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# *Myocardial Hemodynamics during Induced Hypotension: A Comparison between Sodium Nitroprusside and Adenosine Triphosphate*

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**Adenosine triphosphate (ATP) has been reported to be a hypotensive agent similar in effect to sodium nitroprusside (SNP). The purpose of this study was to examine and compare the effects of both SNP and ATP on general coronary hemodynamics, myocardial $O_2$ consumption, and circulating catecholamines. Twelve dogs were anesthetized with 1.0% halothane and given either SNP or ATP by controlled infusion to reduce their systemic blood pressure by 50% for a 2-h period followed by a (blood pressure) recovery period. The ATP-induced hypotension was rapid, easily controlled, not accompanied by tachyphylaxis over the 120 min studied, and resulted in an increase in coronary sinus blood flow (CSBF), which plateaued at 260% above control. The increase in CSBF was almost immediate and remained at this elevated level for the duration of the induced hypotension. During the ATP-induced hypotension, there was no change in heart rate or circulating catecholamines. A 60% reduction in myocardial $O_2$ uptake was observed, presumably from the cardiac unloading. In contrast, SNP-induced hypotension required a marked increase in dose over time, did not significantly increase CSBF, did increase heart rate, and resulted in large increases in circulating plasma catecholamines. Neither agent affected cardiac output. ATP-induced hypotension resulted in no change in cardiac lactic acid uptake, while SNP caused lactic acid production, indicating possible cardiac ischemia or cyanide toxicity. (Key words: Anesthetic techniques: induced hypotension; ATP; nitroprusside. Heart: blood flow; metabolism. Sympathetic nervous system: catecholamines.)**

ADENOSINE TRIPHOSPHATE (ATP), adenosine, and other purine compounds are extremely potent coronary vasodilators and have been implicated in the physiologic regulation of coronary blood flow. Evidence to support a mediator role for adenosine and possibly ATP in local myocardial blood flow control comes from data that demonstrate their release during hypoxia and the potency that they exhibit as coronary vasodilators.[1–3]

ATP given by infusion has been reported to be an effective hypotensive agent that is like sodium nitroprusside (SNP) in that it is a rapid-acting direct vasodilator. In contrast to SNP, ATP seems to have few of the disadvantages of SNP, mainly resistance (high initial dose required), tachyphylaxis, and the associated cyanide toxicity.[4–6] During SNP-induced hypotension, release of both catecholamines and renin have been documented and are believed responsible for the resistance and tachyphylaxis. Clinically, beta-adrenergic receptor blockade has been used to combat the homeostatic reflex effects and renin release associated with SNP use and therefore reduce the SNP dose and toxicity.[7,8] Apparent advantages of ATP- over SNP-induced hypotension include lack of tachycardia, tachyphylaxis, and rebound hypertension,[9] suggesting little or no catecholamine release.

The purpose of this study was threefold: first, to examine and compare the coronary hemodynamics during SNP- and ATP-induced hypotension; second, to determine whether ATP might have a selective advantage over SNP by preferentially vasodilating the coronary vascular bed, thereby further increasing myocardial perfusion during induced hypotension; third, to determine change in the catecholamine release during ATP-induced hypotension and compare it with the release during SNP-induced hypotension.

## Methods

Anesthesia was induced in 12 healthy dogs (21.8 ± 0.9 kg) with intravenous sodium thiopental (15–20 mg/kg) followed by tracheal intubation. The animals were mechanically ventilated to maintain a normal $Pa_{CO_2}$. Halothane in oxygen was maintained at a concentration of 1.5% inspired throughout the instrumentation of the animals. Body temperature was maintained at 38.5 ± 0.5° C by means of a temperature-controlled water blanket. Blood pressure was measured through a femoral arterial cannula connected to a Hewlett Packard® pressure transducer. Cardiac output (CO) was measured by thermodilution with a Swan-Ganz®) catheter introduced through the left external jugular vein placed into the pulmonary artery, and connected to a Santa Barbara® cardiac output computer. A micromanometer-tipped catheter was placed in the left ventricle via the left carotid artery. A Webster®

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catheter[10] was placed into the ostium of the coronary sinus through the right external jugular vein under fluoroscopy (Philips® BU 20S). Its location was confirmed by injection of radioopaque medium (Conrad®). Coronary sinus blood flow (CSBF) was determined by the continuous infusion thermodilution method described by Ganz *et al.*[10]

Blood gases and *p*H were measured on an Instrumentation Laboratories® (Model 825) blood gas machine; blood oxygen contents were measured on a Lex $O_2$ Con-TL. End-tidal halothane and $P_{CO_2}$ were monitored continuously by a Perkin Elmer® Mass Spectrometer (Model 1100). Plasma catecholamines, norepinephrine (NE), and epinephrine (EPI) were measured by high-performance liquid chromatography with electrochemical detection.[11] Whole blood lactic acid was measured by the method of Marbach and Weil.[12]

After each animal was instrumented, the inspired $O_2$ was reduced to 40% in nitrogen and the end-tidal halothane concentration was adjusted to 1.0%. One hour was allowed for stabilization before the start of the experimental protocol. Blood samples were drawn from the pulmonary artery through the Swan-Ganz® catheter (to provide mixed venous samples), from the femoral arterial catheter, and from the coronary sinus catheter. Blood gases and $O_2$ content were determined on arterial and mixed venous blood samples.

