Am J Physiol Heart Circ Physiol
280: H22–H33, 2001.

Role of K^+_{ATP} channels in regulation of systemic, pulmonary, and coronary vasomotor tone in exercising swine

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Received 12 June 2000; accepted in final form 23 August 2000

Duncker, D. J., H. H. Oei, F. Hu, R. Stubenitsky, and P. D. Verdouw. Role of K^+_{ATP} channels in regulation of systemic, pulmonary, and coronary vasomotor tone in exercising swine. *Am J Physiol Heart Circ Physiol* 280: H22–H33, 2001.—The role of ATP-sensitive K^+ (K^+_{ATP}) channels in vasomotor tone regulation during metabolic stimulation is incompletely understood. Consequently, we studied the contribution of K^+_{ATP} channels to vasomotor tone regulation in the systemic, pulmonary, and coronary vascular bed in nine treadmill-exercising swine. Exercise up to 85% of maximum heart rate increased body O_2 consumption fourfold, accommodated by a doubling of both cardiac output and body O_2 extraction. Mean aortic pressure was unchanged, implying that systemic vascular conductance (SVC) also doubled, whereas pulmonary artery pressure increased almost in parallel with cardiac output, so that pulmonary vascular conductance (PVC) increased only 25 ± 9% (both $P < 0.05$). Myocardial O_2 consumption tripled during exercise, which was paralleled by an equivalent increase in O_2 supply so that coronary venous P_{O_2} was maintained. Selective K^+_{ATP} channel blockade with glibenclamide (3 mg/kg iv), decreased SVC by 29 ± 4% at rest and by 10 ± 2% at 5 km/h (both $P < 0.05$), whereas PVC was unchanged. Glibenclamide decreased coronary vascular conductance and hence myocardial O_2 delivery, necessitating an increase in O_2 extraction from 76 ± 2% to 86 ± 2% at rest and from 79 ± 2% to 83 ± 1% at 5 km/h. Consequently, coronary venous P_{O_2} decreased from 25 ± 1 to 17 ± 1 mmHg at rest and from 23 ± 1 to 20 ± 1 mmHg at 5 km/h (all values are $P < 0.05$). In conclusion, K^+_{ATP} channels dilate the systemic and coronary, but not the pulmonary, resistance vessels at rest and during exercise in swine. However, opening of K^+_{ATP} channels is not mandatory for the exercise-induced systemic and coronary vasodilation.

exercise; coronary circulation; pulmonary circulation; systemic circulation

OVER A DECADE AGO, hyperpolarization of the vascular smooth muscle cell membrane caused by opening of ATP-sensitive K^+ (K^+_{ATP}) channels was discovered as a novel mechanism of vasodilation. Subsequently, the pharmacological openers of these K^+_{ATP} channels have been shown to dilate resistance vessels in the systemic (20, 27), pulmonary (13, 20, 24, 28), and coronary (9, 27) vascular beds. Additionally, blockade of K^+_{ATP} channels increases basal tone in the systemic (5, 11, 17, 21, 23, 33), pulmonary (20, 24), and coronary circulations (9, 15), indicating that these channels contribute significantly to the regulation of basal vasomotor tone in these vascular beds. In contrast, information on the role of K^+_{ATP} channels in the adaptation of vasomotor tone during increased metabolic demands produced by exercise is limited. Thus only two studies (9, 10) on dogs reported the role of K^+_{ATP} channels in exercise-induced coronary vasodilation, whereas no study investigated the role of K^+_{ATP} channels in the adaptation of vasomotor tone in the pulmonary and regional systemic vascular beds during exercise. Consequently, in the present study we investigated the role of K^+_{ATP} channels in the regulation of systemic, pulmonary, and coronary vasomotor tone in awake pigs under basal resting conditions and during treadmill exercise, resulting in heart rates up to 85% of the maximum heart rate.

MATERIALS AND METHODS

Crossbred Landrace × Yorkshire pigs were used in the present study. All of the experiments were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* as approved by the Council of the American Physiological Society and the regulations of the Animal Care Committee of the Erasmus University Rotterdam (The Netherlands). Adaptation of animals to the laboratory conditions started 1 wk before the day of surgery and continued until 10 days postoperatively. Full details of the experimental procedures have been published previously (7, 8, 27, 30).

Surgical Procedures

After an overnight fast, 11 pigs (6 male and 5 female, weighing 24 ± 1 kg at the time of surgery and 29 ± 1 kg at the time of study) were sedated with ketamine (20 mg/kg im; Ketalin, Apharmo, Arnhem, The Netherlands), anesthetized with 10 mg/kg iv thiopental sodium (Rhone-Rorer-Poulenc, Amstelveen, The Netherlands), and 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

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the fourth left intercostal space and an 8-Fr fluid-filled polyvinyl chloride 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 inner diameter) 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 P4.5, Konigsberg Instruments, Pasadena, CA) was inserted into the left ventricle via the apical dimple for recording of left ventricular (LV) pressure and the maximum of its first derivative (LV dP/dt_{max}). An 8-Fr catheter was inserted into the left ventricle for calibration of the Konigsberg transducer signal. An 8-Fr catheter was also inserted into the pulmonary artery for measurement of pulmonary artery pressure, withdrawal of mixed venous blood samples, and administration of drugs, and another 8-Fr catheter was inserted into the left atrial appendage for measurement of left atrial pressure and injection of radioactive microspheres to determine regional organ and tissue blood flows (27). For the measurement of coronary blood flow, a Doppler flow probe of 2.0–3.0 mm inner diameter, emitting frequency (F_0) = 10 MHz, was placed around the proximal part of the left anterior descending (LAD) coronary artery (model HVPD-10, Crystal Biotech, Northboro, MA) for measurement of coronary blood flow (7, 8, 16). A small angiocatheter (0.8/1.1 mm, inner/outer diameter) connected to a larger Tygon catheter (0.8/2.4 mm, inner/outer diameter) was inserted directly into the anterior interventricular vein to allow sampling of coronary venous blood. Electrical wires and catheters were tunneled subcutaneously to the back, the chest was closed, and the animals were allowed to recover. All of the 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 buprenorphine (Temgesic; Schering-Plough, Amstelveen, The Netherlands) during the first 48 h and intravenous injections of 25 mg/kg amoxicillin (Clamoxyl, Beecham Farma, Amstelveen, The Netherlands) and 5 mg/kg gentamycin (AUV, Cuijk, The Netherlands) on a daily basis during the first week to prevent infections. The catheters were flushed daily with physiological saline containing 2,000 U/ml heparin sodium (Leo Pharmaceutical Products, Weesp, The Netherlands).

Experimental Protocols

Studies were performed 10–20 days after surgery with animals either resting in a cage or exercising on a motor-driven treadmill.

Degree, duration, and selectivity of K^+_{ATP} channel blockade produced by glibenclamide. To determine the degree and duration of K^+_{ATP} channel blockade produced by glibenclamide, studies were performed in five awake resting pigs. After animals had been lying quietly for 15 min, baseline measurements were collected and the effects of four consecutive intravenous infusions (37.5, 75, 150, and 225 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of the K^+_{ATP} channel opener bimakalim (27) on heart rate, mean aortic blood pressure, cardiac output, and coronary blood flow were studied.

