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The Effect of Adenosine-induced Hypotension on Systemic and Splanchnic Hemodynamics during Halothane or Sevoflurane Anesthesia in the Rat

Mark W. Crawford, M.B.B.S., F.R.C.P.C., Jerrold Lerman, M.D., F.R.C.P.C.,† Victor Saldivia, B.Sc.,‡ Hector Orrego, M.D., F.R.C.P.C.,§ Frederick J. Carmichael, Ph.D., M.D., F.R.C.P.C.‖*

Background: **It has been suggested that the liver may be at risk for ischemic damage during adenosine-induced hypotension. This notion, however, is somewhat inconsistent with the understanding that adenosine is a powerful vasodilator of the splanchnic circulation. To help clarify the effect of adenosine-induced hypotension on splanchnic hemodynamics, we studied the systemic and splanchnic hemodynamic responses to adenosine, both alone and in the presence of halothane or sevoflurane.**

Methods: **Systemic and splanchnic hemodynamics were determined during the infusion of adenosine in 36 rats allocated randomly to one of three study groups: (1) awake, (2) halothane anesthesia (1.0 MAC), or (3) sevoflurane anesthesia (1.0 MAC). Adenosine was infused at a rate sufficient to decrease the mean arterial pressure by 35–38% from awake control values. Cardiac output and organ blood flows were measured using the radiolabeled microsphere technique.**

Results: **Adenosine infusion produced stable hypotension of rapid onset due to a reduction in systemic vascular resistance. Stroke volume increased, but cardiac output remained unchanged in the awake and sevoflurane groups because of a decrease in heart rate. Infusion of adenosine during halothane anesthesia increased cardiac output enough to compensate for the decrease in cardiac output due to halothane alone. In the splanchnic circulation, there was an increase in portal tributary (42%, $P < 0.01$) and hepatic arterial (38%, $P < 0.05$) blood flows during adenosine infusion in awake rats. This resulted in an overall increase in total liver blood flow (42%, $P < 0.01$). Halothane anesthesia was associated with a decrease in portal tributary blood flow (28%, $P < 0.05$). In contrast, sevoflurane anesthesia was associated with an increase in hepatic arterial flow (35%, $P < 0.05$) but with no change in portal tributary blood flow. During halothane anesthesia, adenosine infusion increased portal tributary (90%, $P < 0.01$) and hepatic arterial (37%, $P < 0.05$) blood flows, thereby increasing total liver blood flow to values similar to those in awake adenosine-infused rats. During sevoflurane anesthesia, adenosine infusion increased portal tributary blood flow (48%, $P < 0.01$), but hepatic arterial blood flow did not increase beyond the values observed during sevoflurane anesthesia alone.**

Conclusions: **These findings demonstrate that adenosine is a potent vasodilator of portal tributary and hepatic arterial vasculature in the rat and that the splanchnic hemodynamic effects of adenosine predominate over those of halothane and sevoflurane. (Key words: Anesthetic techniques: deliberate hypotension. Anesthetics, volatile: halothane; sevoflurane. Interactions (drug). Liver: blood flow. Measurement techniques: blood flow; microspheres. Pharmacology: adenosine.)**

* Lecturer in Anesthesia, Department of Anesthesia and the Research Institute, The Hospital for Sick Children; the Department of Anesthesia, University of Toronto.

† Associate Professor of Anesthesia, Department of Anesthesia and the Research Institute, The Hospital for Sick Children; the Department of Anesthesia, University of Toronto.

‡ Research Assistant, the Department of Pharmacology, University of Toronto.

§ Professor of Pharmacology and Medicine, the Department of Pharmacology, University of Toronto.

‖ Associate Professor of Anesthesia, Department of Anesthesia, Toronto Western Hospital; the Departments of Anesthesia and Pharmacology, University of Toronto.

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Address reprint requests to Dr. Carmichael: Department of Anesthesia, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8.

