Role of adenosine in local metabolic coronary vasodilation

TOYOTAKA YADA, KEITH NEU RICHMOND, RICHARD VAN BIBBER, KEITH KROLL†, AND ERIC O. FEIGL
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Yada, Toyotaka, Keith Neu Richmond, Richard Van Bibber, Keith Kroll, and Eric O. Feigl. Role of adenosine in local metabolic coronary vasodilation. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H1425–H1433, 1999.—Adenosine has been postulated to mediate the increase in coronary blood flow when myocardial oxygen consumption is increased. The aim of this study was to evaluate the role of adenosine when myocardial oxygen consumption was augmented by cardiac paired-pulse stimulation without the use of catecholamines. In 10 anesthetized closed-chest dogs, coronary blood flow was measured in the left circumflex coronary artery, and myocardial oxygen consumption was calculated using the arteriovenous oxygen difference. Cardiac interstitial adenosine concentration was estimated from coronary venous and arterial plasma adenosine measurements using a previously described multicompartmental, axially distributed mathematical model. Paired stimulation increased heart rate from 55 to 120 beats/min, increased myocardial oxygen consumption 104%, and increased coronary blood flow 92%, but the estimated interstitial adenosine concentration remained below the threshold for coronary vasodilation. After adenosine-receptor blockade with 8-phenyltheophylline (8-PT), coronary blood flow and myocardial oxygen consumption were not significantly different from control values. Paired-pulse pacing during adenosine-receptor blockade resulted in increases in myocardial oxygen consumption and coronary blood flow similar to the response before 8-PT. Coronary venous and estimated interstitial adenosine concentration did not increase to overcome the adenosine blockade by 8-PT. These results demonstrate that adenosine is not required for the local metabolic control of coronary blood flow during pacing-induced increases in myocardial oxygen consumption.

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† Deceased 15 July 1997.

IN 1963 Berne (4) and Gerlach et al. (9) proposed that adenosine mediates local metabolic control of coronary blood flow, whereby coronary flow and myocardial oxygen consumption are kept in balance. The hypothesis is that adenosine released from cardiomyocytes crosses the interstitial space to activate adenosine receptors on coronary vascular smooth muscle cells and cause vasodilation. The postulate is that an increase in myocardial oxygen consumption produces an incipient fall in myocardial oxygen tension that augments adenosine release from cardiac cells and that the ensuing increase in oxygen delivery via increased coronary flow returns the oxygen tension back toward the operating point in a negative-feedback manner.

The increase in myocardial oxygen consumption secondary to pacing tachycardia represents a relatively "pure" local metabolic vasodilator stimulus to the coronary circulation. In contrast to catecholamine infusions, pacing tachycardia avoids the direct vascular effects of both α-adrenoceptor-mediated vasoconstriction (7) and β-adrenoceptor-mediated vasodilation (30). Furthermore, there is evidence for a link between catecholamines and cardiac adenosine release separate from changes in myocardial oxygen consumption (17, 19, 28, 42, 44).

Accordingly, an experiment was designed in which myocardial oxygen consumption was increased by cardiac pacing in the presence of β-adrenergic receptor blockade. The adenosine hypothesis was tested with arterial and coronary venous plasma adenosine measurements before and during adenosine-receptor blockade. Interstitial adenosine concentration (estimated with a distributed mathematical model) did not reach vasoactive levels before or during adenosine-receptor blockade, indicating that adenosine is not important in local metabolic control of coronary blood flow.