On a different day, baseline hemodynamic measurements were recorded and blood samples were collected, after which animals received an intravenous infusion of glibenclamide (3 mg/kg in 20 ml, administered over 5 min). Five minutes after administration was completed, measurements were made at 3-min intervals over a 12-min period corresponding to the total exercise protocol period (see *Experimental Protocols*). After we completed these measurements, four consecutive infusions of bimakalim (37.5, 75, 150, and 225 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were administered.

To confirm the reported (9, 10) specificity of glibenclamide, six consecutive, 5-min infusions of sodium nitroprusside (0.5, 1, 2, 3, 4, and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were administered intravenously before and 5 min after glibenclamide (3 mg/kg iv) in two awake but resting pigs.

Exercise Protocols

Two exercise protocols were performed on different days and in random order. The aim of the first protocol was to study the effect of K^+_{ATP} channel blockade during exercise. In the second protocol we confirmed the reproducibility of two consecutive exercise tests performed at a 90-min interval (7, 8, 30).

K^+_{ATP} channel blockade. With the pigs resting quietly on the treadmill, resting hemodynamic measurements were obtained, and arterial, mixed venous, and coronary venous blood samples were collected (7, 8). After all of the hemodynamic measurements were repeated and rectal temperature was measured with animals standing on the treadmill, a five-stage treadmill exercise protocol was started (1–5 km/h). Each exercise stage lasted 2–3 min. Hemodynamic variables were continuously recorded and blood samples 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, the animals were allowed to rest on the treadmill. Ninety minutes later, the animals received an intravenous infusion of glibenclamide (3 mg/kg in 20 ml, administered over 5 min) to produce K^+_{ATP} channel blockade. Five minutes after completion of the glibenclamide infusion, resting measurements were obtained, and the exercise protocol was repeated. To prevent glibenclamide-induced decreases in blood glucose levels, the animals received intravenous 10-ml 10% glucose injections at rest and after collection of measurements at 2 and 4 km/h.

On a different day, the effects of K^+_{ATP} channel blockade on regional organ and tissue blood flows were studied in five pigs. For this purpose, radioactive microspheres were injected in pigs when resting quietly on the treadmill and when exercising at 5 km/h before and after 90 min of rest, in the presence of glibenclamide (3 mg/kg iv).

Reproducibility of responses to exercise. Ninety minutes after the pigs had undergone a control exercise period, the animals received 20 ml of physiological saline, after which resting measurements were obtained and the five-stage exercise protocol was repeated.

Blood Gas and Glucose Measurements

Blood samples were maintained in ice-cold syringes until the conclusion of each exercise trial. Measurements of P_{O_2} (mmHg), P_{CO_2} (mmHg), pH, and standard base excess (SBE) were then immediately performed with a blood gas analyzer (Acid-Base Laboratory model 505, Radiometer, Copenhagen, Denmark). O_2 saturation (S_{O_2}) and hemoglobin (Hb, 100 ml/g) were measured with a hemoximeter (OSM2, Radiometer). Arterial glucose measurements were performed with the use of Glucostix (Bayer Diagnostics, Mijdrecht, The Netherlands) and a glucometer (model 5626, Miles).

Data Acquisition and Analysis

All hemodynamic data were recorded and digitized on-line by using an eight-channel data-acquisition program ATCO-

DAS (Dataq Instruments, Akron, OH) and stored on a computer for 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.

Cardiac output was computed as the sum of ascending aortic blood flow (measured with an electromagnetic flow probe) and total coronary blood flow. Because the LAD coronary artery supplies ~40% of the left ventricle, total coronary blood flow was taken as 2.5× flow in the LAD coronary artery. Systemic and coronary vascular conductance were calculated as the ratio of cardiac output and mean aortic pressure and coronary blood flow and mean aortic pressure, respectively. Blood O_2 content (μmol/ml) was computed as [0.621·Hb (g%)·O_2 saturation (%)] + [0.00131·P_{O_2} (mmHg)]. Myocardial O_2 delivery (MD_{O_2}) in the LAD coronary artery perfused area was computed as the product of arterial O_2 content and LAD coronary blood flow; whole body O_2 delivery (BD_{O_2}) was calculated as the product of arterial O_2 content and cardiac output. MV_{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 (BV_{O_2}) was calculated as the product of cardiac output and difference in O_2 content between arterial and mixed venous blood. Myocardial O_2 extraction was computed as the ratio of arteriocoronary venous O_2 content difference and the arterial O_2 content; whole body O_2 extraction was calculated as the ratio of the difference in the arterial and mixed venous O_2 contents and the arterial O_2 content.

Statistical analysis of the exercise and treatment data was performed by using a two-way ANOVA for repeated measures. When a significant effect of exercise was observed, post hoc testing was done by using Dunnett's test. When a significant effect of treatment was observed, post hoc testing was done with the use of either a paired Student's *t*-test or Wilcoxon signed rank test. A two-tailed *P* value of <0.05 was considered statistically significant. All data are presented as means ± SE.

Drugs

Glibenclamide (Sigma-Aldrich, Bornem, Belgium) was dissolved in 20-ml distilled water (30°C, pH 8–9), whereas bimakalim (courtesy of P. Schelling; Merck, Darmstadt, Germany) was dissolved in 30°C saline to produce a concentration of 100 $\mu g \cdot kg^{-1} \cdot ml^{-1}$. Sodium nitroprusside (25 mg/ml) (Department of Pharmacy, Academic Hospital Dijkzigt, Rotterdam, The Netherlands) was diluted in 37°C saline to produce a concentration of 1 $\mu g \cdot kg^{-1} \cdot ml^{-1}$. Fresh drug solutions were prepared daily.

RESULTS

Degree, Stability, and Selectivity of K^+_{ATP} Channel Blockade Produced by Glibenclamide

Bimakalim produced a dose-dependent increase in systemic and coronary vascular conductance (Fig. 1) and a small increase in pulmonary vascular conductance from 0.29 ± 0.04 $l \cdot min^{-1} \cdot mmHg^{-1}$ at baseline up to 0.33 ± 0.06 $l \cdot min^{-1} \cdot mmHg^{-1}$ ($P < 0.05$) during the highest dose of bimakalin (225 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Twenty minutes after administration of glibenclamide (3 mg/kg iv), the bimakalim-induced vasodilation was blunted by 60–70%, whereas the vasodilation produced by sodium nitroprusside remained unmitigated (Fig. 1). Glibenclamide resulted in stable decreases in mixed venous and coronary venous S_{O_2} saturation over the 12-min period (Fig. 2). These data indicate that glibenclamide produced a good and stable degree of selective blockade of K^+_{ATP} channels over a time period corresponding with the total exercise trial period (12 ± 1 min).

