EXPERIMENTAL approaches

Effects of Infusion of Dopamine and Nitroprusside on Size of Experimental Myocardial Infarct*

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Using a canine model for experimentally induced myocardial infarction via ligation of the left anterior descending coronary artery and using a stain for intracellular lactic dehydrogenase to directly measure the size of the infarct, we evaluated the influence of infusion of dopamine and sodium nitroprusside. Infusion of sodium nitroprusside (222 μg/min) produced significant decreases in the mean blood pressure, total peripheral resistance, and left atrial pressure and reduced the volume of the infarct by 58 percent (P < 0.0025). The administration of dopamine (6 μg/kg/min) significantly improved the cardiac index and lowered the systemic vascular resistance and left atrial pressure but did not affect the size of the infarct. Administration of dopamine at a rate of 15 μg/kg/min significantly increased the mean blood pressure and cardiac index and decreased the peripheral resistance and left atrial pressure. The histochemically determined volume of the infarct was reduced by 37 percent (P < 0.0025), but the hearts were very edematous and hemorrhagic. Therapy with nitroprusside appears to have promise in the active treatment of clinical myocardial infarction. The safe use of therapy with high doses of dopamine in patients with acute myocardial infarction must await further study.

Dopamine and nitroprusside have become popular drugs in the treatment of circulatory collapse, including shock following myocardial infarction. These agents have profound peripheral hemodynamic effects and also directly or indirectly influence cardiac function. Thus, both drugs can potentially affect the extent of myocardial ischemia and necrosis following acute myocardial infarction. Since morbidity and mortality correlate with the ultimate size of the infarct, an experiment was designed to examine the influence of clinical dosages of dopamine and sodium nitroprusside on the volume of the myocardial infarct.

MATERIALS AND METHODS

Healthy, anesthetized (diabutol) adult mongrel dogs weighing from 18 to 25 kg (40 to 55 lb) were used in the study. All animals were intubated and ventilated with room air via a respirator (Fig 1). Under fluoroscopic guidance, catheters were introduced into the coronary sinus and the aortic root. The chest was then opened via a median sternotomy, and the anatomy of the left anterior descending coronary artery was examined. Only dogs grossly exhibiting a similar anatomic distribution of this vessel were used. A left atrial catheter was inserted, and baseline measurements were made of the mean aortic blood pressure, left atrial pressure, and cardiac output. Control samples of blood were obtained from the coronary sinus and the aorta. Animals with abnormal

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FIGURE 1. Experimental model of myocardial infarction. SVC, Superior vena cava; RV, right ventricle; IVC, inferior vena cava; and LA, left atrium.
baseline hemodynamic or metabolic values were eliminated.

The left anterior descending coronary artery was occluded at its distal third with a double ligature of 4-0 silk. If present, intercoronary communications between the circumflex marginal branches and the distal portion of the left anterior descending coronary artery were also doubly ligated. Immediately after coronary arterial ligation, the physician (C.H.S.) left the laboratory, and the technician drew a card from a box to determine if the animal was to be treated and which regimen would be used.

Treated animals received a continuous intravenous infusion of either dopamine or nitroprusside throughout the experiment. Dopamine (one ampule [300 mg] added to 250 ml of a 5 percent solution of dextrose in water) was administered to two groups of dogs at rates of 6 µg/kg/min and 15 µg/kg/min, respectively. Sodium nitroprusside (one vial [50 mg] added to 500 ml of a 5 percent solution of dextrose in water) was infused at a rate sufficient to maintain the mean systemic blood pressure at 20 percent below the level measured before ligation. An average dosage of 222 µg of sodium nitroprusside per minute was administered. The entire system for delivery of nitroprusside was shielded from incidental light. A fresh solution of nitroprusside was used four hours after the experiment was begun.

