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Cerebral and Systemic Effects of Hypotension Induced by Adenosine or ATP in Dogs

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The authors evaluated the systemic and cerebral hemodynamic and metabolic effects of 1 h of hypotension to a mean arterial pressure of either 50 mmHg or 40 mmHg induced by intravenous adenosine or ATP in dogs maintained on 70% nitrous oxide and 0.1% halothane. Following the hypotensive period, brain biopsy specimens were taken for the determination of cerebral metabolites and calculation of the energy charge. Hypotension induced by either adenosine or ATP produced a marked 40–62% decrease in systemic vascular resistance with little change in cardiac index or oxygen consumption but resulted in a mild metabolic acidosis. Because of a profound decrease in cerebral perfusion pressure with hypotension (to 31–33 mmHg at an MAP of 50 mmHg and 22–24 mmHg at an MAP of 40 mmHg) CBF decreased 54–65% and was inadequate to meet the unchanged cerebral oxygen demands, resulting in some anaerobic metabolism with an accumulation of lactate. While the ease with which one can induce and maintain hypotension with these agents may be advantageous in clinical practice, the effects of adenosine and ATP on cerebral hemodynamics and metabolism may offer no advantage over other hypotensive agents. (Key words: Anesthetic techniques: hypotension; adenosine; ATP. Blood pressure: induced hypotension. Brain: blood flow; metabolism.)

INDUCED HYPOTENSION is commonly used during surgery to decrease the incidence of bleeding and to provide better operating conditions. Agents employed for this practice have included nitroprusside,[1] trimethaphan,[2] nitroglycerine,[3] halothane,[4] and isoflurane.[5] Potential disadvantages of these include cyanide toxicity,[6] rebound hypertension,[7] tachyphylaxis,[8] increased intracranial pressure,[9] and neuronal damage.[10]

Exogeneously administered adenosine triphosphate (ATP) and its active metabolite, adenosine,[11] are potent vasodilators in most vascular beds,[12] and several animal studies have demonstrated the efficacy of ATP or adenosine in producing deliberate hypotension and the subsequent effects of such hypotension on the heart and on blood flow through the major vascular beds.[13–16] Both ATP[17] and adenosine[18] have been used to produce deliberate hypotension in neurosurgical patients. However, few studies have been done examining the effects of ATP or adenosine-induced hypotension on cerebral circulation or metabolism. ATP-induced hypotension to 50% control value for 15 min was reported in dogs to cause a marked 48% decrease in cerebrovascular resistance (CVR) with maintenance of cerebral blood flow (CBF). This was accompanied by a 13% decrease in cerebral oxygen consumption (CMR_{O_2}).[19] Adenosine-(plus dipyridamole) induced hypotension to a mean arterial pressure (MAP) of 40 mmHg for 90 min was reported in dogs to produce a comparable 53% decrease in CVR, but CBF also decreased significantly by an average of 28% without change in cerebral oxygen consumption.[20] The effect of ATP or adenosine-induced hypotension on the cerebral metabolites has not been investigated.

The purpose of the present study was to investigate the systemic and cerebral hemodynamic and metabolic effects of two levels of hypotension in an animal model used previously to study hypotension induced with trimethaphan, nitroprusside, halothane,[21] and isoflurane.[22]

Methods

Twenty-four unmedicated fasting mongrel dogs of either sex weighing 10.5–15.5 kg were studied. Anesthesia was induced and maintained during the surgical preparation with 1% inspired halothane in 70% nitrous oxide and oxygen. Succinylcholine (40 mg) was given intravenously to facilitate endotracheal intubation and thereafter was continued at an infusion rate of 150 $mg \cdot h^{-1}$ to maintain paralysis. Ventilation was controlled with a Harvard Pump® and initially adjusted to maintain normocarbia (Pa_{CO_2} 40 mmHg) and $Pa_{O_2} > 120$ mmHg. Cannulae were inserted into the left femoral artery for pressure measurements and blood sampling; into the left femoral vein for fluid and drug administration; and into a pulmonary artery via the right external jugular vein for pressure measurements, blood sampling, and measurement of cardiac output by thermodilution (Instrumentation Laboratory Cardiac Output Computer