Plasma catecholamine concentrations were determined in systemic arterial blood samples. Whole blood lactic acid was measured in both systemic arterial and coronary sinus samples. CSBF, blood gases, $O_2$ content ($C_{O_2}$), plasma catecholamines, and whole blood lactic acid were determined in duplicate; CO was determined in triplicate. The arithmetic mean was used where multiple determinations were made. Arterial blood pressure, heart rate (HR), central venous pressure (CVP), pulmonary arterial pressure, and left intraventricular pressure were recorded continuously on a Hewlett Packard® strip chart recorder (Model #7758). Coronary $O_2$ uptake (ml/min) was calculated by the following formula: (arterial − coronary sinus $O_2$ content [ml/dl]) × CSBF (dl/min). Coronary vascular resistance (CVR) (units = $mmHg \cdot min \cdot ml^{-1}$) was calculated by the following formula: (systemic diastolic pressure [mmHg] − coronary sinus outflow pressure [mmHg])/CSBF (ml/min). Cardiac lactic acid uptake (μmol/min) was calculated by the following formula: (systemic arterial lactic [μmol/ml] − coronary outflow lactic acid [μmol/ml]) × CSBF ml/min. Lactic acid extraction ratio was calculated by the following formula: (systemic arterial lactic [mol/ml] − coronary outflow lactic acid [mol/ml])/systemic arterial lactic (mol/ml) × 100.

SNP was obtained from the UCLA pharmacy at a concentration of 20 mg/ml and diluted to 4 mg/ml for infusion. Appropriate measures were taken to protect the SNP from light throughout its use. ATP (disodium salt) was obtained from Kyowa Hakko Kogyo Co., Ltd., in powder form and was freshly prepared each day by dissolving it in saline at a concentration of 200 mg/ml. The *p*H was adjusted from approximately 2.5 to 6.5 with NaOH (Sigma Analytical Grade) to ensure stability of the ATP in solution.

After control measurements, either SNP (N = 6) or ATP (N = 6) was given by continuous infusion at a rate sufficient to decrease the mean arterial blood pressure by 50%. Samples and measurements, as previously described, were taken at 5, 15, 30, 60, 90, and 120 min during the induced hypotension and at 15 and 30 min during recovery. Heparinized whole blood taken from a donor dog was administered in equal amounts to the volume of blood drawn for the samples.

Intragroup differences were statistically examined using analysis of variance for repeated measure followed by Bonferroni modified *t* test. Nonpaired *t* test was used to make intergroup comparisons. Linear regression and correlation analysis were used where indicated. $P < 0.05$ was considered to be significant. Values reported are means ± SEM.

## Results

### Systemic Effects

The control values of mean arterial blood pressure (MABP) and heart rate (HR) were not significantly different between the ATP and SNP groups (94 ± 4 and 97 ± 7 mmHg; 130 ± 5 and 128 ± 7 beats/min, respectively). Similar MABP was achieved in both groups during the 50% reduction throughout the 2-h controlled hypotensive period. This reduction required an infusion dose of 3.6 ± 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$ for ATP and a dose range of 19 ± 4 to 31 ± 3 $g \cdot kg^{-1} \cdot min^{-1}$ for SNP at 15 and 120 min, respectively (see tables 1 and 2). The infusion rate for SNP had to be increased over time to maintain the desired hypotension. Cardiac output was not significantly altered by the reduction in blood pressure by either agent (table 3). Heart rate in the SNP group was increased from initiation of the hypotensive period, attaining statistical significance from control at 30 min. It continued to increase through the 2-h period, reached a maximum of 28% above control at 120 min (fig. 1*A*), and returned to a level not significantly different from control within 15 min after the SNP infusion was discontinued. In contrast to SNP, ATP-induced hypotension resulted in no significant change in HR throughout the hypotensive period.

SNP-induced hypotension resulted in a significant increase in both plasma EPI and NE levels. In general, EPI increased more than NE and both increased with time (figs. 1*B* and *C*). In contrast, ATP-induced hypotension caused no significant changes in plasma NE or EPI levels throughout the course of the experiment.

TABLE 1. Effect of SNP-Induced Hypotension on Arterial, Coronary Sinus and Venous Parameters

