Quantitative Effects of Sodium Nitroprusside on Coronary Hemodynamics and Left Ventricular Function in Dogs

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SUMMARY We studied the effects of nitroprusside on left ventricular contractility, coronary blood flow, and coronary vascular resistance in dogs during right heart bypass in which stroke volume, aortic pressure, and heart rate were controlled. Intravenous nitroprusside increased coronary blood flow and decreased coronary vascular resistance but did not change left ventricular end-diastolic pressure or maximum dP/dt when aortic pressure was held constant. When aortic pressure was allowed to fall during intravenous nitroprusside infusion, coronary flow increased slightly as coronary resistance decreased, but left ventricular contractility increased (left ventricular end-diastolic pressure fell at constant maximum dP/dt). After β-adrenergic blockade, intravenous nitroprusside decreased maximum dP/dt, coronary flow, and coronary resistance when aortic pressure fell during intravenous nitroprusside infusion. When the coronary and systemic circulations were separated and coronary pressure was kept constant, intravenous nitroprusside did not change coronary flow or coronary resistance, but maximum dP/dt decreased when aortic pressure fell. Conversely, intracoronary nitroprusside increased coronary flow and decreased coronary resistance but did not change left ventricular end-diastolic pressure or maximum dP/dt. We conclude that nitroprusside dilates coronary arteries but has no direct effect on left ventricular contractility. When mean aortic pressure is decreased by nitroprusside, β-adrenergic stimulation results in increased left ventricular contractility and indirect coronary dilation. Circ Res 45: 351-359, 1979

RECENT reports have directed attention to the use of sodium nitroprusside to reduce left ventricular afterload and to improve ventricular performance in patients with myocardial infarction (Chatterjee et al., 1973a), congestive heart failure (Guilha et al., 1974) or mitral regurgitation (Chatterjee et al., 1973b) (Goodman et al., 1974), and during the perioperative period of cardiac surgery (Lappas et al., 1976) (Stinson et al., 1976) (Benzing et al., 1976). The beneficial effects of nitroprusside in treatment of failing or ischemic hearts have been attributed primarily to the indirect effect of systolic unloading of the left ventricle by peripheral vasodilation. The effect may be related somewhat to its influence on preload, since clinical (Chatterjee et al., 1973a; Lappas et al., 1975) and some experimental (DaLuz et al., 1975) data indicate that increases in cardiac output during nitroprusside infusion do not occur in the absence of initially elevated left ventricular filling pressures. Ross and Cole (1973) and Rowe and Henderson (1974) reported increased cardiac output during nitroprusside infusion in dogs with normal filling pressures. Previous experiments by Chatterjee et al. (1973a) revealed no inotropic effects of nitroprusside on cat papillary muscle strips or in patients with acute myocardial infarction. However, the studies of Miller et al. (1975) indicate that small increases in left ventricular contractility occurred when left ventricular end-diastolic pressure fell during nitroprusside infusion in patients with chronic ischemic heart disease.

It is reported also that nitroprusside dilates coronary arteries. Ross and Cole (1973), as well as Rowe and Henderson (1974), measured coronary blood flow in anesthetized dogs during infusion if nitroprusside. Coronary blood flow increased in both studies, but there were concomitant increases in cardiac output and heart rate. Rowe and Henderson (1974) demonstrated decreased coronary vascular resistance, but since cardiac output and heart rate also increased, this may have resulted from changes in myocardial oxygen demand rather than from direct vasodilation by nitroprusside. Pagni et al. (1978) observed an increase in regional coronary flow and a decrease in coronary vascular resistance in conscious dogs during nitroprusside infusions. Lappas et al. (1976) studied the effects of...
sodium nitroprusside in three groups of patients during coronary artery operations and suggested that coronary arterial dilation as well as a decrease in preload and afterload may improve left ventricular performance in patients with left ventricular dysfunction.