Following ligation, hourly measurements were made of the mean blood pressure, left atrial pressure, and cardiac output. Samples of blood were taken every two hours. After six hours of coronary arterial occlusion, the dog was killed, and the heart was removed by a physician (C.H.S.) who was unaware of the treatment of the animal. The left ventricle was dissected from the heart, weighed, and sliced transversely into 1-cm sections. The slices were incubated for 15 minutes in a solution of nitroblue tetrazolium (consisting of 720 ml of distilled water, 80 ml of a 0.1 M buffer solution of potassium phosphate, and 250 mg of nitroblue tetrazolium [Sigma]), a stain for intracellular lactic dehydrogenase. The sections were then removed from the bath and washed. The unstained portions of the left ventricular myocardium (Fig 2) were sharply dissected from the slices and weighed. The volume of the infarct was then calculated.

Samples of blood from the coronary sinus were analyzed for pH, oxygen pressure (Po2), carbon dioxide tension (Pco2), oxygen saturation, oxygen content, and levels of lactate and creatine phosphokinase. Systemic (aortic) blood was analyzed for pH, Po2, Pco2, oxygen saturation, and oxygen content. The concentration of lactate in the serum was determined using the method of Barker and Summerson.7 The concentration of creatine phosphokinase in the serum was determined colorimetrically. Using standard formulas, several derived functions were later calculated from the hemodynamic and metabolic data.

Student's t-test was used to statistically analyze all results. In evaluating the hemodynamic and metabolic measurements, a comparison was made between the mean change following infarction in each treated group compared to the mean change in the untreated animals. The mean change was used to evaluate hemodynamic and metabolic results, because it was believed that significant differences occurring over the monitoring interval would be more meaningful than transient phenomena after treatment.

**RESULTS**

### Size of Infarct

Data on the volume of the myocardial infarct are shown in Table 1. With the exception of animals receiving dopamine at a dosage of 15 µg/kg/min, the left ventricular weights of the groups were remarkably similar (range, 99.3 to 101.8 gm) and were comparable to those observed in our previous experiments.8,9 The mean left ventricular weight of the group treated with dopamine at a dosage of 15 µg/kg/min was significantly higher (P < 0.0025) than that of any other group. Cross examination of these hearts revealed edema and scattered hemor-

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Table 1—Effects of Infusion of Dopamine and Nitroprusside on Size of Myocardial Infarct

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Dogs</th>
<th>Left Ventricular Weight, gm</th>
<th>Percentage of Left Ventricle</th>
<th>Size of Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>101.8 ± 3.1</td>
<td>14.8 ± 0.9</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Dopamine 6 µg/kg/min</td>
<td>13</td>
<td>100.7 ± 3.5</td>
<td>15.2 ± 2.0</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Dopamine 15 µg/kg/min</td>
<td>20</td>
<td>117.6 ± 3.7*</td>
<td>11.0 ± 1.8</td>
<td>9 ± 2**</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>20</td>
<td>99.3 ± 4.0</td>
<td>6.3 ± 1.3</td>
<td>7 ± 1**</td>
</tr>
</tbody>
</table>

*P < 0.0025, compared to any other group.
**P < 0.0025, compared to control.

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Figure 2. Experimental myocardial infarct stained with tetrazolium blue.
rhages involving the entire thickness of the left ventricular wall (Fig 3).

The average volume of the infarct in the control animals was 15 ± 1 percent (SE) of the left ventricle. Infusion of nitroprusside decreased the mean size of the infarct to 7 ± 1 percent of the left ventricle (P < 0.0025), a reduction of 58 percent from the control population. Dopamine given at a dosage of 6 μg/kg/min had no effect on the extent of myocardial necrosis. Treatment with dopamine at a dosage of 15 μg/kg/min reduced the volume of the infarct to 9 ± 2 percent of the left ventricle (P < 0.0025), a decrease of 37 percent in the size of the infarct from the control population. No correlation was seen between the volume of the infarct and levels of gases in systemic blood or blood from the coronary sinus, levels which remained relatively unchanged in all groups during the experiments.

