Role of adenosine in the regulation of coronary blood flow in swine at rest and during treadmill exercise

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Duncker, Dirk J., René Stubenitsky, and Pieter D. Verdouw. Role of adenosine in the regulation of coronary blood flow in swine at rest and during treadmill exercise. *Am. J. Physiol.* 275 (*Heart Circ. Physiol.* 44): H1663–H1672, 1998.—A pivotal role for adenosine in the regulation of coronary blood flow is still controversial. Consequently, we investigated its role in the regulation of coronary vasomotor tone in swine at rest and during graded treadmill exercise. During exercise, myocardial O_2 consumption increased from 167 ± 18 μmol/min at rest to 399 ± 27 μmol/min at 5 km/h ($P \leq 0.05$), which was paralleled by an increase in O_2 delivery, so that myocardial O_2 extraction (76 ± 1 and 78 ± 1% at rest and 5 km/h, respectively) and coronary venous P_{O_2} (24.5 ± 1.0 and 22.8 ± 0.3 mmHg at rest and 5 km/h, respectively) remained unchanged. After adenosine receptor blockade with 8-phenyltheophylline (5 mg/kg iv), the relation between myocardial O_2 consumption and coronary vascular resistance was shifted toward higher resistance, whereas myocardial O_2 extraction rose to 81 ± 1 and 83 ± 1% at rest and 5 km/h and coronary venous P_{O_2} fell to 19.2 ± 0.8 and 18.9 ± 0.8 mmHg at rest and 5 km/h, respectively (all $P \leq 0.05$). Thus, although adenosine is not mandatory for the exercise-induced coronary vasodilation, it exerts a vasodilator influence on the coronary resistance vessels in swine at rest and during exercise.

coronary circulation; myocardial oxygen extraction; myocardial oxygen consumption; pulmonary circulation; systemic circulation

THE NORMAL HEART IS characterized by a high myocardial O_2 extraction (ME_{O_2}), requiring a tight coupling of coronary blood flow to changing metabolic needs (16, 26). The close coupling of coronary blood flow and myocardial O_2 demand has been proposed to depend primarily on messengers released from the myocardium, such as adenosine (4, 30). Although adenosine has been shown to contribute to coronary vasodilation in isolated rodent hearts, a pivotal role for adenosine in the regulation of coronary blood flow in the large mammalian in situ heart is still controversial. Thus neither increased adenosine catabolism with adenosine deaminase nor adenosine receptor blockade with the adenosine A_1/A_2-receptor blocker 8-phenyltheophylline (8-PT) altered resting coronary blood flow in anesthetized or awake dogs (2, 22, 24, 33). In addition, during treadmill exercise, coronary blood flow and resistance, as well as myocardial O_2 consumption (MV_{O_2}) and ME_{O_2}, were not altered by adenosine receptor blockade or adenosine deaminase (2), suggesting that adenosine is not mandatory for the regulation of coronary blood flow in the dog heart at rest or during exercise. In contrast, several studies have reported that adenosine receptor blockade produced by theophylline increased coronary vascular resistance and ME_{O_2} and decreased coronary blood flow and coronary venous P_{O2} (Pcv_{O_2}) in the human heart under basal conditions (11–13), whereas only one study reported no change in resting coronary blood flow after adenosine receptor blockade with aminophylline (32). Also, in closed-chest sedated swine, adenosine deaminase produced a small increase in coronary vasomotor tone under basal conditions (17) while markedly blunting the early coronary blood flow response to intracoronary infusions of isoproterenol (18). Recently, we observed in swine that exercise produced increases in MV_{O_2} that were matched by equivalent increments in coronary blood flow so that ME_{O_2} and Pcv_{O_2} were maintained (9). Because interstitial adenosine levels have been reported to increase during β-adrenergic stimulation with dobutamine in anesthetized swine at a time when Pcv_{O_2} or interstitial lactate levels did not change (21), it is possible that adenosine could contribute to the maintained Pcv_{O_2} in swine during exercise. Consequently, in the present study we investigated the role of adenosine in the coupling between myocardial O_2 delivery (MD_{O_2}) and MV_{O_2} in awake swine at rest and during graded treadmill exercise up to 85–90% of maximum heart rate (4a).

MATERIALS AND METHODS

Crossbred Landrace × Yorkshire pigs were used in the present study. All experiments were performed in accordance with the "Guiding Principles in the Care and Use of Laboratory Animals," as approved by the Council of the American Physiological Society and with prior approval of the Animal Care Committee of the Erasmus University Rotterdam. Adaptation of animals to the laboratory conditions started 1 wk before the day of surgery and continued until 10 days postoperative. Full details of the experimental procedures have been published previously (7, 9, 37, 38).

Surgical Procedures

After an overnight fast, seven pigs (23 ± 1 kg; 3 males and 4 females) were sedated with ketamine (30 mg/kg im; Ketalin, Apharmo, Arnhem, The Netherlands), anesthetized with thiopental sodium (10 mg/kg iv; Rhône-Poulenc, Amstelveen, The Netherlands), intubated, and mechanically ventilated with a mixture of O_2 and nitrous oxide (1:2) to which 0.2–1.0% (vol/vol) isoflurane (Forene, Abbott, Amstelveen, The Netherlands) was added. Anesthesia was further maintained with midazolam (2 mg/kg + 1 $mg \cdot kg^{-1} \cdot h^{-1}$ iv; Dormicum, Roche, Mijdrecht, The Netherlands) and fentanyl (10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ iv; Janssen-Cilag, Tilburg, The Netherlands). Under sterile conditions, the chest was opened via the fourth left intercostal

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space, and an 8-Fr fluid-filled polyvinylchloride (PVC) catheter was inserted into the aortic arch for the measurement of central aortic blood pressure and collection of arterial blood samples and secured with a purse-string suture. After the pericardium was opened, an electromagnetic flow probe (14–15 mm ID) was positioned around the ascending aorta for the measurement of ascending aortic blood flow (Transflow 601 Systems, Skalar, Delft, The Netherlands). A high-fidelity pressure transducer (model $P_{4.5}$, Konigsberg Instruments, Pasadena, CA) was inserted into the left ventricle (LV) via the apical dimple for recording of LV pressure and its first derivative (LV dP/d*t*; obtained via electrical differentiation). An 8-Fr PVC catheter was also inserted into the LV for calibration of the Konigsberg transducer signal; two 8-Fr PVC catheters were inserted into the pulmonary artery for measurement of pulmonary arterial pressure, withdrawal of mixed venous blood samples, and administration of drugs. Another 8-Fr catheter was inserted into the left atrium for measurement of left atrial pressure. For the measurement of coronary blood flow, a Doppler flow probe (2.0, 2.5, or 3.0 mm ID, emitting frequency = 20 MHz) was placed around the proximal part of the left anterior descending (LAD) coronary artery (model HVPD-20, Crystal Biotech, Northboro, MA) (23). A small angiocatheter (0.8 mm ID, 1.1 mm OD) connected to a larger Tygon catheter (0.8 mm ID, 2.4 mm OD) was inserted directly into the anterior interventricular vein to allow sampling of coronary venous blood (5). Electrical wires and catheters were tunneled subcutaneously to the back, the chest was closed, and the animals were allowed to recover. All electrical wires and catheters were protected with a vest.

