}{[\text{organ blood flow (ml/100 g per min) \times \text{organ weight (g)}]}\).

Total left ventricular blood flow was determined by summing the products of flow and weight of each individual left ventricular segment. Left ventricular oxygen consumption \((\text{MVO}_2)\), left ventricular work \((\text{LVW})\), and mechanical efficiency \((\text{ME})\) were calculated as follows (Gorlin, 1961): \(\text{MVO}_2\) (ml/100 g per min) = \(\text{LVBF} \times \left(\text{C}_a - \text{C}_w\right) + 1000\); \(\text{LVW} \text{ (kg-m/min)} = \left(\text{LV}_w \times \text{CO} \times 1.36\right)/100\); \(\text{ME} \text{ (%) = } \left[\frac{\text{LV}_w}{\text{LVBF} \times \text{MVO}_2} \times 2.06\right]\), where \(\text{LVBF}\) is total left ventricular blood flow, ml/100 g per min; \(\text{C}_a\), arterial blood oxygen content, ml/liter; \(\text{C}_w\), coronary sinus blood oxygen content, ml/liter; \(\text{LV}_w\), left ventricular systolic mean pressure, mm Hg; \(\text{CO}\), cardiac output, liters/min.

**Experimental Protocol**

Animals were divided into two experimental groups. The same experimental protocol was used in both groups, with the exception that in the infusion period one group received normal saline and the other received a dobutamine infusion \((20 \mu\text{g/kg per min})\). This dose of dobutamine is within the therapeutic range (Gillespie et al., 1977; Leier et al., 1977; Steen et al., 1978). Each animal received two infusions of the same solution, once before and once after the production of acute myocardial infarction. The first infusion began after a 20-minute control period and continued for 20 minutes at 0.19 ml/min, using a Harvard infusion pump. Systemic hemodynamics, including cardiac output, heart rate, aortic blood pressure, left atrial pressure, and left ventricular \(dP/dt\) and \(dP/dt/P\), were measured at 5-minute intervals both during the control and infusion periods. Regional blood flows and blood gas measurements were obtained within the last 5 minutes of the control or infusion period.

Myocardial infarction was produced 20 minutes after the end of the first infusion by inflating the balloon occluder implanted previously around the left anterior descending coronary artery with a predetermined amount of saline which was known to cause complete occlusion of the coronary artery at the time of balloon implantation. This invariably resulted in a decrease in left ventricular \(dP/dt\) and an increase in ST segments of the electrocardiogram. Twenty minutes later, control measurements were again taken over a 20-minute period, followed by the second infusion of normal saline or dobutamine. The solutions were infused at a rate of 0.19 ml/min, identical to that used before coronary artery occlusion. Similarly, systemic hemodynamics, regional blood flows, and blood gas measurements were taken at the same times as those during the first infusion prior to coronary artery occlusion. Subsequently, the infusions were continued for 24 hours at a rate of 0.9 ml/hr using a battery operated Sigmamotor mobile infusion pump (Sigmamotor, Inc.). After the left ventricular and coronary sinus catheters were removed, a jacket was put on the dog and the infusion pump was secured in a pocket of the jacket before the animal was returned to the cage. No antiarrhythmic agents were given during the infusion periods. The dogs were killed at the end of the 24-hour infusion. The infusion bag was weighed before and after the infusion. The difference in weight represented the amount of dobutamine or normal saline the animal received. There were no detectable leaks in the infusion system. All animals received the total amounts of solution intended for the 24-hour infusion. We also inspected the balloon occluders for possible leakage after the dogs had been killed. In addition, coronary angiography was performed in five dogs immediately before they were killed. It showed that the coronary artery occlusion produced by the balloon occluders was complete.

**Statistical Analysis**

The experimental results are given as mean ± SE. The statistical significance of the differences between the saline and dobutamine groups was deter-
mined by two-way analysis of variance for independent groups with repeated measures (Winer, 1971). Dunnett's test (Dunnett, 1964) was used to determine the significance of differences between the pre-infusion control and the serial repeated measurements during the infusion period in each group. Student's t-test was used to analyze the difference between two means in the two groups. Changes are considered statistically significant if \( P \) values are less than 0.05.