INDUCED hypotension is an anesthetic technique that has been shown to reduce operative blood loss and transfusion requirements.[1,2] The safe use of this technique requires a clear understanding of the hemodynamic and organ blood flow responses to the hypotensive agent. Adenosine, a naturally occurring purine nucleoside, has been used to induce hypotension during neurosurgery,[3] pheochromocytoma surgery,[4] and major vascular surgery.[5] Previous studies have focused mainly on the cerebral,[6–8] coronary,[5,9,10] and renal[11] hemodynamic responses to adenosine-induced hypotension. The few studies that have examined splanchnic hemodynamics during adenosine-induced hypotension have yielded variable results. Some studies have re-

ported an increase in liver blood flow during the administration of adenosine.[12–14] Others have reported either no change[15,16] or a decrease[7,17] in liver blood flow during adenosine-induced hypotension. On the basis of the latter studies, it recently has been suggested that the liver may be at risk for ischemic damage during adenosine-induced hypotension.# This notion, however, is somewhat inconsistent with our understanding that adenosine is a powerful vasodilator of the splanchnic circulation and possible mediator of the "hepatic arterial buffer response."[18,19]

The reason for the discrepancy among these studies is unclear. One important difference among the studies is that some studies involved awake animals, whereas others involved animals anesthetized with a variety of anesthetics. Anesthetics differ widely in their effects on the splanchnic circulation.[20] It is possible, therefore, that anesthetic-induced alterations in splanchnic hemodynamics might have contributed in part to the different results. However, the interaction between adenosine and anesthetic agents has not been investigated. We sought to determine whether the systemic and splanchnic hemodynamic responses to adenosine infusion would be altered by the presence of potent inhaled anesthetic agents.

Materials and Methods

After approval of the protocol by the Animal Care Committee, Sprague-Dawley rats (Charles River Breeding Laboratories, Quebec, Canada) weighing 250–340 g were studied. The rats were housed in a temperature- and humidity-controlled environment with a 12-h light–dark cycle and fasted, with water freely available, for 16–18 h before experimentation.

Surgical Preparation

During ether anesthesia, polyethylene catheters (PE 50, Tygon, Beck and Dickson, Parsippany, NJ) were inserted into: (1) the left femoral artery for blood pressure monitoring, blood sampling, and reference sample withdrawal; (2) the left internal jugular vein for infusion of saline or adenosine; and (3) the left ventricle *via* the right common carotid artery for injection of radioactive microspheres, as described previously.[21,22] Placement of the catheter into the left ventricle was verified by observation of the blood pressure waveform. Catheters were capped with rubber injection ports and tunneled subcutaneously to the rat's midback, where they were brought to the skin surface. The incisions were infiltrated with lidocaine and sutured. After surgical preparation (20–25 min), the rats were allowed to recover in a temperature-controlled environment for 3–4 h. There was no obvious evidence of stress or pain during recovery, and the rats resumed their usual behavior. In a previous study, we have shown that indices of stress such as blood glucagon concentration, mean arterial pressure, and heart rate remain unchanged after these operative procedures.[21]

Experimental Design

Thirty-six rats were assigned randomly to one of three study regimens: (1) awake (n = 16), (2) halothane anesthesia (1.0 MAC) (n = 10), or (3) sevoflurane anesthesia (1.0 MAC) (n = 10). The MAC values for halothane and sevoflurane in the rat had been determined previously.[22] The rats were placed individually in cylindrical Plexiglas chambers through which oxygen, at a flow rate of 5 $l \cdot min^{-1}$, was administered to prevent rebreathing of exhaled gases.

In awake rats, a maintenance infusion of normal saline was commenced, and control hemodynamic data were recorded. Cardiac output and organ blood flows were determined using ^{57}Co-labeled microspheres. Adenosine was infused at a rate sufficient to reduce the mean arterial pressure by 35–38%. Hemodynamic data were recorded; cardiac output and organ blood flow measurements were repeated using ^{46}Sc-labeled microspheres; and blood (1.0 ml) was sampled for arterial blood gas determination (blood gas analyzer, Corning Canada, Ontario, Canada).

In the anesthetized groups, a maintenance infusion of normal saline was commenced, and the rats were anesthetized with either halothane (1.0 MAC) or sevoflurane (1.0 MAC). Hemodynamic data were recorded 30 min after the onset of anesthesia, and cardiac output and organ blood flows were determined using ^{57}Co-labeled microspheres. Adenosine was infused at a rate sufficient to reduce the mean arterial pressure by 35–38%. Hemodynamic data were recorded; cardiac output and organ blood flow measurements were repeated using ^{46}Sc-labeled microspheres; and blood (1.0 ml) was sampled for arterial blood gas determination.