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701®). The electrocardiogram (ECG) was recorded continuously from limb leads. Core temperature, measured by a thermistor in the pulmonary artery catheter, and brain temperature, monitored by a parietal epidural thermistor, were maintained at 37° C ± 0.1° C (±SE) with heating pads and lamps. Intracranial pressure (ICP) was measured continuously with an epidural fiberoptic device (LADD® intracranial pressure monitor, LADD Research Industries Inc., Burlington, Vermont), and a four-lead electroencephalogram (EEG) was recorded continuously from electrodes cemented to the exposed skull. Following heparinization with 300–400 units · kg^{-1}, the posterior sagittal sinus was exposed, isolated, and cannulated as previously described[23,24] for direct measurement of cerebral blood flow by a square-wave electromagnetic flowmeter (EP 300® API, Carolina Medical Electronics). The cranium then was closed by sealing the opening with Surgicel® and Super Line® adhesive (Rawn Co.).

Arterial, sagittal sinus, and mixed venous blood gases were measured by electrodes at 37° C (Instrumentation Laboratory, 1303). Blood oxygen contents were calculated from measurements of oxyhemoglobin concentration (CO-oximeter®, Instrumentation Laboratory 282) and oxygen tension.[25] Cerebral oxygen consumption was calculated as the product of CBF and the arterial–sagittal sinus blood oxygen content difference, while total body oxygen consumption ($\dot{V}_{O_2}$) was calculated as the product of cardiac index (CI), expressed as $l \cdot min^{-1} \cdot m^{-2}$, and the arterial–mixed venous blood oxygen content difference. Cerebral perfusion pressure (CPP) was the difference between mean arterial pressure (MAP) at the head level and ICP. Cerebrovascular resistance was the quotient of CPP and CBF, and systemic vascular resistance index (SVRI) was the quotient of MAP at the heart level and cardiac index. Blood glucose and serum lactate and pyruvate contents were determined by standard enzymatic techniques. After completion of the surgical preparation, the inspired halothane concentration was decreased to 0.1%, and a period of 30 min was allowed for the animals to eliminate the halothane. For control values, CBF and CMR_{O_2} were measured at 5-min intervals, while blood gases, CI, $\dot{V}_{O_2}$, MAP, mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), heart rate, core and brain temperatures, ICP, blood glucose, and serum lactate and pyruvate concentrations were measured at 15-min intervals.

Following control measurements, the dogs were divided into four groups. Adenosine in a concentration of 15 mg · ml^{-1} was administered as a continuous infusion to produce an MAP of 50 mmHg in six dogs and an MAP of 40 mmHg in another six dogs. The desired pressure was maintained throughout the 60-min study period and the time needed to take brain biopsies (~11 min) by minor adjustments of the adenosine infusion. The other two groups of six dogs each received a continuous infusion of ATP in a concentration of 20 or 40 mg · ml^{-1} to produce an MAP of either 50 mmHg or 40 mmHg for the 60 min study period plus the time necessary to take brain biopsies. During the period of hypotension, pressures, heart rate, CBF, and CMR_{O_2} were measured at 7.5-min intervals, while CI, $\dot{V}_{O_2}$, blood gases, and samples for glucose, lactate, and pyruvate determinations were measured at 15-min intervals.

Thereafter, the dura was exposed and excised and simultaneous cortical biopsies were taken by a technique that deposits a sample of brain (200–400 mg) into liquid nitrogen within 1 s.[26] The tissue was prepared for analysis in a refrigerated box,[27] and tissue extracts then were assayed by enzymatic fluorometric techniques for phosphocreatine (PCr), ATP, ADP, AMP, glucose, lactate, and pyruvate.[28] The sum of the adenine nucleotides was calculated as [Ad] = [ATP] + [ADP] + [AMP]. The energy charge (EC) of the brain then was expressed as EC = ([ATP] + 0.5 [ADP])/[Ad].[29]

In an additional six dogs, following the surgical preparation under 1% halothane, 70% nitrous oxide anesthesia, total spinal anesthesia was established via a lumbar subarachnoid needle with 2 ml 1% tetracaine HCl and the surgical wound in the head was infiltrated with 2 ml of 1% lidocaine. The halothane then was discontinued and nitrogen was substituted for nitrous oxide for at least 20 min. Thereafter, simultaneous bilateral cortical biopsies were obtained as previously described and cerebral metabolites were analyzed. The combined results from these six animals now serve as our laboratory's normal values for cerebral metabolites.