Postsurgical period. After surgery the animals received analgesia by daily intramuscular injections of 0.3 mg of buprenorphine (Temgesic, Schering-Plough, Amstelveen, The Netherlands) during the first 48 h and intravenous injections of 25 mg/kg of amoxicillin (Clamoxil, Beecham Farma, Amstelveen, The Netherlands) and 5 mg/kg gentamicin (A.U.V., Cuijk, The Netherlands) on a daily basis during the 1st wk to prevent infections. Catheters were flushed daily with physiological saline containing 2,000 IU/ml heparin (Leo Pharmaceutical Products, Weesp, The Netherlands).

Experimental Protocols

Exercise protocols. Studies were performed 10–20 days after surgery with animals exercising on a motor-driven treadmill. Two experimental protocols were performed on different days and in random order. The first protocol was performed to establish that two consecutive exercise tests performed at 90-min intervals produced reproducible results; in the second protocol the effect of nonselective adenosine A_1/A_2-receptor blockade was studied.

Reproducibility of responses to exercise. With swine lying quietly on the treadmill, resting hemodynamic measurements, consisting of ascending aortic blood flow, LV pressure and LV dP/d*t*, blood pressures in the aorta, pulmonary artery, and left atrium, and the coronary Doppler shift, were obtained, and arterial, mixed venous, and coronary venous blood samples were collected (9, 38). Aortic, pulmonary, and left atrial pressures were measured using Combitrans pressure transducers (Braun, Melsungen, Germany) with the reference point at midchest level. In one of the seven animals, samples could not be obtained from the coronary venous catheter. All hemodynamic measurements were repeated, and rectal temperature was measured with animals standing on the treadmill. Subsequently, a five-stage treadmill exercise protocol was started [1, 2, 3, 4, and 5 km/h resulting in 85–90% of maximum heart rate (4a)]; each exercise stage lasted 2–3 min. Hemodynamic variables were continuously recorded, and blood samples were collected during the last 45 s of each exercise stage, at a time when hemodynamics had reached a steady state. After completing the exercise protocol, animals were allowed to rest on the treadmill for 90 min, and then resting measurements were obtained and the five-stage exercise protocol was repeated.

Adenosine receptor blockade. Ninety minutes after swine had undergone a control exercise period, animals received an infusion of 8-PT (5 mg/kg administered over 5 min into a pulmonary artery catheter) to produce adenosine receptor blockade (20). It has previously been shown that this dose of 8-PT produces >95% inhibition of adenosine-induced coronary vasodilation in anesthetized swine (8) and awake dogs (2, 10). Five minutes after completion of the 8-PT infusion, resting measurements were obtained and the exercise protocol was repeated.

Contribution of changes in pH and P_{CO_2} to the 8-PT-induced alterations in ME_{O_2}. Because we observed that 8-PT decreased arterial and coronary venous P_{CO_2} and increased arterial pH, which could potentially increase coronary vasomotor tone, we determined the effects of equivalent hyperventilation-induced decreases in arterial and coronary venous P_{CO_2} and increases in pH on $M\dot{E}O_2$ and Pcv_{O_2} in five swine (2 chronically instrumented ketamine-sedated swine and three pentobarbital-anesthetized intubated open-chest animals) (15). After 5 min of hyperventilation, arterial and coronary venous samples were obtained. In addition, we obtained arterial and coronary venous blood samples before and 5 min after infusion of 1 M sodium hydrogen bicarbonate (Lansberg, Uden, The Netherlands), which produced similar increases in pH in the two chronically instrumented ketamine-sedated swine.

Blood Gas Measurements

Blood samples were maintained in iced syringes until the conclusion of each exercise trial. P_{O_2} (mmHg), P_{CO_2} (mmHg), and pH were then immediately measured with a blood gas analyzer (Acid-Base Laboratory model 505, Radiometer, Copenhagen, Denmark). O_2 saturation (S_{O_2}) and Hb (g/100 ml) were measured with a hemoximeter (model OSM2, Radiometer, Copenhagen, Denmark).

Data Acquisition and Analysis

All hemodynamic data were recorded and digitized (400 Hz/channel) on-line using an eight-channel data-acquisition program (ATCODAS, Dataq Instruments, Akron, OH) and stored on a computer for later postacquisition off-line analysis with a program written in MatLab (Mathworks, Natick, MA). A minimum of 15 consecutive beats were selected for analysis of the digitized hemodynamic signals. From these selected beats the LV peak systolic pressure, mean aortic blood pressure, mean pulmonary arterial and mean left atrial pressure, mean ascending aortic blood flow, and mean coronary Doppler shift were determined for each beat and averaged.

Cardiac output was computed as the sum of ascending aortic blood flow (measured with the electromagnetic flow probe) and total coronary blood flow. Because the LAD coronary artery supplies ~40% of the LV, total coronary blood flow was taken as 2.5 times flow in the LAD coronary artery. Systemic and coronary vascular resistance were calculated as the ratios of mean aortic pressure to cardiac output and mean aortic pressure to LAD coronary blood flow, respectively. Blood O_2 content (μmol/ml) was computed as $(0.621 \cdot Hb_a \cdot S_{O_2}) + (0.00131 \cdot P_{O_2})$, where Hb_a is arterial Hb. $M\dot{D}O_2$ was computed as the product of arterial O_2 content and LAD coronary blood flow; whole body O_2 delivery was calculated as the product of arterial O_2 content and cardiac output. $M\dot{V}O_2$ in the region

perfused by the LAD coronary artery was calculated as the product of coronary blood flow and the difference in O_2 content between arterial and coronary venous blood; whole body O_2 consumption ($B\dot{V}O_2$) was calculated as the product of cardiac output and difference in O_2 content between arterial and mixed venous blood. $M\dot{E}O_2$ was computed as the ratio of arterial-coronary venous O_2 content difference to arterial O_2 content; whole body O_2 extraction ($B\dot{E}O_2$) was calculated as the ratio of arterial-mixed venous O_2 content difference to arterial O_2 content.

Statistical analysis of the exercise data was performed using two-way (exercise and treatment) ANOVA for repeated measures. When a significant effect of exercise was observed, post hoc testing was done using Dunnett's test. When a significant effect of treatment was observed, post hoc testing was done using paired *t*-test or Wilcoxon signed rank test as appropriate. The effect of hyperventilation was tested using paired *t*-test or Wilcoxon signed rank test. $P \leq 0.05$ was considered statistically significant (2-tailed). Values are means ± SE.

Drugs

8-PT (Sigma-Aldrich, Bornem, Belgium) was dissolved in 20 ml of demineralized water at 30°C (pH 10–11). Fresh drug solutions were prepared on each day.