Although important information about nitroprusside has been gained from clinical observations, precise mechanisms of its action have been difficult to determine. The effects of nitroprusside in one vascular bed indirectly may alter its effect on another vascular bed and thereby influence overall effects of the drug. It was the purpose of this study to separate and to measure quantitatively the effects of sodium nitroprusside on coronary blood flow, coronary vascular resistance, left ventricular function, peripheral vascular resistance, and myocardial oxygen consumption under the following conditions: (1) with constant heart rate, mean aortic pressure and cardiac output, to control the major hemodynamic determinants of left ventricular contractility; (2) with decreased aortic blood pressure produced by nitroprusside infusion, other conditions controlled, to approximate the clinical situation of decreased afterload; (3) with the coronary circulation isolated so as not to receive nitroprusside given systemically, so that cardiac and coronary effects of the drug would be indirect in response to changes produced by nitroprusside within the systemic system or its distribution; (4) during direct infusion of nitroprusside into coronary arteries, and not the systemic circulation, to measure possible direct effects of nitroprusside on left ventricular performance; and (5) after sympathetic blockade (other hemodynamic conditions as in no. 2) to assess interaction of nitroprusside and the autonomic nervous system in terms of the drug’s cardiovascular effects.

Methods

Mongrel dogs weighing 25–40 kg were anesthetized intravenously with a warmed mixture of chloralose, 100 mg/kg, and urethane, 1 g/kg. The trachea was intubated and ventilation was maintained by a volume-limited Emerson ventilator. The chest was opened by median sternotomy or left thoracotomy, and heparin, 3 mg/kg, was administered and right heart bypass was begun as previously described (Daggett, 1967). Briefly, the venous blood from the cannulated superior and inferior vena cavae was returned to a venous reservoir primed with heparinized fresh whole blood. Blood from the reservoir was warmed by a heat exchanger, oxygenated by a Bentley bubble oxygenator (Q100L), and returned to the proximally occluded pulmonary artery by a calibrated occlusive roller pump. The isolated right heart received only the coronary venous blood, which was led from the cannulated right heart by gravity drainage to the venous reservoir. Infusion or withdrawal of warmed oxygenated blood through femoral arterial cannulas by a second calibrated occlusive roller pump allowed control of mean aortic pressure. After the sinoatrial node had been crushed, the heart rate was kept constant by atrial pacing with a Medtronic pulse generator, model 5837. Pressures were measured with Statham P23Db strain gauges. A National Institutes of Health catheter in the ascending aorta allowed measurement of mean and phasic aortic pressure. A Y-shaped, wide-bore metal cannula placed in the left ventricle through the apex allowed simultaneous measurement on separate channels of left ventricular (LV) and left ventricular end-diastolic pressure (LVEDP). The pressure measurement system demonstrated a phase shift, which varied linearly up to 30 Hz with uniform amplitude over this range.

Left ventricular dP/dt was obtained by a Hewlett Packard differentiator 8814A, which electronically differentiated the output of the channel recording full-phase LV pressure. The differentiator had a time constant of 0.003 second at a cutoff of 50 Hz. Zero pressure levels were established at the end of each experiment by exposing the tips of the cannulas in situ. Coronary blood flow (CBF) was measured by 1-minute collections from the right heart cannula and normalized by calculation of coronary flow per 100 g LV weight obtained at the end of the experiments. Differences in arterio-venous oxygen content (A-V O₂) were monitored continuously by a Guyton A-V O₂ analyzer (Oxford Instrument Co.) sampling blood from the ascending aorta and from the line draining coronary venous blood. Calibrations of continuous A-V O₂ sampling were done in each experiment by intermittent determinations of A-V O₂ from aortic and coronary venous samples by the method of Van Slyke and Neill (1924). All variables including the standard electrocardiogram were recorded on a Hewlett Packard model 7788A multichannel oscillograph at a paper speed of 100 mm/sec.

The celiac artery was ligated at its origin from the aorta to prevent hepatic engorgement, which frequently occurred after multiple blood transfusions. Serum potassium and glucose levels were obtained every hour during the experiment and were kept within normal range by intravenous administration of 20% glucose and potassium chloride. The liver of each dog was examined at the end of the experiment, and no evidence of necrosis was noted.

The experimental model was altered in other dogs to provide isolated coronary arterial perfusion during right heart bypass. Through a left thoracotomy, a Gregg cannula was placed through a carotid arteriotomy into the left main coronary artery and secured with a ligature. The right coronary artery was ligated proximally and cannulated distally with 240 polyethylene tubing. Both coronary arteries were perfused with a roller pump from the femoral artery of a support dog, and the coronary drainage was collected in a separate reservoir and infused.
into the support dog's femoral vein. Coronary arterial pressure was measured in the perfusion tubing approximately 30 cm from the coronary orifice. In vitro perfusion of blood at 200 ml/min through the cannula system demonstrated a 5-mm pressure gradient between a point in the perfusion tubing 30 cm proximal to its orifice and a point at the distal tip of the cannula. Since this pressure gradient was small and reasonably consistent over the narrow range of coronary flows in these experiments, it was not considered in the calculation of coronary vascular resistance. In this isolated coronary arterial perfusion, the coronary and systemic circuits of the test dogs were separate except for the LV Thebesian flow.

