# Comparative Cardiovascular Effects of SNP, ATP and Phentolamine during Norepinephrine-induced Hypertension in Dogs

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There has been no study comparing the advantage and disadvantage of various antihypertensive agents during surgery for pheochromocytomas because the study is difficult in clinical setting. In the present experiments using dogs, after increasing the arterial blood pressure with norepinephrine, we decreased it to the baseline with sodium nitroprusside (SNP), adenosine triphosphate (ATP), or phentolamine (PE) and compared the hemodynamic changes. A hyperdynamic state was found with ATP and with PE, but not with SNP. The norepinephrine-induced pulmonary hypertension could be successfully treated with SNP, but not with ATP or PE. The reason for these differences are thought to be the different vasodilative properties on peripheral arteries and veins. We conclude that agents that dilates the arteries and veins should be used to regulate the arterial pressure during surgical removal of a pheochromocytoma. (Key words: adenosine triphosphate, norepinephrine, phentolamine, sodium nitroprusside, pheochromocytoma)

(Murata K, Takahashi H, Ikeda K: Comparative cardiovascular effects of SNP, ATP and phentolamine during norepinephrine-induced hypertension in dogs. J Anesth 5: 396–403, 1991)

Blood-pressure control is one of the most crucial points in the management of anesthesia during surgery to remove a pheochromocytoma. Phentolamine (PE) and sodium nitroprusside (SNP) are most often used for this purpose, and afford good results[1]. Recently, there have been reports of satisfactory results obtained with the use of adenosine and adenosine triphosphate (ATP)[2–4]: these agents have a potent vasodilator action, and a rapid onset and disappearance of action. However, to date there has been no clinical evaluation of the relative merits of these vasodilators because this disease is rare and it is very difficult to perform a comparative study in clinical setting[1]. The question of which of these agents affords the best control of hypertension, from the standpoint of hemodynamic changes, during surgery to remove a pheochromocytoma has not been addressed. The object of the present experiments using dogs was to determine which of SNP, ATP or PE would afford the best blood-pressure control during surgical removal of a pheochromocytoma.

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J Anesth 5:396–403, 1991

## Methods

Twelve dogs of either sex weighing approximately 8 kg (7–10 kg) were anesthetized with intravenous pentobarbital (30 $mg \cdot kg^{-1}$) and then tracheas were intubated with cuffed endtracheal tubes. Anesthesia was maintained with enflurane (1% end-tidal) in oxygen. Ventilation was controlled with a

Harvard Respirator (Model 613, Harvard Apparatus). Tidal volume was 20 $ml \cdot kg^{-1}$, and the frequency of respiration was set to maintaine the end-tidal $CO_2$ at 4–5%. The expiratory gas was monitored with a mass spectrometer (Perkin Elmer MGA 1100). Heparin (1 $mg \cdot kg^{-1}$) was given intravenously before the insertion of the catheters to prevent the blood clotting. A venous catheter was inserted via the left external jugular vein for fluid maintenance (Lactate Ringer's solution, 7 $ml \cdot kg^{-1} \cdot hr^{-1}$) and administration of experimental drugs. A canula was inserted percutaneously through the right femoral artery for measurement of the mean arterial pressure (MAP) and sampling of the blood for blood gas analysis. A flow-directed balloon-tipped (Swan-Ganz) thermodilution catheter (93A-131H-7F, Edwards Laboratory, USA) was advanced via the right external jugular vein into the pulmonary artery for measurement of the mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) using a thermodilution technique (Cardiac Computer, 9520A Edwards Laboratory, USA). A transducer-tipped pressure-monitoring catheter (Model 110-4, 420XP, Camino Laboratory, USA) was also placed via the left carotid artery into the left ventricle of the heart for measurement of the left ventricular end-diastolic pressure (LVEDP) and the dp/dt/IP. The dp/dt/IP is the dp/dt max which is the peak value of the first derivative of the left ventricular pressure, divided by the instantaneous developed left ventricular pressure. MAP, MPAP, ECG, heart rate (HR), left ventricular pressure and dp/dt max were monitored and recorded on a multi-channel recorder (78342A Monitor, Hewlett Packard, USA; Carrier Amplifier Differentiator, 8-0411A, Nihon Kohden, Co., Japan; Linearcorder Type WR 3001, Watanabe Instruments Co., Japan). The systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated by conventional formulae.