**Results**

Twenty dogs were divided into two groups of ten, designated to receive either dobutamine or normal saline. In one of the animals that received normal saline, the Silastic balloon occluder was ruptured and myocardial infarction was not produced. This animal was discarded and the acute hemodynamic results reported here were derived from the remaining 19 dogs. However, only 16 animals (eight in each group) survived the 24-hour infusion and were available for infarct sizing. One animal in the dobutamine group died of ventricular fibrillation one hour and 40 minutes after the onset of coronary artery occlusion. Another two animals (one in each group) died overnight. No gross pathology other than myocardial infarction was found at postmortem examination. Ventricular fibrillation probably was the cause of death in these two animals. Balloon occluders were inflated at the time of postmortem examination in all of the dogs. In addition, hemorrhage was noted within the infarct, suggesting that no significant balloon leakage had occurred to produce reperfusion injury.

**Systemic Hemodynamic Responses to Dobutamine Infusion**

Figures 1–3 show the effects of dobutamine infusion (20 \( \mu \)g/kg per min) on systemic hemodynamics before and after coronary artery occlusion. Before occlusion (Fig. 1), dobutamine infusion increased cardiac output, mean aortic blood pressure, and left ventricular \( \frac{dP}{dt} \) and \( \frac{dP}{dt}/P \). Stroke volume also increased significantly from 21 ± 2 to 26 ± 2 ml (\( t = 4.78, \text{d.f.} = 9, P < 0.001 \)). Concomitantly, heart rate and total peripheral vascular resistance decreased slightly (Fig. 3), but there was no change in left atrial pressure (4.2 ± 0.8 to 4.5 ± 1.1 mm Hg). After coronary artery occlusion (Fig. 2), dobutamine infusion again increased cardiac output, left ventricular \( \frac{dP}{dt} \), and \( \frac{dP}{dt}/P \); however, mean aortic blood pressure did not increase significantly. Stroke volume increased from 16 ± 1 to 20 ± 1 ml (\( t = 4.94, \text{d.f.} = 9, P < 0.001 \)), but left atrial pressure did not change (5.1 ± 0.8 to 4.8 ± 0.8 mm Hg). Heart rate increased significantly during dobutamine infusion after coronary artery occlusion (Fig. 3). This is in contrast to the decrease in heart rate observed during dobutamine infusion before coronary artery occlusion. Dobutamine infusion also resulted in a larger decrease in total peripheral vascular resistance after coronary artery occlusion than before occlusion (Fig. 3). No hemodynamic

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Systemic hemodynamic effects of dobutamine (20 \( \mu \)g/kg per min; \( n = 10, 12.2 ± 0.7 \) kg; solid lines) and normal saline (\( n = 9, 10.2 ± 0.8 \) kg; broken lines) infusion in conscious dogs before coronary artery occlusion. Bars indicate SE's. Asterisks indicate values that are statistically different from their corresponding baseline values at \( P < 0.05 \). The baseline values at time zero of infusion are averages of the repeat measurements within the 20-minute control period immediately prior to infusion.

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Systemic hemodynamic effects of dobutamine (20 \( \mu \)g/kg per min; \( n = 10, 12.2 ± 0.7 \) kg; solid lines) and normal saline (\( n = 9, 10.2 ± 0.8 \) kg; broken lines) infusion in conscious dogs after coronary artery occlusion. Bars indicate SE's. Asterisks indicate values that are statistically different from their corresponding baseline values at \( P < 0.05 \). The baseline values at time zero of infusion are averages of the repeat measurements within the 20-minute control period immediately prior to infusion.
Dobutamine infusion increased total left ventricular blood flow, coronary saline infusion either before or after coronary artery occlusion (Figs. 1 and 2). Changes occurred in animals that received normal saline infusion. It actually decreased slightly in the endocardium of moderately ischemic regions. There was also no change in endocardial:epicardial blood flow ratio in these animals.