| Dose | Control | SNP 15 Min 19.0 ± 4.1 | SNP 30 Min 21.7 ± 3.1 | SNP 60 Min 25.8 ± 2.4 | SNP 90 Min 28.9 ± 2.5* | SNP 120 Min 30.7 ± 3.8† | SNP Rec 15 Min | SNP Rec 30 Min |
|---|---|---|---|---|---|---|---|---|
| Arterial | | | | | | | | |
| *p*H | 7.33 ± 0.01 | 7.33 ± 0.01 | 7.32 ± 0.01 | 7.31 ± 0.01 | 7.31 ± 0.01 | 7.31 ± 0.01 | 7.31 ± 0.01 | 7.31 ± 0.01 |
| BE | −5.8 ± 0.3 | −6.4 ± 0.5 | −6.6 ± 0.6 | −6.7 ± 0.4 | −6.8 ± 0.5‡ | −7.5 ± 0.5‡ | −7.8 ± 0.4‡ | −7.4 ± 0.5 |
| $C_{O_2}$ | 17.0 ± 1.0 | 16.0 ± 1.0 | 16.0 ± 1.0 | 15.0 ± 1.0† | 15.0 ± 1.0† | 15.0 ± 1.0† | 15.0 ± 1.0† | 15.0 ± 1.0† |
| $P_{O_2}$ | 166.0 ± 12.0 | 154.0 ± 12.0 | 156.0 ± 12.0 | 158.0 ± 10.0 | 159.0 ± 10.0 | 160.0 ± 8.0† | 174.0 ± 5.0† | 175.0 ± 9.0† |
| $P_{CO_2}$ | 34.0 ± 2.0 | 34.0 ± 2.0 | 33.0 ± 1.0 | 33.0 ± 1.0 | 34.0 ± 2.0 | 33.0 ± 1.0 | 33.0 ± 1.0 | 32.0 ± 2.0 |
| LA | 1.2 ± 0.3 | 1.4 ± 0.3 | 1.3 ± 0.3 | 1.4 ± 0.3 | 1.4 ± 0.2 | 1.5 ± 0.4 | 1.4 ± 0.4 | 1.3 ± 0.3 |
| Coronary sinus | | | | | | | | |
| $C_{O_2}$ | 6.0 ± 1.0 | 7.0 ± 1.0‡ | 8.0 ± 1.0 | 10.0 ± 1.0* | 11.0 ± 1.0† | 10.9 ± 1.0† | 8.0 ± 2.0 | 7.0 ± 2.0 |
| $P_{O_2}$ | 33.0 ± 3.0 | 37.0 ± 5.0§ | 44.0 ± 5.0§ | 51.0 ± 5.0*·§ | 57.0 ± 5.0† | 58.0 ± 6.0† | 45.0 ± 7.0 | 42.0 ± 7.0 |
| LA | 0.5 ± 0.21 | 1.0 ± 0.2 | 1.2 ± 0.3 | 1.3 ± 0.3 | 1.6 ± 0.4 | 1.5 ± 0.4 | 1.2 ± 0.5 | 1.0 ± 0.3 |
| Venous | | | | | | | | |
| $C_{O_2}$ | 12.0 ± 2.0 | 9.0 ± 1.0 | 10.0 ± 1.0 | 10.0 ± 1.0 | 10.0 ± 1.0 | 11.0 ± 1.0 | 11.0 ± 1.0 | 12.0 ± 1.0 |
| $P_{O_2}$ | 55.0 ± 6.0 | 48.0 ± 5.0 | 51.0 ± 1.0 | 52.0 ± 4.0 | 55.0 ± 3.0 | 60.0 ± 6.0 | 62.0 ± 5.0 | 64.0 ± 6.0 |
| Lactic acid | | | | | | | | |
| Extration Ratio | 32.0 ± 9.0 | 23.0 ± 5.0 | 11.0 ± 3.0†·‡ | 9.0 ± 10.0† | −6.0 ± 5.0‡ | 0.0 ± 8.0†·‡ | 14.0 ± 13.0† | 20.0 ± 12.0 |
| Uptake | 24.0 ± 12.0 | 19.0 ± 8.0 | 7.0 ± 3.0 | 11.0 ± 8.3 | −20.0 ± 13.0*·‡ | −19.0 ± 12.0*·§ | 6.0 ± 8.0‡ | 16.0 ± 6.0 |

Base excess (BE) units = mEq/l; oxygen content ($C_{O_2}$) units = ml/dl; $P_{O_2}$ units = mmHg; $P_{CO_2}$ units = mmHg; lactic acid units = μmol/ml; extraction ratio = ((arterial conc. − venous conc.)/arterial conc.) × 100; uptake = μmol/min; dose = μg/kg/min.

Values are means ± SEM.

* $P < 0.05$ when compared with control.

† $P < 0.01$ when compared with control.

‡ $P < 0.05$ when ATP and SNP were compared at the same time periods.

§ $P < 0.01$ when ATP and SNP were compared at the same time periods.

TABLE 2. Effect of ATP-Induced Hypotension on Arterial, Coronary Sinus, and Venous Parameters