Sperry RJ, Longnecker DE: Regional blood flow changes during induced hypotension. Current Opinion in Anesthesiology 1:94–100, 1988.

All measurements were performed after at least 20 min of stable hemodynamics during spontaneous ventilation. In previous studies, values for cardiac output and organ blood flows obtained with the ^{46}Sc-labeled microspheres were similar to those obtained with the ^{57}Co-labeled microspheres, demonstrating the stability of this technique for measuring organ blood flows.** Throughout the current study, normothermia was maintained using radiant heating lamps. Anesthetic concentration was monitored using an infrared medical gas analyzer (model LB 2, SensorMedics, Anaheim, CA) that had been calibrated before use in 1% increments from 0 to 4% using halothane and sevoflurane standards prepared in air. Rectal temperature taken at the end of the experiments was 36.9 ± 0.3° C (mean ± SEM).

Hemodynamic and Organ Blood Flow Measurements

Arterial blood pressure was measured with a pressure transducer and recorded continuously using a physiograph (Narco Biosystems, Houston, TX). Heart rate was determined from the blood pressure waveform. Cardiac output and organ blood flows were measured using 16.5 ± 0.1-μm diameter radiolabeled microspheres (New England Nuclear, Boston, MA). The microspheres, prepared as described in a previous publication,[23] were suspended in 10% dextran containing 1 drop Tween-80, agitated for 10 min using a Vortex mixer, and aspirated into polyethylene tubing for γ scintillation counting (counter model 1185, Nuclear Chicago, Chicago, IL) before injection.

Approximately 50,000 microspheres were infused into the left ventricle over 20 s with an infusion pump. A 0.6-ml reference sample that contained 300–400 microspheres was obtained from the femoral artery using a withdrawal pump that had begun to aspirate blood 10 s before the infusion of microspheres and that continued for 60 s. The presence of this number of microspheres in the reference sample has been shown to yield an accurate estimate of cardiac output.[24] An equal volume of Ficoll (0.6 ml, 13% weight/volume, Sigma Chemical, St. Louis, MO), a nonionic synthetic polymer of sucrose, was flushed through the microsphere infusion tubing to replace the volume of blood sampled. The net counts infused were the difference between the counts obtained before injection into the left ventricle and those remaining in the polyethylene tubing. The infusion of microspheres and the withdrawal of the reference sample had no demonstrable effect on the monitored hemodynamic variables.

At the termination of the study, the rats were killed with intravenous potassium chloride, and the following organs were removed and placed in saline-containing vials for analysis of radioactivity: lungs, heart, liver, kidneys, spleen, stomach, omentum, pancreas, and small and large intestines. All organs were analyzed intact, with the exception of the liver and small intestine, each of which was divided into five sections. The mixing of microspheres in the circulation was considered to be adequate if the difference between the right and left renal blood flows was less than 15%. No animal was eliminated from the study on the basis of this criterion.

Calculations

Mean arterial blood pressure was calculated as diastolic pressure plus one third of the pulse pressure. Correction was made for overlap during counting of the radioisotopes. Cardiac index (Qt) (milliliters per minute per kilogram body weight) was calculated by the equation

$$Qt = \frac{Ci \cdot R}{Cr \cdot w}$$

where Ci = net counts injected; R = reference sample withdrawal rate; Cr = net counts in the reference sample; and w = body weight (kilograms). Organ blood flow (Qo) (milliliters per minutes per kilogram body weight) was calculated by the equation

$$Qo = \frac{Qt \cdot Co}{Ci}$$

where Co = net counts in the organ. Indexed systemic vascular resistance (mmHg per milliliter times minutes times kilograms) was calculated as the ratio of the mean arterial pressure to cardiac index. Central venous pressure was assumed to approximate zero. Stroke volume index (milliliters per kilogram) was calculated as the ratio of the cardiac index to heart rate. Organ vascular resistances (mmHg per milliliter times minutes times kilograms) were calculated as the ratio of the mean arterial pressure to organ blood flow.

Portal tributary blood flow (PTBF) was calculated as the sum of the blood flow to the spleen, stomach, omentum, pancreas, small intestine, and large intestine.

