

## Controlled Hypotension with Adenosine in Cerebral Aneurysm Surgery

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The cardiovascular effects of adenosine-induced controlled hypotension were studied in 10 patients undergoing cerebral aneurysm surgery. Adenosine and its metabolites were measured in arterial plasma using high-pressure liquid chromatography. Whole body and cerebral arteriovenous oxygen content differences (AVDO<sub>2</sub>), arterial lactate levels, and arteriojugular lactate differences were determined. In order to reduce the dose requirement of adenosine, the patients were pretreated with the adenosine uptake inhibitor, dipyridamole (0.3–0.4 mg·kg<sup>-1</sup>). During the infusion of adenosine (0.14 ± 0.04 mg·kg<sup>-1</sup>·min<sup>-1</sup>) the mean arterial blood pressure decreased by 43%, from 82 to 46 mmHg, during a mean hypotensive period of 32 min, without signs of tachyphylaxis. The arterial adenosine level increased from 0.15 ± 0.02 to 2.45 ± 0.65 μM (*P* < 0.01). Hypotension was caused by a profound decrease in peripheral vascular resistance (61 ± 3%, *P* < 0.01), which was accompanied by an increase in cardiac output (44 ± 9%, *P* < 0.01). Heart rate increased moderately by 16 ± 5% (*P* < 0.01). Pulmonary vascular resistance and central venous pressures were unaffected. Arterial lactate and PaO<sub>2</sub> were unchanged, while whole body oxygen consumption was decreased by 13 ± 4% (*P* < 0.05). The AVDO<sub>2</sub> across the brain was decreased by 37 ± 5% (*P* < 0.05) without signs of lactate formation. The authors conclude that adenosine rapidly induces a stable and easily controlled hypotension in humans by dilation of arterial resistance vasculature. (Key words: Anesthetic techniques: adenosine; hypotension. Blood pressure: adenosine; hypotension. Metabolism: lactate; oxygen consumption. Pharmacology: adenosine; dipyridamole.)

DURING the dissection and clipping of cerebral arterial aneurysms, controlled hypotension often is required to reduce the aneurysm wall tension in order to minimize the risk of rupture and bleeding.<sup>1</sup> Controlled hypotension also is used to reduce bleeding during other forms of major surgery. Vasodilators such as sodium nitroprusside (SNP) and nitroglycerin (TNG) currently are used for this purpose; SNP may have some drawbacks such as tachyphylaxis and rebound hypertension,<sup>2,3</sup> while TNG has a slow onset and unpredictable action.

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Purines, *e.g.*, adenosine and adenine nucleotides, are well-known vasodilators.<sup>4,5</sup> In recent years it has been demonstrated that adenosine is an important endogenous vasodilator, involved in the regulation of local flow in several vascular beds, including the heart,<sup>6</sup> brain,<sup>7</sup> and adipose tissue.<sup>8</sup> The potential use of purines to achieve controlled hypotension recently has attracted considerable attention. ATP induces an effective and stable hypotension in rats<sup>9</sup> and dogs,<sup>10,11</sup> and ATP has been used for controlled hypotension in humans.<sup>12</sup> Using a quantitative high-pressure liquid chromatography (HPLC) technique for purine determination, we recently have demonstrated that ATP (given by the iv route) is entirely degraded to adenosine and its metabolites during its transpulmonary passage and that the hypotensive effect of ATP is related to the arterial adenosine concentration.<sup>13</sup> Moreover, we recently have shown in the dog that adenosine-induced hypotension is characterized by rapid induction and a stable hypotensive blood pressure level, which rapidly was reversed when infusion of the drug was discontinued.<sup>14</sup>

The present investigation therefore was designed to study the clinical usefulness of adenosine as an agent to induce controlled hypotension (mean arterial blood pressure 40–50 mmHg) during dissection and clipping of cerebral aneurysms. In order to minimize the dose requirement for adenosine-induced hypotension in this first clinical study, we pretreated the patients with the well-known adenosine uptake inhibitor, dipyridamole (Persantine®).<sup>15</sup>

### Patients and Methods

Ten patients with no known history of cardiopulmonary diseases (seven men and three women, ages 35–58 years), scheduled for intracerebral aneurysm surgery, were selected for the study. The investigation was approved by the Ethical Committee of the Karolinska Hospital and was performed after obtaining the informed consent of the patients.