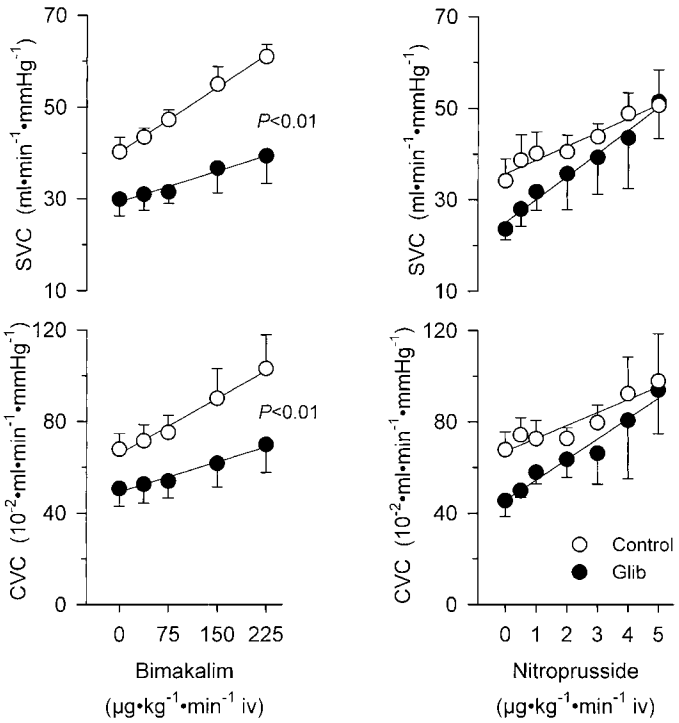

Fig. 1. Effect of glibenclamide (Glib, 3 mg/kg iv, $n = 5$ pigs) on bimakalim-induced (*left*) and sodium nitroprusside (*right*)-induced increases in systemic vascular conductance (SVC, *top*) and coronary vascular conductance (CVC, *bottom*). Note that the increase in conductance by bimakalim was significantly ($P < 0.01$) attenuated by Glib, whereas the increase in conductance by nitroprusside was unaffected. Data are means ± SE.

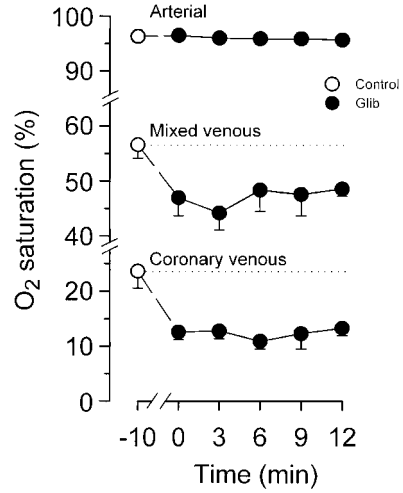

Fig. 2. Stability of Glib-induced (3 mg/kg iv) decreases in mixed venous and coronary venous O_2 saturations. Data are means ± SE; $n = 3$ pigs.

Table 1. *Effect of K^+_{ATP} channel blockade on hemodynamic responses to graded treadmill exercise*

	Rest		Treadmill Exercise, km/h				
	Lying	Standing	1	2	3	4	5
Systemic hemodynamics							
CO, l/min							
Control	4.0 ± 0.2	5.3 ± 0.3*	6.1 ± 0.2*	6.7 ± 0.2*	7.2 ± 0.2*	7.8 ± 0.3*	8.3 ± 0.3*
Glib	3.4 ± 0.2†	4.4 ± 0.2*†	5.5 ± 0.2*†	6.1 ± 0.2*†	6.8 ± 0.3*†	7.6 ± 0.3*	8.1 ± 0.3*
HR, beats/min							
Control	121 ± 5	147 ± 9*	173 ± 8*	196 ± 9*	213 ± 9*	235 ± 10*	245 ± 8*
Glib	100 ± 5†	115 ± 4*†	142 ± 6*†	160 ± 6*†	180 ± 7*†	207 ± 11*†	225 ± 11*†
SV, ml							
Control	33.1 ± 1.0	36.1 ± 1.2*	35.5 ± 1.2*	34.3 ± 1.1	34.2 ± 0.8	33.3 ± 1.0	33.8 ± 0.9
Glib	34.1 ± 0.7	38.4 ± 0.8*	38.8 ± 1.1*†	38.3 ± 0.6*†	38.0 ± 0.9*†	37.0 ± 1.4*†	36.4 ± 1.4*†
LVSP, mmHg							
Control	110 ± 2	115 ± 2*	119 ± 3*	123 ± 3*	124 ± 3*	131 ± 3*	136 ± 3*
Glib	127 ± 4†	126 ± 4†	123 ± 2	125 ± 2	126 ± 2	130 ± 3	134 ± 3*
LV dP/dt_{max}, mmHg/s							
Control	2,940 ± 120	3,700 ± 240*	4,230 ± 250*	4,720 ± 180*	4,930 ± 140*	5,510 ± 180*	5,890 ± 180*
Glib	2,600 ± 70†	2,890 ± 80*†	3,530 ± 150*†	3,890 ± 180*†	4,300 ± 150*†	4,850 ± 150*†	5,450 ± 210*†
MAP, mmHg							
Control	96 ± 2	92 ± 2*	90 ± 3*	91 ± 3*	90 ± 3*	91 ± 3*	92 ± 3*
Glib	116 ± 2†	111 ± 2†	104 ± 3*†	104 ± 3*†	102 ± 2*†	100 ± 3*†	100 ± 3*†
SVC, $ml \cdot min^{-1} \cdot mmHg^{-1}$							
Control	42 ± 2	58 ± 3*	69 ± 4*	74 ± 3*	81 ± 3*	87 ± 4*	91 ± 5*
Glib	29 ± 2†	40 ± 2*†	53 ± 3*†	59 ± 3*†	68 ± 3*†	76 ± 3*†	81 ± 3*†
Pulmonary hemodynamics							
MPAP, mmHg							
Control	16 ± 1	16 ± 2	19 ± 1	23 ± 2*	27 ± 2*	31 ± 2*	34 ± 2*
Glib	17 ± 1	17 ± 2	20 ± 1	22 ± 2*	27 ± 2*	31 ± 2*	33 ± 2*
MLAP, mmHg							
Control	4 ± 1	1 ± 1	2 ± 1	4 ± 2	7 ± 2	11 ± 2*	14 ± 3*
Glib	7 ± 1	5 ± 2	5 ± 1	6 ± 2	9 ± 2	12 ± 2*	14 ± 2*
PVC, $l \cdot min^{-1} \cdot mmHg^{-1}$							
Control	0.35 ± 0.05	0.35 ± 0.03	0.37 ± 0.04	0.37 ± 0.03	0.39 ± 0.03	0.40 ± 0.04*	0.42 ± 0.05*
Glib	0.31 ± 0.03	0.37 ± 0.04	0.37 ± 0.04	0.39 ± 0.05*	0.41 ± 0.06*	0.42 ± 0.06*	0.44 ± 0.06*
Coronary hemodynamics							
CBF, ml/min							
Control	50 ± 4	71 ± 7*	87 ± 9*	94 ± 10*	100 ± 10*	113 ± 13*	118 ± 13*
Glib	44 ± 4†	55 ± 4*†	71 ± 5*†	77 ± 7*†	86 ± 7*†	102 ± 11*†	110 ± 12*†
CVC, $ml \cdot min^{-1} \cdot mmHg^{-1}$							
Control	0.53 ± 0.04	0.77 ± 0.07*	0.98 ± 0.11*	1.05 ± 0.11*	1.12 ± 0.11*	1.26 ± 0.15*	1.32 ± 0.17*
Glib	0.38 ± 0.04†	0.49 ± 0.05*†	0.69 ± 0.06*†	0.76 ± 0.08*†	0.86 ± 0.07*†	1.04 ± 0.11*†	1.12 ± 0.12*†

Values are means ± SE; $n = 9$ pigs. CO, cardiac output; HR, heart rate; SV, stroke volume; LV dP/dt_{max}, maximum rate of rise of left ventricular (LV) pressure; MAP, mean aortic pressure; LVSP, LV systolic pressure; SVC, systemic vascular conductance; MPAP, mean pulmonary artery pressure; MLAP, mean left atrial pressure; PVC, pulmonary vascular conductance; CBF, coronary blood flow of the left anterior descending (LAD) coronary artery perfused myocardium; CVC, coronary vascular conductance; Glib, glibenclamide, 3 mg/kg iv. *$P < 0.05$ vs. Rest; †$P < 0.05$ vs. Control.