MATERIALS AND METHODS

General preparation. Adult male mongrel dogs (n = 10) weighing 22–29 kg were initially sedated with morphine sulfate (3 mg/kg sc). One hour later each dog was fully anesthetized with α-chloralose (100 mg/kg iv; Sigma). An additional dose of morphine (40 mg im) was given, and anesthesia was supplemented with 500 mg of α-chloralose as needed. The metabolic acidosis associated with this anesthesia was corrected with a continuous intravenous infusion of NaHCO₃ and additional bolus injections as needed. Animals were intubated and ventilated with a volume displacement ventilator (model 607; Harvard Apparatus, South Natick, MA) using oxygen-enriched room air so that arterial oxygen tension was maintained >100 mmHg. End-expiratory CO₂ fraction was monitored continuously (model LB-2; Beckman Instruments, Fullerton, CA) and kept near 5% with appropriate adjustments in the ventilatory rate. A segment of Silastic tubing was placed in the left femoral artery for obtaining arterial samples from freely flowing blood. Arterial blood samples were taken periodically and analyzed (model 1306; Instrumentation Laboratories, Waltham, MA) for pH, PCO₂, PO₂, and base excess. Core temperature was monitored with an esophageal thermometer and controlled at 37°C with a YSI controller (model 73A; Yellow Springs, OH) and heating pads placed under the animal. Blood pressure was measured with a strain-gauge manometer (Statham P23 ID; Gould, Cleveland, OH) (Fig. 1). A catheter-tip manometer (model SPC-350; Millar Instruments, Houston, TX) was placed in the left ventricle via the right femoral artery. A catheter was intro-
duced into the abdominal vena cava via the right femoral vein so that, during its intravenous infusion, 8-phenyltheophylline (8-PT) was immediately diluted in a large volume of flowing blood. Heparin sodium (750 U/kg iv) was administered to prevent coagulation. Ibuprofen (12.5 mg/kg iv) was used to prevent any reflex changes in catechol-cell activation caused by the blood flow through artificial tubing. Heparin sodium (750 U/kg iv) was administered to prevent coagulation. Ibuprofen (12.5 mg/kg iv) was administered to prevent any reflex changes in catechol-cell activation caused by the blood flow through artificial tubing.

Circumflex coronary artery blood flow. The circumflex coronary artery was cannulated, closed chest, with a wedgeline (8-PT) was immediately diluted in a large volume of flowing blood. Heparin sodium (750 U/kg iv) was administered to prevent coagulation. Ibuprofen (12.5 mg/kg iv) was given to inhibit the formation of cyclooxygenase products, which could have been released as a result of complement and white blood cell activation caused by the blood flow through artificial tubing. Propranolol (0.5 mg/kg iv) was administered to obtain a low initial heart rate and prevent any reflex changes in catecholamines from altering myocardial oxygen consumption.

Coronary sinus cannulation and pacing catheter. A shortened Sones catheter was inserted into the right external jugular vein and advanced into the coronary sinus with the aid of a fluoroscope (Fig. 1). A metal ring surrounded the tip of the catheter to prevent venous collapse during sampling. Placement of the catheter was confirmed by injection of contrast medium, measurement of coronary sinus Po2, and anatomic location post mortem. To avoid right atrial admixture, the catheter tip was always placed at least 34 mm inside the coronary sinus ostium (21). Blood samples drawn from the coronary sinus catheter were analyzed for Po2, PCO2, pH, oxygen content, lactate concentration, and plasma adenosine concentration. Coronary venous samples were drawn at ≈15 ml/min through the catheter, which had an internal volume of 0.55 ml; thus the transit time through the catheter was ≈2.2 s. A pacing catheter (USCI, Billerica, MA) was placed in the right ventricle via the right jugular vein.

Lactate measurement. Arterial and coronary venous blood samples were drawn into syringes, immediately transferred into NaF-coated vials, and placed on ice to prevent glycolysis. Lactate concentration was determined with a YSI lactate analyzer (model 23A). The machine was calibrated with standards before and after each experiment. Percent myocardial lactate extraction was calculated as [(arterial concentration – coronary venous concentration)/arterial concentration] × 100.

Oxygen content measurement. Arterial and coronary venous blood samples were drawn anerobically into chilled glass syringes and placed on ice. Blood samples were analyzed using the fuel-cell method (Lex-O2-Con; Hospex, Chestnut Hill, MA). Myocardial oxygen consumption (μl O2 · min−1 · g myocardium−1) was calculated by multiplying the coronary blood flow per gram by the coronary arteriovenous oxygen content difference.