One hour before the operation, the patients were premedicated orally with diazepam (10–20 mg). Atropine (0.5 mg) and droperidol (0.1 mg·kg<sup>-1</sup>) were given intravenously before induction of anesthesia. Induction was started with thiopental (5 mg·kg<sup>-1</sup>) followed by

phenoperidine‡ (1–2 mg). Pancuronium bromide (0.1 mg · kg<sup>-1</sup>) was given to facilitate endotracheal intubation. Anesthesia was maintained by supplementary doses of phenoperidine and droperidol, as required. The total dose of droperidol did not exceed 0.2 mg · kg<sup>-1</sup> and was administered within the first 2 h of anesthesia. Phenoperidine was supplemented regularly to prevent the blood pressure from exceeding the preanesthetic level (approx. 1 mg/30–60 min). Controlled hyperventilation was employed with a humidified gas mixture of 60% N<sub>2</sub>O in O<sub>2</sub> to maintain PaCO<sub>2</sub> values at approximately 30 mmHg (±1.5 SEM). Mannitol (1–1.5 g · kg<sup>-1</sup>) was given routinely at the start of the operation (*e.g.*, 1–2 h prior to the controlled hypotension). The patients were operated on in the horizontal supine position.

A 1.2-mm plastic cannula was introduced into the left radial artery to monitor systemic arterial blood pressure (MABP) and collect arterial blood. A balloon-tipped, flow-directed, quadruple lumen Swan-Ganz® catheter (Model 93A-831-7.5 F, VIP) was inserted percutaneously via the left basilic vein, and its correct position in the pulmonary artery was determined by pressure tracings. The catheter was used for the monitoring of mean right atrial pressure (RAP), mean pulmonary artery pressure (PAP), and mean pulmonary capillary wedge pressure (PCWP) for the determination of cardiac output and collection of mixed venous blood and for the infusion of adenosine. Another plastic cannula was introduced percutaneously, in a retrograde direction, into the right internal jugular vein, with the tip placed in the jugular bulb for the collection of blood. The correct position was verified by x-ray.

The ECG was monitored with a standard chest (V<sub>5</sub>) lead. Heart rate was determined from the R-R interval. Blood pressures were measured by transducers placed at the midthoracic level. Cardiac output (QT) was determined in triplicate according to the thermodilution technique with a cardiac output computer (Edwards Lab, model 9510). Isotonic glucose, 10 ml at 1° C, was used as a thermal indicator. The ECG, heart rate, blood pressures, and thermodilution curves were recorded on a Grass® polygraph.

Blood gases were measured with appropriate electrodes for pH, P<sub>CO</sub><sub>2</sub>, and P<sub>O</sub><sub>2</sub> (Radiometer, Copenhagen). The hemoglobin concentration was determined spectrophotometrically. Samples for the determination of adenosine and its metabolites were collected as described by Sollevi *et al.*<sup>13</sup> Adenosine and inosine were purified and analyzed by HPLC as described by Fredholm and Sollevi.<sup>16</sup> Hypoxanthine, xanthine, and uric acid were an-

alyzed by HPLC according to the method of Schweinsberg and Loo.<sup>17</sup> Arterial levels of dipyridamole were determined by HPLC.<sup>18</sup> Blood lactate was measured according to Tfelt-Hansen and Siggard-Andersen.<sup>19</sup>

Measurements and blood samplings were performed immediately before hypotension, as late as possible during hypotension (1–5 min before terminating the infusion) and approximately 30 min after the hypotensive period.

