

## Effectiveness of Sodium Nitroprusside as a Function of Total Peripheral Resistance in the Anesthetized Dog

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To determine the influence of background vasomotor tone on the effectiveness of sodium nitroprusside in decreasing total peripheral resistance, experiments were performed on 12 open-chest dogs under halothane anesthesia. In the first experiment, the vasomotor condition of six dogs was changed by altering the background infusion rate of phenylephrine (0, 40, and 0  $\mu\text{g}/\text{min}$ ). Increasing background phenylephrine infusion from 0 to 40  $\mu\text{g}/\text{min}$  significantly enhanced the effectiveness of nitroprusside in decreasing total peripheral resistance. In contrast, the effectiveness of nitroprusside in decreasing arterial pressure was not altered significantly. In a second experiment on six other dogs, phenylephrine was infused continuously at 40  $\mu\text{g}/\text{min}$ , and the vasomotor condition was changed by the infusion of phentolamine (0, 60–100, 0  $\mu\text{g}/\text{min}$ ). Phentolamine significantly diminished the effectiveness of nitroprusside in decreasing peripheral resistance. In contrast, the effectiveness of nitroprusside in decreasing arterial pressure was not altered significantly. Stepwise linear regression analysis indicated that the background peripheral resistance was the hemodynamic variable that could account partially for the changes in nitroprusside effectiveness. Increasing background total peripheral resistance significantly enhanced the effectiveness of nitroprusside in decreasing total peripheral resistance. (Key words: Anesthetic techniques: hypertension; nitroprusside. Blood pressure. Heart: cardiac output. Hemodynamics: total peripheral resistance. Pharmacology: nitroprusside.)

SODIUM NITROPRUSSIDE (SNP) is a hypotensive agent used in a variety of clinical situations when blood pressure is increased.<sup>1,2</sup> It also is used often in conjunction with positive inotropic agents to treat cardiogenic shock by decreasing the load on the failing heart when arterial pressure is increased only slightly or not at all. Finding the proper dose is occasionally difficult because sensitivity to the drug varies widely between individuals and because SNP often is given in the presence of other agents that may alter its effectiveness.<sup>3,4</sup> Although the effects of SNP on a variety of hemodynamic variables have been studied extensively, there is little information on the influence that the background hemodynamic conditions have on the effectiveness of SNP.

The purpose of this investigation was to examine the effectiveness of SNP in decreasing total peripheral resis-

tance (TPR) and mean arterial pressure (MAP) when the background vasomotor tone is altered by a steady infusion of phenylephrine (alpha-sympathetic agonist) or phentolamine (alpha-sympathetic antagonist) plus phenylephrine.

### Methods

The experiments were carried out on 12 mongrel dogs (mean weight: 22 kg, range: 18–25 kg). After induction of anesthesia with thiopental (15 mg/kg) and endotracheal intubation, anesthesia was maintained with halothane (0.7–1.2% inspired concentration). For each animal the inspired halothane concentration was adjusted to provide appropriate anesthetic depth as monitored by the corneal reflex and response to surgical stimulation and was thereafter held constant. The animals were ventilated with a Harvard® positive-pressure pump, using an equal mixture of  $\text{O}_2$  and  $\text{N}_2\text{O}$  (7–9 l/min). Arterial blood pressure was monitored by a Gould/Statham® P23DB pressure transducer through a 19-gauge polyvinyl chloride catheter inserted into a femoral artery. A Gould/Brush® coupler (which engages an integrating circuit with a 5-s time constant) was used to derive MAP. A 19-gauge polyvinyl chloride catheter was introduced in a femoral vein to administer bolus injections of SNP (200  $\mu\text{g}/\text{ml}$  in 5% dextrose in water). The venous line was filled before the experiment, so that the bolus injections could be delivered without flushing. Other venous catheters were inserted in femoral and cephalic veins to infuse phenylephrine (40  $\mu\text{g}/\text{ml}$  in normal saline) and/or phentolamine (100  $\mu\text{g}/\text{ml}$  in normal saline) continuously by Watson–Marlow® roller pumps. The chest was opened through a left thoracotomy (third intercostal), and a Gould/Statham® electromagnetic flow-probe was placed around the ascending aorta to measure stroke volume. Mean aortic flow (cardiac output, CO) obtained from a Gould/Statham® SP-2202 flowmeter was smoothed further by a low-pass filter with 0.3-Hz cutoff frequency. Flow was calibrated with a Gould/Statham® SP-7010 calibrator. During the course of the experiment, the zero offset of the pulsatile flow-signal was reset periodically by assuming zero diastolic flow. MAP and mean flow signals were sampled by a digital computer at 0.5 Hz. Because central venous pressure was not measured, but in healthy dogs is always much smaller than MAP, total peripheral resistance (TPR) simply was computed as  $\text{MAP}/\text{CO}$ .