The support dog was anesthetized with chloralose, 100 mg/kg, and urethane, 1 mg/kg, and ventilated with a mixture of air and oxygen through an endotracheal tube to maintain PaO2 from 200 to 400 mm Hg, PaCO2 from 35 to 45 mm Hg, and pH from 7.35 to 7.45 by altering the inspired oxygen concentration, changing minute volume, or administering sodium bicarbonate. Systemic arterial pressure in the support dog was maintained near 100 mm Hg mean pressure by altering the height of the venous reservoir and by blood transfusion.

Sodium nitroprusside powder (Nipride) was reconstituted daily in 5% dextrose in water to attain a solution containing 800 µg/ml and administered by a Harvard infusion pump. The reconstituted solution was protected by metal foil as recommended and supplied by the manufacturer. In experiments evaluating the systemic effects of nitroprusside, the infusion was adjusted to maintain systemic vascular resistance 20-30% below control levels. In experiments designed to study the direct coronary effects of nitroprusside, the infusion was adjusted to decrease coronary vascular resistance by approximately 30-40%. Data was recorded during a steady state prior to nitroprusside, at the peak of the nitroprusside effect (when vascular resistance had been lowered by 20-40%), and again after cessation of nitroprusside infusion and return of vascular resistance to or near control levels. Although considerable variation occurred, the dose of nitroprusside required to decrease systemic vascular resistance by 20-30% ranged from 5 to 20 µg/kg per min over 15-45 minutes, and the time required for vascular resistance to return to control levels varied from 2 to 45 minutes. The dose required to decrease coronary vascular resistance by 30-40% ranged from 3 to 11.5 µg/kg per min over 15-45 minutes.

Methods

Data Analysis

Systemic vascular resistance index (SVRI) was calculated by dividing mean aortic pressure (right atrial pressure was assumed to be zero) in mm Hg by systemic flow (sum of pulmonary artery and femoral artery flow) in liters/min and by kg body weight. Coronary vascular resistance index (CVRI) was obtained by dividing mean coronary perfusion pressure in mm Hg by CBF in ml/100 g LV per min. Under conditions of constant mean aortic pressure, LV performance was indexed by peak dP/dt, by LVEDP, and by LV function curves.

When aortic pressure was variable, (dP/dt)/CDP (common developed pressure) was calculated for the control and experimental points and compared in an attempt to correct for the differences in afterload. A modification of the calculations of (dP/dt)/CDP (common isovolumic pressure) as previously described (Mason, 1969) was used. Left ventricular pressure, its dP/dt, and the aortic pressure were recorded simultaneously during control and experimental interventions. The isovolumic phase, beginning with the abrupt increase in left ventricular pressure and ending at a point at which the superimposed left ventricular and aortic pressure curves met, was located for both control and experimental points. The highest isovolumic left ventricular pressure common to both control and experimental points was designated as the CPIP. The end-diastolic pressure at each point was subtracted from the peak isovolumic pressure to yield the CDP for each intervention. The dP/dt corresponding to CDP was found on the respective curves and the ratio dP/dt/CDP for control and experimental points calculated accordingly.

Systolic pressure time index (SPTI) was derived from the mean aortic pressure during ejection, the systolic ejection period and heart rate. Stroke work (SW) in gram-meters (g-m) was calculated by multiplying the mean aortic pressure minus LVEDP (in cm H2O) times stroke volume divided by 100. Myocardial oxygen consumption (MVO2) in ml/100 g LV per min was derived from the product of A-V O2 and CBF/100 g LV. Comparisons within each group were performed using a paired t-test. Results are reported as mean plus or minus the standard error of the mean.