| Dose | Control | ATP 15 Min 3.4 ± 0.8 | ATP 30 Min 3.5 ± 0.7 | ATP 60 Min 3.4 ± 0.8 | ATP 90 Min 3.7 ± 0.9 | ATP 120 Min 3.9 ± 0.8 | ATP Rec 15 Min | ATP Rec 30 Min |
|---|---|---|---|---|---|---|---|---|
| Arterial | | | | | | | | |
| *p*H | 7.36 ± 0.01 | 7.34 ± 0.02 | 7.34 ± 0.03 | 7.34 ± 0.02 | 7.33 ± 0.02 | 7.31 ± 0.02 | 7.29 ± 0.01 | 7.32 ± 0.02 |
| BE | −5.7 ± 0.5 | −6.7 ± 0.02 | −7.1 ± 0.2 | −7.9 ± 0.4* | −8.6 ± 0.4†‡ | −9.3 ± 0.5†‡ | −9.4 ± 0.5†‡ | −7.6 ± 1.1 |
| $C_{O_2}$ | 15.0 ± 2.0 | 14.0 ± 1.0 | 14.0 ± 1.0 | 14.0 ± 1.0 | 14.0 ± 2.0 | 14.0 ± 2.0 | 14.0 ± 1.0 | 14.0 ± 1.0 |
| $P_{O_2}$ | 178.0 ± 7.0 | 181.0 ± 7.0 | 183.0 ± 6.0 | 181.0 ± 8.0 | 178.0 ± 9.0 | 177.0 ± 8.0 | 168.0 ± 9.0 | 170.0 ± 10.0 |
| $P_{CO_2}$ | 33.0 ± 1.0 | 33.0 ± 1.0 | 32.0 ± 1.0 | 31.0 ± 1.0 | 31.0 ± 1.0 | 32.0 ± 1.0 | 34.0 ± 1.0 | 34.0 ± 2.0 |
| LA | 1.5 ± 0.1 | 1.4 ± 0.1 | 1.4 ± 0.1 | 1.3 ± 0.2 | 1.2 ± 0.2† | 1.2 ± 0.1† | 1.0 ± 0.1† | 0.9 ± 0.1† |
| Coronary sinus | | | | | | | | |
| $C_{O_2}$ | 5.0 ± 1.0 | 12.0 ± 2.0†‡ | 12.0 ± 2.0† | 12.0 ± 2.0† | 13.0 ± 2.0† | 13.0 ± 2.0† | 7.0 ± 2.0 | 7.0 ± 2.0 |
| $P_{O_2}$ | 28.0 ± 1.0 | 64.0 ± 4.0†§ | 66.0 ± 4.0†§ | 67.0 ± 4.0†§ | 68.0 ± 5.0† | 67.0 ± 3.0† | 39.0 ± 4.0 | 37.0 ± 4.0 |
| LA | 0.7 ± 0.1 | 1.2 ± 0.1† | 1.1 ± 0.1† | 1.0 ± 0.1† | 1.0 ± 0.1† | 1.0 ± 0.1† | 0.6 ± 0.05 | 0.6 ± 0.05 |
| Venous | | | | | | | | |
| $C_{O_2}$ | 11.0 ± 1.0 | 10.0 ± 1.0 | 10.0 ± 1.0 | 11.0 ± 1.0 | 12.0 ± 2.0 | 12.0 ± 2.0 | 11.0 ± 1.0 | 11.0 ± 1.0 |
| $P_{O_2}$ | 50.0 ± 2.0 | 49.0 ± 2.0 | 55.0 ± 3.0 | 61.0 ± 5.0* | 64.0 ± 5.0† | 70.0 ± 5.0† | 63.0 ± 4.0† | 64.0 ± 3.0† |
| Lactic acid | | | | | | | | |
| Extraction Ratio | 53.0 ± 2.0 | 17.0 ± 5.0† | 23.0 ± 6.0† | 20.0 ± 11.0*‡ | 12.0 ± 3.0† | 21.0 ± 3.0†‡ | 42.0 ± 4.0 | 29.0 ± 6.0* |
| Uptake | 60.0 ± 15.0 | 32.0 ± 6.0 | 60.0 ± 23.0 | 36.0 ± 15.0 | 23.0 ± 2.0‡ | 43.0 ± 5.0§ | 33.0 ± 4.0‡ | 24 ± 3.0 |

Base excess (BE) units = mEq/l; oxygen content ($C_{O_2}$) units = ml/dl; $P_{O_2}$ units = mmHg; $P_{CO_2}$ units = mmHg; lactic acid units = μmol/ml; extraction ratio = ((arterial conc. − venous conc.)/arterial conc.) × 100; uptake = μmol/min; dose = $mg \cdot kg^{-1} \cdot min^{-1}$.

Values are means ± SEM.

* $P < 0.05$ when compared with control.

† $P < 0.01$ when compared with control.

‡ $P < 0.05$ when ATP and SNP groups were compared at the same time periods.

§ $P < 0.01$ when ATP and SNP groups were compared at the same time periods.