Plasma adenosine measurements. Paired arterial and coronary venous adenosine measurements were made at each time point. Plasma adenosine concentration was measured with a modified version of the method of Herrmann and Feigl (18). Blood samples (3.7 ml) were collected with a two-syringe arrangement that simultaneously mixed ice-cold enzymatic stop solution (5.0 ml) with the blood to prevent metabolism of adenosine (32). The stop solution contained dipyridamole (32 μM), iodotubercidin (ITC; 1 μM), and erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA; 10 μM). Dipyridamole acts as an inhibitor of cellular adenosine uptake. ITC is an inhibitor of adenosine kinase, preventing the incorporation of adenosine into AMP. EHNA is an inhibitor of adenosine deaminase, preventing the degradation of adenosine to inosine. Theophylline (20 μM) was included in the stop solution as an internal recovery standard. Blood samples were centrifuged at 15,000 revolutions per minute (rpm) and 0°C for 2 min, and 5 ml of the supernatant plasma were added to 1.8 ml of 4 N perchloric acid to precipitate plasma proteins. The sample was again centrifuged at 15,000 rpm and 0°C for 10 min. The acid supernatant (5 ml) was then added to 4.35 ml of a neutralizing solution containing 0.4 M KH2PO4 and 0.8 mM KOH. The resultant pH was 7.0. An additional centrifugation for 10 min at 15,000 rpm and 0°C precipitated most of the salt. The samples were then purified by applying the neutralized supernatant to C-18 Sep-Pak cartridges. Adenosine and theophylline were eluted into test tubes with 40% methanol. The samples were then concentrated by evaporation and resuspended in 200 μl of HPLC buffer. Adenosine and theophylline were separated on a Hewlett-Packard 1090M HPLC with a C-18 column using an ion-pairing buffer solution of
tetrabutylammonium hydrogen sulfate and KH₃PO₄ with an acetonitrile gradient. Adenosine content was determined by comparison with known adenosine standards, and plasma concentration was calculated using the hematocrit, accounting for dilution steps in sample handling, and was normalized for recovery with the theophylline standard in each sample.

Estimation of interstitial adenosine concentration. Estimates of interstitial adenosine concentration were made using a four-region (capillary, endothelial cell, interstitial space, and parenchymal cell) axially distributed mathematical model (22, 25, 39). The model describes the effects of blood flow, adenosine transport and exchange between tissue regions, and cellular production and consumption on the relations among arterial, venous, and interstitial adenosine concentrations. This model has been used previously to estimate interstitial adenosine concentrations in vivo, and the constraints and assumptions have been described extensively (25, 39). Briefly, the model accounts for myocardial flow heterogeneity and for the change in heterogeneity that occurs with changes in blood flow. Also, the model is constrained with previously obtained estimates of capillary adenosine transport and metabolism adjusted for the level of flow. The estimate of interstitial adenosine concentration is obtained with previously obtained estimates of capillary adenosine concentration (to obtain coronary plasma flow), and arterial plasma adenosine concentration. Cellular adenosine production in the model is adjusted iteratively until the model coronary adenosine concentration matches the measured values of coronary blood flow, hematocrit (to obtain coronary plasma flow), and arterial plasma adenosine concentration.

Table 1. Hemodynamic and metabolic data

<table>
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<th>Baseline</th>
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<tr>
<td></td>
<td>60</td>
<td>180</td>
</tr>
<tr>
<td>Coronary blood flow, ml·min⁻¹·g⁻¹</td>
<td>0.49±0.04</td>
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<tr>
<td>Myocardial O₂ consumption, µl·min⁻¹·g⁻¹</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
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<td>117±5</td>
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<tr>
<td>Heart rate, beats/min</td>
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<tr>
<td>Arterial P₅O₂, mmHg</td>
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<td>145±5</td>
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<tr>
<td>Coronary venous P₅CO₂, mmHg</td>
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<td>Lactate extraction, %</td>
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<td>Arterial adenosine concn, nmol/l</td>
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<td>9±1</td>
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<td>Venous adenosine concn, nmol/l</td>
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<tr>
<td>Interstitial adenosine concn, nmol/l</td>
<td>44±5</td>
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Values are means ± SE for 10 dogs. Con, control; 8-PT, 8-phenyltheophylline.
before and after treatment with the adenosine-receptor antagonist 8-PT (3 mg/kg iv). This dose of 8-PT was previously shown to shift the adenosine coronary vasodilation dose-response curve 12-fold to the right (39). Initially, two sets of arterial and coronary venous blood samples were drawn at the spontaneous heart rate without electrical pacing. These samples are reported as basal. Next, paired ventricular pacing was begun at a heart rate of 120 beats/min. The interval between the two paired stimuli was adjusted while the electrocardiogram and left ventricular pressure were monitored to obtain two depolarizations with a single left ventricular contraction (Fig. 2). During pacing, cardiac carbon dioxide production increases, and the ventilation rate was increased to keep end-expiratory carbon dioxide, and thus arterial PCO₂, as constant as possible. Arterial and coronary venous blood samples were drawn 60, 180, and 300 s after stable paired pacing was achieved. After the 5-min samples were taken, the animal was allowed to return to basal conditions. 8-PT (3 mg/kg iv) was then infused via a catheter in the abdominal vena cava over 10 min with a syringe pump. After an additional 10 min, the same sampling protocol was repeated. At each time point, heart rate, arterial blood pressure, and coronary blood flow were recorded.