Dipyridamole§ (5 mg · ml<sup>-1</sup>) was infused iv (0.3–0.4 mg · kg<sup>-1</sup> over a period of 5–10 min) approximately 20 min prior to the induction of controlled hypotension. This dose of dipyridamole produced clinically relevant drug levels in the plasma (1.2 ± 0.3 μM, SEM)<sup>18</sup> during the hypotensive periods.

Adenosine (5 mM, 1.34 mg · ml<sup>-1</sup> in isotonic saline) was administered by continuous infusion (Critikon roller pump, 2102A,¶ superior vena cava) for 12–71 min ( $\bar{x}$  = 33 ± 8 SEM) at a rate of 0.01–0.32 mg · kg<sup>-1</sup> · min<sup>-1</sup> ( $\bar{x}$  = 0.14 ± 0.04 SEM, corresponding to 8.0 ± 2.7 mg · min<sup>-1</sup>). The infusion was started at a rate of 0.01 mg · kg<sup>-1</sup> · min<sup>-1</sup>, which was doubled at 15-s intervals until the desired MABP level of 40–50 mmHg was reached. The corresponding volume of infused adenosine solution ranged from 0.5 to 17 ml · min<sup>-1</sup> ( $\bar{x}$  = 6 ± 2 SEM). The mean hypotensive period was 32 ± 8 min. The total adenosine dose did not exceed 1.5 g.

Serum creatinine was determined before and on two consecutive days after operation. The standard ECG was recorded the day before and the day after operation.

Systemic vascular resistance (SVR) was derived from the formula  $SVR \text{ (mmHg} \cdot \text{l}^{-1} \cdot \text{min)} = \frac{MABP - RAP}{QT}$  and pulmonary vascular resistance (PVR) from the formula  $PVR = \frac{PAP - PCWP}{QT}$ .

Oxygen content was derived from the formula  $SO_2^{**} \times 1.34 \times Hb + PO_2 \times 0.03$ .<sup>20</sup> The arteriovenous oxygen content difference (AVDO<sub>2</sub>) was determined and used to calculate total oxygen consumption ( $\dot{V}O_2$ ) as the product of AVDO<sub>2</sub> and QT.

## STATISTICS

Data are presented as means ± SEM. The statistical significance (control 1 *vs.* adenosine and control 1 *vs.* control 2) was determined by Student's *t* test for paired data. A *P* value of <0.05 was regarded as significant.

§ Persantine®, commercially available for iv administration in Europe (Boehringer Ingelheim, Ingelheim, W. Germany).

¶ A high-precision roller pump is recommended, since infusion of adenosine with an intermittently operating pump produces an oscillating blood pressure level.

\*\* SO<sub>2</sub> = oxygen saturation.

‡ Synthetic opiate with pharmacodynamics resembling fentanyl but with a longer duration of action and 1/10 of its analgesic potency.

TABLE 1. Purine Levels ( $\mu\text{M}$ ) in Arterial Plasma before, during, and after Adenosine-induced Controlled Hypotension in Nine Patients.

	Control 1	Hypotension	After Hypotension	
			3-9 Min	20-40 Min
Adenosine	$0.15 \pm 0.02$ (9)	$2.45 \pm 0.65^*$ (9)	$0.24 \pm 0.06$ (6)	$0.19 \pm 0.03$ (7)
Inosine	$0.04 \pm 0.01$ (8)	$3.01 \pm 1.48^*$ (8)	$0.69 \pm 0.26^\dagger$ (5)	$0.29 \pm 0.15$ (7)
Hypoxanthine	$1.94 \pm 0.55$ (9)	$6.28 \pm 2.33$ (9)	—	$3.25 \pm 1.00$ (8)
Xanthine	$5.93 \pm 2.04$ (7)	$6.10 \pm 1.67$ (7)	—	$5.49 \pm 1.58$ (7)
Uric Acid	$185.2 \pm 14.2$ (9)	$198.1 \pm 22.7$ (9)	—	$199.5 \pm 28.8$ (8)

\*  $P < 0.01$ ,  $^\dagger P < 0.05$ , denotes significantly different from the control 1 levels.

