Cardiovascular Effects of Hypotension Induced by Adenosine Triphosphate and Sodium Nitroprusside on Dogs with Denervated Hearts

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Department of Anesthesiology, Tottori University School of Medicine, Yonago 683 and *† Department of Anesthesiology, The University of Texas Medical School, Houston, Texas 77028, USA

HASHIMOTO, Y., RIGOR, B.M. and MORENO, J.A. Cardiovascular Effects of Hypotension Induced by Adenosine Triphosphate and Sodium Nitroprusside on Dogs with Denervated Hearts. Tohoku J, exp. Med., 1982, 138 (1), 27–37 — Adenosine triphosphate (ATP) and sodium nitroprusside (SNP) are administered to patients to induce and control hypotension during anesthesia. SNP is authorized for clinical use in USA and UK, and ATP is clinically used in other countries such as Japan. We investigated how these two drugs act on the cardiovascular systems of 20 dogs whose hearts had been denervated by a procedure we had devised. ATP (10 dogs) or SNP (10 dogs) was administered to reduce mean arterial pressure by 30% to 70% of control. Before, during and after induced hypotension, we measured major cardiovascular parameters. Hypotension induced by ATP was accompanied by significant decreases in mean pulmonary arterial pressure (p<0.001), central venous pressure (p<0.001), left ventricular end-diastolic pressure (p<0.001), total peripheral resistance (p<0.001), rate pressure product (p<0.001), total body oxygen consumption (p<0.05), and heart rate (p<0.001); all these variables returned normal within 30 min after ATP was stopped. Cardiac output did not change. During hypotension produced by SNP similar decreases were observed in mean pulmonary arterial pressure (p<0.01), central venous pressure (p<0.001), left ventricular end-diastolic pressure (p<0.01), total peripheral resistance (p<0.001), rate pressure product (p<0.001), and oxygen content difference between arterial and mixed venous blood (p<0.05), while heart rate (p<0.001) and cardiac output (p<0.05) were increased. Recoveries of heart rate and left ventricular end-diastolic pressure were not shown within 60 min after SNP had been stopped. Both ATP and SNP should act on the pacemaker tissue of the heart.

Adenosine triphosphate; sodium nitroprusside; denervated heart; induced hypotension; cardiovascular effects

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hypotension during general anesthesia in Japan (Tanaka 1975; Hashimoto et al. 1978; Maruno et al. 1978; Maruyama et al. 1978). Chaudry et al. (1974, 1977) have used ATP as an energy source for the treatment of shock. Sodium nitroprusside (SNP) has been widely used not only to produce controlled hypotension but also in the treatment of congestive heart failure (Miller et al. 1976) and hypertensive crisis (Page et al. 1955). ATP is clinically used in Japan but not in USA and SNP has been authorized for clinical use in USA but not in Japan yet.

This study is to compare cardiovascular changes arising from induced hypotension by ATP with those by SNP in dogs with denervated hearts (Hashimoto 1982) and was performed in attempt to clarify these mechanisms of direct action on the heart.

METHODS

Mongrel dogs weighing 10–19 kg were anesthetized with 40% alpha chloralose/urethane solution (1:5), 1 ml/kg administered intravenously. Muscle relaxation was produced with 2 mg/kg succinylcholine chloride and maintained with infusion of 100 mg/hr. Artificial ventilation was instituted with a Harvard respirator of 100% oxygen.

For sampling blood and monitoring blood pressure, a polyethylene catheter was inserted into the femoral artery and a Swan-Ganz catheter into the pulmonary artery, respectively. For infusing drugs, including ATP or SNP, and measuring central venous pressure, an indwelling catheter was inserted into each femoral vein. For measuring left ventricular end-diastolic pressure and dP/dt, a Millar Mikro-Tip catheter pressure transducer was inserted into the left ventricle through the right carotid artery.

In order to block sympathetic nerves to the heart, epidural catheters were inserted into T1-T2 and T4-T5 interspaces and used later for drug administration and electrical stimulation.