Effects of K^+_{ATP} Channel Blockade During Exercise

Systemic circulation. Exercise produced an increase in cardiac output from 4.0 ± 0.2 l/min at rest (lying down) to 8.3 ± 0.3 l/min at 5 km/h ($P < 0.01$), which was principally due to an increase in heart rate from 121 ± 5 to 245 ± 8 beats/min ($P < 0.01$, ~85% of maximum heart rate) as stroke volume increased <10% (Table 1). Because LV systolic pressure increased from 110 ± 2 mmHg at rest to 136 ± 3 mmHg at 5 km/h, $P < 0.01$, the maintained stroke volume was the result of an increase in left atrial pressure from 4 ± 1 to 14 ± 3 mmHg ($P < 0.01$) and an increase in LV dP/dt_{max} from 2,940 ± 120 to 5,890 ± 180 mmHg/s ($P < 0.01$). Mean aortic pressure decreased slightly when the animals went from a lying position to a standing position but did not change during exercise. The maintained mean aortic blood pressure in the presence of a doubling of cardiac output implies a doubling of systemic vascular conductance.

Exercise resulted in a decrease in arterial P_{CO_2} from 44 ± 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 $P < 0.05$) (Table 2). Arterial P_{O_2} and S_{O_2} (97 ± 1% at rest and 96 ± 1% at 5 km/h) did not change from their baseline values, but Hb and O_2 content increased by 15 ± 4% and 14 ± 4% at the highest level of exercise compared with resting conditions (both $P < 0.05$). Mixed venous P_{O_2} (Table 2), S_{O_2}, and O_2 content (not shown) decreased progressively during exercise, whereas mixed venous P_{CO_2} and pH were minimally

Table 2. *Effect of K^+_{ATP} channel blockade on blood gas responses to graded treadmill exercise*

		Treadmill Exercise, km/h				
	Rest (Lying)	1	2	3	4	5
Hb, g/100 ml						
Control	7.0 ± 0.4	7.5 ± 0.4*	7.5 ± 0.4*	7.7 ± 0.4*	7.8 ± 0.3*	8.0 ± 0.3*
Glib	6.5 ± 0.3	6.7 ± 0.3	6.8 ± 0.2	7.2 ± 0.3*	7.5 ± 0.3*	7.7 ± 0.3*
Art pH						
Control	7.44 ± 0.01	7.44 ± 0.01	7.45 ± 0.01	7.45 ± 0.01	7.46 ± 0.01*	7.47 ± 0.01*
Glib	7.44 ± 0.01	7.44 ± 0.01	7.45 ± 0.01	7.46 ± 0.01	7.47 ± 0.01*	7.48 ± 0.01*
Art P_{CO_2}, mmHg						
Control	44 ± 1	44 ± 1	43 ± 1	42 ± 1	40 ± 1*	39 ± 1*
Glib	43 ± 1	43 ± 1	41 ± 1	40 ± 1*	39 ± 1*	38 ± 1*
Art P_{O_2}, mmHg						
Control	109 ± 3	106 ± 4	108 ± 3	105 ± 3	104 ± 5	103 ± 4
Glib	115 ± 3	105 ± 2	110 ± 3	108 ± 5	107 ± 4	106 ± 5
MV pH						
Control	7.38 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01
Glib	7.37 ± 0.01	7.35 ± 0.01*†	7.36 ± 0.01	7.35 ± 0.01†	7.35 ± 0.01*†	7.34 ± 0.01*†
MV P_{CO_2}, mmHg						
Control	53 ± 1	53 ± 1	55 ± 1	55 ± 1	54 ± 1	55 ± 1
Glib	54 ± 1	55 ± 1	54 ± 1	55 ± 1	55 ± 1	56 ± 1
MV P_{O_2}, mmHg						
Control	43 ± 1	35 ± 1*	33 ± 1*	31 ± 1*	29 ± 1*	26 ± 1*
Glib	37 ± 1†	31 ± 1*†	30 ± 1*†	28 ± 1*†	25 ± 1*†	23 ± 1*†
CV pH						
Control	7.36 ± 0.01	7.37 ± 0.01	7.38 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01
Glib	7.35 ± 0.01†	7.35 ± 0.01†	7.35 ± 0.01†	7.36 ± 0.01*	7.36 ± 0.01*	7.37 ± 0.01*
CV P_{CO_2}, mmHg						
Control	57 ± 1	56 ± 1	56 ± 1	55 ± 1	54 ± 2	55 ± 1
Glib	59 ± 1	58 ± 1	56 ± 1*	56 ± 1*	54 ± 1*	53 ± 1*†
CV P_{O_2}, mmHg						
Control	25 ± 1	25 ± 1	23 ± 1	24 ± 0	23 ± 1	23 ± 1
Glib	17 ± 1†	17 ± 1†	18 ± 1†	17 ± 1†	19 ± 1†	20 ± 1*†

Values are means ± SE; n = 9 pigs. Hb, hemoglobin; Art, arterial; MV, mixed venous; CV, coronary venous; P, partial pressure; Glib, 3 mg/kg iv. *$P < 0.05$ vs. Rest (Lying); †$P < 0.05$ vs. Control.