Results were analyzed statistically using Student's *t* test for paired data to compare control and final (60 min) hypotensive values in the same dog and by Student's *t* test for unpaired data to compare final values obtained with adenosine to those obtained with ATP and to compare values obtained at 40 mmHg with those obtained at 50 mmHg with either adenosine or ATP. Cerebral concentrations of metabolites at each hypotensive level were compared with normal values for our laboratory by Student's *t* test for unpaired data. A probability of less than 0.05 that differences were due to chance was considered significant.

Results

Hypotension was easily induced and maintained with either ATP or adenosine. A steady state at the desired level of hypotension was achieved within an average of 7 min. This time was longer than necessary, because we purposely increased the ATP or adenosine concentra-

TABLE 1. Control and Final Hypotensive Values for Arterial, Sagittal Sinus Blood Gases, and Hemoglobin at MAP of 40 or 50 mmHg Produced by Adenosine or ATP

	Adenosine (n = 6)		ATP (n = 6)	
	Control	Final	Control	Final
MAP = 50 mmHg				
Pa_{O_2} (mmHg)	158 ± 6	158 ± 8	164 ± 9	174 ± 15
Pa_{CO_2} (mmHg)	40 ± 1	35 ± 1*	39 ± 1	35 ± 1*
pH_a	7.40 ± 0.01	7.35 ± 0.02*	7.41 ± 0.01	7.34 ± 0.02*
BB+ (mEq/l)	46 ± 1	41 ± 1*	46 ± 1	40 ± 1*
Pss_{O_2} (mmHg)	53 ± 4	33 ± 2*	60 ± 1	40 ± 2*
Pss_{CO_2} (mmHg)	47 ± 1	53 ± 2*	44 ± 1	49 ± 2*
pHss	7.36 ± 0.01	7.26 ± 0.02*	7.38 ± 0.01	7.27 ± 0.01*
Hb (g/dl)	13.3 ± 0.6	11.7 ± 0.5*	14.6 ± 0.5	13.3 ± 0.6*
MAP = 40 mmHg				
Pa_{O_2} (mmHg)	164 ± 10	166 ± 5	172 ± 4	176 ± 5
Pa_{CO_2} (mmHg)	39 ± 0	35 ± 1*	40 ± 1	37 ± 2*
pH_a	7.42 ± 0.02	7.37 ± 0.01*	7.40 ± 0.02	7.25 ± 0.02*†‡
BB+ (mEq/l)	47 ± 1	41 ± 1*	46 ± 1	36 ± 1*†‡
Pss_{O_2} (mmHg)	54 ± 4	31 ± 2*	58 ± 3	32 ± 2*‡
Pss_{CO_2} (mmHg)	48 ± 1	58 ± 3*	47 ± 1	59 ± 3*‡
pHss	7.37 ± 0.02	7.26 ± 0.02*	7.36 ± 0.01	7.16 ± 0.02*†‡
Hb (g/dl)	14.8 ± 0.7	13.0 ± 0.8*	13.3 ± 0.9	10.9 ± 0.6*‡

Mean ± SEM.
* Significantly different from control value ($P < 0.05$).
† Significantly different from adenosine hypotensive value ($P < 0.05$).
‡ Significantly different from 50 mmHg value ($P < 0.05$).

tions slowly in a step-wise fashion every 30 s until the desired MAP was obtained. For ATP the mean dose was 2.1 $mg \cdot kg^{-1} \cdot min^{-1}$ to maintain an MAP of 50 mg and 5.1 $mg \cdot kg^{-1} \cdot min^{-1}$ for an MAP of 40 mmHg. The average dose of adenosine was 1.7 $mg \cdot kg^{-1} \cdot min^{-1}$ for an MAP of 50 mmHg and 2.6 $mg \cdot kg^{-1} \cdot min^{-1}$ for an MAP of 40 mmHg.