Coronary Hemodynamic Responses to Dobutamine Infusion

Tables 1 and 2 show that dobutamine infusion increased total left ventricular blood flow, coronary sinus oxygen saturation, left ventricular oxygen consumption, and left ventricular work, and did not change myocardial mechanical efficiency (Gorlin, 1961). These changes occurred both before and after the production of coronary artery occlusion. Similar administrations of normal saline had no effects on any of the measurements.

The effects of dobutamine on regional myocardial blood flows in the ischemic myocardium are shown in Figure 4. In each experiment, left ventricular segments were grouped into four different regions according to their endocardial blood flows, determined at 40 minutes after coronary artery occlusion. Segments having blood flows less than 25 ml/100 g per min were combined for calculation of an average blood flow, and these areas are termed the "severely ischemic regions." Similar calculations were performed for moderately ischemic and mildly ischemic regions that had flows between 25 and 50 ml/100 g per min and between 50 and 75 ml/100 g per min, respectively. Areas with flows higher than 75 ml/100 g per min were considered normal non-ischemic myocardium. Figure 4 shows that in the ischemic regions the endocardial flows were lower than corresponding epicardial flows. The endocardial:epicardial blood flow ratio became progressively smaller as the degree of ischemia worsened. Dobutamine infusion increased blood flow to all regions of the heart. Both endocardial and epicardial blood flows increased proportionately and the endocardial:epicardial flow ratios did not change significantly.

Myocardial blood flow did not increase during normal saline infusion. It actually decreased slightly in the endocardium of moderately ischemic regions (Fig. 5). There was also no change in endocardial:epicardial blood flow ratio in these animals.

Effects of Dobutamine on Infarct Size

Infarct size was measured in the 16 animals that survived the 24-hour infusion of either dobutamine or normal saline. Left ventricular weight did not differ between the two groups, but the infarct size, expressed either by weight or by percent of left ventricular weight, was significantly smaller in the dobutamine group than in the normal saline group (Table 3).

![Graph showing changes in heart rate and total peripheral vascular resistance (PVR) produced by dobutamine infusion (20 μg/kg per min) in 10 conscious dogs before (stippled bars) and after (striped bars) coronary artery occlusion. Bars indicate se's. The baseline heart rate prior to dobutamine infusion was 127 ± 11 beats/min before coronary artery occlusion and 130 ± 8 beats/min after occlusion. This difference in baseline heart rate before and after coronary artery occlusion was not statistically significant. The baseline total peripheral vascular resistance, however, was significantly higher after coronary artery occlusion (4,619 ± 379 dynes cm/sec) than before occlusion (3,728 ± 202 dynes cm/sec, \( t = 2.54, \text{d.f.} = 9, P < 0.05 \)). Asterisks indicate changes that are statistically different from zero at \( P < 0.05 \), whereas the \( P \) values given at the bottom of the columns show the levels of significance for the difference between the two values obtained before and after coronary artery occlusion, as determined by Student's \( t \)-test for paired comparisons.

Changes occurred in animals that received normal saline infusion either before or after coronary artery occlusion (Figs. 1 and 2).

Coronary Hemodynamic Responses to Dobutamine Infusion

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Effects of Dobutamine on Infarct Size

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### Table 1: Coronary Hemodynamic Effects of Dobutamine in Normal Dogs

<table>
<thead>
<tr>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 9)</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Baseline</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>118 ± 11</td>
<td>114 ± 5</td>
</tr>
<tr>
<td>18 ± 3</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>13.0 ± 1.2</td>
<td>12.6 ± 1.2</td>
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<tr>
<td>6.6 ± 0.7</td>
<td>6.8 ± 0.8</td>
</tr>
<tr>
<td>23.7 ± 2.3</td>
<td>25.5 ± 1.8</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Dobutamine</strong></td>
<td><strong>Normal saline</strong></td>
</tr>
<tr>
<td>158 ± 14*</td>
<td>116 ± 5</td>
</tr>
<tr>
<td>21 ± 3*</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>18.3 ± 1.0*</td>
<td>13.0 ± 1.2</td>
</tr>
<tr>
<td>8.4 ± 0.7*</td>
<td>7.1 ± 0.7</td>
</tr>
<tr>
<td>21.3 ± 1.9</td>
<td>25.9 ± 1.6</td>
</tr>
</tbody>
</table>

Values are mean ± se. The number of experiments in each group is given in the parentheses in the subheadings.