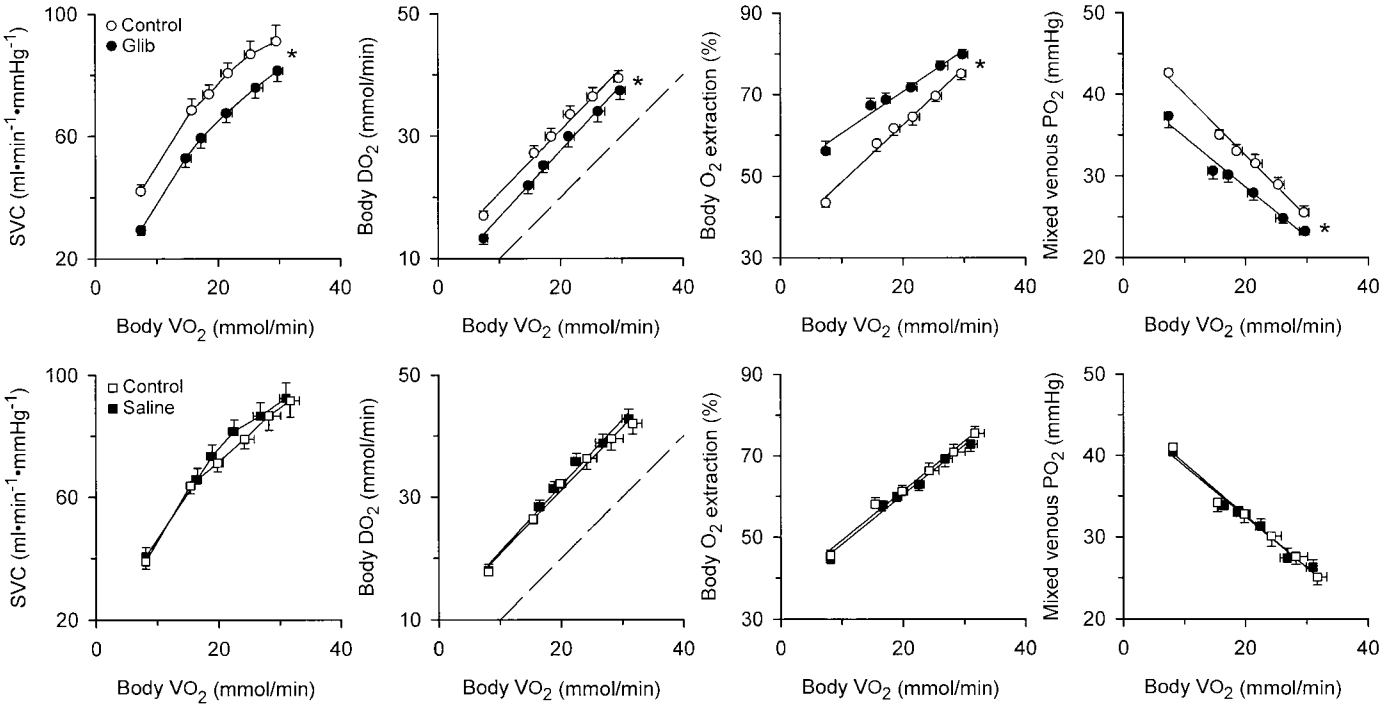

Fig. 3. Effect of ATP-sensitive K^+ (K^+_{ATP}) channel blockade with Glib (3 mg/kg iv, *top*) or an equivalent volume of saline (*bottom*) on the relations between whole body O_2 consumption (BVo_2) and SVC, between BVo_2 and body O_2 delivery (BDo_2; dashed line represents line of identity), between BVo_2 and body O_2 extraction, and between BVo_2 and mixed venous Po_2. Data points were obtained at rest (lying) and during 5 levels of treadmill exercise (1–5 km/h). Data are means ± SE; n = 9 pigs; *$P < 0.05$ vs. Control.

affected. Because both cardiac output and the difference in the arterial and mixed venous O_2 contents nearly doubled, BVo_2 increased fourfold from 7.5 ± 0.3 to 30.1 ± 0.8 mmol/min, respectively ($P < 0.01$, Fig. 3).

Glibenclamide increased mean aortic blood pressure that was the result of a decrease in systemic vascular conductance as cardiac output decreased at rest and lower levels of exercise or remained unchanged at 4 and 5 km/h (Table 1) due to a possibly baroreceptor reflex-mediated decrease in heart rate. The decrease in systemic vascular conductance was compensated by an increase in O_2 extraction, so that body O_2 consumption was maintained. Consequently, mixed venous Po_2 and O_2 content were decreased at rest and during each level of exercise (Table 2). The glibenclamide-induced decrease in systemic vascular conductance and mixed venous Po_2 were similar at rest and all levels of exercise, indicating that K^+_{ATP} channel blockade did not affect the exercise-induced systemic vasodilation (Fig. 3). The increased systemic vasomotor tone resulted in an increased arterio-mixed venous pH difference, which was principally due to an increase in arterio-mixed venous Pco_2 difference (not shown), suggesting that the glibenclamide-induced vasoconstriction did not result in anaerobic metabolism.

Regional blood flows. During exercise at 5 km/h, flow to the various skeletal muscle groups increased (Fig. 4), varying from 5-fold in predominantly white fiber muscle to 20-fold in predominantly red fiber muscle (1). Brain flow increased by ~20% ($P \leq 0.05$), flow to the adrenals and bone did not change, and flow to most visceral organs decreased (Table 3). Arteriovenous anastomotic (AVA) flow, represented by lung flow (27) and cutaneous flow increased by 300% and 25%, respectively.

Glibenclamide had no effect on skeletal muscle blood flow, in any of various skeletal muscle groups independent of fiber-type composition, either at rest or during exercise (Fig. 4). In contrast, glibenclamide decreased flow to most visceral organs at rest and/or during exercise at 5 km/h (Table 3), whereas bone flow was not affected. Glibenclamide also reduced skin flow but had no effect on AVA flow. Vascular conductance in all visceral organs, bone, and skin decreased at rest and/or

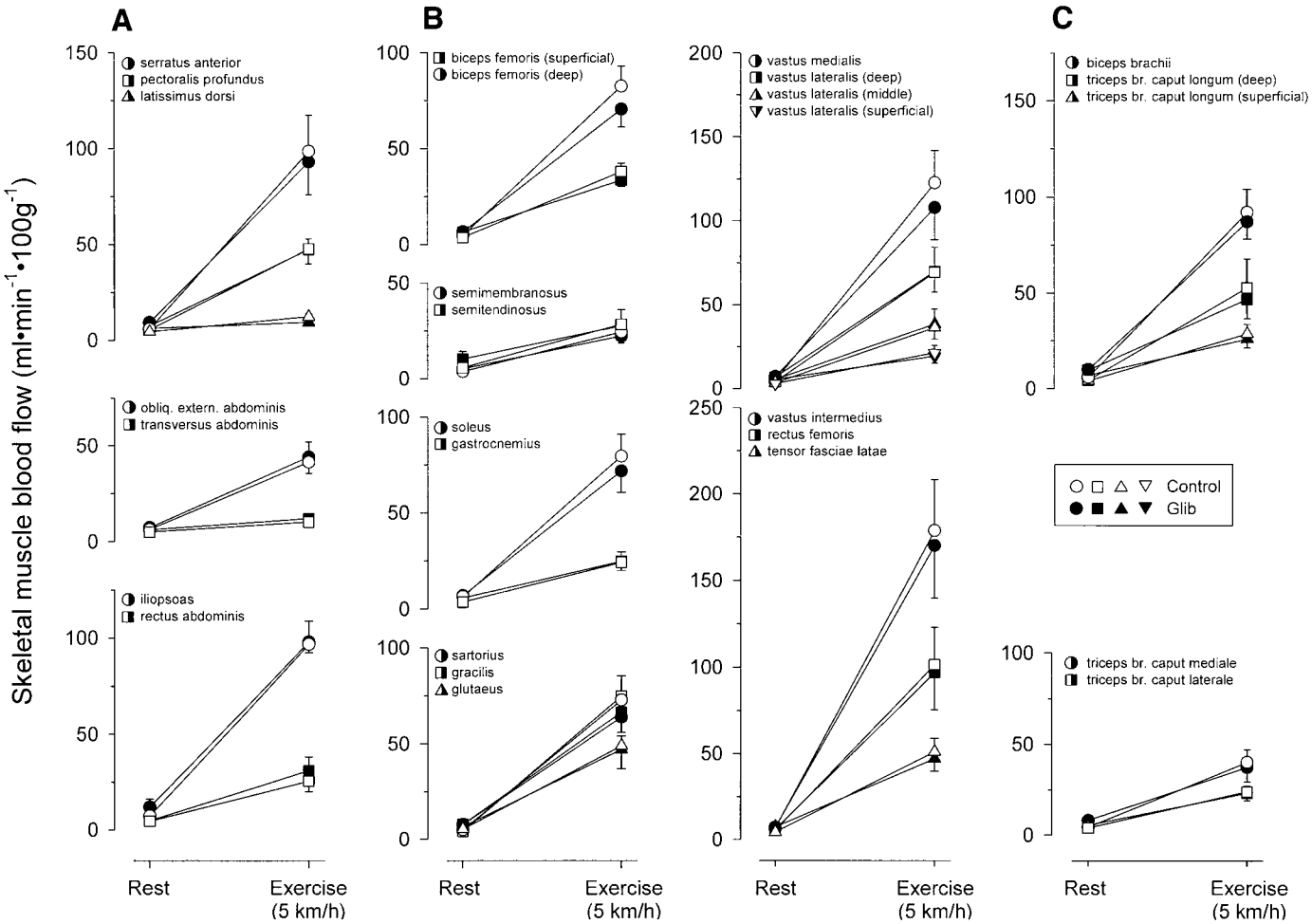

Fig. 4. Effect of K^+_{ATP} channel blockade with Glib (3 mg/kg iv) on blood flow to various skeletal muscle groups of the trunk (*A*), hind legs (*B*), and front legs (*C*). Data points were obtained at rest (lying) and during treadmill exercise at 5 km/h. Glib had no significant effect on blood flow in any of the skeletal muscle groups either at rest or during exercise. Data are means ± SE; $n = 5$ pigs.