TABLE 3. Effect of ATP- and SNP-Induced Hypotension on Hemodynamic Parameters

| | Control | 15 Min | 30 Min | 60 Min | 90 Min | 120 Min | Rec 15 Min | Rec 30 Min |
|---|---|---|---|---|---|---|---|---|
| ATP | | | | | | | | |
| MAP | 94.0 ± 4.0 | 48.0 ± 4.0† | 47.0 ± 1.0† | 51.0 ± 2.0† | 53.0 ± 1.0† | 53.0 ± 1.0† | 98.0 ± 5.0 | 99.0 ± 4.0 |
| CSBF | 61.0 ± 8.0 | 168.0 ± 28.0†§ | 191.0 ± 35.0†§ | 187.0 ± 34.0† | 190.0 ± 27.0† | 193.0 ± 28.0† | 75.0 ± 7.0 | 74.0 ± 7.0 |
| CO | 2.7 ± 0.1 | 2.9 ± 0.1 | 3.1 ± 0.2 | 3.5 ± 0.4 | 3.3 ± 0.4 | 3.5 ± 0.4 | 2.9 ± 0.2 | 2.9 ± 0.2 |
| HR | 130.0 ± 5.0 | 120.0 ± 10.0 | 121.0 ± 9.0‡ | 125.0 ± 10.0§ | 124.0 ± 9.0§ | 123.0 ± 9.0 | 129.0 ± 8.0§ | 128.0 ± 7.0 |
| SV | 21.6 ± 1.1 | 26.4 ± 0.7† | 27.6 ± 1.0† | 30.4 ± 2.3* | 28.4 ± 2.3* | 30.2 ± 2.8* | 23.2 ± 0.6 | 23.6 ± 0.8 |
| LVEDP | 6.5 ± 1.9 | 4.5 ± 1.9 | 4.7 ± 2.6 | 4.8 ± 2.4 | 6.0 ± 2.0 | 5.7 ± 2.0 | 8.5 ± 2.1 | 7.2 ± 2.3 |
| dP/dt | 1,785 ± 195 | 1,455 ± 143† | 1,402 ± 129† | 1,394 ± 145† | 1,438 ± 155† | 1,340 ± 198† | 1,508 ± 172 | 1,534 ± 136 |
| SNP | | | | | | | | |
| MAP | 99.0 ± 4.0 | 50.0 ± 2.0† | 51.0 ± 4.0† | 53.0 ± 3.0† | 53.0 ± 2.0† | 56.0 ± 3.0† | 83.0 ± 6.0 | 89.0 ± 6.0 |
| CSBF | 54.0 ± 5.0 | 56.0 ± 17.0§ | 57.0 ± 15.0§ | 105.0 ± 24.0 | 129.0 ± 30.0 | 145.0 ± 38.0 | 122.0 ± 48.0 | 106.0 ± 41.0 |
| CO | 2.8 ± 0.2 | 2.7 ± 0.4 | 2.9 ± 0.4 | 3.3 ± 0.5 | 3.3 ± 0.5 | 3.8 ± 0.6 | 3.4 ± 0.5 | 3.1 ± 0.5 |
| HR | 128.0 ± 7.0 | 137.0 ± 10.0 | 145.0 ± 9.0*‡ | 155.0 ± 8.0†§ | 160.0 ± 8.0†§ | 164.0 ± 7.0†§ | 133.0 ± 9.0 | 127.0 ± 9.0 |
| SV | 23.2 ± 0.7 | 28.2 ± 3.0 | 28.4 ± 1.6 | 29.6 ± 2.2 | 28.3 ± 2.7 | 31.5 ± 0.5 | 28.0 ± 2.0 | 26.4 ± 1.5 |
| LVEDP | 6.2 ± 1.8 | 1.3 ± 2.4† | 3.3 ± 2.8 | 2.7 ± 2.9 | 1.3 ± 2.8 | 2.0 ± 3.5 | 4.2 ± 2.0 | 5.3 ± 2.1 |
| dP/dt | 1,515 ± 143 | 1,489 ± 126 | 1,550 ± 189 | 1,961 ± 295 | 2,331 ± 395†‡ | 2,459 ± 773* | 1,996 ± 366 | 1,752 ± 314 |

Values are means ± SEM.

Mean arterial blood pressure (MAP) units = mmHg; coronary sinus blood flow (CSBF) units = ml/min; cardiac output (CO) units = l/min; heart rate (HR) units = beats/min; stroke volume (SV) units = ml/min; left ventricular end-diastolic pressure (LVEDP) units = mmHg; dP/dt units = mmHg/s.

* $P < 0.05$ when compared with control.

† $P < 0.01$ when compared with control.

‡ $P < 0.05$ when ATP and SNP groups were compared at the same time periods.

§ $P < 0.01$ when ATP and SNP groups were compared at the same time periods.

Arterial *p*H or $P_{CO_2}$ for both groups did not change significantly over the period studied, although base excess (BE) changed in the ATP group (tables 1 and 2). In the SNP group, a slight but significant reduction in $Ca_{O_2}$ was found with a concomitant slight reduction in arterial $P_{O_2}$ late during the induced hypotension followed by a significant increase over control during the recovery period. In contrast, the ATP group showed no significant reduction in $Ca_{O_2}$ and $P_{O_2}$ (tables 1 and 2). Venous $P_{O_2}$ increased significantly in the ATP group between 60 min and throughout the recovery period, whereas no similar change was found in the SNP group.

## CARDIAC EFFECTS

*Coronary Sinus Blood Flow.* CSBF (fig. 2*A*) was increased significantly after 15 min of ATP-induced hypotension, plateaued at approximately 260% of control at 30 min, and remained there until the infusion was terminated 120 min later, whereupon CSBF returned to levels not significantly different from control within 5 min. SNP did not significantly change CSBF, although some increase occurred over time. The dose of SNP (table 1) to maintain the desired level of hypotension (see above) and CSBF increased over time (fig. 2*A*).

*Coronary Vascular Resistance.* CVR decreased to 18% of control in less than 5 min after starting the ATP infusion and stayed at less than 10% of control throughout the duration of the hypotensive period (fig. 2*B*). Changes in CVR during SNP-induced hypotension were both slower in onset and quantitatively less compared with ATP changes during the initial 30 min (fig. 2*B*). Thereafter, CVR decreased significantly to about 40% of control by 60 min and remained near this level until the SNP infusion was terminated. Within 5 min after termination of hypotension, CVR returned to near control levels for both the SNP and ATP groups.