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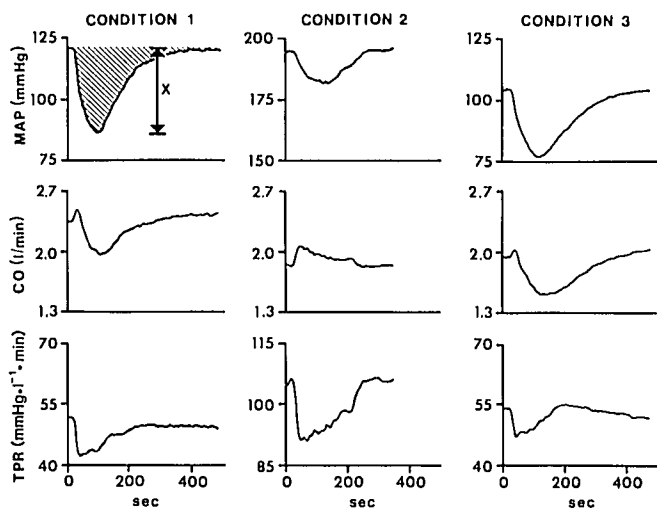


FIG. 1. Hemodynamic responses of a dog to 50 µg sodium nitroprusside before phenylephrine (left column), during 40 µg phenylephrine infusion (middle column), and after stopping phenylephrine infusion (right column). The left upper tracing depicts the way responses to bolus injections of SNP were measured. Distance X measures the maximum decrease in MAP. Shading indicates the area under the MAP response.

The investigation consisted of determining the MAP and TPR responses to SNP at different background vasomotor tones in two sets of experiments. In Experiment A (six dogs), three conditions were examined. In Condition A1, no drugs were infused. In Condition A2, phenylephrine was infused at a rate of 40 µg/min. A period of 20–30 min was allowed from the initiation of phenylephrine infusion for the TPR to stabilize at a higher level. In Condition A3, phenylephrine infusion was discontinued, and a period of 30–60 min was allowed before assuming that a new steady-state had been reached. In Experiment B (another six dogs), phenylephrine was infused continuously at a rate of 40 µg/min throughout the experiment, and the hemodynamic state was altered by the infusion of phentolamine. Condition B1 was reached after infusing phenylephrine for 20–30 min. To reach Condition B2, phentolamine was infused at 60–100 µg/min for 20 to 40 min. The dose of phentolamine was selected to return TPR approximately to the level that existed before phenylephrine infusion. For Condition B3, phentolamine infusion was terminated, and the hemodynamic variables were allowed to stabilize, requiring 40–90 min.