Number of observation in parentheses.

### Results

The control arterial plasma levels of purines are shown in Table 1. Adenosine is present in the  $10^{-7}$  M range during basal conditions. Continuous infusion of adenosine increased the arterial adenosine level to  $2.45 \pm 0.65 \mu\text{M}$ . The adenosine metabolites inosine and hypoxanthine were increased during the infusion, whereas xanthine and uric acid levels were unaffected. Once the desired blood pressure level was reached, the infusion rate could be kept constant throughout the hypotensive period. After termination of the infusion, the arterial adenosine levels returned to control values within 3-9 min (table 1). Inosine was eliminated more slowly from the circulation and remained slightly above basal levels even 20-40 min after the infusion.

The infusion of dipyridamole decreased MABP by approximately 10 mmHg in five of the patients. At the start of the adenosine infusion, MABP was not significantly different from the predipyridamole level ( $82 \pm 3$  vs.  $86 \pm 3$  mmHg). Adenosine induced a decrease in MABP to 46 mmHg ( $43 \pm 3\%$ ) within 1-2 min (table

2). The decrease in MABP was caused by a parallel decrease in both systolic and diastolic pressure. The MABP was stable throughout the hypotensive period. Cardiac output increased from  $4.9$  to  $6.9 \text{ l} \cdot \text{min}^{-1}$  ( $44 \pm 9\%$ ) in parallel with a small increase in heart rate of  $9 \pm 2 \text{ beats} \cdot \text{min}^{-1}$ . The SVR decreased from  $16.7$  to  $6.2 \text{ mmHg} \cdot \text{l}^{-1} \cdot \text{min}$ , corresponding to a decrease of  $61 \pm 3\%$ , whereas PVR was unchanged. RAP, PAP, and PCWP were not influenced by adenosine.

After discontinuation of the infusion, MABP was restored within 1-5 min. Rebound hypertension did not occur, although the MABP was persistently approximately 10 mmHg higher after hypotension than during the control period. However, the posthypotensive MABP was not significantly higher than the MABP before administration of dipyridamole. Heart rate, QT, and SVR returned rapidly to control levels concurrently with the restoration of MABP.

Arterial oxygen tension remained unchanged during adenosine-induced hypotension (table 3).  $\dot{V}\text{O}_2$  was decreased by  $13 \pm 4\%$ , with a decrease in  $\text{AVDO}_2$  of  $37 \pm 5\%$ . The arterial lactate concentration was not affected

TABLE 2. Central Hemodynamic variables before, during, and 30 Min after Adenosine-induced Controlled Hypotension in 10 Patients.

	Control 1	Adenosine	Control 2
Systolic blood pressure (mmHg)	$115 \pm 6$	$78 \pm 6^*$	$130 \pm 7^\dagger$
Diastolic blood pressure (mmHg)	$61 \pm 3$	$34 \pm 2^*$	$71 \pm 3^\dagger$
Mean arterial blood pressure (mmHg)	$82 \pm 3$	$46 \pm 2^*$	$91 \pm 4^\dagger$
Right atrial pressure (mmHg)	$6.8 \pm 1.1$	$7.2 \pm 0.7$	$5.6 \pm 0.8$
Pulmonary artery pressure (mmHg)	$14.4 \pm 1.0$	$16.5 \pm 0.9$	$14.7 \pm 1.4$
Pulmonary capillary wedge pressure (mmHg)	$9.6 \pm 1.1$	$11.0 \pm 1.0$	$9.9 \pm 1.4$
Heart rate ( $\text{beats} \cdot \text{min}^{-1}$ )	$54 \pm 2$	$63 \pm 3^*$	$58 \pm 3$
Cardiac output ( $\text{l} \cdot \text{min}^{-1}$ )	$4.93 \pm 0.51$	$6.86 \pm 0.71^*$	$5.17 \pm 0.54$
Systemic vascular resistance ( $\text{mmHg} \cdot \text{l}^{-1} \cdot \text{min}$ )	$16.65 \pm 1.95$	$6.22 \pm 0.60^*$	$17.70 \pm 1.72$
Pulmonary vascular resistance ( $\text{mmHg} \cdot \text{l}^{-1} \cdot \text{min}$ )	$0.97 \pm 0.15$	$0.82 \pm 0.08$	$0.97 \pm 0.15$

