

## Central and Splanchnic Hemodynamics in the Dog during Controlled Hypotension with Adenosine

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Central and splanchnic hemodynamic effects during controlled hypotension induced by the administration of the endogenous vasodilator adenosine were studied in ten artificially ventilated dogs under neurolept anesthesia. Adenosine was administered as a continuous infusion in the aorta ( $n = 3$ ), in the inferior vena cava ( $n = 3$ ), and after pretreatment with dipyridamole (which inhibits the cellular uptake of adenosine) ( $n = 4$ ) in a dose sufficient to maintain a mean arterial blood pressure (MABP) level of approximately 50 mmHg. Observations were made before and after 20 min of controlled hypotension. Basal arterial plasma levels of adenosine were in the  $10^{-7}$  M range ( $\bar{X} = 0.4 \mu\text{M}$ ). The hemodynamic response was similar in all three settings. Adenosine caused a profound decrease in systemic vascular resistance (SVR) (52%,  $P < 0.01$ ) and preportal vascular resistance (PPR) (64%,  $P < 0.01$ ), while hepatic arterial vascular resistance (HAR) increased by 49% ( $P < 0.05$ ). Cardiac output increased (22%,  $P < 0.05$ ) through increase of stroke volume (77%,  $P < 0.01$ ), while heart rate decreased (28%,  $P < 0.01$ ). Whole-body oxygen uptake decreased (14%,  $P < 0.01$ ). Portal venous blood flow increased by 28% ( $P < 0.05$ ), whereas hepatic arterial blood flow decreased by 70% ( $P < 0.01$ ). In the preportal tissues, oxygen uptake decreased by 21% ( $P < 0.01$ ). In contrast, hepatic oxygen consumption increased (53%,  $P < 0.05$ ). Adenosine-induced hypotension was not associated with changes in plasma renin activity or the plasma concentration of norepinephrine. It is concluded that adenosine causes a rapidly induced and easily maintained hypotension and may be a potentially useful agent for controlled hypotension in patients. (Key words: Anesthetic techniques: hypotension, induced, adenosine. Arteries: hepatic. Liver: metabolism. Polypeptides: renin-angiotensin. Veins: portal.)

THE VASODILATOR PROPERTIES of purines such as adenosine and the adenine nucleotides have been known since the work of Drury and Szent-Györgyi.<sup>1</sup> It is also a well-known fact that exogenously administered purines are degraded and eliminated rapidly in body fluids.<sup>2</sup> In recent years, there has been a growing interest in aden-

osine triphosphate (ATP) as an effective substance for controlled hypotension,<sup>3,4</sup> and ATP also has been used for this purpose in patients.<sup>5</sup> Using a quantitative HPLC method for purine determination, we recently have demonstrated<sup>6</sup> that ATP given by the iv route is degraded entirely to adenosine and its breakdown products during the transpulmonary passage. Furthermore, the hypotensive effect of ATP was related to the arterial adenosine concentration.<sup>6</sup> Since adenosine induces relaxation of vascular smooth muscle,<sup>7</sup> we concluded that adenosine mediates the vasodilator effects of parenterally administered ATP. Moreover, questions have been raised as to whether ATP may have arrhythmogenic effects produced by the chelation of calcium and magnesium.<sup>8</sup> We therefore consider it more appropriate to use adenosine instead of ATP to induce controlled hypotension.

The regional circulatory effects of adenosine have been studied in myocardial,<sup>9,10</sup> cerebral,<sup>11</sup> renal,<sup>12</sup> splanchnic,<sup>13</sup> and subcutaneous<sup>14</sup> vascular beds. There have been few studies on the regional circulatory effects of controlled hypotension with adenosine.<sup>15</sup> In a very recent study<sup>16</sup> it was demonstrated that ischemic tissue damage during profound hypotension with trimetaphan is more apt to occur in the liver than in the brain. The present experimental study was designed to investigate the splanchnic circulatory and metabolic effects as well as central hemodynamics during adenosine-induced hypotension at a mean arterial blood pressure (MABP) of 50 mmHg and to relate these effects to the simultaneous plasma adenosine levels.

