

## Effects of Sodium Nitroprusside on Systemic and Regional Hemodynamics and Oxygen Utilization in the Dog

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The effects of sodium nitroprusside (SNP) on the systemic and regional circulation, as well as on oxygen utilization, were studied in anesthetized dogs. A solution of SNP was infused intravenously to lower the blood pressure first to 75 per cent and then to 50 per cent of control. Seven of 15 dogs demonstrated resistance to SNP: SNP infusion rates ranging from 25 to 120  $\mu\text{g}/\text{kg}/\text{min}$  were necessary in this group (resistant, or R, group) to bring blood pressure to 50 per cent of control, whereas less than 7  $\mu\text{g}/\text{kg}/\text{min}$  SNP were needed to lower the blood pressure to 50 per cent of control in the other eight dogs, which were more sensitive to SNP (sensitive or S, group). In the control state, there was no apparent difference between the two groups in hemodynamic functions, oxygen transport, or oxygen utilization. In the R group, after blood pressure was lowered to 50 per cent of control, cardiac output increased to 150 per cent as a result of increased myocardial contractility, blood flows increased markedly in the myocardium (250 per cent) and brain (145 per cent) and decreased in the liver (hepatic artery, 40 per cent), kidney (50 per cent) and spleen (30 per cent), and myocardial oxygen consumption increased to 250 per cent of control. In the S group, corresponding values remained more or less constant throughout the period of hypotension. These findings may have significant implications in administering SNP to patients who are not responsive to SNP and who have hepatic or renal dysfunction, and/or coronary insufficiency. (Key words: Anesthetic techniques: hypotension, induced, sodium nitroprusside. Blood: viscosity, vascular hindrance. Blood pressure: peripheral vascular resistance. Brain: blood flow. Heart: blood flow; contractility; oxygen consumption. Kidney: blood flow. Liver: blood flow. Intestine: blood flow. Spleen: blood flow.)

SODIUM NITROPRUSSIDE (SNP) is frequently used to induce hypotension during anesthesia,<sup>1,2</sup> and to reduce the afterload during open-heart surgery and following myocardial infarction with myocardial failure.<sup>3-5</sup> Effects of SNP-induced hypotension on hemodynamic functions have been examined in several previous studies.<sup>6-9</sup> However, a systematic approach to investigation of the hemodynamic responses in several vascular beds simultaneously, with the pur-

pose of elucidating the compensatory mechanism in SNP-induced hypotension, is still lacking. Furthermore, although the accumulation of cyanide (CN) as a result of excessive doses of SNP has been fully recognized and studied,<sup>10-12</sup> hemodynamic functions and oxygen utilization in individuals resistant to SNP have not been fully investigated.

Palmer and Lasseter<sup>7</sup> reviewed 350 human cases reported in the medical literature and stated that there was no incidence of tachyphylaxis. Although cases of tachyphylaxis and toxic reactions to SNP have been reported,<sup>10,11</sup> the incidence remains low. Dogs are more resistant than man to induction of hypotension with SNP.<sup>12</sup> In the present study, seven of 15 dogs were resistant to the action of SNP. This enabled us to study systemic and regional hemodynamics and oxygen utilization in dogs that were resistant as well as in those sensitive to SNP. Systemic and regional hemodynamic functions were studied following stepwise decreases of systemic blood pressure induced by graded doses of SNP.

### Methods

Fifteen mongrel dogs weighing 10-15 kg were anesthetized with sodium pentobarbital, 30 mg/kg, intravenously, followed by supplements of approximately 2 mg/kg/hr. Pancuronium bromide, 0.08 mg/kg, was given as a muscle relaxant. Ventilation was provided with a Harvard<sup>®</sup> respirator through a cuffed endotracheal tube to maintain  $\text{Pa}_{\text{CO}_2}$  at 37-40 torr.  $\text{Pa}_{\text{O}_2}$  was maintained in a range of 100-150 torr with oxygen added to the inspired mixture. Esophageal temperature was monitored with a thermistor probe\*\* and maintained at  $37 \pm 1$  C with an electric heating pad. A catheter (frequency response flat to 25 Hz) was introduced into the left ventricle via a femoral artery with the aid of pressure monitoring. A Swan-Ganz catheter†† (7 Fr) was introduced through a femoral vein into the pulmonary artery. The other femoral artery and femoral vein were cannulated for pressure monitoring and infusion of fluid or blood. Ringer's lactate solution (5-10 ml/kg) was infused in the control state to obtain a pulmonary wedge pressure of approximately 9 torr (table 1), with the aim of achiev-

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ing a constant preload state. After the chest was opened through the left fifth intercostal space, the coronary sinus was catheterized directly with a polyethylene catheter and location was ascertained with sinus blood-gas analysis. Heparin, 100 units/kg, initially, and 50 units/kg/h, was given intravenously. Oxygen tension ( $P_{O_2}$ ) and  $CO_2$  tension ( $P_{CO_2}$ ) of blood samples were determined at appropriate intervals with calibrated electrodes at 37 C.‡‡ Hemoglobin concentration (Hb, in g/dl) and oxygen saturation (per cent) of each blood sample were measured with a CO-Oximeter.§§ Systemic arterial blood pressure, right atrial pressures, pulmonary arterial and wedge pressures, and left ventricular pressure were recorded on a Grass polygraph recorder through Statham transducers (frequency response 60 Hz). All pressures were reported as mean values. The rate of rise of left ventricular pressure ( $dP/dt$ )<sup>13</sup> was measured with a differentiator and recorded on the polygraph.