\*  $P < 0.01$ ,  $^\dagger P < 0.05$ , denotes significantly different from control 1.

TABLE 3. Total Arteriovenous Oxygen Content Difference ( $AVD_{T-O_2}$ ), Jugular Arteriovenous Oxygen Content Difference ( $AVD_{J-O_2}$ ), Total Oxygen Consumption ( $\dot{V}_{T-O_2}$ ), Arterial Oxygen Tension ( $P_{aO_2}$ ), Arterial Lactate Concentration (La) and Jugular Arteriovenous Lactate Content Differences ( $AVD_{J-La}$ ) before, during, and after Adenosine-induced Hypotension in Nine Patients.

	Control 1	Adenosine	Control 2
$AVD_{T-O_2}$ (ml · l <sup>-1</sup> )	46.3 ± 2.3	29.3 ± 2.5*	46.8 ± 3.2
$AVD_{J-O_2}$ (ml · l <sup>-1</sup> )	85.2 ± 10.5	58.1 ± 14.1†	74.9 ± 7.7
$\dot{V}_{T-O_2}$ (ml · min <sup>-1</sup> )	220 ± 15	193 ± 16†	235 ± 16
$P_{aO_2}$ (mmHg)	111.0 ± 9.8	97.5 ± 9.0	93.0 ± 5.2
La (mmol · l <sup>-1</sup> )	1.46 ± 0.17	1.73 ± 0.20	1.82 ± 0.20†
$AVD_{J-La}$ (mmol · l <sup>-1</sup> )	0.02 ± 0.04	-0.05 ± 0.05	-0.06 ± 0.04

\*  $P < 0.01$ , †  $P < 0.05$ , denotes significantly different from control 1.

by hypotension. The cerebral  $AVDO_2$  decreased similarly by  $37 \pm 13\%$ , while the arterio-jugular lactate content difference was unaltered.

After the hypotensive period, the metabolic variables returned to the control levels, except for a minor increase in the arterial lactate concentration.

The ECG the day after operation was unchanged. The mean serum creatinine level was  $83 \pm 4 \mu\text{M}$  before operation and  $70 \pm 3$  and  $71 \pm 4 \mu\text{M}$  on the first 2 postoperative days.

### Discussion

The present study demonstrates that adenosine can be used to induce controlled hypotension in humans. Adenosine-induced hypotension is characterized by a rapidly achieved and stable level of hypotension that is rapidly reversible upon discontinuation. The latter phenomenon probably is related to the short plasma half-life of adenosine (10–20 s).<sup>16</sup> Fukunaga *et al.*<sup>12</sup> reported similar properties when using ATP for controlled hypotension in humans. Since all ATP is degraded to adenosine in the circulation before reaching the arterial vascular bed in the dog,<sup>13</sup> it seems reasonable to assume that ATP-induced hypotension is mediated, in fact, by its metabolite adenosine. The vasodilator effect of adenosine in the present study was reversible within a few minutes after termination of the infusion and paralleled the return to basal plasma levels of the substance. After approximately 30 min, plasma purine metabolites had returned toward basal levels. By contrast, ATP administration is associated with considerable phosphate formation during degradation of the compound in the blood stream. High levels of phosphate may cause arrhythmias secondary to chelation of magnesium and calcium.<sup>21</sup> Therefore, we consider it more appropriate to use adenosine in preference to ATP to induce controlled hypotension. Pretreatment with the adenosine uptake inhibitor, dipyridamole, potentiates the vasodilator effect of adenosine in dogs.<sup>14,22</sup> Dipyridamole