The dog was then placed in the supine position and electrocardiographic monitoring began. Rectal temperature was maintained at 38.5±0.5°C with a water circulating mattress. Body fluids were maintained with lactated Ringer’s solution infused intravenously at a rate of 6 ml/kg/hr throughout the experiment. Respiration was adjusted to maintain PaCO2 30–40 mmHg. Sodium bicarbonate was administered to maintain base excess of 0±5 mEq/liter.

After filling the catheter in the T1-T2 interspinous space with 4 ml of 0.9% saline, two electrodes of 125 μm diameter insulated stainless steel wires were introduced and connected to a Grass Model 48 electrical stimulator. Electrical stimuli of 40–100 Hz for 5 msec duration were adjusted in peak voltage between 2 and 10 V to produce a 10% increase in heart rate and blood pressure. Chemical sympathectomy was performed by injecting 4 ml of 0.25% bupivacaine through the epidural catheter in the T1-T2 interspinous space. Effectiveness of sympathectomy was verified 20 min later by the absence of changes in heart rate and mean arterial pressure by means of the repeated electrical stimulation (p<0.001). Both parameters recovered immediately after stimulation had been stopped. However, when electrical stimulation was administered 20 min after epidural anesthesia, heart rate or mean arterial pressure did not change even though the same pulse-stimuli were administered. The bilateral vagal nerves were exposed and sectioned, thus completing denervation of the heart.

Intravenous infusion of 0.3% ATP* in 5% glucose or 0.025% SNP† in 5% glucose was instituted, the rate being adjusted to maintain a steady 30% reduction in mean arterial pressure for 30 min. SNP solutions protected by aluminum foil were prepared immediately before use.

* ATP (disodium adenosine-5'-triphosphate); Adetphos®, Kowa, Japan.
† SNP (sodium nitroprusside dihydrate); Nipride®, Roche, USA.
Cardiovascular Effects of ATP and SNP

Heart rate, arterial systolic pressure, mean arterial pressure, mean pulmonary arterial pressure, left ventricular end-diastolic pressure, left ventricular dP/dt, central venous pressure, total body oxygen consumption (Warren spirometer), arterial and mixed venous blood gases (Corning 180), and hemoglobin and oxyhemoglobin concentrations (IL CO-Oxymeter) were measured before, during, 30 min and 60 min after induced hypotension.

Dependent variables were calculated from standard formulae as follows:

- Oxygen content = \((1.39 \times \text{Hb} \times \text{percent saturation} \times 1/100) + (0.0031 \times \text{PO}_2)\)
- Cardiac output (ml/min) = \(\frac{\text{VO}_2}{(\text{CaO}_2 - \text{CVO}_2) \times 100}\)
- Total peripheral resistance = \(\frac{(\text{MAP} - \text{CVP (mmHg)})/\text{cardiac output (l/min)}}{80}\)
- Rate pressure product = arterial systolic pressure \times heart rate

Statistical significances were evaluated by Student’s t-test for paired observations to compare each measurement during the course with control in the same dog and by using an unpaired Student’s t-test for unpaired data to compare the ATP group with the SNP one. All data are expressed as mean±s.e.

RESULTS

In the 10 dogs receiving ATP (3.07±0.45 mg/kg/min), a gradual decrease of the arterial pressure was produced and the goal of 30% reduction was maintained easily by small adjustments of the infusion rate.

In the 10 dogs receiving SNP (29.7±4.2 µg/kg/min), mean arterial pressure did not stabilize at the desired level within 5 min after the beginning of infusion. Furthermore, the arterial pressure did not return to control values within 30 min after induced hypotension, but remained at 83% of control values (\(p<0.01\)). Data from 6 other dogs were discarded because their mean arterial pressure did not reduce to desired level even with SNP in excess of 50 µg/kg/min.

Table 1 and Fig. 1 show changes in mean arterial pressure for both drugs during hypotension and recovery. Measurements of all these cardiovascular parameters during hypotension and recovery are represented in Table 2.