#### PROCEDURES FOR EXPERIMENTAL VARIATIONS OF BLOOD PRESSURE WITH SNP

The SNP solution was infused intravenously at a constant rate to lower blood pressure, first to 75 per cent and then to 50 per cent of the control value. After each desired level of blood pressure was arrived, a 15 min period was allowed for stabilization before hemodynamic measurements were made. Blood pressure was reduced to 50 per cent of control level with less than 7  $\mu\text{g}/\text{kg}/\text{min}$  SNP infusion in eight of the 15 dogs (SNP-sensitive, or S group), while SNP infusion rates ranging from 25 to 120  $\mu\text{g}/\text{kg}/\text{min}$  were needed in the other seven dogs (SNP-resistant, or R group). In ten of these dogs (five S and five R), more frequent hemodynamic measurements with microspheres (labeled with five radionuclides) were performed to obtain a dose-response curve of SNP.

#### MEASUREMENT OF SYSTEMIC AND REGIONAL FLOWS WITH MICROSPHERES

Microspheres  $16 \pm 1.0 \mu\text{m}$  (mean  $\pm$  SD) in size, labeled with radionuclides  $^{57}\text{Co}$ ,  $^{113}\text{Sn}$ ,  $^{103}\text{Ru}$ ,  $^{96}\text{Nb}$ , and  $^{46}\text{Sc}$  and suspended in 10 per cent dextran solution (MW 78,000) were used.¶¶ The spheres were checked for size, status of aggregation, presence of fragmentation, specificity of radionuclides, and specific activity. Microscopic examination was carried out to assure the complete dispersion of spheres and to count the number of spheres to be injected. Approximately 1

$\times 10^6$  of spheres per 10 kg body weight were used for each injection. Precautions and details in preparing the spheres were reported elsewhere.<sup>14</sup> During the control period and 20 minutes after each decrement of systemic blood pressure, the spheres, diluted in 5–10 ml physiologic saline solution containing 0.05 per cent Tween 80<sup>®</sup>, were injected into the left ventricle via the left ventricular catheter over a period of 30 s, followed by injection of 10 ml physiologic saline solution over a period of approximately 10 s. This 30-s injection period was chosen to avoid excessive injection of spheres during systole and sudden change in hemodynamics. Concentrations of dextran and Tween 80 solutions used here were lower than those needed to cause significant hemodynamic changes.<sup>15,16</sup> For the withdrawal of reference arterial blood samples, the pump was set at a rate ( $Q_{\text{ar}}$ ) of 15 ml/min for 2 min, starting 10 s before the injection of microsphere suspension.

At the end of the experiment, the dog was sacrificed with potassium chloride or an overdose of sodium pentobarbital, injected intravenously. Brain, heart, liver, spleen, intestine (a portion of the jejunum), and kidneys were removed and dissected into 0.5–1.5-g pieces for the measurement of radioactivities with a gamma counter. Radioactivities and the weight of each tissue sample were entered into a PDP-11/10 minicomputer.\*\*\* A computer program was used to resolve the radioactivity of each isotope. From the radioactivity per 100-g tissue sample ( $C_t$ ), the flow rate per 100 g of tissue ( $Q_t$ ) and cardiac output (CO) were calculated, using equations given below:

$$\text{CO} = A_i / (A_{\text{ar}} / Q_{\text{ar}}) \quad (1)$$

$$Q_t = C_t / (A_{\text{ar}} / Q_{\text{ar}}) \quad (2)$$

where  $A_i$  is the radioactivity injected,  $A_{\text{ar}}$ , the total activity of the arterial reference flow sample, and  $Q_{\text{ar}}$ , the pump withdrawal rate for the reference sample. Values of CO obtained by use of this microsphere technique have been shown to correlate well with those obtained by use of the dye-dilution method.<sup>14,15</sup>

The total cerebral blood flow was calculated as the sum of the products of the regional tissue flows and fractional weights for cerebral cortex, caudate nucleus, thalamus, midbrain, limbic system, and cerebellum. To obtain the mean cerebral cortical flow rate, two pieces of samples containing both gray and white matter were taken from each of the following four lobes: frontal, parietal, temporal, and occipital.

The kidney was dissected to give two pieces each of the outer cortex, the inner cortex, and the medulla. Blood flow rate of total kidney ( $Q_{\text{kidney}}$ ) was computed

‡‡ Instrumentation Laboratory, Model 213 blood-gas analyzer, Lexington, Massachusetts.

§§ Instrumentation Laboratory, Model 182.

¶¶ New England Nuclear Corp., Boston, Massachusetts.