A series of SNP bolus injections (20–200 µg) were administered randomly in order to determine a dose-response curve at each condition. A period of 5–15 min was allowed between successive bolus injections to permit TPR and MAP to return to their preinjection levels. Only those bolus injections following which TPR and MAP returned to within 5% of their preinjection level were included in the analysis. Any drift (less than 5%)

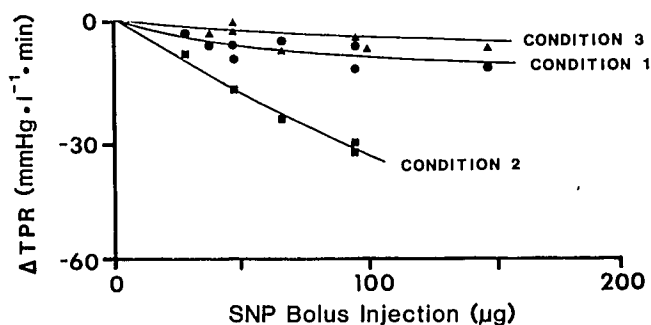


FIG. 2. TPR dose response curves to sodium nitroprusside before phenylephrine (Condition 1, ●), during 40 µg/min phenylephrine (Condition 2, ■), and after stopping phenylephrine (Condition 3, ▲) for one experiment. The dose-response curves were computed by least-squares fitting of a Michaelis-Menten equation to the experimental data.

in TPR or MAP baseline during a bolus injection was assumed to be proportional to the time elapsed since the stimulus and was subtracted from the response. The number of responses used to construct the dose-response curves at each condition for each dog was usually five to eight but never less than three.

The effect of a bolus of SNP on either MAP or TPR was characterized by measuring both the maximum reduction attained (usually 1 to 2 min after the injection) and by the area under the bolus response (fig. 1). Whether expressed as peak or area responses, the results were similar. Hence, only the results derived from the area responses are presented. The dose-response curves were obtained from a least-squares fit to the data (Figs. 2 and 3).<sup>5</sup> Numeric comparisons were made on the basis of responses to 50 and 100 µg SNP, as determined from the dose-response curves. These two doses were chosen because they generally fell on the central portion of the dose-response curves.

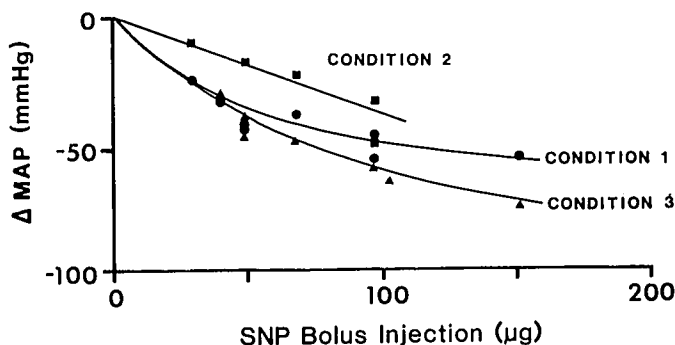


FIG. 3. MAP dose response curves to sodium nitroprusside before phenylephrine (Condition 1, ●), during 40 µg/min phenylephrine (Condition 2, ■), and after stopping phenylephrine (Condition 3, ▲) for the same experiment illustrated in Figure 2. The dose response curves were computed as in Figure 2.

TABLE 1. Background Hemodynamic Variables and their Normalized Values (mean  $\pm$  SD, N = 6) during Three Conditions of Phenylephrine and Phentolamine Infusion.