** Carmichael FJ, Crawford MW, Saldivia V: Unpublished observations. 1990.

Table 1. Effect of Adenosine on Systemic Hemodynamics and Organ Blood Flows

	Awake		Halothane		Sevoflurane	
	Control	Adenosine	1 MAC	1 MAC + Adenosine	1 MAC	1 MAC + Adenosine
MAP	105 ± 2	68 ± 3*	92 ± 5	65 ± 3*‡	104 ± 4§	67 ± 3*‖
SVR	0.46 ± 0.02	0.28 ± 0.02*	0.53 ± 0.04	0.28 ± 0.01*‡	0.44 ± 0.03§	0.29 ± 0.03*‖
SVI	0.69 ± 0.04	0.88 ± 0.06†	0.55 ± 0.04#	0.77 ± 0.04**	0.67 ± 0.03	0.78 ± 0.05††
HR	360 ± 15	302 ± 10*	320 ± 8#	307 ± 11*	352 ± 7	311 ± 6††
Qt	244 ± 12	261 ± 19	173 ± 11†	234 ± 13§	238 ± 8§	241 ± 23
Blood flow						
PT	41.7 ± 2.0	59.4 ± 4.5†	29.9 ± 1.6#	57.1 ± 3.6#**	39.8 ± 3.4	59.0 ± 10.7#‡‡
HA	9.9 ± 1.2	13.7 ± 1.3#	11.5 ± 1.2	15.8 ± 1.5†§	13.4 ± 1.4#	14.4 ± 1.5#
TL	51.6 ± 2.3	73.1 ± 3.5†	41.4 ± 1.8	72.9 ± 4.3†‡	53.2 ± 3.8	73.4 ± 11.2†††
Gastric	3.8 ± 0.3	7.5 ± 0.8*	2.4 ± 0.2	5.7 ± 0.8§	2.5 ± 0.2	6.2 ± 1.5#‡‡
Splenic	5.4 ± 0.3	6.9 ± 1.0	3.1 ± 0.2#	6.1 ± 1.0§	3.8 ± 0.4	5.4 ± 1.0
SI	24.3 ± 1.8	38.4 ± 2.5†	19.1 ± 1.2	35.3 ± 2.2‡#	26.4 ± 2.8	38.6 ± 8.0†††
LI	8.2 ± 0.7	9.0 ± 0.8	6.4 ± 0.7	10.1 ± 1.5§	7.0 ± 1.0	8.9 ± 2.1
Renal	42.5 ± 3.1	42.8 ± 4.3	33.9 ± 3.5	41.3 ± 2.6	44.6 ± 3.6	48.9 ± 6.3

Values are mean ± SEM.

MAP = mean arterial pressure (mmHg); SVR = systemic vascular resistance ($mmHg \cdot ml^{-1} \cdot kg \cdot min$); SVI = stroke volume index ($ml \cdot kg^{-1}$); HR = heart rate ($beats \cdot min^{-1}$; Qt = cardiac index ($ml \cdot min^{-1} \cdot kg^{-1}$); organ blood flows ($ml \cdot min^{-1} \cdot kg^{-1}$): PT = portal tributary; HA = hepatic arterial; TL = total liver; SI = small intestinal; LI = large intestinal.

* $P < 0.001$ *versus* awake control.

† $P < 0.01$ *versus* awake control.

‡ $P < 0.001$ *versus* halothane 1 MAC.

§ $P < 0.05$ *versus* halothane 1 MAC.

‖ $P < 0.001$ *versus* sevoflurane 1 MAC.

\# $P < 0.05$ *versus* awake control.

** $P < 0.01$ *versus* halothane 1 MAC.

†† $P < 0.05$ *versus* sevoflurane 1 MAC.

‡‡ $P < 0.01$ *versus* sevoflurane 1 MAC.

The contribution of blood flows from the pancreas and omentum, which cannot be readily isolated in the rat, was included in the flows to the small and large intestines. The accuracy of this method as an estimate of PTBF is well validated.[23–25] Hepatic arterial blood flow (HABF) was determined from the net counts within the liver. Total hepatic blood flow (TLBF) was calculated as the sum of PTBF and HABF.