RESULTS

Reproducibility of Responses to Exercise

Exercise increased cardiac output from 3.5 ± 0.2 l/min at rest (supine) to 7.9 ± 0.5 l/min at 5 km/h ($P \leq 0.01$), which was principally due to an increase in heart rate from 110 ± 4 to 242 ± 4 beats/min ($P \leq 0.01$) as stroke volume increased ~10% (Table 1). Because afterload increased (reflected by the increase in LV systolic pressure from 120 ± 4 mmHg at rest to 145 ± 5 mmHg at 5 km/h, $P \leq 0.01$), the increase in stroke volume was likely the result of an increase in LV filling pressure (reflected by the increase in left atrial pressure from 6 ± 1 to 14 ± 2 mmHg, $P \leq 0.01$) and an increase in LV contractility (reflected by the increase in LV dP/dt_{max} from 3,080 ± 290 to 6,220 ± 380 mmHg/s, $P \leq 0.01$). Mean aortic pressure decreased slightly when the animals went from a supine to an upright position, but during exercise, aortic pressure increased from 92 ± 4 mmHg while animals were standing to 97 ± 4 mmHg at 5 km/h ($P \leq 0.05$). The 5% increase in mean aortic blood pressure in the presence of a doubling of cardiac output implies that systemic vascular resistance had decreased. In contrast, mean pulmonary arterial pressure increased from 14 ± 1 to 33 ± 2 mmHg ($P \leq 0.01$), and the driving pressure across the pulmonary vascular bed increased virtually in parallel with cardiac output, so that pulmonary vascular resistance was not significantly altered. Blood flow through the LAD coronary artery increased from 45 ± 4 ml/min at rest to 95 ± 11 ml/min during the highest level of exercise ($P \leq 0.01$; Table 1). After 90 min of rest, at a time when all hemodynamic variables had returned to baseline resting values, the second period of exercise

Table 1. *Reproducibility of hemodynamic responses in swine during consecutive periods of graded treadmill exercise*

	Rest		Exercise, km/h				
	Supine	Standing	1	2	3	4	5
Cardiac output, l/min							
Control	3.5 ± 0.2	4.5 ± 0.3†	5.3 ± 0.3†	6.1 ± 0.4†	6.7 ± 0.5†	7.4 ± 0.5†	7.9 ± 0.5†
Saline	3.7 ± 0.3	4.8 ± 0.3†	5.6 ± 0.3†	6.0 ± 0.3†	6.7 ± 0.4†	7.2 ± 0.4†	7.9 ± 0.4†
Heart rate, beats/min							
Control	110 ± 4	134 ± 6†	161 ± 6†	179 ± 3†	205 ± 6†	229 ± 5†	242 ± 4†
Saline	113 ± 5	136 ± 6†	156 ± 5†	165 ± 4†‡	193 ± 6†‡	210 ± 6†‡	234 ± 6†‡
Mean aortic pressure, mmHg							
Control	102 ± 2	92 ± 4†	88 ± 3†	93 ± 2†	95 ± 3†	95 ± 3†	97 ± 4†
Saline	100 ± 2	90 ± 3†	91 ± 3†	91 ± 2†	90 ± 2†	94 ± 3†	94 ± 3†
LV systolic pressure, mmHg							
Control	120 ± 4	118 ± 4	120 ± 4	130 ± 4†	131 ± 4†	139 ± 4†	145 ± 5†
Saline	119 ± 3	120 ± 5	125 ± 6†	125 ± 5†	127 ± 4†	136 ± 5†	141 ± 5†
LV dP/dt_{max}, mmHg/s							
Control	3,080 ± 290	3,790 ± 380†	4,120 ± 400†	4,640 ± 390†	5,020 ± 300†	5,790 ± 370†	6,220 ± 380†
Saline	3,140 ± 270	3,680 ± 340†	4,110 ± 360†	4,100 ± 340†‡	4,580 ± 220†‡	5,200 ± 250†‡	5,670 ± 230†‡
Mean pulmonary arterial pressure, mmHg							
Control	14 ± 1	12 ± 1	16 ± 1	21 ± 1†	27 ± 2†	30 ± 2†	33 ± 2†
Saline	16 ± 1	16 ± 1	19 ± 1†	20 ± 1†	24 ± 2†	29 ± 2†	33 ± 1†
Mean left atrial pressure,* mmHg							
Control	6 ± 1	−2 ± 1†	3 ± 1	4 ± 2	8 ± 2	11 ± 2†	14 ± 2†
Saline	8 ± 1	1 ± 2†	3 ± 2	4 ± 2	6 ± 3	9 ± 2	12 ± 3
Pulmonary vascular resistance,* $mmHg \cdot l^{-1} \cdot min$							
Control	2.7 ± 0.5	2.6 ± 0.2	2.3 ± 0.3	2.4 ± 0.2	2.6 ± 0.3	2.5 ± 0.3	2.3 ± 0.3
Saline	2.4 ± 0.3	2.9 ± 0.1	2.9 ± 0.2	2.7 ± 0.2	2.5 ± 0.2	2.5 ± 0.3	2.4 ± 0.2
Coronary blood flow, ml/min							
Control	45 ± 4	52 ± 6†	63 ± 7†	81 ± 8†	84 ± 9†	88 ± 8†	95 ± 11†
Saline	45 ± 5	55 ± 6†	69 ± 9†	72 ± 6†	83 ± 9†	91 ± 11†	97 ± 14†

Values are means ± SE; $n = 7$ unless otherwise noted. LV, left ventricle; dP/dt_{max}, maximum rate of rise in pressure. *$n = 4$. †$P \leq 0.05$ vs. supine; ‡$P \leq 0.05$ vs. corresponding control.

Table 2. *Reproducibility of blood gas and O_2 transport responses in swine during consecutive periods of graded treadmill exercise*