Although measurements and calculations were made at 7.5-min intervals throughout the hypotensive period, pertinent results for each group of dogs are most apparent by comparing the final 60-min values between the groups and to the control values. These values include any effect duration of hypotension might have.

A significant metabolic acidosis occurred in all groups, despite a concomitant decrease in Pa_{CO_2} (table 1). The most severe acidosis developed with a blood pressure reduction to 40 mmHg by ATP. Noteworthy are the changes occurring in the sagittal sinus blood gases. A significant decrease in sagittal sinus P_{O_2} occurred in all groups, indicating increased oxygen extraction by the brain. This was accompanied by a significant cerebral mixed metabolic and respiratory acidosis. Again, the most severe cerebral acidosis occurred with ATP-induced hypotension to 40 mmHg. In all groups there was a significant decrease in hemoglobin following the 60 min of hypotension, which presumably reflects compensatory

TABLE 2. Systemic Hemodynamic and Metabolic Values at MAP = 50 mmHg

	Adenosine (n = 6)		ATP (n = 6)	
	Control	Final	Control	Final
MAP (mmHg)	109 ± 3	51 ± 0*	105 ± 4	49 ± 0*
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.89 ± 0.32	2.81 ± 0.19	3.05 ± 0.45	2.52 ± 0.39*
SVRI ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	39.5 ± 3.3	18.5 ± 1.4*	38.1 ± 5.5	21.8 ± 3.2*
HR (beats/min)	113 ± 11	119 ± 12	133 ± 15	138 ± 9
PCWP (mmHg)	8 ± 1	8 ± 1	7 ± 1	7 ± 2
$\dot{V}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	144.0 ± 14.6	129.1 ± 14.8	144.8 ± 9.4	146.6 ± 6.2
Lactate (μmol/ml)	3.18 ± 0.49	4.05 ± 0.41	3.63 ± 0.46	4.10 ± 0.37
L/P	12 ± 1	19 ± 1*	13 ± 1	15 ± 1*†
Glucose (mg/dl)	121.4 ± 6.3	124.0 ± 15.3	104.0 ± 10.4	107.6 ± 9.3

Mean ± SEM.
* Significantly different from control value ($P < 0.05$).
† Significantly different from adenosine hypotensive value ($P < 0.05$).

TABLE 3. Systemic Hemodynamic and Metabolic Values at MAP = 40 mmHg

	Adenosine		ATP	
	Control	Final	Control	Final
MAP (mmHg)	97 ± 7	43 ± 1*†	112 ± 4	42 ± 1*†
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.89 ± 0.36	2.86 ± 0.22*	2.86 ± 0.15	3.14 ± 0.59
SVRI ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	25.7 ± 2.1	15.5 ± 1.2*	39.3 ± 1.4	15.0 ± 2.2*
HR (beats/min)	121 ± 8	98 ± 6	126 ± 13	109 ± 8†
PCWP (mmHg)	5 ± 1	6 ± 1	8 ± 1	10 ± 2
$\dot{V}_{O_2}$ ($ml \cdot min^{-1} \cdot m^{-2}$)	171.9 ± 15.8	131.2 ± 12.1	140.3 ± 9.5	100.8 ± 10.5*†
Lactate (μmol/ml)	3.49 ± 0.39	4.10 ± 0.48	2.54 ± 0.38	3.31 ± 0.70
L/P	18 ± 2	27 ± 5	13 ± 1	18 ± 4
Glucose (mg/dl)	105.0 ± 4.8	106.4 ± 6.9	116.5 ± 10.3	119.0 ± 17.5

Mean ± SEM.
No significant differences between the adenosine and ATP hypotensive values.
* Significantly different from control value ($P < 0.05$).
† Significantly different from 50 mmHg value ($P < 0.05$).

hemodilution, withdrawal of blood samples, and hemodilution from the 100-ml normal saline needed to prime the pump, which returns sagittal sinus outflow to the femoral vein.