### Materials and Methods

Ten mongrel dogs weighing 17–28 kg were studied. They had fasted overnight before the experiments and were not premedicated. Anesthesia was induced with thiopental ( $25 \text{ mg} \cdot \text{kg}^{-1}$ ) intravenously and was maintained with 70% nitrous oxide in oxygen and supplementary doses of thiopental ( $5 \text{ mg} \cdot \text{kg}^{-1}$ ) when needed. Muscle relaxants were not used. The dogs were intubated endotracheally. Ventilation was provided with an Engström ventilator (Engström Medical, Stockholm, Sweden) at a frequency of 20 breaths/min. The minute ventilation was set at  $0.3 \text{ l} \cdot \text{kg}^{-1}$  and, if necessary, adjusted to achieve normocapnia.

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## SURGICAL PREPARATION

The abdomen was opened through a right subcostal incision. The gastroduodenal artery was ligated, and the common hepatic artery and the portal vein were dissected without severing perivascular nerves. Catheters for blood sampling and pressure measurements were placed in the abdominal aorta, pulmonary artery, portal vein, and one hepatic vein. In three dogs an additional catheter was placed in the ascending aorta, and its location was verified by pressure tracings. The aortic catheters were introduced through the femoral arteries and the portal venous catheter via a small mesenteric tributary. The hepatic venous catheter was introduced through the right external jugular vein and placed in the correct position by manual guidance. The correct location of this catheter was verified at autopsy. A triplelumen, balloon-tipped catheter was inserted into the pulmonary artery via the right external jugular vein. The position of this catheter was verified by pressure tracing. Calibrated flow probes were placed on the common hepatic artery and portal vein. Blood flows were measured with square-wave electromagnetic flow meters (Nycotron AS, Drammen, Norway). Cardiac output was measured by thermodilution with a cardiac output computer (Model 9520, Edwards Lab., Santa Ana, California). Systemic and pulmonary arterial, central and portal venous blood pressures and blood flows were recorded continuously on a Polygraph (Grass Instrument Co., Quincy, Massachusetts). The heart rate was determined from a pulsatile pressure or EKG tracing. Blood temperature was measured by the thermistor in the pulmonary artery.

## LABORATORY ANALYSES

Blood gases and acid-base balance were determined by an ABL-1 autoanalyzer (Radiometer, Copenhagen, Denmark). Plasma renin activity and catecholamine concentrations were determined in arterial plasma by a radioimmunoassay method (New England Nuclear Angiotensin I<sup>125</sup> Kit) and by high-performance liquid chromatography (HPLC),<sup>17</sup> respectively.

Blood lactate was measured according to Tfelt-Hansen and Sigaard-Andersen<sup>18</sup> with a spectrophotometer (LKB 7400). Plasma samples (2 ml) for the determination of adenosine were collected in 2 ml of ice-cooled saline containing 20  $\mu$ M dipyridamole (to prevent cellular adenosine uptake) and 10  $\mu$ M EHNA (adenosine-deaminase blocker) as described by Sollevi *et al.*<sup>6</sup> The samples then were purified and analyzed as reported by Fredholm and Sollevi.<sup>19</sup>

## EXPERIMENTAL PROCEDURE

When the surgical preparation was completed, neurolept anesthesia (NLA) was induced with phenoperidine 0.05 mg  $\cdot$  kg<sup>-1</sup> and droperidol 0.2 mg  $\cdot$  kg<sup>-1</sup>. After the