Table 3. *Effect of K^+_{ATP} channel blockade on regional blood flows and regional vascular conductances*

	Blood Flow, ml·min^{-1}·100 g^{-1}		Conductance, ml·min·100 g^{-1}·mmHg^{-1}	
	Rest	5 km/h	Rest	5 km/h
Total brain				
Control	96 ± 5	118 ± 3*	1.01 ± 0.04	1.36 ± 0.06*
Glib	100 ± 8	119 ± 10	0.88 ± 0.07†	1.25 ± 0.11†
Kidneys				
Control	370 ± 18	350 ± 32	3.93 ± 0.24	4.02 ± 0.37
Glib	311 ± 14†	306 ± 17†	2.72 ± 0.15†	3.22 ± 0.21†
Urine bladder				
Control	10.0 ± 1.0	11.1 ± 1.7	0.107 ± 0.012	0.127 ± 0.019
Glib	10.0 ± 1.4	9.5 ± 2.1	0.087 ± 0.011†	0.099 ± 0.022†
Adrenals				
Control	182 ± 19	202 ± 24	1.93 ± 0.19	2.32 ± 0.29*
Glib	120 ± 11†	163 ± 19†	1.05 ± 0.12†	1.70 ± 0.19*†
Spleen				
Control	182 ± 27	47 ± 14*	1.93 ± 0.28	0.56 ± 0.19*
Glib	103 ± 21†	24 ± 8*†	0.90 ± 0.18†	0.26 ± 0.09*†
Pancreas				
Control	186 ± 16	104 ± 12*	1.98 ± 0.20	1.21 ± 0.16*
Glib	91 ± 13†	65 ± 7*†	0.80 ± 0.13†	0.69 ± 0.09†
Stomach				
Control	161 ± 15	122 ± 14*	1.71 ± 0.16	1.39 ± 0.15*
Glib	62 ± 6†	63 ± 9†	0.55 ± 0.06†	0.66 ± 0.10†
Ileum				
Control	200 ± 53	143 ± 32*	2.12 ± 0.56	1.60 ± 0.33
Glib	128 ± 31†	102 ± 19†	1.10 ± 0.25†	1.05 ± 0.17†
Colon				
Control	98 ± 12	59 ± 3*	1.04 ± 0.14	0.68 ± 0.03*
Glib	69 ± 8†	64 ± 12	0.60 ± 0.07†	0.64 ± 0.12
Bone				
Control	15.6 ± 1.5	15.4 ± 1.3	0.166 ± 0.017	0.178 ± 0.018
Glib	13.1 ± 0.9	13.3 ± 1.6	0.114 ± 0.006†	0.138 ± 0.015†
Skin				
Control	7.4 ± 1.1	9.2 ± 1.3*	0.079 ± 0.013	0.106 ± 0.016*
Glib	3.8 ± 0.5†	6.0 ± 1.5*†	0.033 ± 0.004†	0.062 ± 0.016*†
Lungs, AVA				
Control	57 ± 9	222 ± 44*	0.61 ± 0.10	2.63 ± 0.61*
Glib	62 ± 11	197 ± 26*	0.55 ± 0.11	2.08 ± 0.32*

Values are means ± SE; $n = 5$ pigs. AVA, arteriovenous anastomoses. *$P < 0.05$ vs. Rest, †$P < 0.05$ vs. Control.

during exercise, but AVA conductance was not significantly altered (Table 3). Glibenclamide had no effect on the exercise-induced increases in vascular conductance in skeletal muscle (not shown).

Pulmonary circulation. Exercise resulted in an increase of mean pulmonary artery pressure from 16 ± 1 to 34 ± 2 mmHg ($P < 0.01$; Table 1). The driving pressure across the pulmonary vascular bed (mean pulmonary artery pressure-mean left atrial pressure) increased slightly less than the increase in cardiac output so that pulmonary vascular conductance increased by 25 ± 9% ($P < 0.05$) (Table 1 and Fig. 5). Glibenclamide had no effect on pulmonary artery pressure or pulmonary vascular conductance, either at rest or during exercise.

Coronary circulation. Blood flow in the LAD coronary artery increased from 50 ± 4 ml/min at rest to 118 ± 13 ml/min during the highest level of exercise ($P < 0.01$). Exercise had no effect on coronary venous P_{CO_2}, pH, P_{O_2} (Table 2, Fig. 6), S_{O_2}, or O_2 content (not shown). MV_{O_2} increased from 162 ± 18 to 465 ± 44 μmol/min, whereas MD_{O_2} increased from 212 ± 20 to 585 ± 53 μmol/min, respectively (both $P < 0.01$). Consequently, myocardial O_2 extraction and coronary venous P_{O_2} were minimally affected during exercise. K^+_{ATP} channel blockade with glibenclamide decreased coronary blood flow and coronary vascular conductance, which resulted in a decrease in O_2 delivery at each level of MV_{O_2} ($P < 0.05$), necessitating an increase in O_2 extraction, which led to a decrease in coronary venous P_{O_2} (Fig. 6). Similar to the systemic circulation, the effect of glibenclamide on coronary vascular conductance was also similar at rest and at each level of exercise, indicating that K^+_{ATP} channel blockade did not modify the exercise-induced coronary vasodilation. The increased coronary vasomotor tone resulted in an increased arteriocoronary venous pH difference, due to the widening of arteriocoronary venous P_{CO_2} gradient as the arteriocoronary venous SBE difference was unchanged (not shown), indicating that the glibenclamide-induced flow reduction did not result in myocardial ischemia.