After the preparation of each animal, one hour was allowed for stabilization before the start of the experimental protocol. The experiment was designed so that each animal received SNP, ATP and PE in sequence. The cross-over comparative study among the three drugs was made in the twelve dogs. And to minimize the effects of the sequence of drug administration, one hour was allowed for recovery between the drug infusion.

Blood gas analysis (ABL 2, Radiometer, Denmark) was performed before the measurement of the baseline values. When metabolic acidosis was present, the pH was corrected with sodium bicarbonate.

After the baseline measurements, norepinephrine (NE) infusion was started through the central venous catheter at the rate of 1 $mcg \cdot kg^{-1} \cdot min^{-1}$ with a micro-infusion pump (Model 102, Atom Co., Japan). NE infusion rate was titrated in 0.2 $mcg \cdot kg^{-1} \cdot min^{-1}$ increments or decrements until the systolic arterial pressure reached approximately 250 mmHg and remained at that level for 3 min. Then the hemodynamic data were obtained (Phase 1). Thereafter, an infusion of one of the three vasodilators was started at the rate of 2 $mcg \cdot kg^{-1} \cdot min^{-1}$ for SNP, 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ for ATP, and 10 $mcg \cdot kg^{-1} \cdot min^{-1}$ for PE. The dose was increased by increments of 2 $mcg \cdot kg^{-1} \cdot min^{-1}$ for SNP, 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ for ATP, and 10 $mcg \cdot kg^{-1} \cdot min^{-1}$ for PE every 2 min until the MAP returned to the baseline value. After the MAP had remained at the baseline level for 3 min, the hemodynamic data were again obtained (Phase 2). Five min elapsed after the simultaneous discontinuation of NE and the vasodilator, the hemodynamic data were determined once more (Phase 3).

All data were expressed as means ± SEM. Student's paired t-test was used to compare baseline values with those determined during the drug infusion. Analysis of variance and Student-Newmann-Keul test were used to compare the effects of the three vasodilators. Changes were considered significant when $P$ was less than 0.05.

## Results

The amount of NE administered, the doses of each vasodilator used and the baseline blood gas values are shown in table 1.

**Table 1.** Doses of norepinephrine, vasodilators, end-tidal concentrations of enflurane and blood gas data of baseline

| | SNP | ATP | PE |
|---|---|---|---|
| Dose of NE ($mcg \cdot kg^{-1} \cdot min^{-1}$) | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.1 ± 0.1 |
| Dose of Vasodilator | 6.5 ± 0.6 | 1.2 ± 0.2 | 42 ± 5 |
| SNP ($mcg \cdot kg^{-1} \cdot min^{-1}$) | | | |
| ATP ($mcg \cdot kg^{-1} \cdot min^{-1}$) | | | |
| PE ($mcg \cdot kg^{-1} \cdot min^{-1}$) | | | |
| ET enflurane (%) | 0.99 ± 0.02 | 0.99 ± 0.03 | 0.96 ± 0.02 |
| Blood gas data | | | |
| pH | 7.37 ± 0.01 | 7.36 ± 0.01 | 7.35 ± 0.01 |
| $P_{CO_2}$ (mmHg) | 36 ± 1 | 35 ± 1 | 35 ± 1 |
| $P_{O_2}$ (mmHg) | 376 ± 33 | 406 ± 32 | 381 ± 31 |
| $HCO_3$ ($mEq \cdot l^{-1}$) | 20 ± 1 | 19 ± 1 | 19 ± 1 |
| BE ($mEq \cdot l^{-1}$) | −4 ± 1 | −5 ± 1 | −5 ± 1 |

Values: means ± SEM. Abbreviations: SNP, sodium nitroprusside; ATP, adenosine triphosphate; PE, phentolamine; NE, norepinephrine; ET enflurane, end-tidal concentration of enflurane. There are no significant differences in the doses of NE, end-tidal concentrations of enflurane and blood gas data between in SNP, ATP and PE.