\*\*\* Digital Equipment Corp., Marlboro, Massachusetts.

from the following equation, as discussed in a previous publication<sup>17</sup>:

$$Q_{\text{kidney}} = 0.39 Q_{\text{oc}} + 0.32 Q_{\text{lc}} + 0.29 Q_{\text{med}} \quad (3)$$

where  $Q_{\text{oc}}$ ,  $Q_{\text{lc}}$ , and  $Q_{\text{med}}$  represent blood flows of the outer cortex, the inner cortex, and the medulla, and 0.39, 0.32, and 0.29 are the fractional weights of these three regions, respectively.

#### EVALUATION OF PRESSURE-FLOW RELATIONSHIP

Pressure-flow ratios or flow resistance ( $R$ , in PRU/100 g) in the overall systemic circulation ( $R_s$ ), the regional circulations ( $R_r$ ), and the pulmonary circulation ( $R_p$ ) were calculated as follows:

$$R_s = (P_A - P_{RA})/CO \quad (4)$$

$$R_r = (P_A - P_{RA})/Q_r \quad (5)$$

$$R_p = (P_{PAP} - P_{PWP})/CO \quad (6)$$

where  $P_A$  is the mean arterial blood pressure;  $P_{RA}$ , right atrial pressure (central venous pressure);  $P_{PAP}$ , the mean pulmonary arterial pressure, and  $P_{PWP}$ , the mean pulmonary wedge pressure. CO is cardiac output and  $Q_r$ , various regional flow rates. A value of 10 torr was used for the portal venous pressure in the calculation of intestinal blood flow.<sup>17,18</sup>

Resistance to flow includes two factors: blood viscosity ( $\eta$ ) and vascular geometry.<sup>17,19,20</sup> The contribution of vascular geometry to flow resistance is called vascular hindrance. Vascular hindrance in the systemic circulation ( $Z_s$ ) was calculated from the following equation:

$$Z_s = R_s/\eta \quad (7)$$

Viscosity of venous blood was measured in an air-bearing coaxial cylinder viscometer, originally designed by Gilinson *et al.*<sup>21</sup> and modified in our laboratory. The viscosity measurement was performed at 37 C and covered shear rates ranging from 200 to 0.5 sec<sup>-1</sup>. Blood viscosity measured at a shear rate of 200 sec<sup>-1</sup> was used as the  $\eta$  value in the control as well as in high-flow states. At low-flow states, the effect of low shear rates on the  $\eta$  value was corrected, assuming that the shear rate change was proportional to the flow ratio.<sup>22</sup> The blood viscosity corresponding to this corrected shear rate was used as  $\eta$ .

Oxygen content (in ml/dl) was calculated as the sum of the hemoglobin-bound oxygen ( $0.0134 \times \text{Hb} \times \text{O}_2$  saturation) and the dissolved oxygen ( $0.003 \times P_{\text{O}_2}$ ). The oxygen transport rate, which is the product of blood flow and arterial oxygen content, indicates the rate of oxygen supply to tissue. Oxygen extraction ratio was calculated as the ratio of the arteriovenous difference in oxygen content to the arterial oxygen

content. Oxygen consumption was calculated as the product of the appropriate flow and arteriovenous difference in oxygen content.

Data were analyzed to compare results obtained at different blood pressures with those at the control pressure and to compare results in S and R groups by use of analysis of variance and the Student *t* test for unpaired data.  $P < 0.05$  was considered significant.

#### Results

In the control state, there was no significant difference between the sensitive (S) and resistant (R) groups in systemic and regional hemodynamics, oxygen transport, or oxygen utilization (tables 1-4).

Hemodynamic functions measured during SNP infusion in each group were divided by their corresponding control values to give indices in addition to the absolute values of SNP-induced alterations.

Although heart rate increased immediately following each reduction of blood pressure (not tabulated), it had returned to the control level by the time our hemodynamic measurements were made. Blood viscosity ( $\eta$ ) remained constant in both S and R groups during hypotension induced by different doses of SNP; therefore, the alteration of vascular resistance reflects the change of vascular hindrance, *i.e.*, the vascular geometry. When blood pressure was lowered by SNP to 75 per cent of control, cardiac output (CO), blood viscosity, heart rate, and stroke volume in both S and R groups remained constant (table 1). Systemic vascular resistance of the R group showed a significant decrease, whereas the corresponding value was not statistically altered in the S group. At 50 per cent of control blood pressure, CO and stroke volume decreased in the S group and increased in the R group. Systemic vascular resistance showed significant decreases (vasodilation) in both R and S groups, but the decrease was much more prominent in the R group ( $P < 0.05$ ). There was no significant change in  $P_{\text{aO}_2}$ ,  $P_{\text{aCO}_2}$ , or *pH* during SNP infusion.