induction of NLA, 30–40 min were allowed to elapse in order to establish a circulatory steady state, whereupon measurements were made. Blood samples for the determination of arterial, portal venous, hepatic venous, and pulmonary arterial oxygen contents and arterial, portal venous, and hepatic venous lactate concentrations were collected together with plasma samples for determining plasma renin activity (PRA) and adenosine and catecholamine concentrations. Cardiac output was determined as a mean of six measurements. These observations, together with the simultaneously recorded circulatory variables, served as the control values with which the changes induced by adenosine were compared. Controlled hypotension then was induced using a 10 mM solution of adenosine. In three dogs, adenosine was infused in the ascending aorta and in seven dogs in the inferior vena cava. Four of these seven dogs received pretreatment with dipyridamole (Persantin®) 0.1–0.2 mg  $\cdot$  kg<sup>-1</sup> given as a slow intravenous bolus dose 5 min before the adenosine infusion. The infusion rate for adenosine was adjusted to achieve a mean arterial blood pressure of approximately 50 mmHg. All measurements then were repeated 20 min after the start of the infusion.

Arterial blood gases and acid-base balance were determined regularly during the surgical preparation and the experimental period. The arterial pH was kept as close to 7.40 as possible. Metabolic acidosis was corrected with 0.6 M sodium bicarbonate. The blood temperature during the experiment was maintained between 36 and 38° C by means of warming pads. To compensate for fluid losses caused by evaporation, exudation, and bleeding, isotonic saline, and Ringer's solution were infused throughout the experiment. The approximate infusion rate was 15 ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup>.

## CALCULATIONS

Vascular resistance was calculated from the formula  $R = \Delta P/Q$ , where R denotes resistance in mmHg  $\cdot$  l<sup>-1</sup>  $\cdot$  min,  $\Delta P$  denotes perfusion pressure in mmHg and Q denotes blood flow in l  $\cdot$  min<sup>-1</sup>. Oxygen content was calculated from the formula  $C_{O_2} = Hb \cdot S_{O_2} \cdot 1.34 + P_{O_2} \cdot 0.03$  by duplicate determinations of hemoglobin concentration and oxygen saturation on a CO-oximeter (IL 282, Lexington, Massachusetts). Oxygen consumption was calculated as the product of the regional arteriovenous oxygen content difference and the corresponding blood flow. Liver oxygen uptake was determined as the sum of the hepatic arterial and portal venous oxygen uptake. Hepatic lactate uptake was calculated in an analogous manner. Oxygen extraction was calculated as oxygen uptake in percentage of oxygen flow and was calculated separately for the hepatic artery and portal vein.

Statistics: Means and standard deviations ( $\bar{X} \pm SD$ ) of control values and results were calculated. To establish

the statistical significance of the observed changes, Student's *t* test for paired data was employed. *P* < 0.05 was considered significant.

### Results

#### DOSES AND PLASMA CONCENTRATIONS OF ADENOSINE

Controlled hypotension was achieved at an adenosine infusion rate of 1.1–1.8  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  when infused in the ascending aorta and 7.9–15.9  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  when given in the vena cava. The required iv dose could be reduced to 0.7–3.2  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  by pretreatment with dipyridamole 0.1–0.2 mg  $\cdot \text{kg}^{-1}$ . The arterial plasma concentration of dipyridamole was then 0.1–0.4  $\mu\text{M}$ . The basal arterial plasma level of adenosine was 0.38  $\mu\text{M}$  (range 0.07–0.66, *n* = 10). The corresponding levels during hypotension were 7.9–41.6  $\mu\text{M}$  ( $\bar{X}$  = 22.6  $\mu\text{M}$ , *n* = 6) without dipyridamole and 3.0–10.7  $\mu\text{M}$  ( $\bar{X}$  = 5.6  $\mu\text{M}$ , *n* = 4) when dipyridamole was used.

Adenosine levels in the portal venous plasma during hypotension were 0.5–5.9  $\mu\text{M}$  ( $\bar{X}$  = 2.1  $\mu\text{M}$ , *n* = 6) without dipyridamole and 0.7–2.6  $\mu\text{M}$  ( $\bar{X}$  = 1.4  $\mu\text{M}$ , *n* = 4) when dipyridamole was used. Mean recovery of adenosine in portal venous plasma amounted to 16% of the arterial levels.