There were not any differences in the mean amount of NE administered and baseline blood gas values between the three experiments.

The hemodynamic values in the baseline and the three phases are shown in table 2. The hemodynamic values obtained in the baseline and phase 1 for each of the three drugs were not significantly different.

In phase 2, whereas the NE-increased MAP values were reduced to the baseline values similarly by the three vasodilators, several differences in the other hemodynamic values were caused by them. Significant increases in HR over the baseline value were observed with SNP and PE. However, no significant change in HR was found with ATP. ATP or PE decreased SVR significantly more than did SNP. CO and dp/dt/IP with ATP were significantly higher than those with SNP. The MPAP was significantly higher than the baseline value with ATP or PE, whereas it showed no significant change with SNP. In addition, the NE-induced increase in the MPAP did not decrease significantly with ATP. The LVEDP, PCWP, CVP and PVR did not differ significantly from the baseline values except for the PCWP with SNP.

In phase 3, there were no significant differences between the three agents.

## Discussion

The present study had several limitations to conclude the relative merits of the three vasodilators to control the blood pressure during the surgical removal of a pheochromocytoma because the dogs did not completely simulate patients with pheochromocytoma. However, we present new information relevant to the choice of antihypertensive agents during resection of pheochromocytoma.

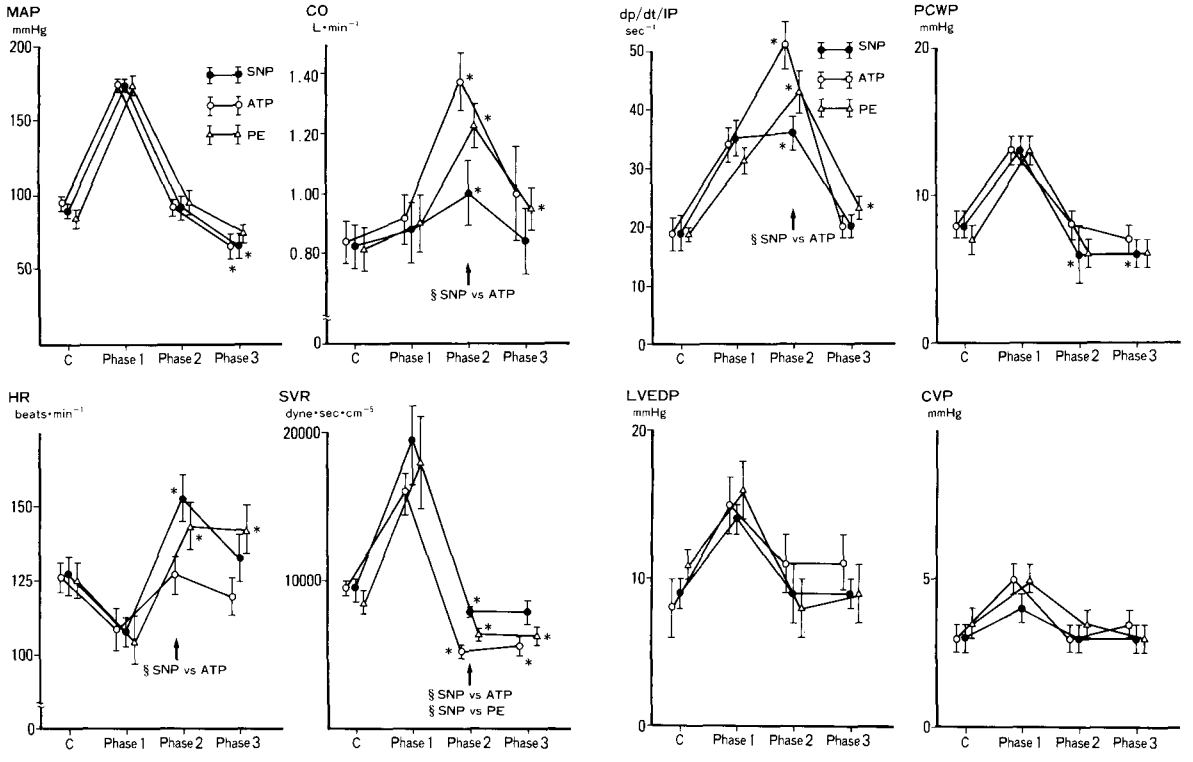
Several authors recommended SNP for the blood-pressure control during the surgery for pheochromocytoma because this drug has a potent vasodilative effects and extremely rapid onset and recovery times[1]. In the present study, we found other advantages of SNP over PE, or ATP.