Blood glucose. Blood glucose did not change during control exercise (6.8 ± 0.8 mmol/l at rest and 5.9 ± 0.6 mmol/l at 5 km/h). With the glucose-supplementation regimen, glucose levels after glibenclamide were simi-

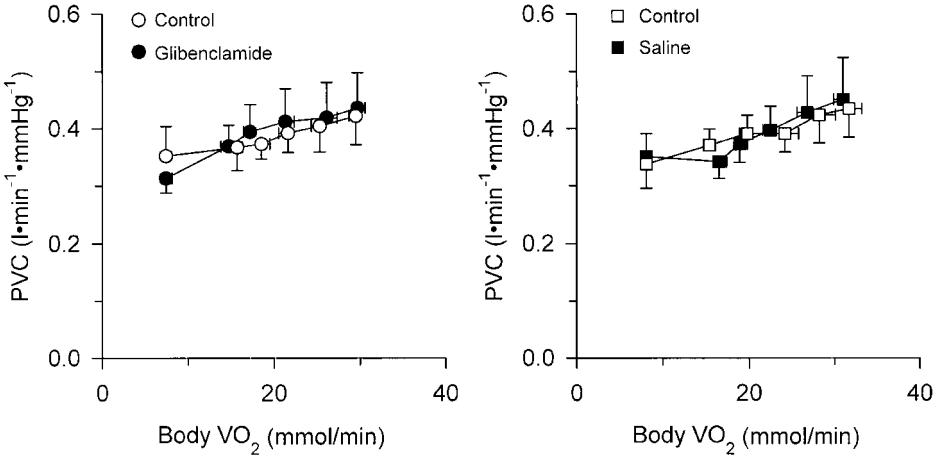

Fig. 5. Effect of K^+_{ATP} channel blockade with Glib (3 mg/kg iv; *left*) or an equivalent volume of saline (*right*) on the relation between BV_{O_2} and pulmonary vascular conductance (PVC). Data points were obtained at rest (lying) and during 5 levels of treadmill exercise (1–5 km/h). Data are means ± SE; $n = 7$ pigs; neither saline nor Glib had a significant effect on the relation between BV_{O_2} and PVC.

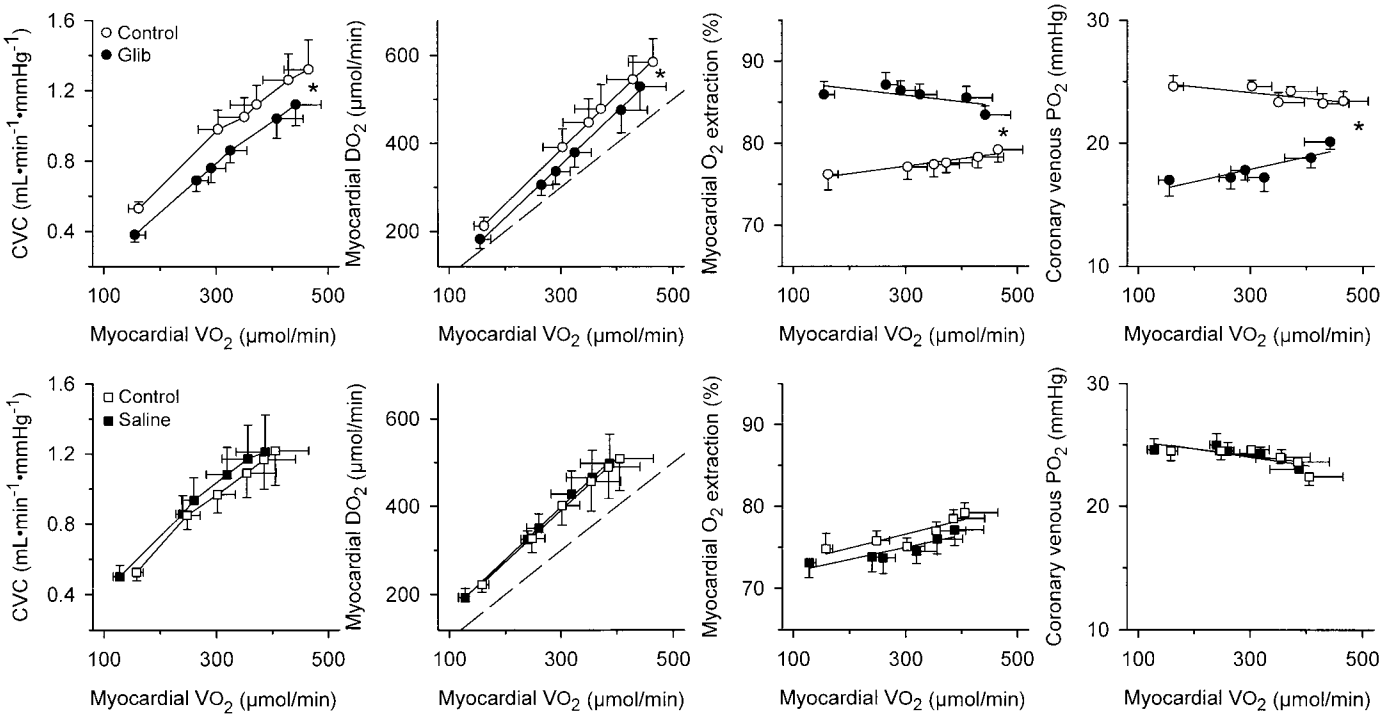

Fig. 6. Effect of K^+_{ATP} channel blockade with Glib (3 mg/kg iv, *top*) or an equivalent volume of saline (*bottom*) on the relations between myocardial V_{O_2} consumption (MV_{O_2}) and CVC; between MV_{O_2} and myocardial O_2 delivery (MD_{O_2}) (dashed line represents line of identity); between MV_{O_2} and myocardial O_2 extraction; and between MV_{O_2} and coronary venous P_{O_2}. Data points were obtained at rest and during 5 levels of treadmill exercise. Data are means ± SE; n = 8 pigs; *$P < 0.05$ vs. control.

lar to levels during control conditions (7.1 ± 0.6 mmol/l at rest and 6.0 ± 0.6 mmol/l at 5 km/h).

Reproducibility of Responses to Exercise

Ninety minutes after the control exercise period, at a time when all hemodynamic variables had returned to baseline resting values, the second period of exercise resulted in almost identical responses to exercise (Tables 4 and 5, and Figs. 3, 5, and 6), with the exception of heart rate and LV dP/dt_{max}, which were slightly (<10%) lower during exercise at 2–5 km/h compared with the first run (Table 4).

DISCUSSION

The present study describes the role of K^+_{ATP} channels in the regulation of coronary, pulmonary, and systemic vasomotor tone in awake pigs at rest and during treadmill exercise. There are three major findings in the present study. First, K^+_{ATP} channel blockade resulted in a decrease in systemic vascular conductance and regional vascular conductances within the systemic bed at rest and during exercise, which was associated with an increase in body O_2 extraction and decreased mixed venous P_{O_2}. However, the exercise-induced increase in systemic vascular conductance, which occurred principally in skeletal muscle, was not affected. Second, K^+_{ATP} channel blockade had no effect on pulmonary vascular conductance either at rest or during exercise. Third, K^+_{ATP} channel blockade resulted in an increased myocardial O_2 extraction and a decreased coronary venous P_{O_2} under resting conditions and during exercise indicating that K^+_{ATP} channels exerted a vasodilator influence that contributed to maintaining MD_{O_2} commensurate with O_2 demands. However, K^+_{ATP} channels were not mandatory for the exercise-induced coronary vasodilation. The implications of these findings will be discussed in detail.

Methodological Considerations

Glibenclamide has been reported to be a selective K^+_{ATP} channel blocker at concentrations up to 5 μM (2, 26). In the present study we used a dose of 3 mg/kg iv. In 30-kg pigs, this dose corresponds to 90 mg in ~2 liters of circulating blood volume, i.e., 90 μmol/l (M_w = 494). However, 98–99% of glibenclamide is bound to plasma proteins (12), so that the concentration of free glibenclamide is in the range of 1–2 μM. These concentrations are well within the range where glibenclamide is selective for K^+_{ATP} channels (2, 26). Moreover, we observed that glibenclamide attenuated the bimakalim-mediated vasodilation without blunting the sodium nitroprusside-mediated vasodilation, indicating that glibenclamide in a dose of 3 mg/kg iv selectively inhibited K^+_{ATP} channels without nonspecifically blunting vascular smooth muscle relaxation.