Left ventricular function curves were generated in duplicate by stepwise 500-ml increments of cardiac output from 1000 to 45000 ml/min during control (before nitroprusside) and during nitroprusside infusion. Curves were plotted by computer using a third order polynomial to construct a least squares "best fit" curvilinear regression (regressing LVEDP on flow). The center of mass (COM) for each curve was calculated by computer over the range of flow (f) of 1000 (f1) to 45000 (f2) ml/min by the formula:

\[
\text{COM}_{\text{LVEDP}} = \frac{1}{\sum \text{LVEDP}(f)} \int_{f_1}^{f_2} \text{LVEDP}(f) \, df
\]

Similarly, the mean LVSW was calculated substituting LVSW for LVEDP in the above formula. Similar analyses of left ventricular function curves previously have been reported by Kay et al. (1978a, 1978b).
the LV function curves were analyzed by comparing LVSW during control and nitroprusside at LVEDP of 5 cm H2O and at 10 cm H2O.

**Experimental Groups**

In all dogs, studies were performed with cardiac output and heart rate held constant for any given experiment. Cardiac output was adjusted to maintain LVEDP between 4 and 11 mm Hg and ranged from 1500 to 3000 ml/min. Heart rate ranged from 150 to 180 beats/min.

Group I dogs (n = 7) underwent right heart bypass with normal coronary perfusion. Aortic pressure was kept constant at 100 mm Hg, while systemic vascular resistance was reduced by nitroprusside infusion into the blood perfusing the pulmonary artery. In these dogs, left ventricular function curves were generated in duplicate as described above, during control (before nitroprusside) and during nitroprusside infusion, and were analyzed as described above.

Group II dogs (n = 11) were treated similarly to those in group I, except that aortic pressure was allowed to fall during nitroprusside infusion, and left ventricular function curves were not performed.

Dogs in groups III, IV, and V were prepared for right heart bypass with the coronary circulation isolated as described and were separately perfused from a support dog. In group III (n = 6), mean aortic pressure was kept constant while nitroprusside was infused into the blood perfusing the pulmonary artery.

Group IV dogs (n = 7), were treated similarly to those in group III. However, during nitroprusside infusion, mean aortic pressure was allowed to fall.

In group V dogs (n = 7), mean aortic pressure was kept constant at 100 mm Hg with the systemic perfusion pump, and coronary arterial pressure was maintained at 100 mm Hg by the coronary perfusion pump. Nitroprusside was infused into the blood perfusing the coronary arteries.

Dogs in group VI (n = 8) were prepared for right heart bypass with normal coronary arterial perfusion and initially treated as those in group II. Nitroprusside was infused into blood perfusing the pulmonary artery to lower SVRI and mean aortic pressure, and measurements were made. After nitroprusside was discontinued and all measurements had returned toward control, the inotropic response (Δ dP/dt) to 3 μg isoproterenol injected into the pulmonary arterial line and the systemic pressor responses (Δ MAP) to bilateral carotid arterial occlusion was tested in each dog. Thereafter, sympathetic blockade was induced by injecting into the pulmonary artery propranolol, 0.5 mg/kg (four dogs); propranolol and mecamylamine, 5 mg/kg (three dogs, two of which had been studied previously with propranolol alone); propranolol, mecamylamine and phenoxybenzamine, 5 mg/kg (three dogs). Thus, 10 studies with nitroprusside in eight blocked dogs were made. The adequacy of β blockade was assured by a 70% reduction in the inotropic response to isoproterenol and the adequacy of a blockade by a rise in mean aortic pressure of less than 10 mm Hg after bilateral carotid arterial occlusion. After a steady state was again obtained and control measurements made, nitroprusside was infused into the pulmonary artery. Two additional dogs were treated like those in group VI but received only a blockade (phenoxybenzamine, 5 mg/kg) prior to nitroprusside infusion.

**Results**

The results for group I are shown in Figure 1. During nitroprusside infusion, group I dogs (n = 7)
underwent right heart bypass with normal coronary perfusion. Aortic pressure was kept constant at 100 mm Hg, while systemic vascular resistance was reduced by nitroprusside infusion into the blood perfusing the pulmonary artery. During nitroprusside infusion, SVRI decreased from 3.50 ± 0.37 to 2.34 ± 0.27 mm Hg/liter per min per kg (P < 0.005), CBF increased from 118.3 ± 9.7 ml/min per 100 g LV to 198.9 ± 32.4 (P < 0.05) and coronary vascular resistance decreased from 0.87 ± 0.08 mm Hg/ml per 100 g LV per min to 0.57 ± 0.08 (P < 0.005). However MVO₂, SW, LVEDP, SPTI, and peak LV dP/dt did not change significantly. After nitroprusside was discontinued, SVRI, CVRI, and CBF consistently returned to near control levels.