*Myocardial $O_2$ Uptake.* The effect of coronary sinus $O_2$ content ($Ccs_{O_2}$) and $P_{O_2}$ paralleled the changes in CSBF, showing a rapid increase plateauing by 15 min in the ATP group (table 2). In the SNP group $Ccs_{O_2}$ and $P_{O_2}$ increased more slowly, also paralleling the CSBF changes (table 1).

During the infusion of both ATP and SNP, the myocardial $O_2$ uptake was reduced (fig. 2*C*). SNP reduced $O_2$ uptake by 37% within 5 min while ATP reduced $O_2$ uptake by 54% at 5 min. The maximum effect of SNP was a 49% reduction at 30 min, while the maximum effect for ATP was 60% reduction at 90 min (fig. 2*C*).

In the SNP group, a significant increase in both $Ccs_{O_2}$ and $P_{O_2}$ was found in the coronary sinus outflow between 60 and 120 min during induced hypotension. In the ATP group an immediate and significant increase was found in both $Ccs_{O_2}$ and $P_{O_2}$ throughout the induced hypotension but returned to control during the recovery period.

*Lactic Acid.* Lactic acid (LA) uptake was found not to change significantly from control during and after ATP-induced hypotension, however, LA extraction ratio did decrease between 30 and 120 min (fig. 3 and table 2). In contrast, during the SNP-induced hypotension, LA uptake converted to LA production (different from control, $P < 0.05$) at 90 and 120 min. LA extraction ratio decreased significantly between 30 and 15 min after SNP infusion, dropping to zero or below at 90 and 120 min (fig. 3 and table 1).

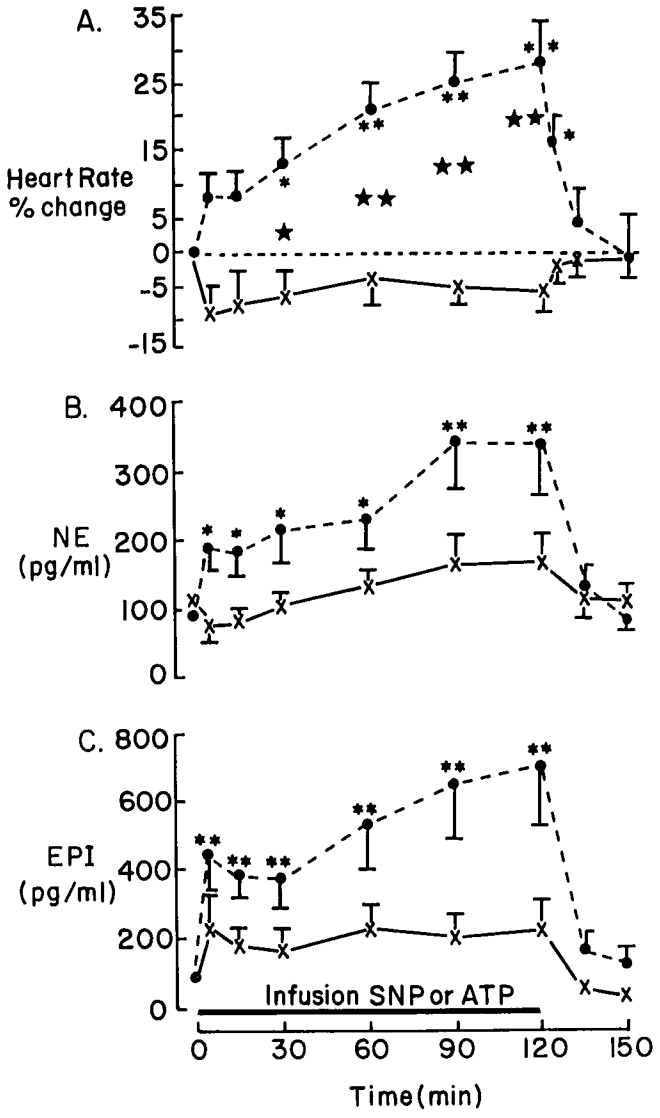


FIG. 1. Heart rate, norepinephrine (NE), and epinephrine (EPI) are plotted as mean values ± SE where time zero represents control, 5–120 min values show responses during the induced hypotension. * and ** = $P < 0.05$ and $P < 0.01$, respectively, when compared with control. ★ and ★★ = $P < 0.05$ and $P < 0.01$, respectively, when compared between ATP (×) and SNP (●) at the same time period.

*Cardiac Contractility.* Cardiac contractility as measured by left ventricular maximal dP/dt was found to *increase* significantly in the SNP group and *decrease* significantly in the ATP group (table 3). Once again these effects happened early on in the ATP-treated dogs, while the SNP-induced effects occurred late. Stroke volume (SV) increased consistently in the ATP group with no change in left ventricular end-diastolic pressure (LVEDP), while in the SNP group there was no change in the SV and a decrease in the LVEDP (table 3).