	Rest	Exercise, km/h				
	Supine	1	2	3	4	5
Hb, g/100 ml						
Control	8.0 ± 0.2	8.2 ± 0.4	8.5 ± 0.3*	8.8 ± 0.2*	8.8 ± 0.3*	9.0 ± 0.3*
Saline	7.7 ± 0.3	8.0 ± 0.3	8.0 ± 0.3	8.3 ± 0.3*†	8.3 ± 0.3*†	8.5 ± 0.2*†
Pa_{CO_2}, mmHg						
Control	43 ± 1	42 ± 1	42 ± 1	41 ± 1*	40 ± 1*	39 ± 1*
Saline	43 ± 1	43 ± 1	42 ± 1	40 ± 1*	40 ± 1*	39 ± 1
pH_a						
Control	7.44 ± 0.01	7.46 ± 0.01*	7.46 ± 0.01*	7.46 ± 0.01*	7.46 ± 0.01*	7.47 ± 0.01*
Saline	7.45 ± 0.01	7.45 ± 0.01	7.46 ± 0.01	7.48 ± 0.01*	7.47 ± 0.01	7.48 ± 0.01*
Pa_{O_2}, mmHg						
Control	104 ± 3	104 ± 3	104 ± 3	107 ± 4	105 ± 4	106 ± 4
Saline	103 ± 3	100 ± 2	107 ± 2	107 ± 4	103 ± 3	104 ± 4
Sa_{O_2}, %						
Control	96 ± 1	97 ± 1	96 ± 1	96 ± 1	96 ± 1	96 ± 1
Saline	97 ± 1	96 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1
Ca_{O_2}, μmol/ml						
Control	4.92 ± 0.14	5.07 ± 0.20	5.20 ± 0.19*	5.40 ± 0.13*	5.39 ± 0.15*	5.51 ± 0.17*
Saline	4.74 ± 0.17	4.90 ± 0.17	4.96 ± 0.21	5.17 ± 0.16*†	5.14 ± 0.16*†	5.23 ± 0.13*†
$P\bar{v}_{CO_2}$, mmHg						
Control	52 ± 1	53 ± 1	53 ± 2	54 ± 2*	55 ± 2*	57 ± 2*
Saline	51 ± 1	53 ± 1	53 ± 1	53 ± 1	53 ± 2	55 ± 1*
$pH_{\bar{v}}$						
Control	7.39 ± 0.01	7.39 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.36 ± 0.01*
Saline	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.38 ± 0.01
$P\bar{v}_{O_2}$, mmHg						
Control	41 ± 1	34 ± 1*	33 ± 1*	31 ± 2*	29 ± 2*	25 ± 1*
Saline	42 ± 1	34 ± 1*	34 ± 1*	32 ± 1*	28 ± 1*	28 ± 1*
$S\bar{v}_{O_2}$, %						
Control	52 ± 1	40 ± 1*	38 ± 1*	34 ± 2*	29 ± 2*	23 ± 1*
Saline	54 ± 1	40 ± 1*	39 ± 1*	37 ± 1*	30 ± 1*	29 ± 2*
$C\bar{v}_{O_2}$, μmol/ml						
Control	2.62 ± 0.09	2.09 ± 0.10*	2.03 ± 0.13*	1.90 ± 0.16*	1.62 ± 0.15*	1.35 ± 0.12*
Saline	2.61 ± 0.09	2.03 ± 0.04*	2.00 ± 0.07*	1.96 ± 0.12*	1.61 ± 0.10*	1.54 ± 0.12*
Pcv_{CO_2}, mmHg						
Control	56 ± 2	56 ± 2	55 ± 2	55 ± 1	56 ± 1	57 ± 1
Saline	54 ± 2	55 ± 2	55 ± 2	55 ± 1	54 ± 1	55 ± 2
pH_{cv}						
Control	7.37 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
Saline	7.37 ± 0.01	7.38 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
Pcv_{O_2}, mmHg						
Control	24.1 ± 0.7	24.3 ± 0.9	24.6 ± 0.5	24.0 ± 0.7	23.7 ± 0.7	23.4 ± 1.1
Saline	24.4 ± 0.8	24.5 ± 0.9	24.6 ± 0.9	24.4 ± 0.8	24.9 ± 0.7	23.7 ± 0.8
Scv_{O_2}, %						
Control	22.0 ± 1.4	22.2 ± 1.0	22.9 ± 1.1	21.7 ± 1.1	20.6 ± 1.1	20.4 ± 1.0
Saline	23.9 ± 1.5	23.3 ± 1.4	24.0 ± 2.1	23.7 ± 1.6	23.4 ± 1.9	22.6 ± 1.9
Ccv_{O_2}, μmol/ml						
Control	1.10 ± 0.06	1.15 ± 0.08	1.20 ± 0.07	1.22 ± 0.08	1.15 ± 0.08	1.17 ± 0.09
Saline	1.13 ± 0.06	1.15 ± 0.05	1.19 ± 0.11	1.23 ± 0.08	1.24 ± 0.10	1.22 ± 0.10
$B\dot{V}O_2$, mmol/min						
Control	7.9 ± 0.5	13.3 ± 0.8*	16.7 ± 0.9*	21.5 ± 2.0*	25.2 ± 2.0*	30.9 ± 2.1*
Saline	7.7 ± 0.4	13.7 ± 1.0*	16.6 ± 1.2*	19.1 ± 1.1*	23.5 ± 1.6*	26.5 ± 1.4*†
$B\dot{E}O_2$, %						
Control	47 ± 1	59 ± 1*	61 ± 1*	65 ± 3*	70 ± 2*	76 ± 1*
Saline	45 ± 1	58 ± 1*	60 ± 1*	62 ± 1*	69 ± 1*	71 ± 2*
$M\dot{V}O_2$, μmol/min						
Control	172 ± 15	233 ± 28*	301 ± 35*	348 ± 43*	372 ± 37*	420 ± 61*
Saline	156 ± 17	239 ± 31*	256 ± 24*	313 ± 40*	353 ± 44*	394 ± 62*
$M\dot{E}O_2$, %						
Control	77 ± 2	77 ± 1	76 ± 1	77 ± 1	79 ± 1	79 ± 1
Saline	76 ± 2	76 ± 1	75 ± 2	76 ± 2	76 ± 2	77 ± 2

Values are means ± SE; n = 7. Pa_{CO_2}, pH_a, Pa_{O_2}, Sa_{O_2}, and Ca_{O_2}, arterial P_{CO_2}, pH, P_{O_2}, O_2 saturation, and O_2 content; $P\bar{v}_{CO_2}$, $pH_{\bar{v}}$, $P\bar{v}_{O_2}$, $S\bar{v}_{O_2}$, and $C\bar{v}_{O_2}$, mixed venous P_{CO_2}, pH, P_{O_2}, O_2 saturation, and O_2 content; Pcv_{CO_2}, pH_{cv}, Pcv_{O_2}, Scv_{O_2}, and Ccv_{O_2}, coronary venous P_{CO_2}, pH, P_{O_2}, O_2 saturation, and O_2 content; $B\dot{V}O_2$ and $B\dot{E}O_2$, whole body O_2 consumption and extraction; $M\dot{V}O_2$ and $M\dot{E}O_2$, myocardial O_2 consumption and extraction. *$P \leq 0.05$ vs. supine; †$P \leq 0.05$ vs. corresponding control.

resulted in almost identical hemodynamic responses to exercise, with the exception of heart rate and LV dP/dt_{max}, which were slightly (<10%) lower during exercise at 2–5 km/h than during the first run (Table 1).

Exercise resulted in a decrease in arterial P_{CO_2} from 43 ± 1 mmHg at rest to 39 ± 1 mmHg at 5 km/h and an increase in arterial pH from 7.44 ± 0.01 to 7.47 ± 0.01 (both $P \leq 0.05$; Table 2). Arterial S_{O_2} did not change, but Hb and, hence, O_2 content increased by 12% at the highest level of exercise compared with resting conditions. Mixed venous P_{O_2}, S_{O_2}, and O_2 content decreased during exercise, whereas mixed venous P_{CO_2} increased and pH decreased slightly. Because cardiac output and the arteriovenous O_2 content difference nearly doubled, $B\dot{V}O_2$ increased fourfold from 7.9 ± 0.5 to 30.9 ± 2.1 mmol/min ($P \leq 0.01$; Table 2, Fig. 1). All variables returned to baseline resting values within 90 min; a second period of exercise resulted in nearly identical responses, with the exception of a slightly lower Hb and arterial O_2 content at 3–5 km/h and a slightly lower $B\dot{V}O_2$ at 5 km/h (Table 2, Fig. 1).

Exercise had no effect on coronary venous P_{CO_2}, pH, P_{O_2}, S_{O_2}, or O_2 content (Table 2, Fig. 2). $M\dot{V}O_2$ increased from 172 ± 15 to 420 ± 61 μmol/min, whereas $M\dot{D}O_2$ increased from 214 ± 25 to 535 ± 81 μmol/min (both $P \leq 0.01$). Consequently, $M\dot{E}O_2$ (i.e., the ratio of $M\dot{V}O_2$ to $M\dot{D}O_2$) was not altered during exercise. All variables returned to baseline resting values within 90 min. Despite the slightly lower heart rate, LV dP/dt_{max}, and arterial O_2 content during the second control run, there were no differences between the two control runs with respect to coronary vascular resistance, $M\dot{E}O_2$, $M\dot{D}O_2$, and Pcv_{O_2} when plotted as a function of $M\dot{V}O_2$ (Fig. 2).

Adenosine Receptor Blockade

Except for a 10% increase in heart rate, 8-PT had no effects on systemic and pulmonary hemodynamics at rest (Table 3). During exercise, heart rate at 5 km/h and coronary blood flow at 1 km/h were slightly higher than during control conditions.