With hypotension there was the expected significant 40–62% decrease in the systemic vascular resistance index (tables 2 and 3; fig. 1). However, the cardiac index also was reduced significantly during ATP-induced hypotension to 50 mmHg and during adenosine-induced hypotension to 40 mmHg. It should be noted that, although the cardiac index during adenosine-induced hypotension to 40 mmHg was significantly lower than control, the control value was unusually high; thus, the hypotensive value of 2.86 $l \cdot min^{-1} \cdot m^{-2}$ was similar to the other control values. There was no evidence of congestive heart failure during hypotension, since neither PCWP nor heart rate changed significantly, although there was a trend toward slower heart rates at the lower blood pressures. No arrhythmias were observed. Reductions in whole body oxygen consumption occurred during hypotension, but the decrease was significant only in the ATP-induced hypotension to 40 mmHg (table 3, fig. 1). Both the serum lactate levels and the L/P ratio increased during hypotension in all groups.

The ICP tended to increase in all but the 40-mmHg ATP-induced hypotension group. This, together with the height of the head above the heart (15 cm), contributed to the very low cerebral perfusion pressures during hypotension: 31–33 mmHg in the 50 mmHg hypotension groups, and 22–24 mmHg in the 40 mmHg groups (tables 4 and 5, fig. 2). This partially was compensated by a 24–35% decrease in CVR. Nevertheless, the CBF decreased 55–65%. The largest reductions (60–65%) occurred in both 40 mmHg hypotension groups.

The CMR_{O_2} did not differ from control levels throughout the hypotensive period (tables 4 and 5; fig. 2). This apparent maintenance of oxygen demand, despite a decrease in CBF, was compensated by an increased extraction of oxygen as indicated by a decrease in sagittal sinus P_{O_2} (table 1).

In all groups, cerebral lactate concentrations and L/P ratios increased significantly during hypotension, an indication of anaerobic metabolism occurring in the brain. Concentrations of cerebral ATP tended to decrease in all groups, but the energy charge and the phosphocreatine concentration remained within normal limits.

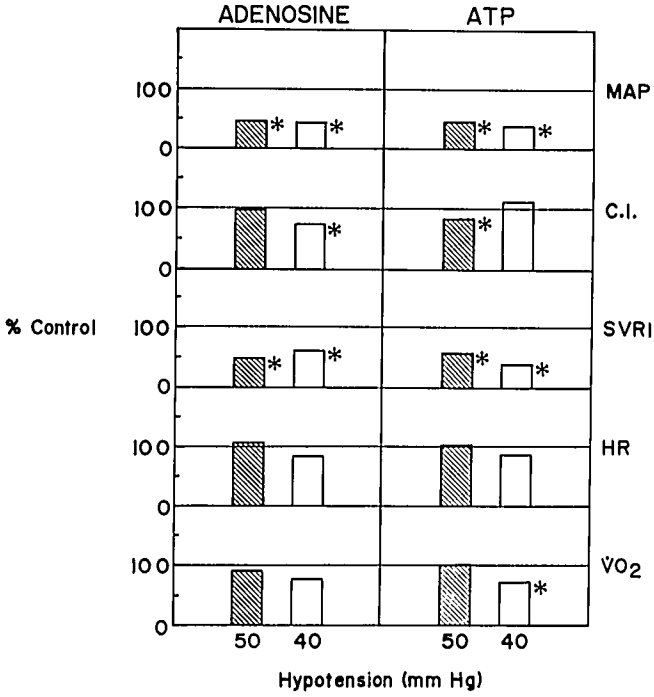

FIG. 1. Changes in systemic hemodynamic and metabolic variables during hypotension to either 50 mmHg (dark bars) or 40 mmHg (open bars) are presented as per cent of the control normotensive value. Any significant change ($P < 0.05$) is denoted by an asterisk.