* Values that are statistically different from the corresponding baseline values at \( P < 0.05 \), as determined by two-way analysis of variance for two independent groups and Dunnett's test.
Table 2: Coronary Hemodynamic Effects of Dobutamine in Dogs with Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Group 1 (n = 10)</th>
<th>Baseline</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular blood flow (ml/100 g per min)</td>
<td>113 ± 11</td>
<td>157 ± 17*</td>
</tr>
<tr>
<td>Coronary sinus O₂ saturation (%)</td>
<td>16 ± 2</td>
<td>19 ± 3*</td>
</tr>
<tr>
<td>Left ventricular work (kgm/min)</td>
<td>11.5 ± 1.1</td>
<td>16.2 ± 1.7*</td>
</tr>
<tr>
<td>Left ventricular O₂ consumption (ml/100 g per min)</td>
<td>5.6 ± 0.6</td>
<td>7.4 ± 0.7*</td>
</tr>
<tr>
<td>Mechanical efficiency (%)</td>
<td>22.4 ± 1.7</td>
<td>22.6 ± 2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2 (n = 9)</th>
<th>Baseline</th>
<th>Normal saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular blood flow (ml/100 g per min)</td>
<td>112 ± 5</td>
<td>114 ± 7</td>
</tr>
<tr>
<td>Coronary sinus O₂ saturation (%)</td>
<td>18 ± 2</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Left ventricular work (kgm/min)</td>
<td>12.3 ± 0.9</td>
<td>11.9 ± 0.8</td>
</tr>
<tr>
<td>Left ventricular O₂ consumption (ml/100 g per min)</td>
<td>6.2 ± 0.6</td>
<td>6.1 ± 0.5</td>
</tr>
<tr>
<td>Mechanical efficiency (%)</td>
<td>16 ± 2</td>
<td>25.4 ± 2.2</td>
</tr>
</tbody>
</table>

Values are mean ± SE. The number of experiments in each group is given in the parentheses in the subheadings.

* Values that are statistically different from the corresponding baseline values at P < 0.05, as determined by two-way analysis of variance for two independent groups and Dunnett’s test.

In addition, infarct size was related to risk zones in the two experimental groups. The risk zone did not differ significantly between the dobutamine (32 ± 5% of left ventricle, n = 5) and normal saline (30 ± 3% of left ventricle, n = 7) groups. Infarct size constituted 56 ± 4% of the risk zone in the dobutamine group and 78 ± 6% of the risk zone in the normal saline group (Table 3). This difference between the two groups was statistically significant (t = 2.76, d.f. = 10, P < 0.05).

Effects of Dobutamine on Organ Blood Flows

Dobutamine infusion increased blood flow significantly only to skeletal muscle (from 4 ± 1 to 9 ± 3 ml/100 g per min) and myocardium (Table 1) before coronary artery occlusion. In contrast, after coronary artery occlusion, dobutamine infusion also increased blood flow significantly to several other organs, including the lungs, kidneys, gastrointestinal tract, skin, and bone (Table 4; Fig. 6).

On the other hand, normal saline infusion produced no significant changes in blood flow to any of the organs studied prior to coronary occlusion. It also did not increase organ blood flows in dogs with acute myocardial infarction; instead, blood flow decreased in the spleen, kidneys, small intestine, and splanchnic circulation (Table 4).