**Drugs.** α-Chloralose (Sigma) was dissolved in warm 0.9% saline. Heparin (SoloPak Laboratories, Franklin Park, IL) was given as an intravenous bolus dose of 750 U/kg. Ibuprofen (Sigma) was dissolved in 0.2 M NaHCO₃ at a concentration of 25 mg/ml (pH was adjusted to 7.5–8.0 with 1 N HCl) and given as an intravenous bolus dose of 0.5 mg/kg. 8-PT (3 mg/kg; Sigma) was placed in 1.5 ml of equal parts 1 N NaOH, ethanol, and propylene glycol and gently warmed until dissolved. Final volume was adjusted to 30 ml with warm 0.9% saline. The adenosine stop solution was made in cold isotonic saline and included 1 µM ITC (Research Biochemicals), 10 µM EHNA (Sigma), 32 µM dipyridamole (Sigma), and 20 µM theophylline (Sigma).

**Data analysis.** Hemodynamic variables were recorded with Windaq data analysis software (Dataq Instruments). Analog signals from the recording instruments were digitized and stored on disk at a rate of 200 samples/s. The values for mean coronary blood flow, heart rate, arterial blood pressure, and coronary blood flow were recorded.

![Fig. 3. Hemodynamic and metabolic responses to pacing before and after adenosine-receptor blockade with 8-phenyltheophylline (8-PT). Cardiac pacing increased coronary blood flow (A), myocardial oxygen consumption (B), and heart rate (C) similarly before and after 8-PT. Cardiac pacing had little effect on mean arterial blood pressure (D) during control and after 8-PT. P values are from a Student-Newman-Keuls test after Bonferroni adjustment for 10 variables. B, baseline measurement.](http://ajpheart.physiology.org/)

**Fig. 3.** Hemodynamic and metabolic responses to pacing before and after adenosine-receptor blockade with 8-phenyltheophylline (8-PT). Cardiac pacing increased coronary blood flow (A), myocardial oxygen consumption (B), and heart rate (C) similarly before and after 8-PT. Cardiac pacing had little effect on mean arterial blood pressure (D) during control and after 8-PT. P values are from a Student-Newman-Keuls test after Bonferroni adjustment for 10 variables. B, baseline measurement.
The data are expressed as means ± SE for 10 dogs. The data in Figs. 3–6 are plotted as the individual means and SE for each time point. For statistical comparisons, the two baseline points before pacing were averaged and called baseline for each variable. For each variable a repeated-measures analysis of variance was performed to estimate residual variation after accounting for dog, treatment (control vs. 8-PT), and time. The effect of pacing was tested by comparing the average baseline value to pacing value for the same condition (control or 8-PT) with the Student-Newman-Keuls test for multiple comparisons (SigmaStat, SPSS). The effect of 8-PT was evaluated by comparing control versus 8-PT at each time point, also using the Student-Newman-Keuls test. A Bonferroni correction factor of 10 was used to adjust for interdependencies among the 10 response variables shown in Figs. 3–7 and Table 1 (arterial PO2 and PCO2 were not considered response variables). That is, all Student-Newman-Keuls tests were performed to yield an overall error rate of ≤5% (16).

RESULTS

Data tracings from one dog appear in Fig. 2. Hemodynamic and metabolic data for all 10 dogs are summarized in Table 1. During control conditions (before 8-PT), there was a 92% increase in coronary blood flow during the first minute of cardiac paired pacing (Fig. 3A). During adenosine-receptor blockade with 8-PT (3 mg/kg), coronary blood flow was not altered during baseline conditions and increased by 81% in response to pacing. Control myocardial oxygen consumption increased 104% during the first minute of pacing (Fig. 3B). After 8-PT administration, baseline myocardial oxygen consumption was not significantly different from that during control conditions and increased 94% during the first minute of pacing. Mean baseline heart rate during control conditions was 55 ± 4 beats/min, rising to a baseline value of 62 ± 4 beats/min after 8-PT (Fig. 3C). Mean aortic blood pressure was little changed throughout the experiment (Fig. 3D).