8-PT decreased P_{CO_2} and increased pH in arterial, mixed venous, and coronary venous blood (Table 4). Arterial P_{O_2}, S_{O_2}, and O_2 content were maintained, but mixed venous P_{O_2}, S_{O_2}, and O_2 content were lower in the presence of adenosine receptor blockade, reflecting an increase in $B\dot{E}O_2$ (Table 4, Fig. 1). The latter could only in part be explained by the increments in $B\dot{V}O_2$, inasmuch as the relation between $B\dot{V}O_2$ and $B\dot{E}O_2$ shifted upward toward higher $B\dot{E}O_2$ (not shown). The relation between $B\dot{V}O_2$ and systemic vascular resistance was also shifted upward toward higher resistance values (Fig. 1), suggesting that adenosine receptor blockade produced systemic vasoconstriction, which limited systemic O_2 delivery, thereby resulting in an increase in $B\dot{E}O_2$ and, hence, a decrease in mixed venous P_{O_2}.

Administration of 8-PT resulted in increases in $M\dot{V}O_2$ that reached levels of statistical significance during exercise at 1 and 3 km/h. Thus the increase in coronary blood flow and $M\dot{D}O_2$ at 1 km/h was likely due to an increase in O_2 requirements. Importantly, after admin-

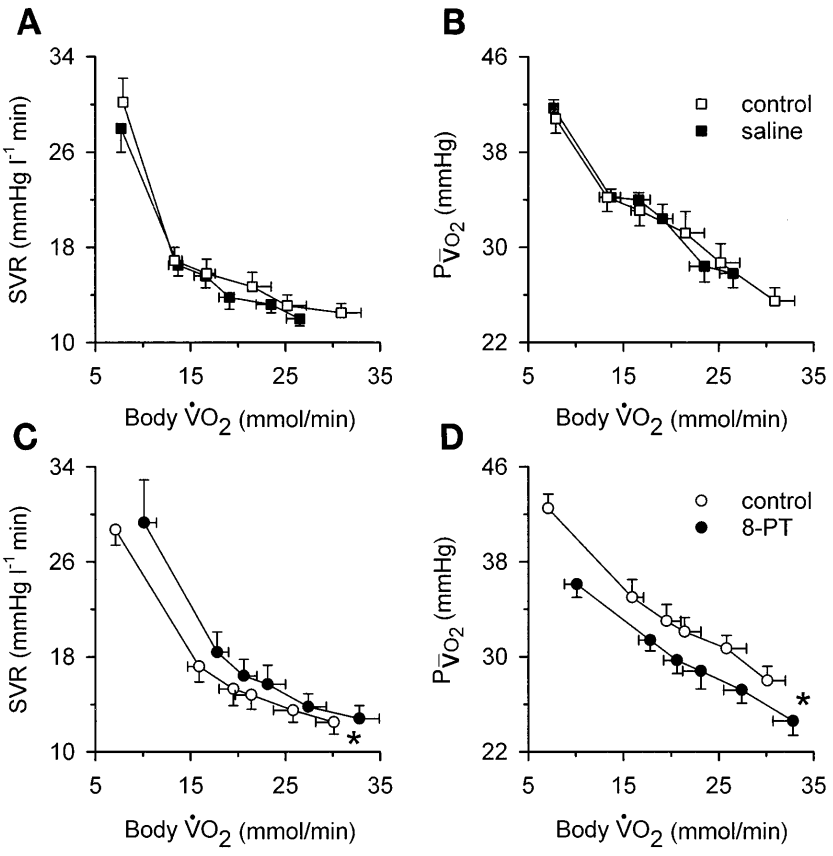

Fig. 1. Effects of saline (*A* and *B*) and adenosine receptor blockade produced by 8-phenyltheophylline (8-PT, 5 mg/kg iv; *C* and *D*) on relations between whole body O_2 consumption (body $\dot{V}O_2$) and systemic vascular resistance (SVR) and between whole body $\dot{V}O_2$ and mixed venous P_{O_2}. Values (means ± SE) were obtained at rest (supine) and during 5 levels of treadmill exercise. *$P \leq 0.05$ vs. control.

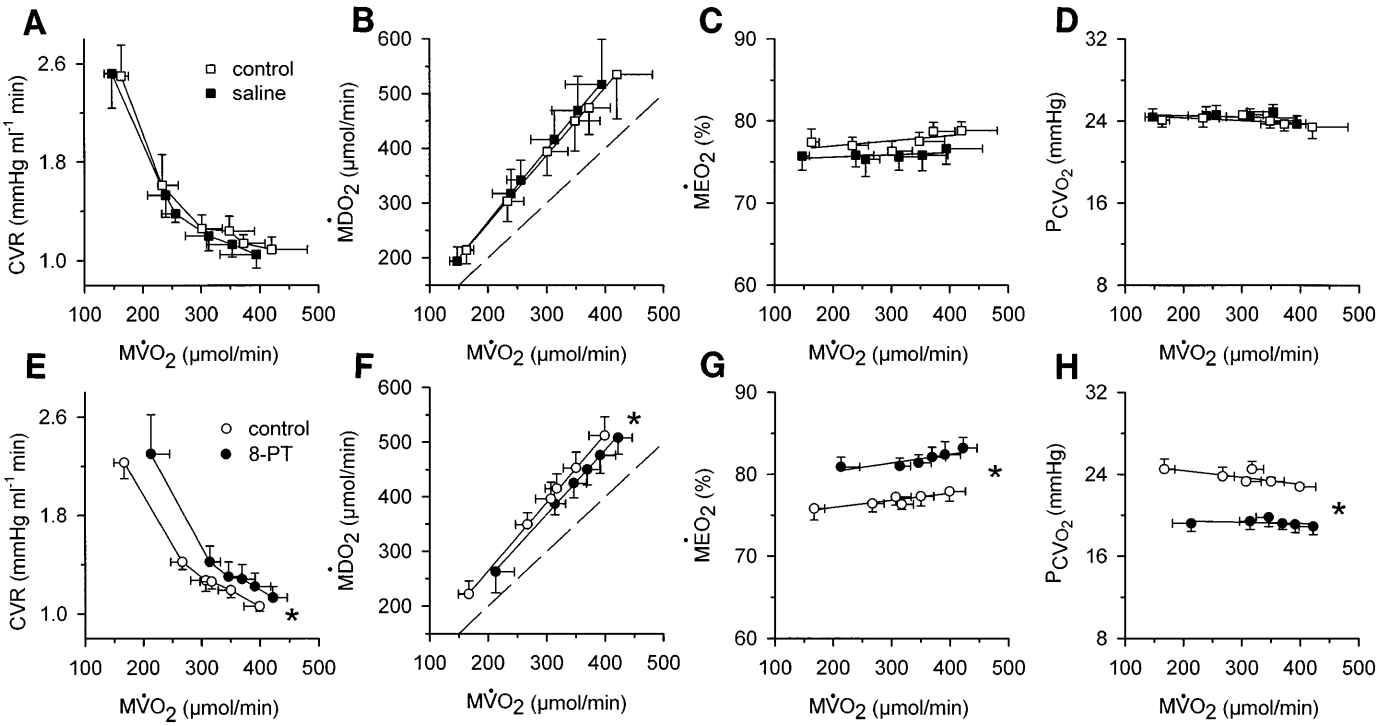

Fig. 2. Effects of saline (*A–D*) and adenosine receptor blockade produced by 8-PT (5 mg/kg iv; *E–H*) on relations between myocardial O_2 consumption ($M\dot{V}O_2$) and coronary vascular resistance (CVR), myocardial O_2 delivery ($M\dot{D}O_2$), myocardial O_2 extraction ($M\dot{E}O_2$), and coronary venous P_{O_2} (Pcv_{O_2}). Values (means ± SE) were obtained at rest (supine) and during 5 levels of treadmill exercise. * $P \leq 0.05$ vs. control.