Changes in Regional Blood Flow in Response to Coronary Artery Occlusion

The effects of acute coronary artery occlusion on regional blood flow were determined by comparing the pre-infusion baseline values obtained before coronary artery occlusion with those obtained after occlusion. Results of both the dobutamine and normal saline groups were pooled. Significant reductions in blood flow occurred after coronary artery occlusion in the lungs (47 ± 10 to 34 ± 6 ml/100 g per min), kidneys (547 ± 42 to 399 ± 26 ml/100 g per min), bone (15 ± 3 to 10 ± 2 ml/100 g per min), and the splanchnic circulation (81 ± 6 to 56 ± 5 ml/100 g per min). These changes were associated with corresponding increases in organ vascular resistance in the lungs (2.5 ± 0.5 to 4.0 ± 0.7 mm Hg/ml per min), kidneys (0.31 ± 0.03 to 0.41 ± 0.02 mm Hg/ml per min), bone (15 ± 4 to 30 ± 14 mm Hg/...
Discussion

The present study shows that dobutamine exerts a significant inotropic action both before and after coronary artery occlusion, but its effects on heart rate and arterial blood pressure differ between the two experimental conditions. Before coronary artery occlusion, dobutamine increased mean aortic blood pressure and decreased heart rate and total peripheral vascular resistance. Blood flow increased significantly to skeletal muscle and myocardium. The decrease in heart rate probably was caused by the increased vagal tone or by withdrawal of sympathetic activity that resulted from the stimulation of baroreceptors during dobutamine infusion. As shown in our previous study (Liang and Hood, 1979), baroreceptor activation probably also led to peripheral vasodilation, predominantly in skeletal muscle (Vatner et al., 1970; Tabeuchi and Manning, 1971), and contributed to the decrease in total peripheral vascular resistance.

The decrease in total peripheral vascular resistance during dobutamine infusion was greater in dogs after coronary artery occlusion than before. Simultaneously, blood flow increased to the lungs, myocardium, kidneys, gastrointestinal tract, skin, femoral muscle, and bone, suggesting a generalized vasodilation during dobutamine infusion in the dogs with acute myocardial infarction. It is well known that acute myocardial infarction is associated with an increased sympathetic activity (Griffin and Leung, 1971; Liang and Hood, 1974). Our finding that blood flow decreased in some organs after coronary artery occlusion is consistent with this sympathtic vasoconstriction. The progressive decreases in blood flow to the spleen, kidneys, and splanchnic circulation during normal saline infusion after coronary artery occlusion probably were caused by the further increase in sympathetic drive that occurred during the early phase of acute myocardial infarction. The increase in cardiac output produced by dobutamine would be expected to cause sympathetic withdrawal in dogs with acute myocardial infarction as was the case prior to coronary artery occlusion. Since sympathetic activity was more marked, as evidenced by vasocostriction, during acute myocardial infarction than before coronary occlusion, withdrawal of the heightened sympathetic activity after coronary artery occlusion probably explains the greater fall in total peripheral vascular resistance.

Heart rate increased slightly during dobutamine infusion in dogs with acute myocardial infarction, suggesting that the positive chronotropic effect of dobutamine was not completely buffered by baroreceptor activation as it was prior to coronary occlusion. It is known that vagal tone is diminished during acute myocardial infarction (Liang and Hood, 1974), and this may also impair slowing of heart rate due to baroreceptor activation. Furthermore, mean aortic blood pressure did not increase during dobutamine infusion after coronary artery occlusion, whereas it increased before occlusion. Thus, the baroreceptors probably were stimulated to a lesser extent after occlusion than before. These alterations in resting vagal tone and baroreceptor stimulation might explain the divergent changes in heart rate before and after coronary artery occlusion. However, the possibility that the sinus node β adrenergic receptor sensitivity was enhanced during acute myocardial infarction, causing a stronger
TABLE 3 Effects of Dobutamine on Infarct Size

<table>
<thead>
<tr>
<th>Organ</th>
<th>Group 1. Dobutamine infusion (n = 8)</th>
<th>Group 2. Normal saline infusion (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV weight (g)</td>
<td>Mean ± SE 10 ± 1 14 ± 1 16 ± 1 56 ± 4</td>
<td>Mean ± SE 17 ± 2 16 ± 2* 26 ± 3* 78 ± 6*</td>
</tr>
<tr>
<td>Risk zone (g)</td>
<td>10 12 14 15</td>
<td>10 14 14 14</td>
</tr>
</tbody>
</table>

LV stands for "left ventricular," and n is the number of experiments in that group. Risk zone was the area of myocardium at risk within the flow distribution of the left anterior descending coronary artery.