A marked difference between the S and R groups was found in the regional blood flow distributions (table 2). In the S group, regional blood flows of various organs, *i.e.*, heart, brain, liver, intestine, and kidney, remained almost constant at 75 and 50 per cent of blood pressure. In the R group, blood flows to the heart and brain increased as the blood pressure decreased, especially in the heart, where the flow more than doubled the control value. Blood flows through the liver (hepatic artery) and kidney in the R group were about half of their corresponding values at control state. Blood flow in the spleen decreased

TABLE 1. Systemic Hemodynamics, Oxygen Transport and Oxygen Consumption during SNP-induced Hypotension (Means  $\pm$  SEM)

|                            | Blood Pressure (torr) | Cardiac Output (ml/min/kg) | Vascular Resistance (PRU $\ddagger$ - kg) | Vascular Hindrance (PRU - kg - cp) | Heart Rate (min $^{-1}$ ) | Stroke Volume (ml/Beat)   | Left Atrial Pressure (torr) | O <sub>2</sub> Transport (ml/min/kg) | O <sub>2</sub> Extraction Ratio | O <sub>2</sub> Consumption (ml/min/kg) |
|----------------------------|-----------------------|----------------------------|---|------------------------------------|---------------------------|---------------------------|-----------------------------|--------------------------------------|---------------------------------|--|
| Control                    |                       |                            |   |                                    |                           |                           |                             |                                      |                                 |  |
| Sensitive                  | 113 $\pm$ 8           | 123 $\pm$ 9                | 0.92 $\pm$ 0.04                           | 0.24 $\pm$ 0.04                    | 150 $\pm$ 13              | 11.7 $\pm$ 0.5            | 9.1 $\pm$ 0.7               | 21.4 $\pm$ 1.7                       | 0.32 $\pm$ 0.02                 | 7.40 $\pm$ 1.65                        |
| Resistant                  | 122 $\pm$ 8           | 137 $\pm$ 14               | 0.91 $\pm$ 0.03                           | 0.27 $\pm$ 0.02                    | 153 $\pm$ 5               | 12.4 $\pm$ 1.0            | 8.9 $\pm$ 0.9               | 23.4 $\pm$ 2.4                       | 0.34 $\pm$ 0.05                 | 7.62 $\pm$ 1.87                        |
| Blood pressure 75 per cent |                       |                            |   |                                    |                           |                           |                             |                                      |                                 |  |
| Sensitive                  | 84 $\pm$ 6*           | 117 $\pm$ 12               | 0.84 $\pm$ 0.08                           | 0.22 $\pm$ 0.02                    | 138 $\pm$ 19              | 11.0 $\pm$ 1.0            | 8.0 $\pm$ 0.8               | 19.5 $\pm$ 1.5                       | 0.34 $\pm$ 0.02                 | 6.14 $\pm$ 0.57                        |
| Resistant                  | 91 $\pm$ 6*           | 136 $\pm$ 9                | 0.65 $\pm$ 0.05*                          | 0.18 $\pm$ 0.01                    | 158 $\pm$ 6               | 11.2 $\pm$ 1.0            | 7.0 $\pm$ 1.0               | 20.2 $\pm$ 2.5                       | 0.35 $\pm$ 0.04                 | 6.84 $\pm$ 0.77                        |
| Blood pressure 50 per cent |                       |                            |   |                                    |                           |                           |                             |                                      |                                 |  |
| Sensitive                  | 56 $\pm$ 7*           | 104 $\pm$ 15*              | 0.74 $\pm$ 0.08*                          | 0.19 $\pm$ 0.02*                   | 147 $\pm$ 16              | 10.4 $\pm$ 0.4*           | 7.6 $\pm$ 0.7               | 17.1 $\pm$ 2.2*                      | 0.34 $\pm$ 0.04                 | 6.40 $\pm$ 1.37*                       |
| Resistant                  | 60 $\pm$ 6*           | 168 $\pm$ 11 $\ddagger$    | 0.36 $\pm$ 0.07 $\ddagger$                | 0.08 $\pm$ 0.02 $\ddagger$         | 162 $\pm$ 16              | 16.2 $\pm$ 1.6 $\ddagger$ | 7.6 $\pm$ 1.6               | 28.2 $\pm$ 1.7 $\ddagger$            | 0.34 $\pm$ 0.04                 | 8.93 $\pm$ 0.96 $\ddagger$             |

\* Significantly different from control data,  $P < 0.05$ . $\ddagger$  Significantly different from control data and also from sensitive group at the same pressure,  $P < 0.05$ .  
 $\ddagger$  PRU is defined as torr  $\cdot$  min  $\cdot$  ml $^{-1}$ .

in both S and R groups as systemic blood pressure decreased.

Determination of vascular resistance showed a progressive vasodilation in the heart and brain as the blood pressure was lowered, and this was more marked in the R group than in the S group (table 3). In the liver (hepatic artery), intestine and kidney, vascular resistance remained essentially constant in both groups at 75 per cent of blood pressure and in the R group as the blood pressure was further decreased to 50 per cent, whereas the S group showed significant vasodilation in these three regions at 50 per cent blood pressure. In the splenic circulation, vascular resistance was unchanged at 75 per cent blood pressure, and a trend of vasoconstriction, although not statistically significant, was evident as the blood pressure further decreased to 50 per cent.