Changes in cardiovascular parameters in the ATP group

The following values significantly decreased during hypotension: heart rate (21%, \(p<0.001\)), mean pulmonary arterial pressure (13%, \(p<0.001\)), central venous pressure (19%, \(p<0.001\)), left ventricular end-diastolic pressure (30%, \(p<0.001\)),

### Table 1. Changes in mean arterial pressure with ATP and SNP

<table>
<thead>
<tr>
<th>Control measures</th>
<th>During hypotension</th>
<th>After hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 min</td>
<td>5.0 min</td>
</tr>
<tr>
<td><strong>ATP group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>155.5</td>
<td>±4.4</td>
<td>±3.2*</td>
</tr>
<tr>
<td><strong>SNP group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>157.5</td>
<td>±6.6</td>
<td>±5.6*</td>
</tr>
<tr>
<td><strong>Group comparisons</strong></td>
<td>‡</td>
<td>†</td>
</tr>
</tbody>
</table>

Mean±s.e. (mmHg).

* \(p<0.001\), † \(p<0.01\) (in differences between control and each stage).

‡ \(p<0.05\) (in differences between ATP and SNP groups).
Fig. 1. Changes in mean arterial pressure during and after hypotension induced by ATP and SNP. Symbols without brackets showing probabilities are for comparisons between control and the indicated stage for the same drug. Symbols in brackets showing probabilities are for comparisons between the ATP and SNP groups.

### TABLE 2. Cardiovascular measurements with hypotension induced by ATP and SNP

<table>
<thead>
<tr>
<th></th>
<th>Control measurements</th>
<th>During hypotension (percent of control) 0–30 min</th>
<th>After hypotension (percent of control) 30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td>ATP 192.6 ± 8.6 beats/min</td>
<td>88.5 ± 2.1*</td>
<td>97.3 ± 2.9</td>
<td>98.5 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>SNP 192.4 ± 9.2</td>
<td>117.0 ± 2.7*</td>
<td>115.0 ± 3.8†</td>
<td>113.4 ± 4.2†</td>
</tr>
<tr>
<td><strong>MPAP</strong></td>
<td>ATP 19.2 ± 1.4 mmHg</td>
<td>87.0 ± 1.3†</td>
<td>113.6 ± 10.0</td>
<td>116.8 ± 9.5</td>
</tr>
<tr>
<td></td>
<td>SNP 22.7 ± 1.3</td>
<td>93.0 ± 1.8†</td>
<td>103.5 ± 1.7</td>
<td>100.6 ± 1.6</td>
</tr>
<tr>
<td><strong>CVP</strong></td>
<td>ATP 8.3 ± 0.5 cmH2O</td>
<td>80.9 ± 3.8*</td>
<td>99.7 ± 2.2</td>
<td>101.4 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>SNP 9.7 ± 0.5</td>
<td>85.9 ± 1.8*</td>
<td>99.1 ± 3.0</td>
<td>98.8 ± 5.0</td>
</tr>
<tr>
<td><strong>LVEDP</strong></td>
<td>ATP 7.2 ± 0.9 mmHg</td>
<td>69.9 ± 3.0*</td>
<td>105.1 ± 8.2</td>
<td>113.0 ± 11.7</td>
</tr>
<tr>
<td></td>
<td>SNP 8.8 ± 1.3</td>
<td>43.5 ± 13.4†</td>
<td>47.9 ± 12.6†</td>
<td>59.1 ± 10.5†</td>
</tr>
<tr>
<td><strong>LV dp/dt</strong></td>
<td>ATP 2,600 ± 223 mmHg/sec</td>
<td>90.7 ± 6.0</td>
<td>93.3 ± 4.5</td>
<td>91.8 ± 5.8</td>
</tr>
<tr>
<td></td>
<td>SNP 2,640 ± 28</td>
<td>102.9 ± 7.6</td>
<td>101.7 ± 7.9</td>
<td>108.1 ± 5.3</td>
</tr>
<tr>
<td><strong>VO2</strong></td>
<td>ATP 110.5 ± 4.6 ml/min</td>
<td>93.0 ± 2.2†</td>
<td>97.2 ± 2.1</td>
<td>98.4 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>SNP 106.3 ± 7.7</td>
<td>93.5 ± 4.4</td>
<td>102.6 ± 2.0</td>
<td>104.3 ± 2.2</td>
</tr>
<tr>
<td><strong>CaO2-CO2</strong></td>
<td>ATP 4.9 ± 0.2 ml/100ml</td>
<td>91.7 ± 5.2</td>
<td>99.9 ± 4.7</td>
<td>99.3 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>SNP 5.8 ± 0.5</td>
<td>82.6 ± 5.6†</td>
<td>99.0 ± 6.2</td>
<td>104.6 ± 4.6</td>
</tr>
<tr>
<td><strong>CO</strong></td>
<td>ATP 2,316 ± 131 ml/min</td>
<td>102.8 ± 4.5</td>
<td>98.3 ± 2.6</td>
<td>100.7 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>SNP 1,903 ± 166</td>
<td>115.8 ± 5.5†</td>
<td>104.6 ± 5.4</td>
<td>101.2 ± 4.6</td>
</tr>
<tr>
<td><strong>TPR</strong></td>
<td>ATP 5,203 ± 24 dynes-sec-cm⁻²</td>
<td>67.9 ± 3.5*</td>
<td>100.6 ± 2.0</td>
<td>100.9 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>SNP 6,716 ± 560</td>
<td>61.3 ± 1.3*</td>
<td>82.0 ± 5.7†</td>
<td>93.5 ± 6.3</td>
</tr>
<tr>
<td><strong>RPP</strong></td>
<td>ATP 35,081 ± 1,904</td>
<td>67.9 ± 3.7*</td>
<td>95.1 ± 3.2</td>
<td>98.3 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>SNP 34,008 ± 2,100</td>
<td>87.1 ± 2.4*</td>
<td>99.5 ± 4.0</td>
<td>105.2 ± 5.0</td>
</tr>
</tbody>
</table>