therefore was used in the clinical study to reduce the infusion rates of adenosine. Nevertheless, two patients required as much as  $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  of the 5 mM adenosine solution. These high infusion rates can be avoided, however, by using a 20 mM solution.<sup>††</sup>

The adenosine-induced hypotension was achieved at low micromolar arterial plasma concentrations. The effect was entirely due to a sharp decrease in SVR, while QT increased by 40%. This is similar to the effect in the dog,<sup>14</sup> the reaction probably being mediated by adenosine receptors located on the smooth muscle of the resistance vasculature.<sup>23</sup> Adenosine, in a similar concentration range as in this study, caused relaxation of isolated arteries *in vitro*,<sup>24</sup> and small increases in plasma adenosine (less than micromolar concentrations) have clear-cut vasodilatory effects in the canine myocardium<sup>25</sup> and subcutaneous adipose tissue.<sup>8</sup>

The enhanced cardiac output, in combination with maintained right and left heart filling pressures, is in contrast with the hemodynamic effects of controlled hypotension with SNP and TNG noted in our earlier clinical studies (table 4). The lack of effect on venous pressure suggests a minimal effect on the venous vascular bed, such that venous return and ventricular filling pressures are unaffected. This is similar to the effect observed in the dog.<sup>14</sup> The limited effect of adenosine on venous vascular tone may be due to the rapid degradation of adenosine and/or a less adenosine-sensitive venous vascular bed, as discussed previously.<sup>14</sup>

The adenosine infusion rate was constant during the hypotension, which suggests the absence of tachyphylaxis. Adenosine inhibits renin release in the kidney<sup>28</sup> and adenosine-induced hypotension in the dog prevents elevation of circulating plasma renin activity,<sup>14</sup> thereby

†† Since completing the study on this series of patients, we have performed another 20 cases of controlled hypotension using the 20 mM solution without pretreatment with dipyridamole. The hemodynamic effects are similar to those described by the above data, but higher doses of adenosine are required ( $0.2\text{--}0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ).

TABLE 4. Hemodynamic Effects of Adenosine-, SNP- (from Lagerkranser *et al.*<sup>26</sup>), and TNG- (from Lagerkranser<sup>27</sup>) Induced Controlled Hypotension during Cerebral Aneurysm Surgery with Similar Anesthetic Techniques (Data Presented as Per Cent from Control)

	Adenosine n = 10	SNP n = 17	TNG n = 20
MABP	-43*	-36*	-36*
RAP	+6	-39*	-45*
PAP	+15	-27*	-34*
PCWP	+14	-44*	-45*
HR	+9*	+22*	+19*
QT	+44*	-15*	-24*
SVR	-61*	-29*	-16*
PVR	-15	+11	+12

\*  $P < 0.01$ .

reducing the risk of tachyphylaxis, which most probably involves the activation of the renin-angiotensin system.<sup>29</sup>

The increase in cardiac output occurred in parallel with a decrease in  $AVDO_2$ . The decrease in  $AVDO_2$  was caused both by the increase in cardiac output and a 13% decrease in whole body oxygen consumption. This previously has been reported in dogs<sup>14,30</sup> and suggests that adenosine may inhibit metabolic demands in various tissues. Regional administration of adenosine inhibits energy-consuming processes, such as gastrointestinal motility<sup>31</sup> and catecholamine-stimulated lipolysis<sup>32</sup> as well as myocardial metabolism<sup>33</sup> in the dog. Furthermore, adenosine administration caused a pronounced decrease in SVR, implying a corresponding decrease in left ventricular afterload and thereby diminished cardiac work and myocardial oxygen demand. Thus, adenosine may decrease oxygen consumption in certain tissues during periods of reduced perfusion pressure. The unaffected arterial lactate level during hypotension further indicates that organ perfusion was adequate. The small posthypotensive increase in arterial lactate levels probably is related to the effect of prolonged hyperventilation on systemic lactate levels.<sup>34</sup>