A significant difference between the S and R groups was found in the effect of SNP-induced hypotension on the rates of systemic and myocardial oxygen transport and utilization (table 4). In the R group, the oxygen transport rate ( $T_{O_2}$ ) in the systemic circulation showed a significant increase at 50 per cent blood pressure, while a decrease of systemic  $T_{O_2}$  was found in the S group. The R group showed a marked increase in myocardial  $T_{O_2}$  (2.5 times) at 50 per cent blood pressure. The S group had a constant myocardial  $T_{O_2}$  throughout the course of hypotension. Because the oxygen extraction ratios were constant in both systemic and myocardial circulations at various blood pressures, changes in oxygen consumption rate in systemic and myocardial circulations closely reflected those of corresponding  $T_{O_2}$  values. Thus, a marked increase of myocardial oxygen consumption occurred only in the R group as blood pressure was reduced to 50 per cent of control.

The relationship between systemic blood pressure and the dose of SNP administered is shown in figure 1. In the S group, a SNP dose of not more than 7  $\mu$ g/kg/min was sufficient to decrease the blood pressure to 50 per cent of control, but the mean SNP dose of 70  $\mu$ g/kg/min was necessary to achieve the same reduction in blood pressure in the R group. In figures 1 and 2, various values found for the two groups are compared according to the doses of SNP administered. At SNP doses  $<$  10  $\mu$ g/kg/min, CO did not show a significant change in either group. As the dose was increased, a significant increase of CO was seen in the R group. Systemic vascular resistance decreased in proportion to the dose of SNP infused in both groups. Pulmonary vascular resistance ( $R_p$ ) remained essentially constant during SNP infusion.

Coronary and cerebral blood flows increased with larger doses of SNP (fig. 2); a threefold increase of

TABLE 2. Regional Blood Flows during SNP-induced Hypotension (Means ± SEM)

|                            | Regional Blood Flow (ml/100 g/min) |         |         |           |           |           |
|----------------------------|------------------------------------|---------|---------|-----------|-----------|-----------|
|                            | Heart                              | Brain   | Liver‡  | Intestine | Kidney    | Spleen    |
| Control                    |                                    |         |         |           |           |           |
| Sensitive                  | 107 ± 7                            | 40 ± 7  | 35 ± 6  | 79 ± 16   | 491 ± 42  | 162 ± 25  |
| Resistant                  | 95 ± 7                             | 39 ± 3  | 41 ± 8  | 73 ± 11   | 411 ± 53  | 146 ± 20  |
| Blood pressure 75 per cent |                                    |         |         |           |           |           |
| Sensitive                  | 97 ± 8                             | 48 ± 6  | 31 ± 6  | 69 ± 8    | 482 ± 29  | 102 ± 13* |
| Resistant                  | 110 ± 15                           | 41 ± 5  | 37 ± 7  | 58 ± 7    | 326 ± 51  | 101 ± 14* |
| Blood pressure 50 per cent |                                    |         |         |           |           |           |
| Sensitive                  | 111 ± 18                           | 42 ± 2  | 34 ± 8  | 66 ± 11   | 431 ± 36  | 77 ± 15*  |
| Resistant                  | 220 ± 25†                          | 56 ± 8† | 20 ± 3† | 53 ± 18   | 243 ± 32† | 57 ± 18*  |

\* Significantly different from control data,  $P < 0.05$ .

† Significantly different from control data and also from sensitive

group at the same pressure,  $P < 0.05$ .

‡ Blood flow through the hepatic artery.

coronary blood flow was seen at an infusion rate of 100 µg/kg/min. Blood flows in the liver (hepatic artery) and intestine were maintained at different doses of SNP, except that the hepatic flow decreased in the R group with the higher SNP dose. Renal and splenic flows decreased progressively. Therefore, the two groups appeared to have similar changes in blood flow to these organs in relation to SNP dose. Values for regional vascular resistance in the two groups also demonstrated similar relations to the dose of SNP in most of the regions studied. In the myocardium, however, the R group tended to have higher flow than the S group at a given SNP dose (fig. 2).

The ventricular pressure was lowered during SNP infusion in both groups. The rate of rise of ventricular pressure (dP/dt) showed a statistically significant increase only in the R group (table 4 and figure 3) when the blood pressure was lowered to 50 per cent of control.