Typical left ventricular function curves and the calculated center of mass (COM) from one experiment for control and nitroprusside infusion are shown in Figure 2 and are not significantly different. The mean COMLVEDP for the seven experiments was 8.1 ± 1.0 cm H2O for control and 9.8 ± 1.8 cm H2O during nitroprusside infusion. The mean COMLVSW from seven experiments was 20.32 ± 64 g-m for control and 19.98 ± 0.58 g-m during nitroprusside infusion. Neither the COMLVEDP nor the COMLVSW for the seven experiments was significantly different (P = 0.2). Left ventricular function curves also were analyzed by comparing LVSW at a single LVEDP. At LVEDP of 5.0 cm H2O, mean LVSW (n = 7 dogs) during control was 15.66 ± 1.72, and, during nitroprusside 15.30 ± 0.93. At LVEDP of 5.0 cm H2O, LVSW during control and nitroprusside were not significantly different (P = 0.402). At LVEDP of 10 cm H2O, mean LVSW was 25.19 ± 2.02 during control and 23.36 ± 2.94 during nitroprusside. There was no statistically significant difference between LVSW during control and nitroprusside (P = 0.285).

Group II dogs were treated in the same manner as those in group I, except that aortic pressure was allowed to fall (Fig. 3). In spite of a decrease in mean aortic pressure (and, therefore, coronary perfusion pressure) from 100 to 77.0 ± 0.8 mm Hg (P < 0.001), CVRI decreased from 1.017 ± 0.062 to 0.706 ± 0.058 (P < 0.001), allowing an increase in CBF from 104 ± 7.6 ml/min per 100 g LV to 116.9 ± 9.3 (P < 0.05). Not unexpectedly, LVEDP, SW, MVO₂, and SPTI all decreased significantly (P < 0.05) in association with the fall in aortic pressure. Since peak dP/dt and (dP/dt)/CDP did not de-
crease significantly as LVEDP fell, there was an increase in LV contractility. After completion of these experiments, nitroprusside was infused in large doses to five dogs to assess the interrelationship among nitroprusside, coronary perfusion pressure, and CBF. In every instance it was possible to decrease mean aortic blood pressure from 100 mm Hg to 50 mm Hg without decreasing CBF. However, the doses of nitroprusside required to produce this level of hypotension frequently were large (20-30 μg/kg per min).

Results of experiments in groups III and IV are shown in Figure 4. In group III during constant mean aortic pressure, nitroprusside was infused into the pulmonary artery at a rate sufficient to decrease SVRI from 2.90 ± 0.20 to 2.08 ± 0.14 (P < 0.05), a reduction of 28.3%. During nitroprusside infusion, all other parameters, including CBF and CVRI, remained constant. During nitroprusside infusion in group IV (n = 7), mean aortic pressure was allowed to fall from 99.3 ± 0.7 to 78.4 ± 1.2 mm Hg.

**GROUP IV**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>During</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVRI</td>
<td>3.59</td>
<td>2.66</td>
<td>3.59</td>
</tr>
<tr>
<td>CVRI</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>CBF</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>LVEDP</td>
<td>8</td>
<td>6</td>
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</tr>
<tr>
<td>SW</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>PEAK LV dP/dt</td>
<td>3000</td>
<td>3000</td>
<td>3000</td>
</tr>
<tr>
<td>LV dP/dt/CDP</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>MV02</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>SPTI</td>
<td>2500</td>
<td>2500</td>
<td>2500</td>
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</tbody>
</table>

**(P < 0.001)**, while SVRI decreased from 3.59 ± 0.57 to 2.66 ± 0.35 (P < 0.025), a 25.9% decrease. These dogs showed no significant change in CBF or CVRI, but MV02, SW, SPTI, and peak dP/dt fell significantly (P < 0.05). Although LVEDP decreased from 9.3 ± 1.6 to 7.9 ± 1.2, this was not statistically significant. After nitroprusside was discontinued, all measurements returned to control levels.