#### CIRCULATORY EFFECTS (TABLE 1)

MABP decreased from 110 to 53 mmHg (53%) within 1 min from infusion start. Cardiac index increased from 113 to 138  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (22%). The heart rate decreased by 28% from 121 to 87  $\text{beats} \cdot \text{min}^{-1}$ , and stroke volume index increased from 0.94 to 1.66  $\text{ml} \cdot \text{kg}^{-1}$ . There was an increase in right atrial pressure from 2.0 to 4.0 mmHg and in PCWP from 3.5 to 4.7 mmHg. Portal venous pressure was unchanged. The hepatic arterial blood flow decreased by 70%, while the portal venous blood flow increased by 28%. The total hepatic blood flow was unchanged. Systemic vascular resistance decreased by 62% and preportal vascular resistance by 64%. The hepatic arterial resistance increased by 49%. The hemodynamic response to adenosine demonstrated a similar pattern irrespective of whether infusion was given in the aorta or vena cava, with or without dipyridamole pretreatment.

#### METABOLIC EFFECTS (TABLE 2)

The total oxygen consumption decreased by 14% and the arteriovenous oxygen content difference by 32%. Preportal tissue oxygen uptake also was decreased, while hepatic oxygen uptake was increased by 53%, causing an increase in hepatic oxygen extraction from the portal vein.

TABLE 1. Central and Splanchnic Circulatory Data during Adenosine Infusion in 10 Dogs.

	Control	Adenosine
Mean arterial blood pressure (mmHg)	110 ± 12	53 ± 4*
Pulmonary capillary wedge pressure (mmHg)	3.5 ± 1.3	4.7 ± 1.7†
Right atrial pressure (mmHg)	2.0 ± 2.1	4.0 ± 2.5*
Portal venous pressure (mmHg)	10.3 ± 3.8	9.8 ± 4.2
Cardiac index ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	113 ± 27	138 ± 40†
Stroke volume index ( $\text{ml} \cdot \text{kg}^{-1}$ )	0.94 ± 0.23	1.66 ± 0.63*
Heart rate ( $\text{beats} \cdot \text{min}^{-1}$ )	121 ± 12	87 ± 19*
Hepatic arterial blood flow ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	12.3 ± 5.1	3.7 ± 1.3*
Portal venous blood flow ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	29.9 ± 8.9	38.3 ± 15.7†
Total hepatic blood flow ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	42.2 ± 11.2	42.0 ± 15.9
Portal venous fraction of cardiac output (%)	27 ± 8	29 ± 10
Systemic vascular resistance ( $\text{mmHg} \cdot \text{l}^{-1} \cdot \text{min}$ )	44.8 ± 11.3	17.0 ± 4.5*
Hepatic arterial vascular resistance ( $\text{mmHg} \cdot \text{l}^{-1} \cdot \text{min}$ )	452 ± 172	672 ± 244†
Preportal vascular resistance ( $\text{mmHg} \cdot \text{l}^{-1} \cdot \text{min}$ )	160 ± 51	58 ± 27*

Values are expressed as mean ± SD; kg denotes kilogram of body weight.

\* Level of significance *P* < 0.01, compared with control values.

† Level of significance 0.01 < *P* < 0.05, compared with control values.

There was a small but significant increase in arterial lactate concentration from 1.3 to 1.7 mM. The hepatic lactate uptake was unchanged. There were no signs of enhanced renin levels in plasma during hypotension. Arterial plasma concentration of norepinephrine was unchanged, while epinephrine was increased from 1.6 to 4.7 nM.