	Experiment A Phenylephrine			Experiment B Phentolamine and Phenylephrine		
	Condition 1	Condition 2	Condition 3	Condition 1	Condition 2	Condition 3
TPR <sub>0</sub> (mmHg · l <sup>-1</sup> · min)	78 $\pm$ 19	166 $\pm$ 44	96 $\pm$ 20	110 $\pm$ 19	67 $\pm$ 12	91 $\pm$ 11
TPR <sub>n</sub>	0.48 $\pm$ 11	1.00 $\pm$ 0*	0.59 $\pm$ 0.07	0.99 $\pm$ 0.03	0.57 $\pm$ .08*	0.85 $\pm$ 0.07
MAP <sub>0</sub> (mmHg)	81 $\pm$ 10	122 $\pm$ 26	86 $\pm$ 13	142 $\pm$ 10	94 $\pm$ 8	116 $\pm$ 6
MAP <sub>n</sub>	0.71 $\pm$ 17	0.95 $\pm$ 12†	0.71 $\pm$ 0.08	0.99 $\pm$ 0.03	0.66 $\pm$ 0.05*	0.82 $\pm$ 0.09
CO <sub>0</sub> (l/min)	1.30 $\pm$ 28	0.88 $\pm$ 28	1.03 $\pm$ 22	1.46 $\pm$ 24	1.65 $\pm$ 0.26	1.41 $\pm$ 0.25
CO <sub>n</sub>	0.99 $\pm$ 0.03	0.65 $\pm$ 15†	0.84 $\pm$ 0.14	0.88 $\pm$ 0.07	1.00 $\pm$ 0.0*	0.85 $\pm$ 0.12

In Experiment A, no drugs were given in Conditions 1 and 3, but 40  $\mu$ g/min phenylephrine was infused in Condition 2. In Experiment B, phenylephrine was given at 40  $\mu$ g/min in all conditions, but in Condition 2 60–100  $\mu$ g phentolamine also was infused. Significant differences from Condition 1, as determined by Newman-Keuls tests for each experiment using the normalized variables, are indicated by \* ( $P < 0.01$ ) and † ( $P < 0.05$ ). (For each normalized variable and for both drugs, Condition 2 also was significantly different ( $P < 0.05$ ) from Condition 3.) In Experiment B, TPR<sub>n</sub> and MAP<sub>n</sub> in Condition 3 were also different from those in Condition 1, most likely because the effects of phentolamine did not completely disappear.

Analysis of variance, followed by pairwise comparisons using the Newman-Keuls test<sup>6</sup> (with N = 6), was applied to the TPR and MAP responses to examine differences among the three conditions in each of the two experiments. To compensate for differences between animals,

all responses were normalized by dividing each response,  $\Delta$ TPR and  $\Delta$ MAP, to a given dose of SNP by the maximum response to that dose in that subject, yielding  $\Delta$ TPR<sub>n</sub> and  $\Delta$ MAP<sub>n</sub>. (Since these quantities are ratios that express relative effectiveness, they are always positive.) In addition, stepwise linear regression was performed to determine if any of the background hemodynamic variables, TPR<sub>0</sub>, MAP<sub>0</sub>, and CO<sub>0</sub>, at each of the three conditions could account for the altered effectiveness of SNP among the conditions. The background hemodynamic variables also were normalized by dividing the measured variables by the highest value of that variable for a given experiment, yielding TPR<sub>n</sub>, MAP<sub>n</sub>, and CO<sub>n</sub>.