Cardiac output, stroke volume, organ blood flows, and vascular resistances were indexed to body weight (kilograms). Because the relationship of organ weight to body weight did not change during the study period, there were no differences in the conclusions derived with this expression as opposed the expression of blood flows per gram organ.

Data are presented as mean ± SEM. Data were analyzed with one-way analysis of variance using SAS programming (SAS Institute, Cary, NC). Comparisons with awake control and between anesthetized animals were done by the least-significant-difference method.[26] $P < 0.05$ was considered statistically significant.

Results

Effect of Adenosine in Awake Rats

In awake rats, adenosine was infused at a rate of 1.2 ± 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ to decrease the mean arterial pressure by 35% compared with control values ($P < 0.001$) (table 1). Infusion of adenosine was associated with a 39% ($P < 0.001$) decrease in systemic vascular resistance (table 1). Stroke volume index increased by 28% ($P < 0.01$) and heart rate decreased by 16% ($P < 0.001$), with the result that cardiac index remained unchanged (table 1). In the splanchnic circulation, infusion of adenosine was associated with a marked decrease in both portal tributary and hepatic arterial vascular resistances (table 2). PTBF and HABF increased

Table 2. Effect of Adenosine on Vascular Resistances

	Awake		Halothane		Sevoflurane	
	Control	Adenosine	1 MAC	1 MAC + Adenosine	1 MAC	1 MAC + Adenosine
PT	2.5 ± 0.2	1.3 ± 0.1*	3.1 ± 0.3†	1.2 ± 0.1*‡	2.8 ± 0.2	1.4 ± 0.3*§
HA	13.7 ± 1.6	5.6 ± 0.5*	9.4 ± 1.6†	4.3 ± 0.3*‖	9.1 ± 0.9#	5.1 ± 0.6*,**
Gastric	30.9 ± 3.4	10.3 ± 1.0*	38.9 ± 3.0	11.5 ± 1.3*‡	44.4 ± 3.4#	12.8 ± 4.7*§
Splenic	19.4 ± 1.4	13.2 ± 2.7	30.3 ± 1.8#	14.2 ± 3.3‡	31.2 ± 3.4#	14.7 ± 2.7§
SI	4.5 ± 0.5	1.9 ± 0.2*	4.9 ± 0.4	1.9 ± 0.1*‡	4.5 ± 0.5	2.1 ± 0.4*§
LI	12.8 ± 1.5	8.5 ± 0.8	16.5 ± 2.6	7.7 ± 1.3‖	18.1 ± 2.3†	10.4 ± 2.8**
Renal	2.6 ± 0.2	1.9 ± 0.3†	2.7 ± 0.3	1.7 ± 0.1#	2.3 ± 0.2	1.7 ± 0.3

Values are mean ± SEM.

Vascular resistances (mmHg · ml^{-1} · kg · min): PT = portal tributary; HA = hepatic arterial; SI = small intestinal; LI = large intestinal.

* $P < 0.001$ *versus* awake control.

† $P < 0.05$ *versus* awake control.

‡ $P < 0.001$ *versus* halothane 1 MAC.

§ $P < 0.001$ *versus* sevoflurane 1 MAC.

‖ $P < 0.01$ *versus* halothane 1 MAC.

# $P < 0.01$ *versus* awake control.

** $P < 0.05$ *versus* sevoflurane 1 MAC.

by 42% ($P < 0.01$) and 38% ($P < 0.05$) respectively (table 1). These changes resulted in an increase in TLBF of 42% ($P < 0.01$) during the infusion of adenosine (table 1). The increase in PTBF resulted primarily from an increase in small intestinal blood flow of 58% ($P < 0.01$) (table 1). Gastric blood flow increased during adenosine infusion, but splenic, large intestinal, and total renal blood flow did not increase significantly (table 1). Adenosine did not affect microsphere accumulation in the lungs, either in awake or anesthetized rats, suggesting that under the conditions of the current study adenosine did not produce systemic shunting. Arterial blood gases during adenosine infusion in awake rats were *p*H = 7.42 ± 0.02; carbon dioxide tension = 35 ± 3 mmHg; and oxygen tension = 389 ± 15 mmHg.