Direct chronotropic response to dobutamine than in normal dogs, cannot be excluded.

The positive chronotropic effect of dobutamine also has been shown in dogs with acute myocardial infarction by Willerson et al. (1976) and Vatner and Baig (1979). The increase in heart rate produced by dobutamine in our experiments, however, was much smaller than that produced by the same dose of dobutamine reported by Willerson et al. (1976). The difference in the heart rate response between their study and ours probably is related in part to the use of pentobarbital anesthesia in the former study. It has been shown that dobutamine caused a greater increase in heart rate in anesthetized dogs (Robie et al., 1974; Tuttle and Mills, 1975) than in normal conscious dogs (Vatner et al., 1974; Hinds and Hawthorne, 1975). This may relate to the vagolytic effect of barbiturate and the effect of the anesthetic agents in obtunding the baroreceptor reflexes, thus allowing the direct chronotropic effect of dobutamine.

TABLE 4 Effects of Dobutamine on Regional Blood Flow in Dogs with Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Organ</th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Dobutamine</td>
<td>Baseline</td>
</tr>
<tr>
<td>Brain</td>
<td>61 ± 4</td>
<td>67 ± 4</td>
</tr>
<tr>
<td>Lungs (bronchial)</td>
<td>45 ± 8</td>
<td>61 ± 15*</td>
</tr>
<tr>
<td>Spleen</td>
<td>244 ± 55</td>
<td>233 ± 26</td>
</tr>
<tr>
<td>Adrenals</td>
<td>423 ± 41</td>
<td>435 ± 43</td>
</tr>
<tr>
<td>Kidneys</td>
<td>385 ± 39</td>
<td>438 ± 41*</td>
</tr>
<tr>
<td>Liver (hepatic)</td>
<td>18 ± 6</td>
<td>23 ± 9</td>
</tr>
<tr>
<td>Stomach</td>
<td>38 ± 8</td>
<td>56 ± 12*</td>
</tr>
<tr>
<td>Small intestine</td>
<td>41 ± 5</td>
<td>54 ± 8*</td>
</tr>
<tr>
<td>Large intestine</td>
<td>74 ± 10</td>
<td>84 ± 12*</td>
</tr>
<tr>
<td>Splanchnics</td>
<td>55 ± 6</td>
<td>66 ± 9*</td>
</tr>
<tr>
<td>Skin</td>
<td>4 ± 1</td>
<td>7 ± 2*</td>
</tr>
<tr>
<td>Femoral muscle</td>
<td>5 ± 1</td>
<td>12 ± 4*</td>
</tr>
<tr>
<td>Femur</td>
<td>10 ± 2</td>
<td>14 ± 3*</td>
</tr>
</tbody>
</table>

Values are mean ± SE ml/100 g per min. The number of experiments for each group is given in the parentheses in the subheadings.

* Values that are statistically different from their corresponding baseline values at P < 0.05, as determined by two-way analysis of variance and Dunnett's test. The splanchic flow includes flows to the liver, stomach, small intestine, large intestine, pancreas, spleen, ureters, and urinary bladder.
the true mixed venous blood oxygen content was not determined in our experiments. Our values of left ventricular oxygen consumption obtained after coronary artery occlusion might not be quantitatively precise, but probably were qualitatively correct.