TABLE 4. Cerebral Hemodynamic and Metabolic Values at MAP = 50 mmHg

	Adenosine (n = 6)		ATP (n = 6)	
	Control	Final	Control	Final
ICP (mmHg)	4 ± 1	7 ± 1	2 ± 1	4 ± 1
CPP (mmHg)	93 ± 3	31 ± 2*	92 ± 3	33 ± 2*
CBF (ml·min^{-1}·100 g^{-1})	119.0 ± 20.1	54.3 ± 5.9*	152.4 ± 8.7	68.6 ± 7.6*
CVR (mmHg·ml^{-1}·min·100 g)	2.4 ± 0.3	1.7 ± 0.3*	1.7 ± 0.1	1.3 ± 0.1*
CMR_{O_2} (ml·min^{-1}·100 g^{-1})	4.74 ± 0.27	5.02 ± 0.40	5.18 ± 0.20	5.70 ± 0.47
ATP (μmol/g)	(2.01 ± 0.01)†	1.89 ± 0.04*	(2.01 ± 0.01)†	1.87 ± 0.08
Phosphocreatine (μmol/g)	(2.99 ± 0.12)†	3.24 ± 0.08	(2.99 ± 0.12)†	3.39 ± 0.24
Energy charge	(0.87 ± 0.001)†	0.88 ± 0.01	(0.87 ± 0.001)†	0.87 ± 0.01
Lactate (μmol/g)	(1.23 ± 0.04)†	2.34 ± 0.32*	(1.23 ± 0.04)†	1.93 ± 0.10*
L/P	(11 ± 0.4)†	33 ± 9*	(11 ± 0.4)†	26 ± 2*

Mean ± SEM.
No significant differences between the adenosine and ATP hypotensive values.
* Significantly different from control value ($P < 0.05$).
† Normal values obtained from six dogs under spinal anesthesia (1984).

Discussion

Both adenosine and ATP rapidly and smoothly produced the desired level of hypotension. Once obtained, the hypotensive level was very easy to maintain with little alteration in infusion rates and without evidence of tachyphylaxis. We did not supplement these drugs with dipyridamole, which retards the rapid inactivation of adenosine by inhibiting the membrane-bound active transport mechanism for adenosine. It has been used in other studies to potentiate the action of adenosine, thereby decreasing the dose and infusion volume required.[14] We found that hypotension could be achieved and maintained without using excessive amounts of adenosine or fluids. However, we did use a concentrated solution (15 mg·ml^{-1}) of adenosine, which required warming to 40° C to remain in solution. It has been shown that intravenously administered ATP is degraded to adenosine in the plasma before reaching the arterial side of the vascular bed. It is assumed, therefore, that the hypotensive effect of exogenous ATP is due to adenosine.[11]

The reduction in MAP by intravenously administered adenosine and ATP both was produced primarily by a decrease in systemic vascular resistance index, which fell 42–53% at an MAP of 50 mmHg and 40–62% at an MAP of 40 mmHg. Cardiac index remained essentially the same or decreased only modestly in all groups. There was no significant change in heart rate at either level of hypotension, although numerically there was a decrease in heart rate at MAP of 40 mmHg with both adenosine and ATP. This is consistent with Fukunaga *et al.*, who reported a dose-related decrease in heart rate with either adenosine or ATP in rabbits.[15] This inhibition of reflex tachycardia during hypotension is reported to allow for easier induction and maintenance of hypotension. The administration of ATP has been reported to cause significant arrhythmias in rats (multifocal premature ventricular beats, bigeminy, or bradycardia), which is felt to be due to the chelation of

TABLE 5. Cerebral Hemodynamic and Metabolic Values at MAP = 40 mmHg

	Adenosine (n = 6)		ATP (n = 6)	
	Control	Final	Control	Final
ICP (mmHg)	3 ± 1	8 ± 1*	8 ± 2	6 ± 2
CPP (mmHg)	83 ± 7	22 ± 1*†	91 ± 3	24 ± 4*†
CBF (ml·min^{-1}·100 g^{-1})	135.4 ± 19.5	54.2 ± 3.1*	126.9 ± 13.0	43.8 ± 5.3*†
CVR (mmHg·ml^{-1}·min·100 g)	1.7 ± 0.3	1.1 ± 0.1	2.1 ± 0.3	1.6 ± 0.1‡
CMR_{O_2} (ml·min^{-1}·100 g^{-1})	6.06 ± 0.34	5.90 ± 0.24	5.01 ± 0.33	4.45 ± 0.36‡
ATP (μmol/g)	(2.01 ± 0.01)§	1.93 ± 0.04	(2.01 ± 0.01)§	1.99 ± 0.05
Phosphocreatine (μmol/g)	(2.99 ± 0.12)§	3.17 ± 0.10	(2.99 ± 0.12§	3.04 ± 0.22
Energy charge	(0.87 ± 0.001)§	0.88 ± 0.01	(0.87 ± 0.001)§	0.88 ± 0.01
Lactate (μmol·g)	(1.23 ± 0.04)§	2.16 ± 0.32*	(1.23 ± 0.04)§	3.15 ± 0.88*
L/P	(11 ± 0.4)§	26 ± 2*	(11 ± 0.4)§	26 ± 7*