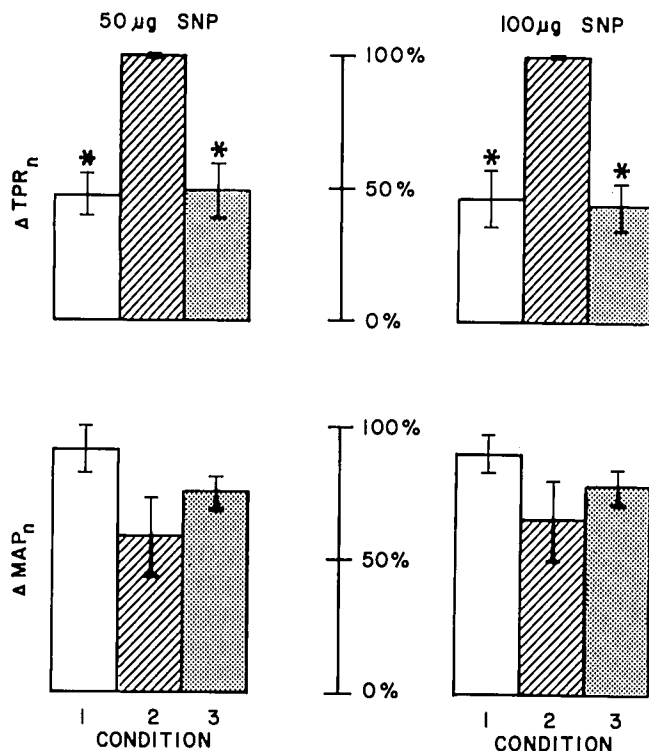


FIG. 4. Relative effectiveness (mean and SD) of SNP (expressed as  $\Delta$ TPR<sub>n</sub> and  $\Delta$ MAP<sub>n</sub>) in decreasing TPR and MAP in three hemodynamic conditions caused by changes in phenylephrine infusion in Experiment A. (Phenylephrine, at 40  $\mu$ g/min, was infused in Condition 2). Asterisks indicate significant difference by Newman-Keuls tests ( $P < 0.05$ , N = 6) from Condition 2. Differences between Conditions 1 and 3 were not significant.

## Results

The background hemodynamic variables for each condition are shown in table 1. Phenylephrine infusion in Condition A2 increased TPR<sub>n</sub> and MAP<sub>n</sub> and decreased CO<sub>n</sub>. Phentolamine infusion in Condition B2 caused opposite changes: it decreased TPR<sub>n</sub> and MAP<sub>n</sub> and increased CO<sub>n</sub>.

In Experiment A, phenylephrine infusion enhanced the effectiveness of SNP in decreasing TPR as seen from the dose-response curve (fig. 2) and from the normalized responses to 50 and 100  $\mu$ g SNP ( $P < 0.01$  for each dose; analysis of variance) shown in figure 4. In contrast, phenylephrine did not alter the effectiveness of SNP significantly in decreasing MAP at either SNP dose ( $P = 0.25$  and  $P = 0.10$ , respectively) (see figs. 3 and 4).

In Experiment B, phentolamine infusion significantly reduced the effectiveness of 100  $\mu$ g SNP in decreasing TPR, although the TPR response to 50  $\mu$ g SNP was not altered significantly ( $P < 0.05$  and  $P = 0.07$ , respec-

tively; analysis of variance). In contrast, phentolamine infusion did not significantly alter the effectiveness of SNP in decreasing MAP at either SNP dose ( $P < 0.50$  and  $P = 0.10$ , respectively) (see fig. 5).

To determine the relationship between sensitivity to SNP and background hemodynamic variables, the normalized TPR and MAP responses ( $\Delta TPR_n$  and  $\Delta MAP_n$ ) were expressed as a function of normalized background variables  $TPR_n$ ,  $MAP_n$ , and  $CO_n$ , using regression analysis. For  $\Delta TPR_n$ , simple linear regression analysis for a SNP dose of 50  $\mu\text{g}$  disclosed statistically significant positive correlations with  $TPR_n$  ( $r = 0.71$ ,  $P < 0.001$ ) and  $MAP_n$  ( $r = 0.54$ ,  $P < 0.001$ ) and negative correlations with  $CO_n$  ( $r = -0.48$ ,  $P < 0.01$ ). Stepwise regression analysis showed that  $TPR_n$  was the most significant independent variable associated with changes in  $\Delta TPR_n$ . The addition of  $MAP_n$  and  $CO_n$  did not improve significantly the estimate of  $\Delta TPR_n$  from the equation  $\Delta TPR_n = 0.82 TPR_n + 10.0\%$  ( $r = 0.71$ ,  $P < 0.001$ ). Similar levels of significance were obtained with 100  $\mu\text{g}$  SNP bolus injections.

For  $\Delta MAP_n$ , simple linear regression analysis showed only a very weak inverse correlation with  $TPR_n$  ( $r = -0.34$ ,  $P < 0.05$ ) and  $MAP_n$  ( $r = -0.35$ ,  $P < 0.05$ ) and a similarly weak positive correlation with  $CO_n$  ( $r = 0.32$ ,  $P < 0.05$ ). Adding the other independent variables to any of the equations did not significantly improve the estimate of  $\Delta MAP_n$ . Similar weak correlations were obtained with 100  $\mu\text{g}$  SNP bolus injections.