Our results further show that infarct size was significantly smaller in the dogs receiving dobutamine infusion than in those receiving normal saline. Although infarct size was not measured directly, Maroko et al. (1974) showed that epicardial ST segment elevation increased during dobutamine infusion in anesthetized, open-chest dogs with acute myocardial infarction. This increase in epicardial ST segment elevation, however, was less than that produced by an equi-inotropic dose of isoproterenol, suggesting that dobutamine is less injurious than isoproterenol in acute myocardial infarction. Increases in epicardial ST segment elevation also were reported by Willerson et al. (1976), using a large dose of dobutamine which increased myocardial blood flow. In addition, the same investigators found that a small dose of dobutamine did not increase heart rate to the same extent as the large dose and did not increase epicardial ST segment elevation, but also did not increase myocardial blood flow to any region of the heart. Thus, they were unable to choose a dose of dobutamine that increased coronary blood flow but did not exert detrimental effects on heart rate and epicardial injury parameters. Their results further suggest that the increase in myocardial blood flow to ischemic tissue was insufficient to supply enough oxygen for the increased oxygen requirement and indicate that dobutamine might be injurious to the ischemic myocardium. However, in their experiments, heart rate increased markedly during infusion of the large dose of dobutamine. Vatner and Baig (1979) showed that, when inotropic stimulation by dobutamine is coupled with tachycardia, blood flow falls and contractile function deteriorates in ischemic myocardium. Tachycardia is detrimental during acute infarction for two reasons: it increases myocardial oxygen demands, and reduces the diastolic coronary perfusion period. Changes in the diastolic perfusion period probably are unimportant in normal myocardium, in which blood flow can increase commensurately, but may be critical in ischemic myocardium, in which blood flow rate is limited. Thus, it is probable that the marked tachycardia was responsible for the deleterious effect of dobutamine upon ischemic myocardium in the anesthetized dog experiments reported by Willerson et al. (1976). In contrast, heart rate increased only slightly during dobutamine infusion in our conscious dogs with acute myocardial infarction.

Unlike isoproterenol, dobutamine did not reduce blood flow to ischemic myocardium in dogs with acute infarction, despite vasodilation in the normal myocardium. These results suggest that β-adrenergic agents that cause coronary vasodilation do not
always cause a "coronary steal" (Cohen et al., 1976), nor do they necessarily enhance myocardial injury. The reduction in infarct size produced by dobutamine in our study probably was related to the increased blood flow to the ischemic myocardium. Left atrial pressure did not change significantly during dobutamine infusion, suggesting that the effect of dobutamine on infarct size could not be explained by a reduction in heart size, wall stress, and myocardial oxygen demand resulting from the inotropic action of the drug.

In addition to the increased myocardial blood flow, dobutamine reduces the amount of norepinephrine released from cardiac sympathetic fibers that usually occurs after myocardial ischemia (Tuttle, 1978). Norepinephrine is thought to be injurious to ischemic myocardium because it has both β adrenergic inotropic effects that would increase oxygen requirements, and an α adrenergic vasoconstrictor effect that would reduce oxygen supply. Thus, Tuttle (1978) speculates that this reduction in norepinephrine release may contribute at least in part to the protective effect of dobutamine on ischemic myocardium.

In summary, our results indicate that dobutamine not only improves the global performance of the heart but also reduces the infarct size during acute infarction. In clinical studies, Gillespie et al. (1977) showed that dobutamine increased cardiac performance and exerted no deleterious effects in patients with acute myocardial infarction. Dobutamine also increased coronary sinus blood flow and decreased myocardial extraction of lactate in patients with stable coronary artery disease, but did not change the mechanical efficiency of the heart in these patients (Tubau et al., 1979). However, in patients with severe coronary artery disease, dobutamine produced an inhomogeneity of regional coronary flow such that areas supplied by obstructed coronary arteries received proportionally less flow than non-jeopardized areas, despite the fact that total coronary blood flow increased (Meyer et al., 1976). This limited increase in myocardial flow in severely ischemic regions, coupled with the markedly inotropic effect of dobutamine, might result in deterioration of the mechanical function in ischemic myocardium. Thus, it appears that patient selection might be critical to using dobutamine in a way that does not increase myocardial injury and might in fact contain or reduce it. Further studies are warranted to evaluate the influence of dobutamine on the relationship between the myocardial oxygen demand and oxygen availability under varying hemodynamic conditions.