There was also a decrease in the cerebral  $AVDO_2$  (37%) without any evidence of lactate production during the hypotension, again implying an adequate supply of oxygen to the brain. Since cerebral blood flow was not measured, we cannot differentiate between an increase in blood flow and/or a decrease in cerebral oxygen consumption.

Although adenosine may decrease the glomerular filtration rate,<sup>35</sup> there were no gross signs of impaired kidney function in any patient as judged by the postoperative serum creatinine levels.

This investigation demonstrates that adenosine is effective in inducing controlled hypotension in humans. The rapidity of onset and termination, stability of action, maintenance of cardiac output, and decrease in oxygen demand differentiate adenosine from other hypotensive

agents. These excellent properties justify further clinical investigation.

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## References

1. Ferguson GG: The rationale for controlled hypotension. Anesthetic considerations in the surgical repair of intracranial aneurysms. *Int Anesthesiol Clin* 20:89-93, 1982
2. Rudehill A, Gordon E, Lagerkranser M: Sodium nitroprusside as a hypotensive agent in intracranial aneurysm surgery. *Acta Anaesthesiol Scand* 23:404-410, 1979
3. Khambatta HJ, Stone JC, Khan E: Hypertension during anesthesia on discontinuation of sodium nitroprusside induced hypotension. *ANESTHESIOLOGY* 51:127-130, 1979
4. Drury AN, Szent-Györgyi A: The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. *J Physiol (Lond)* 68:213-237, 1929
5. Green HW, Stoner HB: Biological Actions of Adenine Nucleotides. London, HK Lewis & Co, 1950
6. Olsson RA: Local factors regulating cardiac and skeletal muscle blood flow. *An Rev Physiol* 43:385-395, 1981
7. Berne RM, Winn HR, Rubio R: Metabolic regulation of cerebral blood flow, Vasodilatation. Edited by Vanhoutte PM, Leusen I. New York, Raven Press, 1981, pp 231-243
8. Sollevi A, Fredholm BB: Role of adenosine in adipose tissue circulation. *Acta Physiol Scand* 112:293-298, 1981
9. Hoffman WE, Satinover I, Miletich DJ, Albrecht RF, Gans BJ: Cardiovascular changes during sodium nitroprusside or adenosine triphosphate infusion in the rat. *Anesth Analg* 61:99-103, 1982
10. Fukunaga AF, Flacke WE, Bloor BC: Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside. *Anesth Analg* 61:273-278, 1982
11. Puchstein C, Van Aken H, Anger C, Thyss J, Lawin P: Kontrollierte hypotension mit ATP, Tier experimentelle untersuchung an hunden. *Anästhesiologie Intensivther Notfallmed* 17:281-284, 1982
12. Fukunaga AF, Ikeda K, Matsuda I: ATP-induced hypotensive anesthesia during surgery. *ANESTHESIOLOGY* 57:3A 65, 1982
13. Sollevi A, Lagerkranser M, Andreen M, Irestedt L: Relationship between arterial and venous adenosine levels and vasodilation during ATP- and adenosine-infusion in dogs. *Acta Physiol Scand* 120:171-176, 1984
14. Lagerkranser M, Irestedt L, Sollevi A, Andreen M: Central and splanchnic hemodynamics in the dog during controlled hypotension with adenosine. *ANESTHESIOLOGY* 60:547-552, 1984
15. Schrader JR, Berne RM, Rubio R: Uptake and metabolism of adenosine by human erythrocyte ghosts. *Am J Physiol* 223:159-166, 1972
16. Fredholm BB, Sollevi A: The release of adenosine and inosine from canine subcutaneous adipose tissue by nerve stimulation and noradrenaline. *J Physiol (Lond)* 313:351-367, 1981
17. Schweinsberg PD, Loo TL: Simultaneous analysis of ATP, ADP, AMP and other purines in human erythrocytes by HPLC. *J Chromatogr* 181:103-107, 1980
18. Pedersen AK: Specific determination of dipyridamole in serum by high-performance liquid chromatography. *J Chromatogr* 162:98-103, 1979