First, in the systemic circulation, SNP returned hemodynamic state to the baseline values. When the arterial blood pressure was

**Table 2.** Cardiovascular responses after norepinephrine, norepinephrine + vasodilator infusion and five minutes after discontinuation of drugs

| | | Control | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|
| MAP | SNP | 89 ± 5 | 173 ± 3 | 92 ± 5 | 65 ± 6* |
| (mmHg) | ATP | 95 ± 5 | 174 ± 3 | 92 ± 4 | 67 ± 8* |
| | PE | 86 ± 6 | 176 ± 6 | 95 ± 6 | 75 ± 5 |
| HR | SNP | 127 ± 6 | 108 ± 6 | 153 ± 8*[a] | 133 ± 8 |
| (beat·min$^{-1}$) | ATP | 126 ± 5 | 109 ± 7 | 127 ± 6 | 120 ± 6 |
| | PE | 125 ± 8 | 105 ± 8 | 144 ± 8* | 143 ± 8* |
| CO | SNP | 0.82 ± 0.07 | 0.88 ± 0.11 | 1.01 ± 0.11*[a] | 0.84 ± 0.11 |
| (*l*·min$^{-1}$) | ATP | 0.84 ± 0.07 | 0.92 ± 0.08 | 1.37 ± 0.10* | 1.00 ± 0.16 |
| | PE | 0.81 ± 0.07 | 0.90 ± 0.10 | 1.23 ± 0.07* | 0.95 ± 0.07* |
| SVR | SNP | 9000 ± 720 | 19000 ± 2900 | 7900 ± 250*[a] | 6900 ± 840 |
| (dyne·sec·cm$^{-5}$) | ATP | 9100 ± 490 | 16000 ± 1400 | 5400 ± 320* | 5700 ± 690* |
| | PE | 8600 ± 640 | 18000 ± 3200 | 6400 ± 400*[b] | 6300 ± 460* |
| dp/dt/IP | SNP | 19 ± 2 | 35 ± 3 | 36 ± 3*[a] | 20 ± 2 |
| (sec$^{-1}$) | ATP | 19 ± 2 | 34 ± 3 | 51 ± 5* | 20 ± 2 |
| | PE | 19 ± 1 | 31 ± 2 | 43 ± 3* | 23 ± 2* |
| LVEDP | SNP | 9 ± 1 | 14 ± 1 | 9 ± 2 | 9 ± 1 |
| (mmHg) | ATP | 8 ± 2 | 15 ± 2 | 11 ± 2 | 11 ± 2 |
| | PE | 11 ± 1 | 16 ± 2 | 8 ± 2* | 9 ± 2 |
| PCWP | SNP | 8 ± 1 | 11 ± 1 | 6 ± 1* | 6 ± 1 |
| (mmHg) | ATP | 8 ± 1 | 11 ± 1 | 8 ± 1 | 7 ± 1 |
| | PE | 7 ± 1 | 11 ± 1 | 6 ± 1 | 6 ± 1 |
| CVP | SNP | 3 ± 1 | 4 ± 1 | 3 ± 1 | 3 ± 1 |
| (mmHg) | ATP | 3 ± 1 | 5 ± 1 | 3 ± 1 | 4 ± 1 |
| | PE | 4 ± 1 | 5 ± 1 | 4 ± 1 | 3 ± 1 |
| MPAP | SNP | 14 ± 1 | 18 ± 1 | 13 ± 1[a] | 12 ± 1* |
| (mmHg) | ATP | 14 ± 1 | 18 ± 1 | 17 ± 1* | 14 ± 1 |
| | PE | 14 ± 1 | 19 ± 1 | 16 ± 1*[b] | 14 ± 1 |
| PVR | SNP | 670 ± 87 | 810 ± 150 | 730 ± 120 | 690 ± 100 |
| (dyne·sec·cm$^{-5}$) | ATP | 680 ± 100 | 710 ± 95 | 590 ± 61 | 720 ± 110 |
| | PE | 840 ± 180 | 820 ± 180 | 670 ± 100 | 690 ± 120 |