Mean ± s.e.

* p<0.001, † p<0.01, ‡ p<0.05 (in differences between control and each stage).

Abbreviations: HR, heart rate; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; LVEDP, left ventricular end-diastolic pressure; LV dp/dt, maximal value of the rate of left ventricular pressure; VO2, total body oxygen consumption; CaO2-CO2, oxygen content difference between arterial and mixed venous blood; CO, cardiac output; TPR, total peripheral resistance; RPP, rate pressure product.
total body oxygen consumption (7%, p<0.05), total peripheral resistance (32%, p<0.001), and rate pressure product (32%, p<0.001). All of these recovered immediately after ATP infusion had been stopped. Left ventricular dP/dt, oxygen content difference between arterial and mixed venous blood, or cardiac output did not change significantly during or after hypotension.

Changes in cardiovascular parameters in the SNP group

The following increased during hypotension: heart rate (17%, p<0.001) and cardiac output (16%, p<0.05). Heart rate still remained high 30 min (+15%, p<0.01) and also 60 min (+13%, p<0.05) after hypotension. Cardiac output returned to control values 30 min after hypotension.

The followings decreased during hypotension: mean pulmonary arterial pressure (7%, p<0.001), left ventricular end-diastolic pressure (57%, p<0.01), oxygen content difference between arterial and mixed venous blood (17%, p<0.01), total peripheral resistance (39%, p<0.001), and rate pressure product (13%, p<0.001). Left ventricular end-diastolic pressure remained low 30 min (−52%, p<0.01) and 60 min (−41%, p<0.01) after the induced hypotension. Total peripheral resistance showed some recovery, but still was low (−18%, p<0.05) 30 min after hypotension.