19. Tfelt-Hansen P, Siggaard-Andersen O: Lactate and pyruvate determination in 50  $\mu$ l whole blood. *Scand Clin Lab Invest* 27:15-19, 1971
20. Foëx P, Prys-Roberts C, Hahn CEW, Fenton M: Comparison of oxygen content of blood measured directly with values derived from measurement of oxygen tension. *Br J Anaesth* 42:803-804, 1970
21. Dedrick DF, Mans AM, Campbell PA, Hawkins RA, Biebuyck JF: Does ATP-induced hypotension cause potentially serious metabolic complications? *ANESTHESIOLOGY* 57:3A 66, 1982
22. Kadatz R: Die pharmakologischen Eigenschaften der neuen coronarerweiternden substanz 2,6-Bis (diaethanolamino)-4,8-dipiperidinopyrimido (5,4-d)pyrimidin. *Arzneimittelforsch* 9:39, 1959
23. Olsson RA, Davies CJ, Khouri EM, Patterson RE: Evidence for an adenosine receptor on the surface of dog coronary myocytes. *Circ Res* 39:93-98, 1976
24. Herlithy JT, Bockman EL, Berne RM, Rubio R: Adenosine relaxation of isolated vascular smooth muscle. *Am J Physiol* 230:1239-1243, 1976
25. Olsson RA, Khouri EM, Bedynek JL Jr, McLean J: Coronary vasoactivity of adenosine in the conscious dog. *Circulation Res* 45:468-478, 1979
26. Lagerkranser M, Gordon E, Rudehill A: Cardiovascular effects of sodium nitroprusside in cerebral aneurysm surgery. *Acta Anesthesiol Scand* 24:426-432, 1980
27. Lagerkranser M: Cardiovascular effects of nitroglycerin as a hypotensive agent in cerebral aneurysm surgery. *Acta Anesthesiol Scand* 26:453-457, 1982
28. Tagawa H, Vander AJ: Effects of adenine compounds on renal function and renin secretion in dogs. *Circ Res* 26:327-338, 1970
29. Lagerkranser M, Andreen M, Irestedt L, Sollevi A, Tidgren B: Adenosine inhibits renin release during controlled hypotension and hemorrhagic shock in the dog. *ANESTHESIOLOGY* 59:3A 13, 1983
30. Rowe GG, Afonso S, Gurtner HP, Chelins CJ, Lowe WC, Castillo CA, Creighton CW: The systemic and coronary hemodynamic effect of adenosine triphosphate and adenosine. *Am Heart J* 64:228-234, 1962
31. Granger HJ, Norris CP: Role of adenosine in local control of intestinal circulation in the dog. *Circ Res* 46:764-770, 1980
32. Sollevi A, Fredholm BB: The antilipolytic effect of endogenous and exogenous adenosine in canine adipose tissue in situ. *Acta Physiol Scand* 113:53-60, 1981
33. Gross CJ, Warltier DC, Hardman HF: Effect of adenosine on myocardial oxygen balance. *J Pharmacol Exp Ther* 196:445-454, 1976
34. Cohen RD, Simpson R: Lactate metabolism. *ANESTHESIOLOGY* 43:661-673, 1975
35. Osswald H, Hermes HH, Nabakowski G: Role of adenosine in signal transmission of tubuloglomerular feedback. *Kidney Int* 22:136-142, 1982