Effect of Halothane Anesthesia

Halothane anesthesia alone (1.0 MAC) was associated with a decrease in mean arterial pressure of 13% ($P < 0.01$), while systemic vascular resistance remained unchanged (table 1). Stroke volume index and heart rate decreased by 20% ($P < 0.05$) and 11% ($P < 0.05$), respectively. These changes resulted in a decrease in cardiac index of 29% ($P < 0.01$) compared with control measurements (table 1). In the splanchnic circulation, portal tributary vascular resistance increased by 24% ($P < 0.05$) (table 2) and PTBF decreased by 28% ($P < 0.05$) (table 1). HABF and TLBF did not change significantly (table 1). The effect of halothane on gastric, splenic, intestinal, and on renal blood flows and vascular resistances is shown in tables 1 and 2, respectively.

Effect of Adenosine during Halothane Anesthesia

During anesthesia with 1.0 MAC halothane, adenosine was infused at a rate of 0.45 ± 0.05 mg · kg^{-1} · min^{-1} ($P < 0.001$ *vs.* awake rats) to decrease the mean arterial pressure by 38% compared with awake control values ($P < 0.001$) (table 1). Infusion of adenosine was associated with a 47% decrease in systemic vascular resistance ($P < 0.001$) compared with values observed during halothane anesthesia alone (table 1). Stroke volume index increased by 40% ($P < 0.01$), whereas heart rate remained unchanged, resulting in an increase in cardiac index of 35% ($P < 0.05$) compared with values observed during halothane anesthesia alone (table 1). In the splanchnic circulation, both portal tributary and hepatic arterial vascular resistances decreased during infusion of adenosine (table 2), and the respective blood flows increased by 90% ($P < 0.01$) and 37% ($P < 0.05$) (table 1). These changes resulted in an increase in TLBF of 76% ($P < 0.001$), which more than compensated for the decrease in TLBF produced by halothane alone (table 1). The changes in gastric, splenic, intestinal and renal blood flows induced by adenosine during halothane anesthesia are shown in table 1. Arterial blood gases were *p*H = 7.35 ± 0.03; carbon dioxide tension = 46 ± 3 mmHg; and oxygen

tension = 391 ± 12 mmHg. The values for arterial *p*H and arterial oxygen tension did not differ significantly from awake values.

Effect of Sevoflurane Anesthesia

Sevoflurane anesthesia alone (1.0 MAC) had minimal effects on the systemic hemodynamic variables studied (table 1). In the splanchnic circulation, both portal tributary vascular resistance (table 2) and PTBF (table 1) remained unchanged during sevoflurane anesthesia. Hepatic arterial vascular resistance, however, decreased by 34% ($P < 0.05$) (table 2) and HABF increased by 35% ($P < 0.05$) (table 1) compared with control values. The increase in HABF was not sufficient to change TLBF significantly (table 1). The effect of sevoflurane on gastric, splenic, intestinal, and renal blood flows and on vascular resistances is shown in tables 1 and 2, respectively.

Effect of Adenosine during Sevoflurane Anesthesia

During anesthesia with 1.0 MAC sevoflurane, adenosine was infused at a rate of 0.57 ± 0.05 mg · kg^{-1} · min^{-1} ($P < 0.001$ *vs.* awake rats) to decrease the mean arterial pressure by 36% compared with awake control values ($P < 0.001$) (table 1). Infusion of adenosine was associated with a 34% ($P < 0.001$) reduction in systemic vascular resistance compared with values observed during sevoflurane anesthesia alone (table 1). The changes in stroke volume index, heart rate, and cardiac index were similar to those observed in the awake state (table 1). In the splanchnic circulation, portal tributary vascular resistance decreased during infusion of adenosine (table 2), and PTBF increased by 48% ($P < 0.01$) (table 1). HABF did not increase beyond the values observed during sevoflurane anesthesia alone (table 1). TLBF, however, increased by 38% ($P < 0.05$) (table 1). The changes in gastric, splenic, intestinal, and renal blood flows induced by adenosine during sevoflurane anesthesia are shown in table 1. Arterial blood gases were *p*H = 7.36 ± 0.05; carbon dioxide tension = 45 ± 4 mmHg; and oxygen tension = 411 ± 12 mmHg. The values for arterial *p*H and arterial oxygen tension did not differ significantly from those in awake or halothane anesthetized rats.