No significant difference was regarded between control and recovery levels, and recovery took place 30 and 60 min after hypotension: mean pulmonary arterial pressure, oxygen content difference between arterial and mixed venous blood, and rate pressure product.

Left ventricular dP/dt or total body oxygen consumption did not change significantly during or after hypotension.

![Fig. 2. Changes in heart rate during and after hypotension induced by ATP and SNP. Otherwise similar to in Fig. 1.](image-url)
Comparison of the ATP and SNP

There were respectively significant differences between the ATP and SNP groups in heart rate during hypotension ($p<0.001$), 30 min after hypotension ($p<0.01$), and 60 min after hypotension ($p<0.05$, Fig. 2); in left ventricular end-diastolic pressure 30 min after hypotension ($p<0.01$) and 60 min after hypotension ($p<0.01$, Fig. 3); and in rate pressure product during hypotension ($p<0.05$, Fig. 4).
DISCUSSION

Since Berne (1963) proposed that adenosine is a metabolic regulator of coronary blood flow, Angelakos and Glassman (1965) have postulated that the cardiovascular effects of adenosine, AMP, ADP, and ATP probably are due to the adenosine moiety of the molecules and are not related to their contents of high energy phosphate bonds. Burnstock (1979) has proposed that purinergic nerve and purinergic receptor belong to the autonomic efferent nerve and receptor. On the other hand, investigations have been performed in which exogenous ATP is believed to have improved circulatory performances by yielding energy to cells. Circulatory parameters changed by ATP infusion and recovered within 30 min after stopping its infusion. The action of ATP is very transient because this substance may be rapidly metabolized by ATPase. As Kontos et al. (1978) described in the intravenous infusion in cats with undenervated heart, we could readily control the action of ATP in dogs with denervated heart. For the reason of its controllability, ATP has been clinically used for the induced hypotension in Japan.

Although SNP is widely accepted as a potent and short-acting hypotensive agent, we found it difficult to control arterial pressure with SNP in the dogs with denervated heart. Furthermore, 6 of our dogs required such excessive doses of SNP to approach the desired degree of hypotension that we excluded their data. We suspect that SNP may induce hypotension by affecting the autonomic nerves, in addition to direct vasodilating actions on the vascular smooth muscles because the denervation of the heart is likely to reduce its hypotensive action.

Heart rate

Emmelin and Feldberg (1948) speculated that the bradycardia in the canine heart produced by ATP results mainly from stimulation of afferent vagal fibers. On the other hand, James (1965) observed sinus bradycardia in dogs from direct perfusion of the sinus node with ATP. Sinus bradycardia and a first or second grade A-V block occurred during rapid infusion of 1% ATP through the catheter in the femoral vein reaching into the right atrium in our preparatory dog experiments (Hashimoto et al. 1978). In addition, we found that during hypotension with ATP heart rate decreased in dogs whose hearts had been denervated by our methods. This evidence suggests that ATP may act directly on the sinus node and conduction system of the heart.

The cause of tachycardia from SNP has not been elucidated. Schlant et al. (1962) proposed that arterial pressure lowered acutely with SNP causes tachycardia as a reflex response. In our experiments, SNP increased heart rate although autonomic reflex was ruled out by denervation of the heart. This is consistent with the suggestion by Adams et al. (1974) that SNP may act directly on the pacemaker tissue of the heart.
Cardiac output

In our experiments, cardiac output remained unchanged during ATP hypotension, but Rowe et al. (1962) reported an increase in cardiac output from adenine nucleotides in dogs.

Studies of SNP influence on cardiac output have shown various results. Rowe and Henderson (1974) reported that SNP increased cardiac output by 30% in anesthetized dogs with intact nerve and decreased total peripheral resistance, pulmonary vascular resistance, and right atrial pressure. These effects are similar to those reported in both anesthetized other animals (Ross and Cole 1973) and anesthetized humans (Wildsmith et al. 1973; Stone et al. 1976). On the other hand, more recent studies have shown that cardiac output in anesthetized animals decreased (Michenfelder and Theye 1977; Wang et al. 1977). In our study during SNP hypotension, cardiac output increased. We postulate that the increased heart rate probably contributed to this increase in cardiac output, in which total peripheral resistance decreased more than in mean arterial pressure in percentage (39% and 30%, respectively).