Table 3. *Hemodynamic effects of adenosine receptor blockade in swine during graded treadmill exercise*

	Rest		Exercise, km/h				
	Supine	Standing	1	2	3	4	5
Cardiac output, l/min							
Control	3.5 ± 0.1	4.3 ± 0.2†	5.4 ± 0.3†	6.2 ± 0.3†	6.6 ± 0.4†	7.1 ± 0.4†	7.6 ± 0.3†
8-PT	3.9 ± 0.3	4.5 ± 0.2†	5.6 ± 0.2†	6.1 ± 0.2†	6.5 ± 0.2†	7.2 ± 0.3†	7.8 ± 0.3†
Heart rate, beats/min							
Control	111 ± 5	129 ± 7†	163 ± 6†	181 ± 8†	200 ± 11†	228 ± 9†	243 ± 6†
8-PT	123 ± 8‡	132 ± 6†	167 ± 3†	191 ± 7†	212 ± 9†	234 ± 9†	253 ± 7†‡
Mean aortic pressure, mmHg							
Control	98 ± 4	93 ± 4	94 ± 4	95 ± 5	96 ± 5	96 ± 5	95 ± 5
8-PT	108 ± 8	103 ± 10	104 ± 8	101 ± 7	102 ± 8	100 ± 7	100 ± 7
LV systolic pressure, mmHg							
Control	115 ± 5	111 ± 4	119 ± 6	123 ± 6†	127 ± 5†	130 ± 4†	136 ± 5†
8-PT	125 ± 9	124 ± 10	132 ± 10	131 ± 8	134 ± 9†	139 ± 6†	144 ± 4†
LV dP/dt_{max}, mmHg/s							
Control	2,910 ± 400	3,120 ± 350	4,110 ± 520†	4,610 ± 440†	5,180 ± 340†	5,700 ± 270†	6,290 ± 350†
8-PT	3,100 ± 450	3,300 ± 410	4,410 ± 510†	4,960 ± 450†	5,440 ± 530†	6,080 ± 330†	6,600 ± 280†
Mean pulmonary arterial pressure, mmHg							
Control	16 ± 1	17 ± 1	20 ± 2	23 ± 1†	28 ± 2†	33 ± 2†	35 ± 2†
8-PT	16 ± 1	14 ± 1	18 ± 1	21 ± 1†	24 ± 2†	29 ± 2†	33 ± 2†
Mean left atrial pressure,* mmHg							
Control	7 ± 3	2 ± 2	1 ± 2	3 ± 2	6 ± 3	10 ± 3	11 ± 2†
8-PT	4 ± 1	2 ± 2	1 ± 1	3 ± 2	6 ± 2	8 ± 2	13 ± 2†
Pulmonary vascular resistance,* $mmHg \cdot l^{-1} \cdot min$							
Control	2.8 ± 0.7	3.5 ± 0.5	3.3 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	3.0 ± 0.4	2.9 ± 0.4
8-PT	3.2 ± 0.3	2.9 ± 0.2	2.8 ± 0.2	2.7 ± 0.2	2.6 ± 0.2	2.5 ± 0.2	2.5 ± 0.2
Coronary blood flow, ml/min							
Control	45 ± 3	52 ± 4†	66 ± 2†	75 ± 4†	77 ± 5†	81 ± 4†	90 ± 4†
8-PT	51 ± 6	56 ± 5†	74 ± 4†‡	80 ± 5†	82 ± 5†	85 ± 8†	91 ± 7†

Values are means ± SE; $n = 7$ unless otherwise noted. 8-PT, 8-phenyltheophylline (5 mg/kg iv). * $n = 4$. † $P \leq 0.05$ vs. supine; ‡ $P \leq 0.05$ vs. corresponding control.

Table 4. *Effects of adenosine receptor blockade on O_2 balance in swine during graded treadmill exercise*