During control conditions the baseline coronary venous PO2 was 20 ± 2 mmHg, and after 8-PT the baseline value fell to 17 ± 1 mmHg (P < 0.05) (Fig. 4A). Myocardial lactate extraction remained positive and >45% throughout the experiments, indicating that the myocardium was not ischemic (Fig. 4B). Ischemic myocardium is known to release large amounts of adenosine and would have confounded the adenosine results (24).

Arterial and venous plasma adenosine measurements and estimates of interstitial adenosine concentration are shown in Figs. 5 and 6. Arterial plasma adenosine concentration was little changed throughout the experiment (Fig. 5A). During control conditions, coronary venous plasma adenosine concentration increased from 16 nM during baseline conditions to 25 nM during the first minute of pacing, decreasing to 20 nM for the remainder of pacing. Correspondingly, the baseline interstitial adenosine concentration of 44 nM increased to 72 nM during the first minute (Fig. 6) but remained below the threshold concentration necessary for coronary vasodilation (Fig. 7) (39). After adenosine-receptor blockade with 8-PT, baseline adenosine levels were not significantly different from that of control (Fig. 6). The absence of an increase in adenosine concentration after adenosine-receptor blockade does not support the hypothesis that adenosine levels rise to overcome receptor blockade.

DISCUSSION

The major finding of this study is that adenosine is not essential for local metabolic control of coronary blood flow. Paired-pulse cardiac stimulation in the presence of β-adrenoceptor blockade was used to augment myocardial oxygen consumption and obtain local metabolic coronary vasodilation without adrenergic activation. This experimental design was used for local metabolic control, because previous studies suggest a link between catecholamines and adenosine levels inde-
dependent of myocardial oxygen consumption (17, 19, 28, 42, 44). The adenosine results in the present study were compared with a previously determined exogenous and endogenous adenosine dose-response curve for the in vivo dog heart (39), and estimated interstitial adenosine did not reach vasoactive concentrations either during control pacing or during pacing after adenosine-receptor blockade by 8-PT. An important new finding is that, after adenosine-receptor blockade, neither coronary venous nor estimated interstitial adenosine levels increased to overcome the blockade, as has been previously suggested (29).

Effect of paired-pulse ventricular pacing. The primary purpose in using the pacing stimulus was to augment myocardial contractility and oxygen consumption (2, 34). Paired-pulse stimulation has an advantage over single-pulse pacing in that larger increases in myocardial oxygen consumption are possible. The two closely spaced electrical pulses cause two action potentials per myocardial contraction and thus augment contractility via increased intracellular calcium concentration. This stimulus, when combined with the b-adrenergic blocking agent propranolol, provided the means for achieving increases in coronary blood flow in response to a local metabolic stimulus without catecholamine effects.

The present study confirms the findings of Feldman et al. (8), who observed that cardiac pacing in normal human subjects did not increase coronary venous plasma adenosine concentration. However, Feldman et al. (8) did observe an increase in coronary venous adenosine concentration during pacing in patients with coronary artery disease, demonstrating that adenosine is a sensitive indicator of myocardial ischemia. The present study adds adenosine-receptor blockade and a quantitative comparison with an independently determined dose-response curve. The present study also confirms the finding of Manfredi and Sparks (28) that canine coronary venous adenosine concentration does not increase during cardiac pacing, again with the addition of adenosine-receptor blockade and a quantitative comparison with an independently determined dose-response curve.

Estimates of interstitial adenosine concentration. Simple inspection of the coronary venous plasma adenosine concentration during paired pacing shown in Fig. 5 indicates little or no role for adenosine in local metabolic vasodilation. However, there was a transient increase in coronary venous plasma concentration after...
1 min of paired pacing during control conditions before adenosine-receptor blockade. Thus it will be useful to determine whether this reflects a vasoactive interstitial adenosine concentration.

It is not feasible to directly measure interstitial adenosine concentration, and several methods have been used to estimate interstitial adenosine. Interstitial adenosine concentration has been estimated by measuring adenosine concentration in buffer solutions placed in contact with the epicardial surface (12, 14, 17, 40). The epicardial method is limited, because it takes a few minutes for the adenosine concentration in an epicardial well to come to steady state, and requires thoracotomy (3, 12). Estimates of interstitial adenosine concentration have also been made from fluid pumped through microdialysis tubing threaded through the myocardium (43). The microdialysis method has the disadvantage of causing injury to the myocardium, leading to cell leakage and high local adenosine levels.