Discussion

Adenosine, an endogenous nucleoside involved in several biologic processes, has been used to induce controlled hypotension during surgery[3–5,8,10] and to diagnose and treat supraventricular tachycardias.[27] In contrast to the use of other vasodilators, such as sodium nitroprusside and nitroglycerin, adenosine infusion produces stable hypotension of rapid onset with no evidence of biochemical or hematologic toxicity and with no tachyphylaxis or rebound hypertension. Adenosine has an extremely short half-life[28] due to rapid uptake into cells, resulting in a rapid termination of action when administration is discontinued.

Despite these attributes, adenosine has not been accepted as a hypotensive agent of great clinical significance. This lack of enthusiasm may be attributed in part to the wide spectrum of biologic effects produced by this ubiquitous nucleoside. Among these are effects such as atrioventricular nodal block,[27] coronary "steal,"[29] and transient renal vasoconstriction.[30] In addition, some authors have suggested the possibility of splanchnic ischemia during adenosine infusion.#

The current study was designed to determine the systemic and splanchnic hemodynamic responses to adenosine administration, both alone and in the presence of potent inhaled anesthetics. Two inhaled anesthetics that have considerably different effects on splanchnic hemodynamics[22] were chosen to study their interaction with adenosine. A well established method involving radioactive microspheres, was used to determine systemic and splanchnic hemodynamics.[21–25] Awake, control values were determined in unrestrained animals, and these agreed with those previously reported.[12,14,21,23–25] All hemodynamic measurements were obtained during spontaneous ventilation. This experimental design avoided hemodynamic alterations due to positive pressure ventilation and ensured that all measurements were unaffected by the presence of other drugs. It did, however, lead to a small increase in arterial carbon dioxide tension in the anesthetized animals. This degree of hypercarbia is less than that associated with significant hemodynamic effects on the splanchnic circulation[31] and is therefore unlikely to have contributed to the observed hemodynamic alterations. In addition, none of the animals, either awake or anesthetized, became hypoxic.

Adenosine infusion produced stable hypotension of rapid onset resulting from systemic arterial vasodilation, as shown previously in animals[6,9,15,16] and in humans.[3,8,10,13] This effect is mediated *via* A_2 adenosine receptors present in endothelial and vascular smooth muscle cells.[32] Stroke volume increased most likely

because of the afterload reduction, but cardiac output, because of a decrease in heart rate, remained unchanged in the awake and sevoflurane groups. Halothane attenuated the bradycardia induced by adenosine, and infusion of adenosine during halothane anesthesia resulted in an increase in cardiac output that was sufficient to compensate for the decrease due to halothane alone. The bradycardia induced by adenosine infusion[6,9,15,17,33] contrasts with the increase in heart rate induced by a variety of other vasodilators. This effect is mediated *via* A_1 adenosine receptors present in the sinoatrial node[27] and may facilitate the induction of hypotension. However, activation of A_1 receptors in the atrioventricular node produces a transient, but undesirable, block of atrioventricular nodal conduction in humans.[34] The development of analogues of adenosine selective for the A_2 receptors may make it possible to avoid this unwanted effect on atrioventricular nodal conduction while maintaining the more desirable A_2-mediated attributes of the parent nucleoside. Like adenosine, however, these A_2-selective analogues would still have the potential to induce coronary steal and myocardial ischemia in susceptible individuals with coronary artery disease.[29]

Whereas it is generally accepted that adenosine is a potent vasodilator of the coronary circulation,[9,10] the marked sensitivity of the splanchnic circulation to adenosine is less widely appreciated. The role of adenosine in the control of HABF, the hepatic arterial buffer response, is well established.[35,36] This physiologic response to adenosine is mediated *via* A_2 adenosine receptors present in the hepatic arterial microvasculature.[37] In keeping with this vasodilator role, adenosine administration in the current study produced considerable vasodilation of both preportal and hepatic arterial vasculature, resulting in a marked increase in PTBF and HABF. These dose-related responses to adenosine have been shown to be attenuated by the A_1–A_2-adenosine receptor antagonist 8-phenyltheophylline.[12,14,35,38] The increase in PTBF in the current study resulted primarily from an increase in small intestinal and gastric blood flows, demonstrating that adenosine did not affect all splanchnic vascular beds equally. The increase in HABF is of particular importance because oxygen delivery to the liver depends to a large extent on HABF.[20] Contrary to the suggestion,‖ therefore, that adenosine-induced hypotension may place the liver at risk for ischemic damage, the current study demonstrates that at the level of hypotension studied, adenosine-induced hypotension is associated with an increase in blood flow and oxygen supply to the splanchnic organs.