## Discussion

The utilization of SNP to produce controlled hypotension has been associated with many problems, ranging from catecholamine release and tachycardia to cyanide toxicity and acidosis. The need for a better agent is apparent. The adenosine-related compounds have been shown to be promising in particular with regard to their potent coronary vasodilating ability and, second, their ability to produce hypotension without tachycardia. ATP and adenosine have been successfully used both clinically[13,14] and in laboratory animals to produce deliberate hypotension. Both agents are equally effective for this purpose, have virtually identical hemodynamic effects,

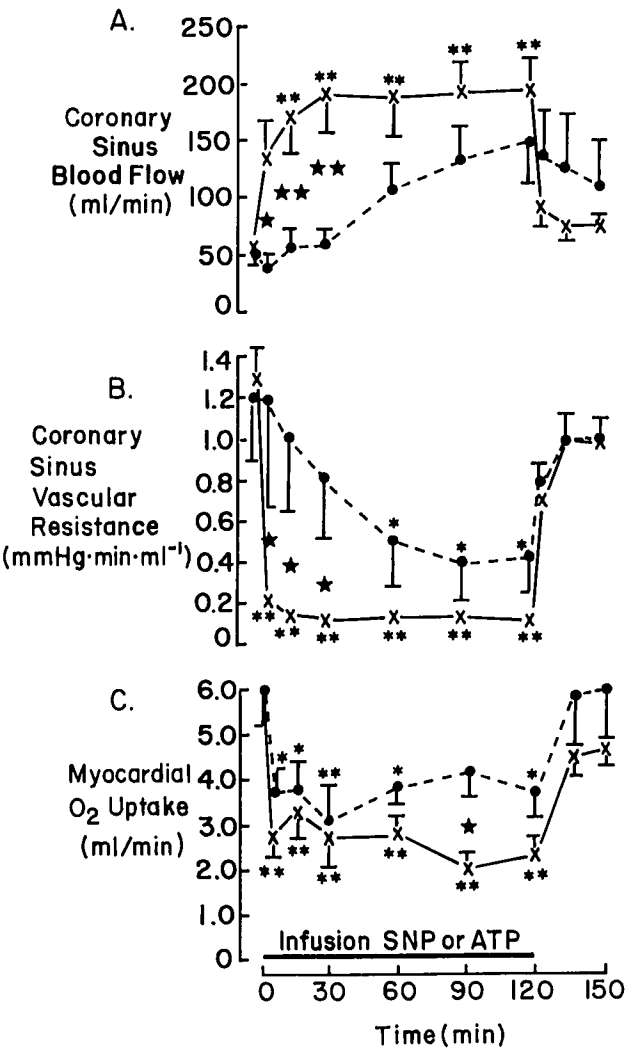


FIG. 2. Mean values ± SE where time zero represents control, 5–120 min values show responses during the induced hypotension. * and ** = $P < 0.05$ and $P < 0.01$, respectively, when compared with control. ★ and ★★ = $P < 0.05$ and $P < 0.01$, respectively, when compared between ATP (×) and SNP (●) at the same time period.

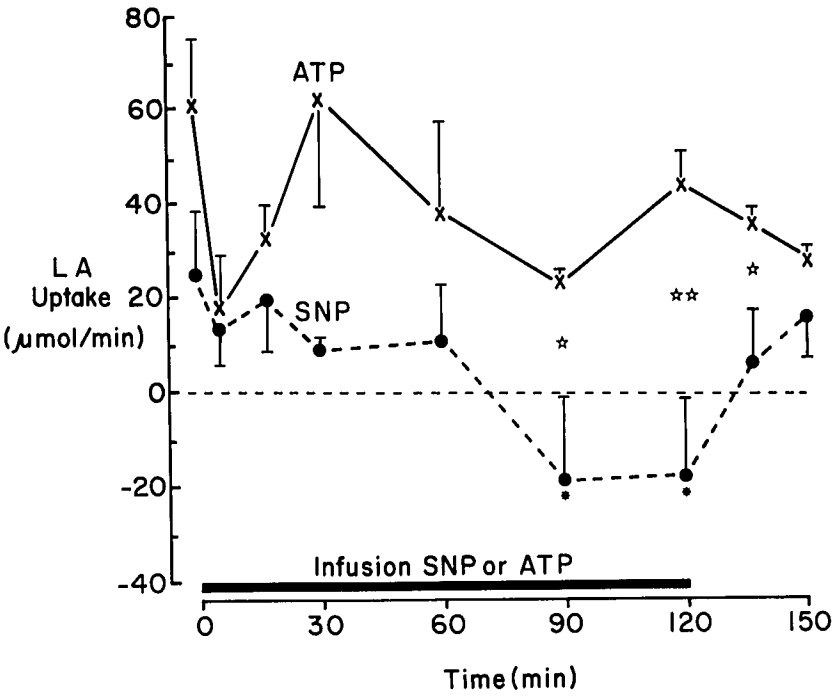


FIG. 3. Myocardial lactic acid uptake (above zero) and production (below zero) before, during, and after either SNP- or ATP-induced hypotension. * and ** = $P < 0.05$ and $P < 0.01$, respectively, when compared with control. ★ and ★★ = $P < 0.05$ and $P < 0.01$, respectively, when compared between ATP and SNP at the same time period.

and are approximately equipotent (on a molar basis). ATP when infused systemically is rapidly metabolized to adenosine, making adenosine the likely active metabolite when ATP is used in this fashion. ATP, being 20–25 times more soluble on a molar basis than adenosine, was used in these experiments because it allowed the preparation of a solution, similar in potency to SNP, a solution concentrated enough that the required infusion volumes would be similar with both agents.