In group V dogs with constant mean aortic and coronary arterial pressure, nitroprusside was infused into the blood perfusing the coronary arteries at a rate sufficient to reduce CVRI by 37% from 0.88 ± 0.07 to 0.63 ± 0.03 (P < 0.005). Nitroprusside doses ranged from 100 to 400 μg/min (Fig. 5). During this infusion, it was necessary to increase CBF from 117.3 ± 10.6 ml/min per 100 g LV to 159.5 ± 9.0 (P < 0.001) to maintain coronary arterial pressure at 100 mm Hg (Fig. 4). Since the systemic and coronary circulations were separate, the systemic circulation did not receive nitroprusside and SVRI...
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Discussion

These experiments indicate that nitroprusside directly dilates coronary arteries, since nitroprusside increased coronary blood flow and decreased coronary vascular resistance when preload, afterload, and heart rate were held constant. Quantitatively, a decrease in systemic vascular resistance of approximately 25% by intravenous nitroprusside was accompanied by a 34% reduction in coronary vascular resistance and a 60% increase in coronary blood flow when mean aortic pressure was kept constant. These nitroprusside-induced changes in coronary vascular resistance occurred independently of changes in myocardial contractility. When LVEDP, mean aortic pressure, and heart rate were constant, left ventricular dP/dt did not change. Left ventricular function curves also did not change from control curves during nitroprusside infusion. Furthermore, the coronary dilating effect was not dependent upon systemic vascular changes. Infusion of nitroprusside into the isolated coronary perfusion circuit consistently diluted coronary arteries while systemic vascular resistance was unchanged.

The data further indicate that when preload and heart rate were constant, the coronary dilating effect of nitroprusside was sufficient to increase coronary blood flow by 13%, in spite of a 25% reduction in coronary perfusion pressure. Indeed, it was possible to decrease mean coronary perfusion pressure from 100 to 50 mm Hg during infusion of nitroprusside without causing coronary blood flow to fall. It is postulated that the increase in coronary blood flow under these conditions was related in part to the direct dilating effect of nitroprusside and in part to sympathetic stimulation. When mean aortic pressure was reduced 24% by nitroprusside in dogs with β-adrenergic blockade, CBF decreased and coronary vascular resistance decreased by 14%. In dogs with prior β blockade studied by Hess et al. (1977), nitroprusside infusions did not change CBF.

Other investigators have stressed the importance of decreasing myocardial oxygen demand with nitroprusside by reducing left ventricular afterload. The present studies confirm this decrease in myocardial oxygen consumption as mean aortic pressure falls. However, these studies also demonstrate the effects of increased coronary blood flow during nitroprusside infusion, confirming the findings of Rowe and Henderson (1974). However, it is important to note that the increased myocardial blood flow and decreased myocardial oxygen utilization in our experiments occurred under conditions of carefully controlled heart rate and cardiac output.

Nitroprusside had no direct effect on myocardial contractility in these experiments. When preload, afterload, and heart rate were kept constant, left ventricular dP/dt did not change in spite of significant decreases in systemic and coronary vascular resistances. Additionally, left ventricular function curves performed at the peak of the nitroprusside effect did not differ from those performed prior to nitroprusside infusion. These findings are compatible with the results of in vitro studies in which nitroprusside had no inotropic effect on cat papillary muscle preparations (Chatterjee et al., 1973a). Furthermore, in our experiments, when coronary perfusion pressure was constant and coronary blood flow increased during nitroprusside infusion, no change in myocardial contractility was observed. Since nitroprusside had no negative inotropic effect on cat papillary muscles in vitro, it is unlikely that in our experiments a myocardial depressant effect of nitroprusside prevented an increase in myocardial contractility resulting from increased coronary blood flow. In previous studies by Bacaner et al. (1965) using an isovolumetric dog heart preparation, myocardial contractility increased with increased coronary blood flow, but the increase in coronary blood flow was accompanied by a rise in coronary perfusion pressure. However, in studies by Downey (1976) of dogs with ejecting ventricles, contractile force was relatively independent of flow at higher coronary blood flows. Therefore, we would conclude that increasing coronary blood flow within the limits described in our study is unlikely to affect directly myocardial contractility.

Although the present data show that LV contractility did not change when mean aortic pressure was held constant, they suggest that indirect effects of nitroprusside infusion resulted in increased contractility when mean aortic pressure was allowed to fall. This positive inotropic effect was manifested in group II dogs by a decrease in LVEDP with con-
constant left ventricular dP/dt during nitroprusside infusion. Left ventricular dP/dt would be expected to decrease in response to reduced aortic pressure when other determinants of myocardial contractility are constant (Wallace et al., 1963). Since dP/dt remained constant or increased (in some dogs) as EDP fell in group II, an increase in contractility occurred. The increase in myocardial contractility could not be confirmed by comparing left ventricular function curves between control and nitroprusside infusion since the difference in afterload would be likely to significantly alter left ventricular performance (Foster et al., 1977). However, this indirect inotropic effect would explain the increased contractility during nitroprusside infusion noted in clinical studies by Miller et al. (1975).