### Discussion

The safety margin of induced hypotension has been of great concern in clinical medicine.<sup>1,2,23</sup> Hemodynamic and metabolic studies of the brain,<sup>24,25</sup> myocardium, and total body<sup>6,7</sup> have shown no significant alteration when systemic blood pressure was higher than 50 per cent of control. Wang *et al.*<sup>9</sup> studied the cardiovascular effects of SNP and trimethaphan in pentobarbital-chloralose-anesthetized dogs and concluded that SNP-induced hypotension (75 per cent of control) decreased CO, and coronary and mesenteric blood flows while maintained renal blood flow. The discrepancy between these regional flow changes found by Wang *et al.*<sup>9</sup> and the constant blood flows through the heart, brain, liver, intestine, and kidney in our S group at 50 per cent blood pressure could be explained by the difference in experimental procedures. In comparison with the present studies,

TABLE 3. Regional Vascular Resistance during SNP-induced Hypotension (Means ± SEM)

|                            | Regional Vascular Resistance (PRU§/100 g) |              |              |              |              |             |
|----------------------------|---|--------------|--------------|--------------|--------------|-------------|
|                            | Heart                                     | Brain        | Liver‡       | Intestine    | Kidney       | Spleen      |
| Control                    |   |              |              |              |              |             |
| Sensitive                  | 1.07 ± 0.08                               | 2.51 ± 0.29  | 3.14 ± 0.47  | 1.68 ± 0.24  | 0.24 ± 0.04  | 0.71 ± 1.24 |
| Resistant                  | 1.11 ± 0.09                               | 2.67 ± 0.20  | 3.39 ± 0.79  | 1.68 ± 0.23  | 0.28 ± 0.05  | 0.75 ± 0.07 |
| Blood pressure 75 per cent |   |              |              |              |              |             |
| Sensitive                  | 0.86 ± 0.08                               | 1.74 ± 0.21* | 2.66 ± 0.92  | 1.21 ± 0.31  | 0.17 ± 0.03  | 0.81 ± 0.06 |
| Resistant                  | 0.81 ± 0.07*                              | 2.01 ± 0.18* | 2.37 ± 0.23  | 1.37 ± 0.16  | 0.25 ± 0.04  | 0.82 ± 0.09 |
| Blood pressure 50 per cent |   |              |              |              |              |             |
| Sensitive                  | 0.54 ± 0.08*                              | 1.36 ± 0.11* | 1.69 ± 0.54* | 0.83 ± 0.07* | 0.14 ± 0.02* | 0.91 ± 0.15 |
| Resistant                  | 0.25 ± 0.02†                              | 1.02 ± 0.12* | 2.76 ± 0.26* | 1.02 ± 0.21* | 0.23 ± 0.03  | 0.98 ± 0.12 |

\* Significantly different from control data,  $P < 0.05$ .

† Significantly different from control data and also from sensitive group at the same pressure,  $P < 0.05$ .

‡ Blood flow through the hepatic artery.

§ PRU is defined as torr min·ml<sup>-1</sup>.

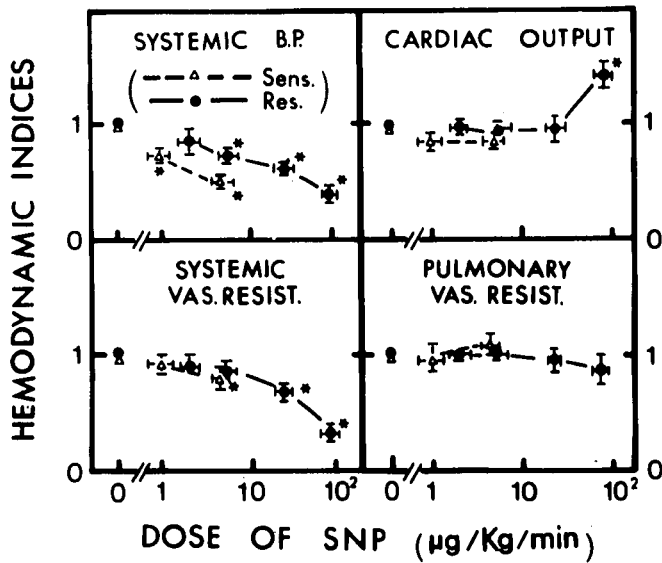


FIG. 1. Effects of different doses of SNP on the hemodynamic indices of systemic blood pressure, cardiac output, systemic vascular resistance, and pulmonary vascular resistance. Hemodynamic indices are calculated by dividing various values by those obtained at the control state. Vertical bars are SEM. \* Significantly different from control data,  $P < 0.05$ . \*\* Significantly different from control data and also from the sensitive group,  $P < 0.05$ . Sens = sensitive group; Res = resistant group.

Wang *et al.*<sup>9</sup> infused SNP at a more rapid rate (4–10  $\mu\text{g}/\text{kg}/\text{min}$ ) within a shorter period, and measurements were made immediately; therefore, their results tended to reflect the dynamic state of acute hypotension, whereas our measurements were made in a more steady state. Furthermore, since no separation of sensitive or resistant responses to SNP was made in their dogs, their results could be a combination of the responses of both S and R groups.

In the present investigation, normal oxygen supplies to the various organs were maintained, and the

constant oxygen extractions in the systemic and myocardial circulations indicate an unchanged relationship between oxygen supplies and demands. These results, along with those previously reported by others,<sup>2,7,8</sup> support the appropriateness of using SNP to induce hypotension to a blood pressure level of 50 per cent of control or higher, provided no resistant response to SNP occurs.