### Discussion

Adenosine induced hypotension was characterized by rapid induction, a stable blood pressure level, and a rapid evanescent action upon discontinuation (fig. 1). There was no need for dose adjustments, once the desired blood pressure was reached. Dose requirements were decreased by giving adenosine in the ascending aorta as compared with administration in a central vein, indicating a rapid elimination of adenosine during the transpulmonary passage. The basal arterial plasma levels of adenosine were in the  $10^{-7}$ – $10^{-6}$  molar range. A 50% reduction of MABP was achieved by an increase of arterial adenosine to approximately  $2 \cdot 10^{-5}$  M, corresponding to a 50-fold increase. Dipyridamole pretreatment decreased both the dose requirements and the equipotent arterial plasma level of adenosine ( $5 \cdot 10^{-6}$  M) during hypotension by its

TABLE 2. Metabolic Data, Plasma Renin Activity, and Catecholamine Concentrations during Adenosine Infusion

	Control	Adenosine
Arterial-mixed venous oxygen content difference ( $\text{ml} \cdot \text{l}^{-1}$ )	$36.1 \pm 15.6$	$24.6 \pm 8.3^*$
Whole body oxygen consumption ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	$3.6 \pm 0.6$	$3.1 \pm 0.4^*$
Hepatic oxygen uptake ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	$1.00 \pm 0.42$	$1.53 \pm 0.58^\dagger$
Preportal oxygen uptake ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	$0.73 \pm 0.22$	$0.58 \pm 0.17^\dagger$
Hepatic arterial oxygen extraction (%)	$34 \pm 7$	$43 \pm 16$
Portal venous oxygen extraction (%)	$17 \pm 10$	$35 \pm 15^\dagger$
Arterial lactate concentration (mM)	$1.3 \pm 0.3$	$1.7 \pm 0.5^*$
Hepatic lactate uptake ( $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ )	$0.6 \pm 10.0$	$5.5 \pm 15.0$
Plasma renin activity ( $\text{ng} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$ )	$3.7 \pm 2.4$	$3.8 \pm 1.8$
Epinephrine (nM)	$1.6 \pm 1.0$	$4.7 \pm 40^\dagger$
Norepinephrine (nM)	$1.3 \pm 0.5$	$2.3 \pm 1.7$

Values are expressed as mean  $\pm$  SD; kg denotes kilograms of body weight.

\* Levels of significance  $P < 0.01$ , compared with control values.

† Levels of significance  $0.01 < P < 0.05$ , compared with control values.

inhibitory effect on adenosine uptake.<sup>20</sup> The fact that only 25% of the arterial plasma levels of adenosine produced the same hypotensive effect when dipyridamole was used suggests that this treatment prevents extensive purine elimination in the circulation, from the site of sampling (aorta) to the effector site in the resistance bed of the vasculature.

Thus, only a 20-fold elevation of the basal adenosine concentration in the peripheral vascular bed was associated with a 50% reduction of MABP.

The stable hypotensive action of adenosine and the lack of tachyphylaxis are in contrast with the effects of

other hypotensive agents, such as sodium nitroprusside<sup>21</sup> and nitroglycerin.<sup>22</sup> Renin release repeatedly has been shown to occur during SNP-induced hypotension in clinical,<sup>23</sup> as well as experimental,<sup>24,25</sup> studies, and the subsequent formation of angiotensin II has been claimed to cause tachyphylaxis.<sup>24</sup> In the present study, there were no signs of renin release, as PRA was unchanged during adenosine infusion, and this probably accounts for the stable action of adenosine. The inhibition of renin release is consistent with the study of Tagawa and Vander,<sup>26</sup> who found decreased renin secretion in the canine kidney after the infusion of adenosine in the renal artery and of Hedqvist *et al.*<sup>27</sup> who made similar observations in the saline-perfused rabbit kidney *in situ*. The modest increase in plasma catecholamine levels also indicates that the  $\beta$ -adrenergic stimulation of renin release<sup>28</sup> was small.