Acknowledgments

We thank Samuel Rivers, Stephanie Arnold, and Debra Ginsburg for their technical assistance and Bernice Kus for her secretarial help. The following chemicals were generously supplied by pharmaceutical companies: dobutamine (Dobutrex) by Lilly Research Laboratories, Indianapolis, Indiana; and indocyanine green (Cardio-Green) by Hynson, Westcott and Dunning, Division of Becton, Dickinson and Company, Baltimore, Maryland.

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DOBUTAMINE INFUSION DURING ACUTE MYOCARDIAL INFARCTION/Liang et al.
**Indomethacin Decreases Arterial Blood Pressure and Plasma Renin Activity in Rats with Aortic Ligation**

**EDWIN K. JACKSON, JOHN A. OATES, AND ROBERT A. BRANCH**

**SUMMARY** Severe renovascular hypertension was produced in rats by complete aortic ligation between the origin of the renal arteries. Six days after coarctation, a carotid cannula was implanted and mean arterial blood pressure (MABP) and plasma renin activity (PRA) were determined. Subsequently, indomethacin (5 mg/kg in oil) or vehicle was administered subcutaneously three times in the following 24-hour period. On day 7, MABP and PRA were again determined. Indomethacin reduced MABP from 179.0 ± 6.7 to 158.4 ± 8.8 mm Hg (P < 0.002, n = 11) and PRA from 21.2 ± 7.3 to 9.3 ± 2.9 ng Al/ml per hr (P < 0.045, n = 10), whereas vehicle treatment did not alter either MABP or PRA (n = 6). There was a significant association between the decrease in MABP and the percentage decrease in PRA following indomethacin treatment (r = 0.766, P < 0.016). A similar study was performed in aortic ligated rats in which the left kidney was removed at the time of ligation. In these animals, 6 days after surgery, MABP and PRA were 128.0 ± 5.9 mm Hg and 0.11 ± 0.06 ng Al/ml per hr (n = 6), respectively, and indomethacin had no effect on either MABP or PRA. These data provide evidence that the prostaglandin system is involved in the release of renin and in the pathogenesis of elevated blood pressure in this model of renin-dependent hypertension. *Circ Res* **49**: 180-185, 1981

CONSIDERABLE evidence exists which implica-
states prostaglandins as important mediators of renin secretion. Central to this hypothesis is the observation that prostaglandin cyclooxygenase inhibitors prevent the renin secretion induced by several stimuli, including intrarenal baroreceptor activation (Data et al., 1978; Berl et al., 1979; Henrich et al., 1979), macula densa activation (Henrich et al., 1979; Olson et al., 1980), blockade of the angiotensin II short-loop negative feedback mechanism (Campbell et al., 1979a, Abe et al., 1980), and, in some species, ß-adrenoceptor stimulation (Campbell et al., 1979b; Feuerstein and Feuerstein, 1980). Since the renin-angiotensin system may be responsible for the elevated arterial blood pressure in certain types of experimental and clinical hypertension, inhibition of renin release by cyclooxygenase inhibitors represents a potential antihypertensive action of this class of drugs. Hypothetically then, in renin-dependent hypertension in which the hyperreninemia is prostaglandin mediated, cyclooxygenase inhibitors should alleviate both the hyperreninemia and hypertension.

Total ligation of the aorta between the origin of the renal arteries in rats produces severe renovascular hypertension which is renin dependent (Carretero et al., 1971; Sweet et al., 1976; Fernandes et
Dobutamine infusion in conscious dogs with and without acute myocardial infarction. Effects on systemic hemodynamics, myocardial blood flow, and infarct size.

C S Liang, J M Yi, L G Sherman, J Black, H Gavras and W B Hood, Jr

doi: 10.1161/01.RES.49.1.170

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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