### Discussion

The hemodynamic responses to SNP are determined by the direct primary effects of the drug on the vasculature and by the secondary adjustments caused by preload/afterload effects on the heart and by cardiovascular reflexes. Verhaeghe and Shepherd, working with isolated blood vessels from dogs, showed that SNP decreased the isometric force of contraction caused by electrical stimulation, potassium, or norepinephrine.<sup>7</sup> They also showed that the degree of relaxation was independent of the level of contraction and was not changed by phentolamine, propranolol, or atropine.

In our experiments, phenylephrine increased and phentolamine decreased the effectiveness of SNP in reducing TPR. These results are not contradictory with those of Verhaeghe and Shepherd, because force in the muscle wall of the isolated vessel is not equivalent to TPR in the intact animal. The two are linked in a very complex manner that involves Laplace's law relating the tangential force in the vessel wall to diameter and pressure, the relationship between vessel diameter and TPR, the compliance of the vessels, and the baroreceptor reflex system linking pressure and TPR.<sup>8</sup> The net effect

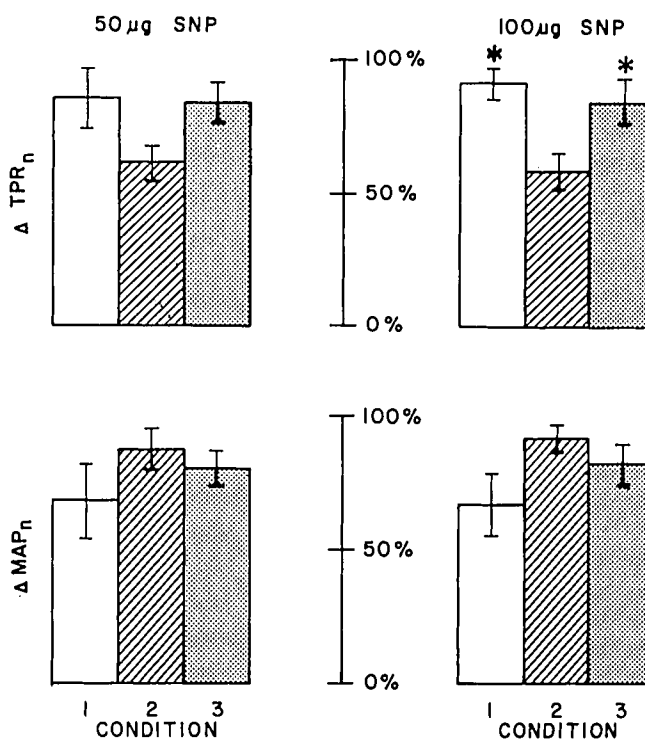


FIG. 5. Relative effectiveness (mean  $\pm$  SD) of SNP in decreasing TPR and MAP (expressed as  $\Delta TPR_n$  and  $\Delta MAP_n$ ) in three hemodynamic conditions caused by changes in phentolamine infusion in Experiment B. (Phentolamine, at 60–100  $\mu\text{g}/\text{min}$ , was infused in Condition 2. In all conditions, a 40  $\mu\text{g}/\text{min}$  phenylephrine infusion was maintained.) Asterisks indicate significant difference by Neuman-Keuls tests ( $P < 0.05$ ,  $N = 6$ ) from Condition 2. Differences between Conditions 1 and 3 were not significant.

was that the larger the background TPR, the more effective was SNP in reducing TPR. The positive correlation between the normalized TPR response and normalized TPR background was highly significant.

Unlike for the TPR response, there was no statistically significant relationship between the MAP response to SNP and the background infusion rate of either phentolamine or phenylephrine. The trend that existed was opposite that for the TPR response. There was a very weak correlation between normalized MAP response and normalized background TPR level, which was negative. The background MAP level was not a good predictor of the SNP-induced decrease in MAP either.