	Rest	Exercise, km/h				
	Supine	1	2	3	4	5
Hb, g/100 ml						
Control	7.8 ± 0.4	8.4 ± 0.3*	8.7 ± 0.3*	8.8 ± 0.2*	9.0 ± 0.2*	9.3 ± 0.3*
8-PT	8.0 ± 0.3	8.3 ± 0.4	8.5 ± 0.4*	8.6 ± 0.5*	9.0 ± 0.3*	9.1 ± 0.4*
Pa_{CO_2}, mmHg						
Control	46 ± 1	46 ± 2	43 ± 2	44 ± 2	42 ± 2	42 ± 1*
8-PT	36 ± 2†	36 ± 1†	38 ± 1†	36 ± 1†	37 ± 1†	35 ± 1†
pH_a						
Control	7.45 ± 0.01	7.46 ± 0.01	7.47 ± 0.01	7.47 ± 0.01	7.48 ± 0.01	7.47 ± 0.01
8-PT	7.53 ± 0.01†	7.52 ± 0.01†	7.50 ± 0.01†	7.52 ± 0.01†	7.51 ± 0.01†	7.52 ± 0.01†
Pa_{O_2}, mmHg						
Control	103 ± 3	98 ± 4	101 ± 5	96 ± 5	101 ± 3	99 ± 2
8-PT	114 ± 3	112 ± 5	102 ± 5	106 ± 4	101 ± 5	105 ± 4
Sa_{O_2}, %						
Control	96 ± 1	95 ± 1	96 ± 1	95 ± 1	96 ± 1	95 ± 1
8-PT	98 ± 1	97 ± 1	96 ± 1	97 ± 1	96 ± 1	97 ± 1
Ca_{O_2}, μmol/ml						
Control	4.77 ± 0.26	5.13 ± 0.22*	5.27 ± 0.21*	5.28 ± 0.15*	5.50 ± 0.17*	5.60 ± 0.20*
8-PT	4.99 ± 0.22	5.13 ± 0.23	5.23 ± 0.21	5.33 ± 0.28	5.48 ± 0.19*	5.63 ± 0.23*
$P\bar{v}_{CO_2}$, mmHg						
Control	52 ± 2	54 ± 2	55 ± 1*	54 ± 2*	55 ± 2*	56 ± 2*
8-PT	46 ± 1†	48 ± 1†	50 ± 1*†	49 ± 2*†	50 ± 2*†	51 ± 2*†
$pH_{\bar{v}}$						
Control	7.40 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.37 ± 0.01
8-PT	7.45 ± 0.01†	7.44 ± 0.01†	7.43 ± 0.01*†	7.43 ± 0.01*†	7.42 ± 0.01*†	7.41 ± 0.01*†
$P\bar{v}_{O_2}$, mmHg						
Control	42 ± 1	35 ± 1*	33 ± 1*	32 ± 1*	31 ± 1*	28 ± 1*
8-PT	36 ± 1†	31 ± 1*†	30 ± 1*†	29 ± 1*	27 ± 1*†	25 ± 1*†
$S\bar{v}_{O_2}$, %						
Control	56 ± 1	41 ± 2*	39 ± 2*	36 ± 2*	33 ± 2*	28 ± 2*
8-PT	48 ± 2†	37 ± 2*†	35 ± 2*†	33 ± 3*	30 ± 2*†	25 ± 2*†
$C\bar{v}_{O_2}$, μmol/ml						
Control	2.76 ± 0.18	2.22 ± 0.16*	2.14 ± 0.15*	2.01 ± 0.12*	1.91 ± 0.13*	1.67 ± 0.15*
8-PT	2.44 ± 0.14†	1.96 ± 0.15*†	1.89 ± 0.16*	1.81 ± 0.22*	1.70 ± 0.17*	1.43 ± 0.14*†
Pcv_{CO_2}, mmHg						
Control	56 ± 2	56 ± 2	57 ± 2	57 ± 2	54 ± 2	56 ± 2
8-PT	49 ± 1†	50 ± 1†	51 ± 1†	50 ± 2†	51 ± 2	50 ± 1†
pH_{cv}						
Control	7.40 ± 0.01	7.41 ± 0.01	7.39 ± 0.01	7.40 ± 0.01	7.40 ± 0.01	7.40 ± 0.01
8-PT	7.45 ± 0.01†	7.44 ± 0.02†	7.44 ± 0.01†	7.44 ± 0.01†	7.43 ± 0.01	7.42 ± 0.01†
Pcv_{O_2}, mmHg						
Control	24.5 ± 1.0	23.8 ± 0.9	23.3 ± 0.4	24.5 ± 0.8	23.3 ± 0.4	22.8 ± 0.3
8-PT	19.2 ± 0.8†	19.4 ± 0.8†	19.8 ± 0.9†	19.2 ± 0.6†	19.1 ± 0.8†	18.9 ± 0.8†
Scv_{O_2}, %						
Control	23.4 ± 1.4	22.5 ± 0.9	21.8 ± 0.8	22.5 ± 0.5	21.8 ± 1.2	21.0 ± 1.1
8-PT	18.8 ± 1.1†	18.4 ± 0.9†	17.9 ± 0.9†	17.4 ± 1.1†	16.9 ± 1.5†	16.3 ± 1.3†
Ccv_{O_2}, μmol/ml						
Control	1.18 ± 0.10	1.23 ± 0.04	1.19 ± 0.05	1.27 ± 0.03	1.26 ± 0.06	1.24 ± 0.06
8-PT	0.96 ± 0.06	0.99 ± 0.04†	0.99 ± 0.03†	0.98 ± 0.05†	0.96 ± 0.07†	0.94 ± 0.05†
$B\dot{V}O_2$, mmol/min						
Control	7.1 ± 0.3	15.9 ± 1.5*	19.5 ± 1.5*	21.4 ± 1.7*	25.8 ± 2.1*	30.1 ± 1.9*
8-PT	10.1 ± 1.3†	17.8 ± 1.2*†	20.6 ± 1.4*	23.1 ± 1.9*	27.4 ± 1.9*	32.8 ± 2.5*†
$B\dot{E}O_2$, %						
Control	42 ± 1	57 ± 2*	60 ± 2*	62 ± 2*	65 ± 2*	70 ± 2*
8-PT	51 ± 2†	62 ± 2*†	64 ± 2*†	66 ± 3*	69 ± 3*†	75 ± 2*†
$M\dot{V}O_2$, μmol/min						
Control	167 ± 18	267 ± 20*	307 ± 26*	317 ± 20*	350 ± 22*	399 ± 27*
8-PT	213 ± 32	314 ± 18*†	346 ± 22*	369 ± 23*†	391 ± 27*	422 ± 24*
$M\dot{E}O_2$, %						
Control	76 ± 1	76 ± 1	77 ± 1	76 ± 1	77 ± 1	78 ± 1
8-PT	81 ± 1†	81 ± 1†	81 ± 1†	82 ± 1†	82 ± 2†	83 ± 1†

Values are means ± SE; $n = 7$. *$P \leq 0.05$ vs. supine; †$P < 0.05$ vs. corresponding control.

istration of 8-PT, $M\dot{D}O_2$ was slightly lower at each level of $M\dot{V}O_2$ than under control conditions ($P \leq 0.05$) so that $M\dot{E}O_2$ increased and Pcv_{O_2} decreased (Table 4, Fig. 2), indicating an increase in vasomotor tone in the coronary resistance vessels that restricted $M\dot{D}O_2$. In support of this finding, the relation between $M\dot{V}O_2$ and coronary vascular resistance was shifted toward higher vascular resistance values (Fig. 2).

Table 5. *Effects of hyperventilation on blood gases and $M\dot{E}O_2$*

	Baseline	Hyperventilation
Pa_{CO_2}, mmHg	47 ± 5	38 ± 5*
pH_a	7.44 ± 0.03	7.51 ± 0.04*
Pa_{O_2}, mmHg	95 ± 5	109 ± 4*
Pcv_{CO_2}, mmHg	56 ± 5	47 ± 6*
pH_{cv}	7.38 ± 0.03	7.44 ± 0.04*
Pcv_{O_2}, mmHg	22.3 ± 0.7	22.4 ± 1.7
$M\dot{E}O_2$, %	77 ± 2	75 ± 2

Values are means ± SE; $n = 5$. *$P \leq 0.05$ vs. baseline.

Contribution of Changes in pH and P_{CO_2} to 8-PT-Induced Alterations in $M\dot{E}O_2$

Mechanical hyperventilation decreased arterial P_{CO_2} from 47 ± 5 to 38 ± 5 mmHg and increased pH from 7.44 ± 0.03 to 7.51 ± 0.04 (all $P \leq 0.05$); similar changes were observed in the coronary venous blood. However, no changes were observed in Pcv_{O_2} or $M\dot{E}O_2$ (Table 5). Similarly, an increase in arterial pH from 7.39 ± 0.03 to 7.50 ± 0.04 produced by infusion of 1 M HCO_3^- in two sedated swine had no effect on Pcv_{O_2} (23.6 ± 0.6 and 23.3 ± 1.8 mmHg before and after HCO_3^- administration, respectively) or on $M\dot{E}O_2$ (77 ± 3 and 77 ± 4%, respectively). These findings indicate that 8-PT-induced changes in P_{CO_2} and pH were not responsible for its vasoconstrictor actions.

DISCUSSION

The present study describes the contribution of adenosine in maintaining the balance between $M\dot{V}O_2$ and $M\dot{D}O_2$ in awake swine at rest and during treadmill exercise. The major findings of the present study were as follows: *1*) $M\dot{E}O_2$ and Pcv_{O_2} were not altered from resting levels during treadmill exercise at up to 80–90% of maximum heart rate (4a), indicating that the exercise-induced increases in $M\dot{V}O_2$ were matched by equivalent increases in $M\dot{D}O_2$. *2*) Adenosine receptor blockade increased $M\dot{E}O_2$ and decreased Pcv_{O_2} under resting conditions as well as during exercise, indicating that endogenously released adenosine exerted a vasodilator influence that contributed to maintaining $M\dot{D}O_2$ commensurate with O_2 demands. *3*) Adenosine was not mandatory for the exercise-induced coronary vasodilation. *4*) Changes in arterial or coronary venous P_{CO_2} or pH could not account for these findings.