Preload, afterload, and Frank-Starling’s law

Preload is determined by intraventricular volume and afterload by systolic ventricular wall tension. In our study, we used left ventricular end-diastolic pressure as an index of preload; mean arterial pressure, total peripheral resistance, and left ventricular end-diastolic pressure were used as indices of afterload in combination. Preload and afterload decreased significantly during hypotension induced by both ATP and SNP.

Frank-Starling’s law relates the filling volume of the heart directly to the cardiac work of the corresponding ventricle. Therefore, we can say that the filling

Fig. 5. The effects of hypotension induced by ATP and SNP on the Frank-Starling curve. Otherwise similar to in Fig. 1.
volume of the heart is indicated by left ventricular end-diastolic pressure and cardiac work is indicated by cardiac output. In our experiments with SNP, the Frank-Starling curve moved up and leftwards during hypotension (Fig. 5). These results tend to support the use of SNP for patients with congestive heart failure (Miller et al. 1976) or hypertensive crisis (Page et al. 1955). During hypotension with ATP, the Frank-Starling curve moved to the left.

**Rate pressure product**

Gobel et al. (1978) showed that rate pressure product correlates well with myocardial oxygen consumption during exercise of patients with ischemic heart disease. In our experiments, rate pressure product decreased more during hypotension with ATP, due to the dramatic reduction in heart rate, than during SNP hypotension. So, we conclude that ATP may be useful for treatment of congestive heart failure or hypertensive crisis.

**Cardiac contractility**

Left ventricular dP/dt is used to indicate cardiac contractility and is affected by variations in preload, afterload, and heart rate. Adams et al. (1974) reported that left ventricular dP/dt is reduced by SNP in a dose-dependent manner. In our study, left ventricular dP/dt did not change significantly during and after hypotension, in either the ATP or the SNP group. It is speculated that cardiac contractility may have increased, which is indicated by the fact that left ventricular dP/dt did not change in spite of a decrease in heart rate, preload, and afterload.

**Mean pulmonary arterial pressure**

Mean pulmonary arterial pressure decreased during hypotension in both the ATP and the SNP groups. This may be due to a significant decrease in total peripheral resistance, including pulmonary vascular resistance, and ventricular end-diastolic pressure.

**Oxygen consumption**

During hypotension with ATP, total body oxygen consumption decreased. Since oxygen content difference between arterial and mixed venous blood remained unchanged, ATP might contribute in part to the body’s energy resources. Chaudry et al. (1974, 1977) stated that ATP administered exogenously entered into the cells and its beneficial effect appeared but not only through vasodilatation because more potent vasodilatory agents, such as ADP or AMP, failed to produce any beneficial effect.

During our studies of hypotension with SNP, oxygen content difference between arterial and mixed venous blood decreased, but total body oxygen consumption did not decrease significantly or metabolic acidosis did not occur. Our results are similar to those in previous studies of hypotension induced by SNP. (Stone et al.
That is, tissue hypoxia was not observed during or after hypotension. The decrease in oxygen content difference may be due to an increase in cardiac output. There is a fear of SNP to be toxic because of cyanmethemoglobinemia, CN⁻ binding to tissue cytochrome oxidase, and thiocyanate (Schubert and Brill 1968; Smith and Kruszyna 1974). On the other hand, ATP exists naturally in the human body. Therefore, ATP should be studied further to elucidate its mechanism and to establish its use as a therapeutic drug.

Acknowledgments

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References

15) Michenfelder, J.D. & Theye, R.A. (1977) Canine systemic and cerebral effects of
hypotension induced by hemorrhage, trimethaphan, halothane, or nitroprusside.  