Mean ± SEM.
* Significantly different from control value ($P < 0.05$).
† Significantly different from 50 mmHg value ($P < 0.05$).
‡ Significantly different from adenosine hypotensive value ($P < 0.05$).
§ Normal values obtained from six dogs under spinal anesthesia (1984).

calcium and magnesium by high levels of phosphate produced by the degradation of ATP.[30] At no time did we observe any arrhythmias during the administration of ATP.

Our results contrast with Ma *et al.*[16] (ATP) and Lagerkranser *et al.*[13] (adenosine), who reported an increase in cardiac output secondary to significant afterload reduction. The tendency toward a decrease in cardiac index we observed in three groups is in agreement with Tanaka and Mori[31] and Kassell *et al.*[20] who reported a slight decrease in cardiac output.

We also observed a mild but significant systemic metabolic acidosis (significant decrease in arterial *p*H and buffer base and mild increase in lactate). This is in agreement with Kassell *et al.*,[14,20] who reported a mild but significant metabolic acidosis after 1 h of dipyridamole/adenosine-induced hypotension to 40 mmHg in dogs, which was felt to be due to decreased peripheral perfusion; with Fukunaga *et al.*,[32] who reported a mild metabolic acidosis in dogs exposed to ATP-induced hypotension to 35 mmHg, and with Dedrick *et al.*,[30] who noted that rats exposed to 1 h of ATP-induced hypotension, maintained their *p*H only because of a decrease in Pa_{CO_2}, resulting in a net base deficit of greater than -10 mEq·l^{-1}. They hypothesized that this acidosis was due to the hydrolysis of ATP with production of phosphate. The amount of acidosis we observed was numerically greater with ATP than adenosine. This acidosis was greater than that we had observed previously in dogs with hypotension induced to the same levels by isoflurane[22] but much less than that observed wtih hypotension to 40 mmHg induced by trimethaphan, halothane, or nitroprusside.[21] ATP-induced hypotension to 57 mmHg in patients has not resulted in metabolic acidosis,[17] while adenosine-induced hypotension to 46 mmHg produced a mild elevation of the arterial lactate concentration.[18] Perhaps the discrepancy in results in patient groups was due to the different hypotensive levels achieved in each group.

The ICP decreased numerically during induced hypotension in three groups but was significant only in the adenosine-induced hypotension to 40 mmHg group. This is in agreement with Van Aken *et al.*,[33] who reported a dose-related increase in ICP during ATP-induced hypotension in dogs with either normal or increased ICP (>20 mmHg). This is felt to be due to vasodilation of both the resistance and capacitance cerebral vessels, the latter being responsible for an increased cerebral blood volume despite a decreased cerebral blood flow. Assuming the same is true in humans, adenosine and ATP should be avoided in patients with intracranial mass lesions before the dura is opened.