Values; means ± SEM. Abbreviation: MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance; dp/dt/IP, dp/dt max of the left ventricular pressure divided by the instantaneous developed pressure of left ventricle; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; Phase 1, norepinephrine infusion; Phase 2, norepinephrine + vasodilator infusion; Phase 3, five minutes after discontinuation of the drugs; SNP, sodium nitroprusside; ATP, adenosine triphosphate; PE, phentolamine. *, $P < 0.05$ compared to control; a, $P < 0.05$ between in SNP and ATP; b, $P < 0.05$ between in SNP and PE.



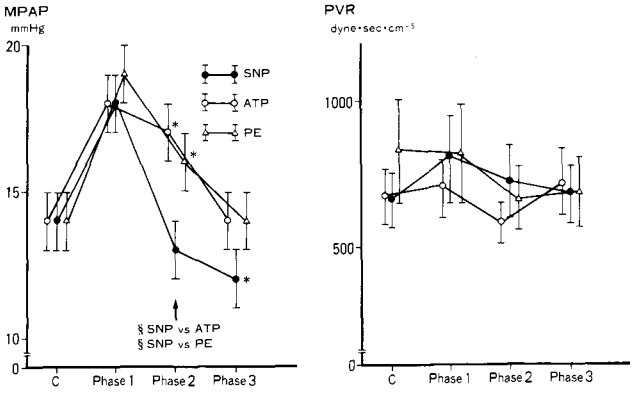




**Fig.** Cardiovascular Responses after Norepinephrine, Norepinephrine + Vasodilator, and Five Minutes after Discontinuation of the Drugs.

C, control; Phase 1, Norepinephrine infusion; Phase 2, Norepinephrine + Vasodilator infusion; Phase 3, five minutes after discontinuation of the drugs; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance; dp/dt/IP, dp/dt max in the left ventricular pressure divided by the instantaneous developed pressure of left ventricle; LVEDP, left ventricular end-diastolic pressure; CVP, central venous pressure; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; SNP, sodium nitroprusside; ATP, adenosine triphosphate; PE, phentolamine.

*$P < 0.05$ compared to baseline, \$$P < 0.05$ compared between SNP, ATP and PE.

reduced by SNP, CO and SVR values close to the base line values. On the other hand, CO was higher and SVR lower when ATP or PE was used, thus produced a hyperdynamic state. NE acts on the alpha-adrenergic receptors of peripheral blood vessels, causing vasoconstriction of both the veins (capacitance vessels) and arteries (resistance vessels), and produce a increased afterload and preload on the heart. SNP produces its antihypertensive effects by vasodilative effects on the vessels of both the venous and the arterial system[5–7]. ATP and PE, however, act primarily on the arterial system and are reported to have weak actions on the venous system[8–11]. Thus, in order to produce the same degree of reduction of blood pressure, a greater reduction of SVR is necessary when using ATP or PE than using SNP[12–13]. Furthermore, a state of increased cardiac output is believed to occur with ATP or PE not only because they do not reduce the preload on the heart, but also because they increased the dp/dt/IP. We thought that ATP or PE would be more likely to produce a hyperdynamic state than SNP when used to control the blood pressure during surgical removal of pheochromocytoma.