The "safe" maximal dosage of SNP in the human has been reported to be between 3.0 and 3.5 mg/kg,[15,16] with an even lower value in dogs.[17] The mean total amount of SNP used over the 120-min induced hypotension was 3.3 mg/kg, indicating that the possibility of cyanide toxicity must be considered. Nonspecific laboratory tests have been suggested to be the best indicators of cyanide toxicity. These tests include systemic acidosis and increased blood lactate levels.[18,19] Systemic acidosis did not occur in any animals during the experiments. Our control arterial blood lactate levels were lower than those found by Michenfelder[17] and were closer to those reported by Vobel et al.[20] Michenfelder demonstrated an elevation in lactate levels in conjunction with SNP toxicity; no quantitatively similar elevation in lactate levels was found during or after SNP-induced hypotension in the present study. This would suggest that SNP toxicity was not present in this study.

Marked differences were observed in the present study between SNP- and ATP-induced hypotension. In spite of a lowered perfusion pressure (about a 50% reduction), CSBF during ATP infusion was significantly increased at 15 min and plateaued at a level 260% of control. There was a delayed increase in CSBF in response to the SNP infusion that never reached statistical significance. This indicates that ATP was a more potent coronary vasodilator than SNP under these conditions.

The rapid large increase in CSBF during the ATP infusion, despite the lowered perfusion pressure, is consistent with many reports that adenine compounds are capable of profound coronary dilation.[21,22] The decrease in CVR for ATP was nearly immediate, while in the SNP group the decrease was gradual. Coronary $P_{O_2}$ and $Ccs_{O_2}$ also were increased markedly and rapidly, and this change was followed by a stable plateau in the ATP group. These effects on $P_{O_2}$ and $Ccs_{O_2}$ closely paralleled the effects seen on CSBF previously discussed.

Hypotension is the stimulus that activates the baroreceptor-mediated homeostatic reflex system. Thus, SNP-induced hypotension frequently is accompanied by tachycardia mediated by this system.[7,8,23,24] In the present experiments, significant increases in HR and circulating catecholamines, NE and EPI, were observed during the SNP-induced but not ATP-induced hypotension. This difference is likely to be responsible for the differences in myocardial $O_2$ uptake (see below). The coronary bed is known to have alpha- and beta-adrenergic receptors that respond to both neuronal and humoral activation. Further, beta-adrenergic stimulation of the myocardium re-

sults in both increased heart rate and contractility (with associated $O_2$ uptake). An increase in dP/dt was found in the SNP group (table 3), as should be expected from the demonstrated increase in catecholamines. The ATP group had neither an increase in catecholamines nor an increase in dP/dt or HR (fig. 1*A, B,* and *C;* table 3).

Several authors[25-28] have shown that adenosine and ATP act presynaptically to inhibit sympathetic transmitter release. This was confirmed by here by the observation that ATP-induced hypotension did not result in increased plasma NE.

A reduction in myocardial $O_2$ uptake was seen with both agents. The main reason for this is the reduced external work load during hypotension. The only time at which the ATP effect was significantly greater was at 90 min. This difference is consistent with the lower heart rate and contractility and the lower catecholamine levels seen in this group in comparison with the SNP-treated group. Reduction in myocardial $O_2$ consumption while cardiac output is maintained may be beneficial. Further, ATP- but not SNP-induced hypotension resulted in continued LA uptake by the myocardium, indicating a general state of aerobic metabolism, while during SNP-induced hypotension LA production was transiently seen (as indicated by both the negative LA extraction ratio and LA uptake), suggesting possibly an insufficient oxygen supply and anaerobic metabolism. The decrease in LA extraction ratio in the ATP-treated group is probably due solely to the large increase in CSBF and is not a result of a change in myocardial metabolism. This demonstrates a potential weakness in LA extraction ratios when CSBF increases considerably.

There are several limitations to the present study. We did not study a range of coronary perfusion pressures and therefore the relationship between pressure and coronary flow was not determined. We therefore do not know at what pressure the maximal CSBF occurs nor can we project the lower limits to which diastolic blood pressure may be dropped without compromising myocardial perfusion. The large increase in CSBF with ATP could be due in part to nonnutritious perfusion. This question has been studied in dogs using continuously infused intracoronary adenosine and was found *not* to be the case.[29] In this study the effects demonstrated were on normal myocardium. Nevertheless, it is possible that under certain pathologic conditions the vasodilation demonstrated could result in steal from poorly perfused myocardial tissue. Under the conditions studied, ATP-induced hypotension provided a different hemodynamic profile when compared with SNP. Using ATP to decrease blood pressure (50%) resulted in the following: 1) a rapid substantial increase in CSBF (260% above control) with no change in heart rate, CO, or circulating catecholamines; 2) a 60% reduction in myocardial $O_2$ consumption; and 3) continued aerobic metabolism as indicated by LA levels. Certainly ATP warrants further study.

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