Adenosine has been proposed as one of the messengers that couples myocardial O_2 demand to vasomotor tone of the coronary resistance vessels (4, 30). Adenine nucleotides do not cross the cell membrane of cardiac myocytes, but adenosine formed from the action of nucleotide phosphorylase on AMP can be transported out of myocytes into the interstitial space (36). On entering the interstitial space, adenosine can interact with A_2 receptors on coronary vascular smooth muscle to produce vasodilation and an increase in coronary blood flow (30). Previous studies in dogs have demonstrated that endogenous adenosine production is not mandatory for maintaining resting coronary blood flow. Thus studies in anesthetized open-chest dogs have generally failed to demonstrate an effect of intracoronary adenosine deaminase (22, 24, 33) or intravenous aminophylline to block adenosine receptors (19, 34) on basal coronary blood flow, although some studies have reported an increase in coronary vascular resistance after administration of the selective adenosine receptor antagonist sulfophenyltheophylline (27). Similarly, in doses that caused marked inhibition of exogenous adenosine-induced coronary vasodilation, intracoronary adenosine deaminase or intravenous 8-PT had no effect on resting coronary blood flow, $M\dot{E}O_2$, or Pcv_{O_2} in awake dogs (2).

In the in vivo canine heart, adenosine release is enhanced during conditions of increased myocardial O_2 demand (1, 14, 28, 39). However, demonstration of an essential role for adenosine in mediating exercise-induced coronary vasodilation requires that interruption of the adenosine effect interferes with exercise-induced coronary vasodilation. Bache et al. (2) examined the effects of adenosine receptor blockade with 8-PT as well as augmented adenosine catabolism produced by intracoronary adenosine deaminase in exercising dogs. Adenosine antagonism inhibited coronary vasodilation evoked by ischemia; adenosine deaminase caused a 33–39% decrease in reactive hyperemia after 5- to 20-s coronary occlusions, whereas 8-PT caused a 40–62% decrease in reactive hyperemia. Neither agent significantly changed heart rate or arterial pressure during treadmill exercise. Furthermore, neither the absolute values for $M\dot{V}O_2$, coronary blood flow, and Pcv_{O_2} nor the relationship between these variables was altered by adenosine receptor blockade or adenosine deaminase (2). These findings indicate that adenosine is not obligatory for the increase in coronary blood flow produced by exercise in the dog heart.

In contrast to the results obtained in the dog heart, there is ample evidence that adenosine contributes to regulation of coronary vasomotor tone in the human heart. Edlund et al. (11–13) examined the effect of adenosine receptor blockade with theophylline on coronary sinus blood flow measured at rest and during supine bicycle exercise in normal young adult human subjects. Theophylline (3–6 mg/kg iv) caused a small increase in heart rate (13) and the rate-pressure product (12), but, despite increased myocardial O_2 demands, coronary blood flow and coronary venous S_{O_2} were lower, whereas coronary vascular resistance and $M\dot{E}O_2$ were higher, after theophylline at rest and during exercise (11–13). The results of the present study obtained in awake swine support the findings by Edlund and co-workers and suggest that endogenous adenosine exerts a vasodilator influence on the coronary circulation at rest and during exercise but is not mandatory for the increase in coronary blood flow and decrease in coronary vascular resistance produced by exercise in swine and humans. These findings could be interpreted to suggest that adenosine contributes to a basal offset point of coronary vasomotor tone but that adenosine does not contribute to the decrease in vasomotor tone produced by exercise. However, in closed-chest

sedated swine, increased adenosine catabolism with intracoronary administration of adenosine deaminase, which had no effect on the steady-state coronary blood flow response to isoproterenol (after 10 min of infusion), markedly blunted the early (at 1 min) coronary blood flow response to intracoronary infusions of isoproterenol (18). In the present study we obtained measurements after 2–3 min of exercise, so we cannot exclude the possibility that adenosine may have contributed to the early adaptation of vasomotor tone (≤1 min) during treadmill exercise. In addition, it is possible that adenosine also contributes to coronary vasodilation during steady-state exercise but that other vasodilator mechanisms, e.g., NO or ATP-sensitive K^+ channel activation, act to compensate and mediate the vasodilation when adenosine receptors are blocked (26). Future studies, employing a combination of blockers of these different vasodilator systems, are needed to determine whether adenosine contributes to the coronary vasodilation produced by exercise in swine. However, the present study clearly demonstrates that adenosine is not mandatory for steady-state exercise-induced vasodilation in swine.

In dogs the exercise-induced increase in coronary blood flow does not fully match the increase in myocardial O_2 demand, so even during mild-to-moderate exercise (<70% of maximum heart rate) $M\dot{E}O_2$ increases and, hence, Pcv_{O_2} decreases (2, 14, 28). In contrast, in humans, minimal changes in $M\dot{E}O_2$ occur at mild-to-moderate levels of exercise, although an increase in $M\dot{E}O_2$ and a decrease in coronary venous O_2 content have been reported in humans during heavy exercise (>85% of maximum heart rate) (26). Similar to humans, $M\dot{E}O_2$ and Pcv_{O_2} did not change significantly in swine during treadmill exercise in the present study. Interestingly, Hall et al. (21) reported that interstitial levels of adenosine increased during β-adrenergic stimulation with dobutamine in anesthetized swine in the presence of maintained Pcv_{O_2} and interstitial lactate levels, suggesting that adenosine could have contributed to the maintained Pcv_{O_2} during exercise in the present study. However, the results of the present study do not support such a role for adenosine, inasmuch as 8-PT resulted in similar decreases in Pcv_{O_2} at rest and during exercise.

In the present study, adenosine receptor blockade increased coronary as well as systemic vascular resistance at rest and during exercise. Because we did not measure regional blood flows, we cannot determine which vascular beds responded with an increased vascular resistance. However, during exercise a major part of cardiac output is directed toward the active skeletal muscle groups (26). Adenosine has been invoked in the regulation of skeletal muscle vascular tone during exercise. Thus the exercise-induced skeletal muscle hyperemia was blunted by increased adenosine catabolism with adenosine deaminase (35), whereas a decrease in adenosine uptake produced by dipyridamole increased skeletal muscle blood flow during exercise (25). The results from the present study are consistent with a vasodilator influence exerted by adenosine on skeletal muscle resistance vessels during treadmill exercise.

Adenosine receptor blockade had no effect on pulmonary vascular resistance, which would appear to indicate that endogenous adenosine did not contribute to regulation of pulmonary vascular resistance at rest or during exercise. However, A_1 and A_2 receptors, both of which are present in the pulmonary bed, mediate pulmonary smooth muscle contraction and relaxation, respectively (3). Because 8-PT is a nonselective A_1/A_2-receptor antagonist, we cannot exclude the possibility that endogenous adenosine may contribute to regulation of pulmonary resistance vessel tone but that lack of effect of 8-PT on the pulmonary bed could be due to its opposing vasomotor actions via simultaneous A_1 and A_2 blockade. Future studies using selective A_1- and A_2-receptor antagonists are required to determine the role of A_1- and A_2-receptor subtypes.

In conclusion, $M\dot{E}O_2$ and Pcv_{O_2} were not altered from resting levels in swine exercising on a treadmill at levels up to 80–90% of maximum heart rate, indicating that the exercise-induced increases in $M\dot{V}O_2$ were matched by equivalent increases in $M\dot{D}O_2$. Adenosine receptor blockade resulted in an increased $M\dot{E}O_2$ and a decreased Pcv_{O_2} under resting conditions and during exercise, indicating that endogenously released adenosine exerted a vasodilator influence that contributed to maintaining $M\dot{D}O_2$ commensurate with O_2 demands. However, adenosine was not mandatory for the exercise-induced coronary vasodilation in swine.

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