The decrease in MAP together with an increase in

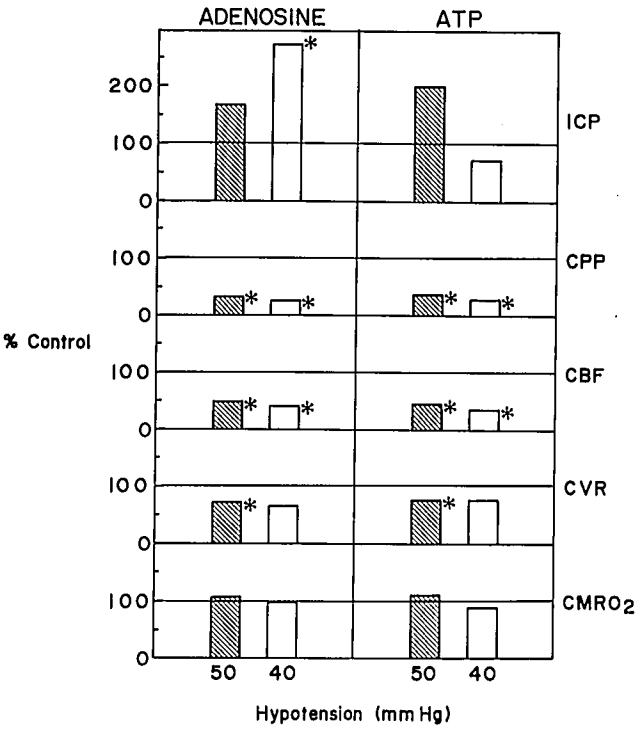

FIG. 2. Changes in cerebral hemodynamic and metabolic variables during hypotension to either 50 mmHg (dark bars) or 40 mmHg (open bars) are presented as per cent of the control normotensive value. Any significant change ($P < 0.05$) is denoted by an asterisk.

ICP resulted in a profound decrease in cerebral perfusion pressure. The CPP was 31–33 mmHg at MAP of 50 mmHg and 22–24 mmHg at MAP of 40 mmHg. Despite a concomitant decrease in CVR, the cerebral blood flow decreased significantly 55–65% in all groups. However, this per cent decrease was exaggerated by the relative hyperdynamic state during the control period in which the anesthetic conditions were less than 1 MAC (70% nitrous oxide, 0.1% halothane). While the decrease in CBF was greater than that reported by others, the actual CBF levels achieved (44–69 ml·100 g^{-1}·min^{-1}) at an MAP of 40 mmHg were similar to those reported by Kassell for adenosine.[20] However, the CBF was much less than that reported for ATP,[19] where the CBF decreased only 4%, with a 50% decrease in MAP.

The cerebral oxygen metabolism did not change during hypotension in any group. This is consistent with Maruno *et al.*,[19] who reported no change in CMR_{O_2} with ATP-induced hypotension, and Kassell *et al.*,[20] who reported that with adenosine-induced hypotension there was either no change or a significant increase in CMR_{O_2}. Their reported values are similar to those observed in this study. It has been shown that intracarotid injections of ATP produce an accumulation of cAMP in brain cells,[34] which results in increased oxygen con-

sumption and increased anaerobic metabolism both by the increased action of adenylate cyclase and by the effect of cAMP on other systems within the cell.[35] The cerebral blood flow, although 44–69 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, was apparently inadequate to fully supply the oxygen demand. Analysis of cerebral metabolites from cortical brain biopsies revealed a small but significant increase in cerebral lactate indicative of anaerobic metabolism. This, together with a modest decrease in ATP concentration, does not support the presumption of Kassell *et al.*[20] that the degree of cerebral vasodilation associated with adenosine hypotension is in proportion to that required to sustain an adequate level of blood flow to the brain. Our observation of disturbed metabolism with either ATP or adenosine-induced hypotension is similar to that observed for trimethaphan and nitroprusside[21] but is in contrast to hypotension induced by isoflurane in which the cerebral energy state remains normal. The latter is explained by the decrease in CMR_{O_2}, produced by isoflurane, which occurs in parallel with the decrease in oxygen delivery.[22]

In conclusion, both ATP and adenosine easily and rapidly can induce hypotension. It is easy to control the hypotension, and there is no evidence of tachyphylaxis. Because of the marked decrease in systemic vascular resistance, cardiac index usually is maintained, although a mild lactic acidosis may develop. In this respect, adenosine and ATP may be superior or equal to other agents. However, the decreased cerebral blood flow at profound hypotensive levels as produced by ATP or adenosine may be inadequate to meet the sustained cerebral oxygen demands resulting in some cerebral anaerobic metabolism. In this respect, adenosine or ATP may be inferior to isoflurane-induced hypotension, which decreases metabolism together with CBF. Adenosine or ATP may not be the agent of choice in those surgical procedures, which may compromise the cerebral circulation.

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