**Hemodynamic Indices**

In control animals the mean blood pressure dropped sharply during the first two hours after myocardial infarction and then rose steadily throughout the remainder of the monitoring period (Fig 4). The mean change in systemic blood pressure in these dogs was 1 ± 5 mm Hg. Animals receiving nitroprusside sustained a mean decrease in blood pressure of 33 ± 3 mm Hg (P < 0.005). The effect of infusion of dopamine on systemic blood pressure was related to dosage. Dogs treated with dopamine at a dosage of 6 μg/kg/min exhibited no change in the systemic blood pressure for the first three hours and then experienced a sharp decline. The mean change was -4 ± 6 mm Hg. Animals receiving dopamine at a dosage of 15 μg/kg/min maintained a mean blood pressure above the control level throughout the monitoring period, with a mean change of 21 ± 5 mm Hg (P < 0.005).

Following ligation of the left anterior descending coronary artery, untreated animals exhibited a steady decline in the cardiac index, with an average drop of 1.69 ± 0.17 L/min/sq m. Dogs receiving nitroprusside experienced a mean change in the cardiac index of -1.38 ± 0.27 L/min/sq m. In both groups receiving dopamine, the cardiac index was significantly higher (P < 0.0025) than that observed in the untreated dogs. Animals receiving dopamine at a dosage of 6 μg/kg/min sustained an average decrease of 0.70 ± 0.20 L/min/sq m, while
those treated with 15μg/kg/min exhibited a mean change of -0.34 ± 0.18 L/min/sq m.

The total peripheral resistance index rose progressively in all groups. In control animals the mean change was 1,747 ± 229 dynes-sec/cm²/sq m. Both infusion of dopamine and infusion of nitroprusside significantly decreased the magnitude of vasoconstriction following myocardial infarction. In the group receiving nitroprusside, the mean change in the total peripheral resistance index was 254 ± 254 dynes-sec/cm²/sq m (P < 0.0025). Dogs given dopamine at a dosage of 6μg/kg/min experienced an average increase in the systemic vascular resistance of 597 ± 210 dynes-sec/cm²/sq m (P < 0.0025), while those treated with 15μg/kg/min exhibited an increase of 1,054 ± 170 dynes-sec/cm²/sq m (P < 0.025).

In untreated animals the left atrial pressure rose progressively following infarction, with an average increase of 3.2 ± 0.8 cm H₂O. Treatment with either dopamine or nitroprusside significantly lowered left atrial pressure. In the group receiving nitroprusside, the mean change was -1.7 ± 0.7 cm H₂O (P < 0.0005). Dopamine administered at rates of 6μg/kg/min or 15μg/kg/min reduced the mean left atrial pressure by 0.4 ± 0.6 cm H₂O and 0.6 ± 0.8 cm H₂O (P < 0.005), respectively.

In animals given dopamine at a dosage of 6μg/kg/min, the mean heart rate rose from 142 to 163 beats per minute during the experiment. Dogs treated with dopamine at a dosage of 15μg/kg/min experienced an average increase in heart rate from 150 to 195 beats per minute. In both groups the heart rate rose immediately after the onset of infusion of dopamine and remained above the control value thereafter. In the animals receiving nitroprusside, the mean heart rate rose from 138 to 154 beats per minute during infusion.

Myocardial Metabolism

In all groups, occlusion of the distal portion of the left anterior descending coronary artery produced an immediate progressive rise in the concentration of creatine phosphokinase in blood from the coronary sinus (Fig 5). In control dogs the level of creatine phosphokinase increased 100 ± 10 units/ml during the six hours of monitoring. Treatment with nitroprusside resulted in a nearly significant (P < 0.025) difference in infarct dogs.
lowering of the concentration of creatine phosphokinase in blood from the coronary sinus, with a mean increase of only 78 ± 10 units/ml. Both infusions of dopamine produced a significant rise in the concentration of creatine phosphokinase in blood from the coronary sinus. In the group receiving dopamine at the lower dosage of 6μg/kg/min, the level of creatine phosphokinase increased 140 ± 16 units/ml, and in dogs receiving 15μg/kg/min, the level of creatine phosphokinase rose 148 ± 12 units/ml. All groups exhibited increases in the lactate concentration of blood from the coronary sinus and in the myocardial arteriovenous oxygen difference following myocardial infarction. Treatment did not significantly affect either measurement.