#### CARDIOVASCULAR EFFECTS

Adenosine caused a dose-related decrease in systemic blood pressure due to a profound decrease in systemic vascular resistance. Cardiac output and stroke volume were increased, while the heart rate was decreased. These hemodynamic effects of adenosine are similar to those obtained in the rat using ATP for controlled hypotension.<sup>4</sup>

Since adenosine has not been shown to possess any positive myocardial inotropic effects,<sup>29</sup> the rather pronounced increases in cardiac output and stroke volume must be attributed to afterload reduction in the presence of a preserved or even increased preload. Many vasodilator agents with direct effects on vascular tone, such as SNP or TNG, act on both resistance and capacitance vessels, resulting in a decrease in preload as well as afterload<sup>30</sup> and an unchanged or even decreased cardiac output.<sup>31-33</sup> The increase in RAP and PCWP in the present study do not indicate major venodilation by adenosine,

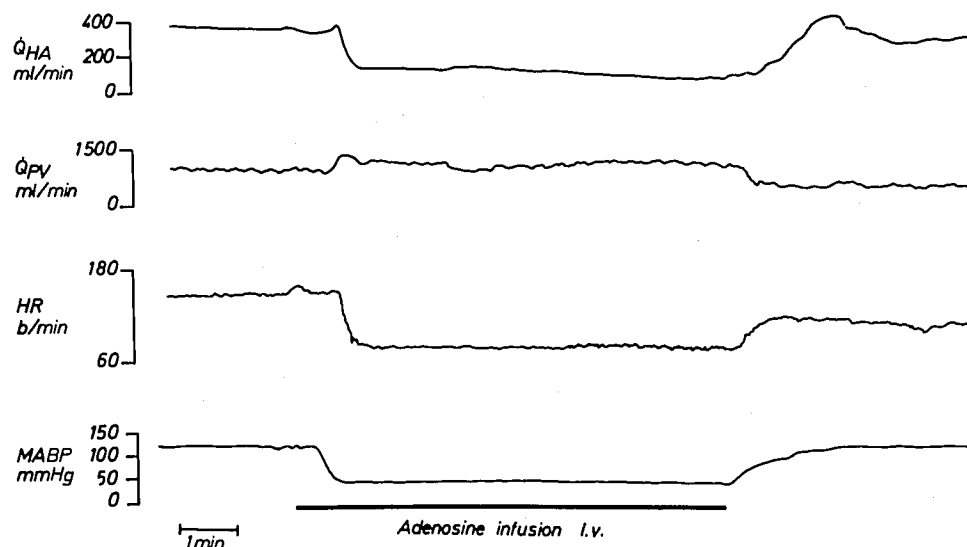


FIG. 1. Effects of an iv infusion of adenosine on mean arterial blood pressure (MABP), heart rate (HR), portal venous ( $\dot{Q}_{PV}$ ), and hepatic arterial ( $\dot{Q}_{HA}$ ) blood flows in one representative experiment. Note the biphasic response in hepatic arterial blood flow, with a transient increase, indicating hepatic arterial vasodilation, followed by a decrease, most probably caused by the concomitant increase in portal blood flow.

although it has been reported to cause relaxation of isolated canine saphenous veins.<sup>34</sup> The rather weak effect of parenterally administered adenosine on venous tone could be explained partly by a lower concentration of adenosine in venous plasma. A concentration gradient across tissues, due to extensive and rapid elimination, is indicated by the fact that only 16% of the arterial adenosine content during hypotension was recovered in portal venous plasma.

The chronotropic effect of adenosine is remarkable, since many peripherally acting hypotensive agents tend to induce reflex tachycardia,<sup>35</sup> while adenosine caused a dose-dependent bradycardia. This is in agreement with previous findings<sup>1,36</sup> and may be due to a direct inhibitory effect on the sinus node<sup>37</sup> as well as inhibition of cardiac sympathetic neurotransmission.<sup>38</sup> Whole-body oxygen consumption was decreased, together with the arteriovenous oxygen content difference, signifying a hyperkinetic circulatory pattern. The decrease in whole body oxygen uptake must be due to additive effect of corresponding reductions in regional oxygen uptake in several tissues, which will be discussed further in this article.