A previous study reported a reduction in liver blood flow during profound hypotension induced by adenosine in dogs anesthetized with halothane.[6] Because halothane anesthesia has been associated with a reduction in liver blood flow,[20] it is conceivable that either halothane or the degree of hypotension, or both, might have contributed to the profound reduction in liver blood flow observed in that study. Indeed, this notion prompted us to investigate the interaction between adenosine and potent inhaled anesthetics during more moderate degrees of hypotension. Under the conditions of the current study, adenosine infusion was associated with an increase in splanchnic blood flow, even in the presence of halothane anesthesia. In fact, the adenosine-induced increase in PTBF was more than sufficient to reverse completely the reduction in PTBF produced by halothane. This finding demonstrates that the splanchnic circulatory effects of adenosine predominate over those of halothane. The reason, therefore, for the reduction in liver blood flow reported in the dogs[6] remains speculative, but most likely it is attributable to the degree of hypotension studied or to the metabolic acidosis[39] that developed during hypotension in the dogs.

In agreement with a previous study in rats,[40] renal blood flow and renal vascular resistance remained unchanged during adenosine infusion. In other species, including human beings, adenosine has been shown to produce renal vasoconstriction associated with a dose-dependent decrease in renal blood flow, glomerular filtration rate, renin secretion, and urine output.[30,41] The reduction in renal blood flow is transient, returning to or above preinfusion levels during continuous infusion of adenosine,[30] and has no long-term effect on renal function in humans.[41] Studies in animals suggest that the initial renal vasoconstriction is mediated *via* the A_1-adenosine receptor present in preglomerular arterioles. In contrast, analogues of adenosine selective for the A_2 receptor have been shown to produce renal vasodilation and an increase renal blood flow,[42] suggesting that the use of A_2-selective analogues of adenosine to induce hypotension during anesthesia could potentially avoid the reductions in renal blood flow, glomerular filtration rate, and urine output associated with adenosine administration.

An inhibition of the hepatic arterial buffer response by halothane and enflurane has been shown.[43,44] The current results with halothane would support this pro-

posal. However, in the current study we observed three distinct patterns of blood flow relationships between the portal vein and the hepatic artery. First, both PTBF and HABF increased during infusion of adenosine. Second, PTBF decreased while HABF remained unchanged during halothane anesthesia. Third, PTBF remained unchanged while HABF increased during sevoflurane anesthesia, a response similar to that reported for isoflurane.[14] Moreover, other patterns of blood flow relationships between the portal vein and the hepatic artery have been reported to follow various physiologic and pharmacologic interventions in awake animals.[14] Those findings in awake animals, together with the findings of the current study, support the hypothesis that independent regulation of the two hepatic circulations may occur in a variety of circumstances.[14]

In the current study, sevoflurane produced minimal systemic hemodynamic changes when compared with halothane at an equipotent concentration of 1.0 MAC. This finding is consistent with previous studies in newborn swine[45] and rats[22] but contrasts with the findings in chronically instrumented and ventilated dogs.[46] In the splanchnic circulation, the effects of sevoflurane are consistent with those reported previously.[22,47] Although various authors have shown small differences in the effects of sevoflurane on HABF and portal venous blood flow, this inhalational agent has consistently been shown to maintain total blood flow and oxygen delivery to the liver.[22,46–48] This finding is similar to that reported for isoflurane[14,43,44] but contrasts with that reported for halothane.[20,43,46]

In summary, we have shown that adenosine is a potent vasodilator of the portal tributary and hepatic arterial vasculature in the rat and that blood flow to these circulations increases even when adenosine is infused at rates that reduce the mean arterial pressure by 35–38%. These splanchnic circulatory effects of adenosine predominate over those of halothane and sevoflurane.

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