The use of SNP to induce hypotension, however, is sometimes complicated by the resistance to SNP, *i.e.*, a larger dose of SNP is necessary to bring the blood pressure to the desired level, as evidenced in the R group of the present experiments. Several hemodynamic and metabolic changes were observed during infusion of large doses of SNP. These included increase of cardiac output, redistribution of systemic blood flows to the heart and brain, and increase of myocardial oxygen consumption. The increase of cardiac output resulted mainly from an increased stroke volume, which can be explained by enhanced myocardial contractility.

In the coronary circulation, marked vasodilation resulted in dose-dependent increases in coronary blood flow. This increase in flow brought more oxygen supply to the myocardium to meet the elevated oxygen demand. Myocardial oxygen consumption ( $MV_{O_2}$ ) is regulated by several factors<sup>26</sup>: the contractile state of the heart, developed wall tension (affected by preload and afterload), and heart rate. In the R group, the afterload (systemic blood pressure) as well as the preload of the myocardium were decreased or maintained, and heart rate remained constant at 50 per cent blood pressure, yet  $MV_{O_2}$  was markedly increased. This increase of  $MV_{O_2}$  after infusion of large doses of SNP was also found in a study by Tinker *et al.*<sup>27</sup> Within 15 min of infusion of a huge dose (20 mg/kg/hour) of SNP, Tinker *et al.*<sup>27</sup> found that  $MV_{O_2}$

TABLE 4. Myocardial Oxygen Transport, Oxygen Consumption, and  $dP/dt$  of Left Ventricular Pressure (LVP) during SNP-induced Hypotension (Means  $\pm$  SEM)

|                            | O <sub>2</sub> Transport (ml/min/kg) | O <sub>2</sub> Extraction Ratio | O <sub>2</sub> Consumption (ml/min/kg) | $dP/dt$ of LVP (torr/sec) |
|----------------------------|--------------------------------------|---------------------------------|--|---------------------------|
| Control                    |                                      |                                 |  |                           |
| Sensitive                  | 208 $\pm$ 22                         | 0.61 $\pm$ 0.05                 | 134 $\pm$ 18                           | 1962 $\pm$ 251            |
| Resistant                  | 187 $\pm$ 13                         | 0.59 $\pm$ 0.10                 | 119 $\pm$ 7                            | 1980 $\pm$ 203            |
| Blood pressure 75 per cent |                                      |                                 |  |                           |
| Sensitive                  | 188 $\pm$ 15                         | 0.58 $\pm$ 0.02                 | 123 $\pm$ 9                            | 1876 $\pm$ 176            |
| Resistant                  | 183 $\pm$ 12                         | 0.54 $\pm$ 0.06                 | 117 $\pm$ 10                           | 1996 $\pm$ 216            |
| Blood pressure 50 per cent |                                      |                                 |  |                           |
| Sensitive                  | 224 $\pm$ 29                         | 0.58 $\pm$ 0.02                 | 134 $\pm$ 15                           | 1712 $\pm$ 212            |
| Resistant                  | 428 $\pm$ 35†                        | 0.60 $\pm$ 0.03                 | 274 $\pm$ 17†                          | 2752 $\pm$ 276†           |

\* Significantly different from control data,  $P < 0.05$ .

† Significantly different from control data and also from sensitive group at the same pressure,  $P < 0.05$ .

had almost doubled, coronary blood flow tripled, and both serum cyanide (CN) and catecholamine levels increased almost ten times. These changes were also associated with concomitant decreases of the preload and afterload of the myocardium and a constant heart rate. Their findings and the results from the present investigation suggest that an elevated myocardial contractility may be the cause of increased  $MV_{O_2}$  in response to large doses of SNP.

Cerebral vessels are primarily under the influence of local metabolic and myogenic autoregulation,<sup>28</sup> whereas the role of sympathetic control is controversial and probably much less important than it is in the other organs.<sup>29</sup> Cerebral vasodilation also occurs in a dose-dependent relationship with SNP. Whether this vasodilation is a result of increased oxygen demand in the brain or simply due to a direct effect of SNP on cerebral blood vessels is not known. In the liver, intestine, and kidney, SNP led to generalized vasodilation in the S group, but larger doses of SNP failed to cause any significant change of vascular resistance even at 50 per cent blood pressure in the R group. Such a discrepancy in vascular responses to SNP infusion in the splanchnic and renal regions, along with marked vasodilation in the heart and brain, contributes to a marked redistribution of flows to vital organs, *i.e.*, heart and brain, and leaves splanchnic and renal organs less perfused. The systemic flow redistribution and increases in CO and  $MV_{O_2}$  that occurred following infusion of large doses of SNP could be the results of a combination of enhanced sympathetic activity,<sup>27</sup> which has region-specific  $\alpha$ - and  $\beta$ -adrenergic actions,<sup>18,30</sup> and nonselective vasodilating effects of SNP, as well as the attenuation of the vasodilatory action of SNP by CN.<sup>31</sup>

The infusion of SNP, even at rates as high as 100  $\mu\text{g}/\text{kg}/\text{min}$ , did not cause any significant change of