#### SPLANCHNIC CIRCULATION AND METABOLISM

Portal blood flow and preportal vascular resistance were changed concurrently with the cardiac output and systemic vascular resistance. On the other hand the hepatic arterial vascular bed was subjected to marked vasoconstriction, which resulted in a profound decrease in the hepatic arterial blood flow. However, the portal venous blood flow increased, leaving the total hepatic blood flow unchanged. Since infusion of adenosine into the hepatic artery causes vasodilation,<sup>13</sup> this suggests that the effect of systemically administered adenosine on the hepatic arterial vascular bed was abolished by the hepatic vascular reciprocal mechanism,<sup>39</sup> causing vasoconstriction and reduced hepatic arterial blood flow due to the simultaneous increase in portal venous blood flow. A metabolic control of the hepatic arterial resistance by *pH*, *P*<sub>CO<sub>2</sub></sub>, and oxygen content in the portal blood has been suggested by Gelman and Ernst.<sup>40</sup> In the present study, portal blood flow increased along with a reduction in preportal oxygen uptake. This hyperperfusion of the preportal tissues, leaving less desaturated portal blood to enter the hepatic sinusoids, may have caused the hepatic arterial vasoconstriction both because of an increase in blood flow and an increase in sinusoidal blood *P*<sub>O<sub>2</sub></sub>.

Our data on preportal oxygen uptake are in agreement with those obtained in dogs during adenosine infusion in the superior mesenteric artery.<sup>41</sup> An increase in plasma adenosine concentration to the same levels as in the present study resulted in a 10–50% decrease in canine intestinal oxygen uptake. Similar results from autoperfused feline ileum were reported by Granger *et al.*<sup>42</sup> who suggested shunting of the intestinal blood flow from metabolically active mucosal–submucosal sites to intestinal

muscular tissue with a relatively small oxygen demand as one important cause of decreased intestinal oxygen uptake. It is also possible that a direct metabolic action of adenosine may occur. Such a metabolic effect, leading to a decrease in oxygen uptake, has been demonstrated previously in myocardial tissue, irrespective of cardiac dynamics.<sup>29</sup>

In contrast with the preportal tissues, the liver responded to adenosine-induced hypotension by an increased oxygen uptake, in spite of the decreased hepatic arterial blood flow. Firstly, this implies an absence of liver metabolic interaction with hepatic arterial resistance, as suggested by Lauth,<sup>43</sup> who found that the hepatic arterial blood flow responded poorly to changes in liver oxygen demand. Secondly, the increased hepatic oxygen uptake shows that the liver responds in a different manner from other tissues exposed to exogenous adenosine. This may be explained by an enhancement of oxygen consuming processes in the liver, such as increased gluconeogenesis,<sup>44</sup> stimulation of hepatic adenylate cyclase,<sup>45</sup> and incorporation of adenosine and its metabolites into intracellular ATP. The absence of lactate release from the liver indicates preserved liver function during adenosine-induced hypotension.

In summary, adenosine caused a stable hypotensive effect, which was achieved by a profound decrease in systemic vascular resistance. Subsequently, cardiac output increased together with stroke volume, while the heart rate was reduced. The preportal vascular bed responded in parallel with the central circulation. The total and preportal oxygen uptake was decreased, *i.e.*, adenosine induced a hyperkinetic circulatory pattern. In contrast, the hepatic arterial bed was subjected to vasoconstriction concomitantly with an increase in hepatic oxygen consumption. Thus, the hepatic arterial vascular tone did not appear to be influenced directly by adenosine but rather was governed by the magnitude of the portal venous inflow. Hepatic lactate uptake was unchanged, indicating preserved hepatic function. Plasma renin activity also was unchanged, which probably accounted for the stable hypotensive level during the infusion of adenosine. Pretreatment with dipyridamole reduced dose requirements of adenosine but did not otherwise modulate the hemodynamic response. The results of this study indicate that adenosine may become an attractive agent for controlled hypotension in clinical practice.

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