The inconsistent effect of background MAP on the MAP response is due to alterations in background cardiac output caused by phenylephrine and phentolamine and cardiac output changes caused by SNP injection. Because the relationship between  $\Delta MAP$  and  $\Delta TPR$  is complex (see "Appendix"), the effect of background vasomotor tone need not be the same on these two variables.

The CO response to SNP is determined by two direct effects of SNP, in addition to reflexive alterations. The

reduction in arterial resistance (relaxation of arterial vessels) has a tendency to increase CO, while the increase in venous capacitance (relaxation of veins) has a tendency to decrease CO. Whether the net effect is positive or negative is dependent not only on the preexisting arterial and venous tones but also on myocardial status. In our healthy animals when the vasomotor tone was not elevated by phenylephrine, CO generally decreased with SNP. This is in agreement with previous reports.<sup>9,10</sup> However, with heart failure, SNP may increase CO.<sup>10</sup> Thus, our results must be applied with caution to situations other than those described here.

The effects of some other alterations in physiologic state on the effectiveness of SNP have been described.<sup>3,11-14</sup> These alterations included changes in anesthesia, carotid sinus baroreceptor reflex, captopril pretreatment, and dobutamine levels. There do not seem to be other reports dealing with the effectiveness of SNP as a function of background TPR level.

Our findings may have clinical importance. In many situations, the effectiveness of SNP is judged by the MAP response. Although our data indicate that increasing the background MAP tends to diminish the effectiveness of SNP in decreasing arterial pressure, the variability of this relationship precludes an accurate prediction of the response to SNP as a function of background MAP. The large variability in MAP response is attributed to the unpredictability of the changes in CO under the influence of SNP. In cases, however, where CO is constant (cardiopulmonary bypass) or where autoregulatory changes in CO are unlikely to occur (low ventricular filling pressure), MAP becomes proportional to TPR. Under these conditions, our results showing a positive correlation between the TPR response and the background TPR level also indicate a similar correlation for MAP. This information might be helpful in predicting changes in the MAP response as a function of changes in the background level of the arterial pressure under halothane anesthesia.

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### Appendix

This Appendix gives a relationship between  $\Delta$ MAP and  $\Delta$ TPR when the cardiac output also is changed by SNP injection.

By definition,  $MAP = TPR \cdot CO$ . Assuming that injection of SNP causes small changes in these variables from a steady level of  $MAP_0$ ,  $TPR_0$ , and  $CO_0$ :

$$\Delta MAP = \Delta TPR \cdot CO_0 + \Delta CO \cdot TPR_0$$

where  $MAP = MAP_0 + \Delta MAP$ ,  $TPR = TPR_0 + \Delta TPR$  and  $CO = CO_0 + \Delta CO$ . As seen earlier, an increase in  $TPR_0$  is associated with an increased TPR response, *i.e.*, a more negative  $\Delta TPR$ . The increased  $\Delta TPR$ , however, does not necessarily cause an increased (more negative)  $\Delta MAP$  for two reasons. First, in the term  $\Delta TPR \cdot CO_0$  the background CO multiplies  $\Delta TPR$ , and, as table 1 shows,  $CO_0$  was less during those conditions when  $\Delta TPR$  was greater (*i.e.*, during increased TPR). Second, the term  $\Delta CO \cdot TPR_0$ , which is associated with the CO response to SNP, also contributes to the  $\Delta MAP$ . The sign of this term is dependent on whether  $\Delta CO$  is positive or negative. As may be seen in figure 1,  $\Delta CO$  can become more positive (or less negative) when  $TPR_0$  or  $MAP_0$  is increased, which makes the second term also more positive (or less negative). This reduces the MAP response, *i.e.*,  $\Delta MAP$  becomes less negative as  $TPR_0$  is increased.