**DISCUSSION**

In recent years, there has been a change in the basic concepts underlying the treatment of acute myocardial infarction. Both researchers and clinicians have adopted a more aggressive posture and have begun to treat the infarct itself, rather than just its complications. Numerous pharmacologic and mechanical therapeutic interventions have been investigated in an attempt to find a means of reducing the extent of myocardial necrosis. Although such studies are important, it is equally necessary to evaluate drugs currently used in patients with acute myocardial infarction to ensure that they do not adversely affect the ischemic-necrotic focus. Thus, we examined the influence of clinical dosages of dopamine and nitroprusside on the size of the infarct.

Nitroprusside has been used primarily in the treatment of malignant hypertension and severe congestive heart failure. In patients experiencing pump failure following an acute myocardial infarction, infusion of nitroprusside has produced significant improvements in cardiac performance; an increase in the cardiac index and reductions in the left ventricular filling pressure, pulmonary capillary wedge pressure, peripheral vascular resistance, myocardial demand for oxygen, and systemic blood pressure. Although one study demonstrated a reduction in myocardial blood flow, most investigators have found a significant improvement in coronary blood flow and a decrease in coronary vascular resistance during infusion of nitroprusside. Yeh et al noted coronary arterial vasodilation in both normal and diseased vessels in patients during administration of sodium nitroprusside. Angina pectoris, which developed in four patients during cardiac catheterization, was immediately relieved and the ST-segment depression reversed after injection of 5μg to 10μg of the drug into the left main coronary artery.

The effect of nitroprusside on the size of the infarct has been evaluated in a limited number of patients with acute myocardial infarction. Chiariello et al noted an increase in ST-segment elevation in ten patients during a ten-minute infusion of nitroprusside. Similar changes were seen in seven dogs receiving intravenous administration of nitroprusside after ligation of the left anterior descending coronary artery. However, Awan and associates found a significant reduction in myocardial ischemic injury as assessed by ST-segment mapping in 12 patients. Mukherjee et al used prolonged (two to seven days) therapy with nitroprusside in five patients with acute myocardial infarction and persistent hypertension, pain in the chest, and severe ventricular arrhythmias. Treatment lowered the blood pressure, relieved the pain, abolished the arrhythmias, and reduced ST-segment elevations.

Our results support the clinical findings of Awan et al. Infusion of nitroprusside resulted in a highly significant decrease in the volume of the infarct in dogs with uncomplicated myocardial infarction. Hemodynamically, infusion of nitroprusside significantly lowered the mean blood pressure, total peripheral resistance, and left atrial pressure and slightly increased the cardiac index. Under the conditions of the present study, it is apparent that the beneficial hemodynamic and metabolic actions of administration of nitroprusside outweighed potential adverse effects from the slight increase in heart rate and the moderate reduction in systemic blood pressure. Whether or not infusion of nitroprusside would reduce the volume of the infarct in acute myocardial infarction complicated by pump failure or shock is purely conjectural at this point. Since favorable hemodynamic changes have been noted during administration of nitroprusside in patients with heart failure and shock following myocardial infarction, it is probable that extension of the infarct would be reduced or prevented under these circumstances. The present study was concerned with the influence of therapy with nitroprusside on the size of the infarct in an uncomplicated acute myocardial infarction. Our results suggest that therapy with nitroprusside should be evaluated in patients with uncomplicated acute myocardial infarction as a means of reducing the extent of myocardial necrosis.

Based on its hemodynamic effects, dopamine has become a popular drug in the treatment of cardiogenic shock. In both experimental and clinical studies, infusion of dopamine has produced increases in heart rate, mean blood pressure, cardiac output, left ventricular end-diastolic pressure, and urinary output and a reduction in the systemic vas-
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References