Second, in regard of pulmonary circulation, our results demonstrated that SNP treated effectively the NE-induced pulmonary hypertension. But both ATP and PE were difficult to treat that. Particularly with ATP, the NE-induced pulmonary hypertension was unchanged despite a return of the systemic blood pressure to the baseline. There were two possible explanations of this phenomenon. NE-induced pulmonary hypertension occured partially due to the displacement of blood from the systemic vascular system to the pulmonary vascular system by the vasoconstriction of systemic capacitance vessels[14]. Thus, neither ATP nor PE could attenuate the volume load on the pulmonary vascular systems because their dilating action on the capacitance blood vessels is weak. The aforementioned increase in pulmonary blood flow also results in pulmonary hypertension. Therefore, it is considered that ATP or PE can not effectively treated the NE-induced pulmonary hypertension during surgery for pheochromocytomas. It was reported that adenosine reduced the catecholamine-induced increase in MPAP effectively, but this response was slower at onset and required five to ten minutes to achieve the full effect when adenosine was used as the antihypertensive agent during pheochromocytoma removal[4]. Secondarily, it was considered that SNP inhibited effectively the pulmonary vasoconstriction induced by NE infusion, but ATP or PE did not. It is known that SNP dilated the pulmonary vasculature, especially in the conditions of enhanced pulmonary vasoconstriction[5,15]. PE also dilated pulmonary vasoconstriction induced by NE[16]. But ATP induced the pulmonary vasoconstriction[17].

On the other hand, we found advantages of ATP as an antihypertensive agent during surgery for pheochromocytoma. ATP did not make tachycardia in phase 2. ATP has several characteristics compared to other vasodilators. ATP and adenosine, known to act on the cardiac conduction system and to decrease HR with atrioventricular delay, are used to treat supraventricular tachyarrhythmias[18]. ATP has been also reported to inhibit the epinephrine-induced ventricular ectpies in experiments with animals[19]. In contrast, neither SNP or PE has been found to have a direct action on the heart. In the present study, tachycardia occurred when the arterial blood pressure was reduced by SNP or PE. The causes of the tachycardia were thought to be beta-adrenergic action of NE and disappearance of baroreceptor mediated reflex induced by the hypertension. When arterial blood pressure was reduced by ATP, however, its action on the cardiac conduction system inhibited the increase in HR induced by the beta-adrenergic action of NE. The use of ATP or adenosine for blood-pressure control during surgery to remove a pheochromocytoma is thought to offer the advantage of reducing the incidence of tachycardia: it has been reported that tachycardia was prevented to some extent when ATP was used to control the arterial blood pressure during surgical

removal of pheochromocytomas[2-3].

As part of hemodynamic control during surgery for pheochromocytoma, beta-adrenergic blocking agents are used to treat the life-threatening tachycardia or ventricular arrythmias. ATP is known to have negative chronotropic and inotropic effects on the myocardium *in vitro*[20]. But conflicting reports have appeared on the effects of ATP on myocardial contractil force. Sohn et al. reported that ATP inhibited ventricular arrythmia induced by epinephrine and antagonizedthe epinephrine-induced increase in HR[19]. However, in a experimental hypotension induced by ATP or SNP, Kien et al. reported that as compared to SNP, cardiac contractility was greater with ATP[12]. This is in contrast to the negative inotropic effects reported when adenine compounds were administered to isolated mammalian hearts. Sohn also reported that when ATP was administered to reduce an increase in blood pressure induced by infusion of epinephrine, the epinephrine-induced increase in the left ventricular dp/dt max was not inhibited by ATP. The findings of these reports are in accord with our results.

In consideration of the hemodynamic changes that may occur in the course of blood pressure management during surgery for pheochromocytoma. We concluded that agents must be used which dilates both systemic arteries and veins, and pulmonary vessels in order to offset the increased preload and afterload on the heart and the pulmonary hypertension caused by NE. Of the three vasodilators we tested, SNP appears to be the agent suited for a single use. ATP affords the advantage of preventing tachycardia, but it must be used in combination with an agent that has a vasodilative action on the venous system. PE must be also used in combination with a venodilative agent.

(A portion of this work was presented at the 37th meeting of Jpn Soc Anesthesiol. in 1990)

(Received Mar. 26, 1991, accepted for publication May 2, 1991)

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