To avoid the problems associated with these methods, a multicompartment model has been developed and is based on multiple indicator dilution experiments done with radioactive adenosine plus plasma and interstitial tracers (25, 45). The model for estimating interstitial adenosine has the advantages of a rapid response time, being applicable in closed-chest animals, and giving global values from a mixed coronary venous sample. Dogs were chosen for the present experiments because the half-life of adenosine in canine blood is 3 min (20, 31), which is much longer than in several other species (10, 31, 41). Because the transit time in the coronary venous catheter was ~2.2 s before the sample was mixed with stop solution, little adenosine was lost in the sampling procedure. The present estimated baseline cardiac interstitial adenosine concentration in closed-chest anesthetized dogs was found to be 44 nM, well below the 117 nM threshold for coronary vasodilation found by Stepp et al. (39) (Fig. 7A). There was a transient increase in interstitial adenosine concentration to 72 nM after 1 min of cardiac pacing, but this was also below the 117 nM threshold for coronary vasodilation (Fig. 7A).

Adenosine hypothesis with adenosine-receptor blockade. Adenosine-receptor blockade has been used in previous studies with cardiac pacing but has not been combined with adenosine concentration measurements. Two studies found a diminished coronary flow response after adenosine-receptor blockade with aminophylline (26, 33), and a diminished response was found with 8-p-sulfophenyltheophylline (27). A study using aminophylline in humans failed to demonstrate a decrement in the coronary flow response to cardiac pacing (35).

8-PT is a potent antagonist compared with other adenosine-receptor blocking agents, such as theophylline and aminophylline, and has very low activity as an inhibitor of phosphodiesterase (13, 37). Therefore, baseline myocardial metabolism did not increase significantly after 8-PT in the present study (Fig. 3B). The 3 mg/kg intravenous dose of 8-PT was previously shown to shift the coronary vasodilation dose-response curve 12-fold to the right for exogenous adenosine and >12-fold for endogenous adenosine (39). The metabolic response to pacing was not affected by 8-PT, because myocardial oxygen consumption and coronary blood flow showed similar responses to pacing both before and after 8-PT (Fig. 3, A and B). However, there was a consistent decrease in coronary venous Po2 of ~4 mmHg after adenosine-receptor blockade (Fig. 4A), which is unexplained by the present experimental design. The sustained decrease in coronary venous Po2 might be interpreted as evidence that resting baseline coronary blood flow is partially controlled by adenosine but that local metabolic vasodilation during cardiac pacing is not mediated by adenosine. This interpretation is unlikely for two reasons: 1) previous studies employing adenosine deaminase (5, 11, 15, 23, 36) have found little evidence for adenosine control of coronary flow during baseline conditions; and 2) the interstitial adenosine concentrations determined in the present study were below the threshold value for coronary vasodilation before or during adenosine-receptor blockade (Fig. 7).
The limitations of the present study are that an anesthetized preparation was used and that only a doubling of myocardial oxygen consumption was achieved with cardiac pacing. It is possible that adenosine may play a role in local metabolic coronary vasodilation when there are larger increases in myocardial oxygen consumption, such as those occurring during exercise. Adenosine-receptor blockade with 8-PT does not alter the coronary vascular response during exercise (1). However, the control of coronary blood flow during exercise involves more than local metabolic vasodilation, including feedforward β-adrenoceptor vasodilation (6). The intention with the present study was to examine local metabolic coronary control in the absence of catecholamine effects in a β-adrenoceptor-blocked preparation.

In conclusion, cardiac pacing increased myocardial oxygen consumption and coronary blood flow without increasing interstitial adenosine concentration to vasoactive levels. Potent adenosine-receptor blockade with 8-PT did not affect any of the responses to pacing, indicating that adenosine is not essential for the coronary hyperemia induced by pacing. The lack of an augmented coronary venous or interstitial adenosine response after 8-PT indicates that adenosine concentration did not increase to overcome the receptor blockade and contribute to the coronary flow response. Therefore, mechanisms other than adenosine must be responsible for local metabolic regulation of coronary blood flow.

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