It is likely that a circulating inotropic substance, not nitroprusside itself, was responsible for the inotropic effect noted in the present experiments when the aortic pressure was allowed to fall. Contractility did not change when systemic infusions of nitroprusside were made into dogs with an isolated coronary circulation. Under these conditions, LVEDP, dP/dt, and (dP/dt)/CDP all fell significantly in response to the fall in aortic pressure during nitroprusside infusion. If the inotropic effect resulted from a reflex neurogenic response instead of a circulating substance, an increase in contractility might have occurred in dogs in this group. These data further suggest that it was a β-adrenergic substance released as aortic pressure fell during nitroprusside infusion that was responsible for increased contractility and in part for increased coronary blood flow. This interpretation was substantiated by β-adrenergic blockade of dogs prior to nitroprusside infusion. As nitroprusside reduced aortic pressure, both coronary blood flow and (dP/dt)/CDP decreased. In two dogs, prior α-adrenergic blockade had the opposite effect of increasing coronary blood flow and contractility during nitroprusside infusion.

The fall in aortic pressure and increase in contractility that occurred during nitroprusside infusion produced conflicting influences on MVO₂. The increased inotropic effect would tend to increase MVO₂, but in these experiments MVO₂ actually decreased. Heart rate did not affect MVO₂ since it was held constant. Another important determinant of MVO₂, left ventricular wall stress, could not be calculated since left ventricular dimensions were not measured. However, the decrease in left ventricular pressure which accompanied the fall in afterload would tend to decrease wall tension. The systolic pressure-time index, which previously has been shown to correlate well with MVO₂ over a wide range of heart rates, aortic pressures, and cardiac outputs (Sarnoff et al., 1958), significantly decreased. The fact that MVO₂ decreased in spite of increased contractility indicates that, under these circumstances, the influence of decreasing afterload was a more important determinant of MVO₂ than the increased demand resulting from a positive inotropic effect. In other experiments, similar decreases in MVO₂ following nitroprusside infusion in dogs (Hess et al., 1977) were accompanied by significant decreases in myocardial wall tension. However, in those dogs, previous β-adrenergic blockade prevented the secondary inotropic response observed in our experiments.

The results of these experiments may have important clinical implications. The concept of improving cardiac efficiency by decreasing myocardial oxygen demand with nitroprusside has been substantiated. In addition, these data suggest that if cardiac output is maintained constant and mean aortic pressure is kept within 20–30% of normal, an additional effect may be an increase in myocardial blood supply. However, in these studies, only total coronary blood flow was measured; myocardial flow distribution was not studied. Furthermore, these effects of nitroprusside occurred in dogs with normal hearts and do not describe the effects of the drug on failing human myocardium with or without ischemia. The lack of improvement of cardiac performance with nitroprusside in patients or animals without elevated left ventricular filling pressure (Chatterjee et al., 1973a; Lappas et al., 1976) may be related to the venodilatory effects of nitroprusside which would tend to decrease preload and cardiac output. Since preload was controlled in our experiments, the venodilatory effect of nitroprusside was nullified. It would be gratifying to know that, when cardiac output is constant during nitroprusside infusion, significant decreases in mean aortic pressure will not decrease coronary blood flow. In actual practice, it is rarely necessary to decrease aortic pressure by more than 25% during nitroprusside infusion (Guha et al., 1974; Goodman et al., 1974) and, in some cases with severely depressed myocardial function, aortic pressure may actually increase during nitroprusside infusion (Lappas et al., 1975).

In summary, these experiments indicate that nitroprusside effectively dilates systemic and coronary arteries. Under conditions of controlled cardiac output and heart rate, moderate reductions in aortic pressure by nitroprusside result in decreased left ventricular afterload with slight increases in coronary blood flow. Under these circumstances, release of a circulating β-adrenergic substance appears to contribute to coronary dilation during nitroprusside administration; conversely, β-adrenergic blockade was shown to attenuate the coronary vasodilator effect of nitroprusside. Nitroprusside has no direct effect on myocardial contractility, but may indirectly increase contractility by β-adrenergic stimulation when aortic pressure falls.

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