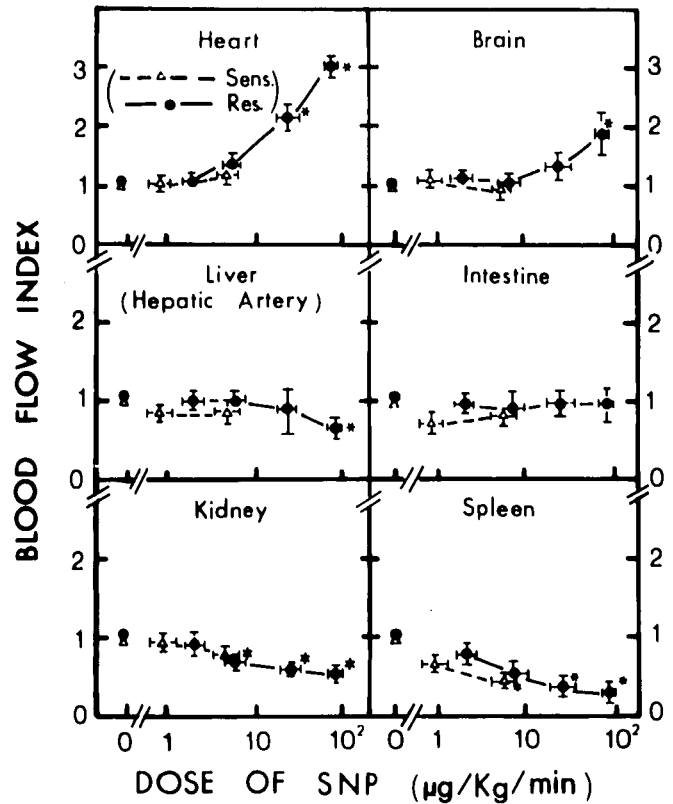


FIG. 2. Effects of different doses of SNP on blood flows through the myocardium, brain, liver (hepatic artery), intestine, kidney, and spleen. Blood flow indices are calculated by dividing various values by those obtained at the control state. Symbols as in figure 1.

pulmonary vascular resistance. This indicates a lack of vasodilating effect of SNP on the pulmonary vasculature in the absence of significant hypoxic vasoconstriction.<sup>32</sup>

In conclusion, in the dog a decrease of blood pressure to 50 per cent of control with infusion of  $< 7 \mu\text{g}/\text{kg}/\text{min}$  SNP did not alter blood flow and

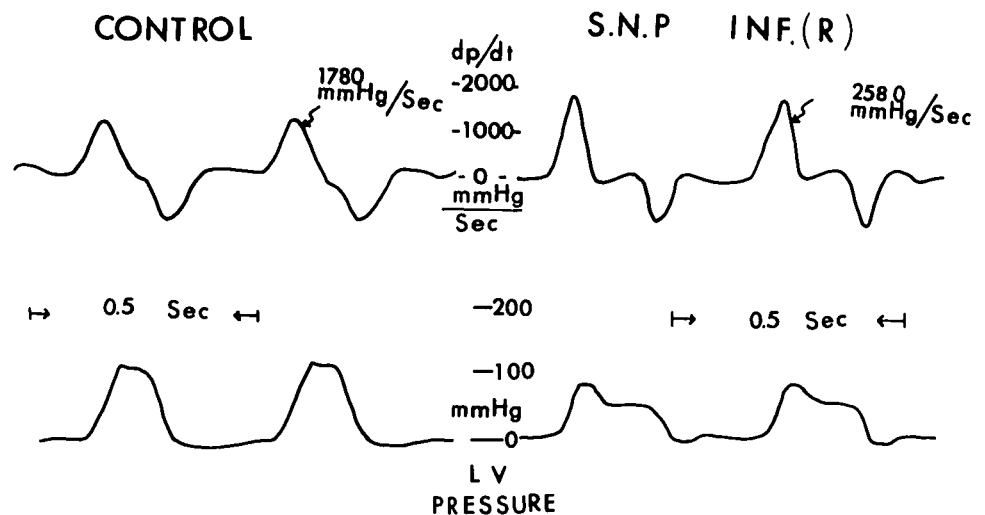


FIG. 3. Representative tracings of ventricular pressure and its first derivative ( $dP/dt$ ) in the control and SNP-induced hypotensive states. R = resistant group.

oxygen utilization in the systemic and myocardial circulations. Where larger doses of SNP (25–120  $\mu\text{g}/\text{kg}/\text{min}$ ) were needed to lower blood pressure to 50 per cent of control, an increase of CO, a redistribution of blood flows to the heart and brain, and an increase of myocardial oxygen consumption occurred. These results suggest that patients resistant to SNP may be at risk due to an increase of myocardial oxygen requirement and marked decreases of blood flows to the liver (hepatic artery) and kidneys. Therefore, in addition to the belief that induced hypotension may aggravate latent disease processes, *e.g.*, coronary insufficiency and impairment in hepatic or renal function due to low perfusion pressure, these anatomic or functional diseases could be further aggravated by acute hemodynamic changes, as observed in the present studies, if huge doses of SNP were necessary to decrease blood pressure to the level desired.

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