Systemic Circulation

K^+_{ATP} channels have been implicated in the regulation of vasomotor tone under basal resting conditions

Table 4. *Reproducibility of hemodynamic responses to graded treadmill exercise*

	Rest		Treadmill Exercise, km/h				
	Lying	Standing	1	2	3	4	5
			Systemic hemodynamics				
CO, l/min							
Control	3.8 ± 0.2	5.1 ± 0.3*	5.7 ± 0.2*	6.5 ± 0.2*	7.2 ± 0.2*	7.9 ± 0.4*	8.4 ± 0.4*
Saline	3.9 ± 0.2	5.0 ± 0.3*	5.9 ± 0.3*	6.5 ± 0.3*	7.2 ± 0.3*	7.8 ± 0.3*	8.3 ± 0.4*
HR, beats/min							
Control	120 ± 6	143 ± 5*	172 ± 6*	192 ± 5*	220 ± 6*	239 ± 7*	253 ± 6*
Saline	117 ± 5	141 ± 8*	168 ± 6*	180 ± 7*†	210 ± 7*†	232 ± 8*	250 ± 8*
SV, ml							
Control	31.8 ± 1.4	35.7 ± 1.8*	33.2 ± 1.3	34.2 ± 1.3*	32.8 ± 0.8	33.0 ± 1.0	33.3 ± 1.1
Saline	33.2 ± 1.2	35.1 ± 0.8*	35.3 ± 1.0*†	35.9 ± 1.0*	34.2 ± 1.1	33.6 ± 1.2	33.4 ± 1.2
LVSP, mmHg							
Control	112 ± 3	114 ± 3	117 ± 3	124 ± 4*	125 ± 4*	132 ± 4*	137 ± 5*
Saline	113 ± 4	115 ± 4	120 ± 6*	120 ± 5*	123 ± 5*	130 ± 5*	135 ± 6*
LV dP/dt_{max}, mmHg/s							
Control	3,080 ± 190	3,800 ± 240*	4,200 ± 240*	4,780 ± 250*	5,250 ± 270*	5,730 ± 270*	6,210 ± 320*
Saline	3,020 ± 200	3,660 ± 240*	4,210 ± 240*	4,310 ± 240*†	4,870 ± 190*†	5,360 ± 190*†	5,750 ± 210*†
MAP, mmHg							
Control	98 ± 2	91 ± 3*	89 ± 2*	92 ± 2*	92 ± 2*	91 ± 2*	93 ± 2*
Saline	97 ± 3	90 ± 2*	91 ± 2*	88 ± 2*	88 ± 1*	90 ± 2*	90 ± 2*
SVC, $ml \cdot min^{-1} \cdot mmHg^{-1}$							
Control	39 ± 2	57 ± 4*	64 ± 3*	71 ± 3*	79 ± 3*	87 ± 5*	92 ± 5*
Saline	41 ± 3	56 ± 4*	66 ± 4*	73 ± 4*	82 ± 4*	87 ± 4*	92 ± 5*
			Pulmonary hemodynamics				
MPAP, mmHg							
Control	16 ± 1	13 ± 1	17 ± 1	21 ± 1*	27 ± 2*	30 ± 1*	34 ± 1*
Saline	15 ± 1	17 ± 1	20 ± 1*	21 ± 1*	26 ± 2*	31 ± 1*	34 ± 1*
MLAP, mmHg							
Control	4 ± 1	−1 ± 1*	1 ± 1*	3 ± 2	7 ± 2	10 ± 1*	12 ± 1*
Saline	4 ± 1	1 ± 2*	2 ± 1	4 ± 1	6 ± 2	10 ± 1*	13 ± 1*
PVC, $l \cdot min^{-1} \cdot mmHg^{-1}$							
Control	0.34 ± 0.04	0.38 ± 0.04	0.37 ± 0.03	0.39 ± 0.03	0.39 ± 0.03	0.42 ± 0.05*	0.44 ± 0.05*
Saline	0.35 ± 0.04	0.33 ± 0.04	0.34 ± 0.03	0.37 ± 0.03	0.40 ± 0.04*	0.43 ± 0.06*	0.45 ± 0.07*
			Coronary hemodynamics				
CBF, ml/min							
Control	52 ± 4	68 ± 7*	76 ± 7*	88 ± 9*	99 ± 13*	106 ± 15*	112 ± 17*
Saline	49 ± 6	65 ± 8*	80 ± 9*	84 ± 12*	96 ± 14*	107 ± 17*	109 ± 17*
CVC, $ml \cdot min^{-1} \cdot mmHg^{-1}$							
Control	0.53 ± 0.05	0.75 ± 0.07*	0.85 ± 0.08*	0.97 ± 0.10*	1.09 ± 0.14*	1.17 ± 0.17*	1.22 ± 0.20*
Saline	0.50 ± 0.06	0.72 ± 0.10*	0.86 ± 0.11*	0.94 ± 0.13*	1.08 ± 0.16*	1.17 ± 0.19*	1.21 ± 0.21*

Values are means ± SE; $n = 9$ pigs for systemic hemodynamics; $n = 7$ pigs for pulmonary and coronary hemodynamics. *$P < 0.05$ vs. Rest; †$P < 0.05$ vs. Control.

in a variety of regional vascular beds within the systemic circulation including the mesenteric (11, 21), renal (11, 23), and skeletal muscle bed (5, 11, 17, 33), although the latter is not a ubiquitous finding (6, 19, 20, 31, 32). In the present study, we observed that in awake resting pigs, K^+_{ATP} channel activity exerts a vasodilator influence in the brain, a variety of visceral organs as well as bone and skin. In contrast, K^+_{ATP} channel blockade had no effect on blood flow and vascular conductance of various skeletal muscle groups, indicating a minimal contribution of K^+_{ATP} channels to the regulation of basal vasomotor tone in resistance vessels of skeletal muscle.

K^+_{ATP} channel blockade also decreased systemic vascular conductance during treadmill exercise but did not blunt the exercise-induced doubling of systemic vascular conductance. The latter is principally due to an increase in vascular conductance in active skeletal muscle groups and to a lesser extent to increases in cerebral, AVA, and cutaneous vascular conductance (1, 18, and present study). Recent studies in anesthetized animal models suggest that K^+_{ATP} channels can contribute to metabolic vasodilation in skeletal muscle produced by electrical muscle stimulation (3, 5, 31, 33). Although the vasoconstrictor effect of K^+_{ATP} channel blockade in the present study persisted during treadmill exercise, indicating that K^+_{ATP} channels exert a vasodilator influence at rest and during exercise, K^+_{ATP} channel blockade had no effect on the increase in vascular conductance in the brain, skeletal muscle, skin, and of AVA. These findings demonstrate that the opening of K^+_{ATP} channels is not mandatory for the exercise-induced vasodilation in these regional beds. It is possible that under normal conditions opening of these channels does contribute but that after K^+_{ATP} channel blockade other vasodilator mechanisms are recruited

Table 5. *Reproducibility of blood gas responses to graded treadmill exercise*

		Treadmill Exercise, km/h				
	Rest (Lying)	1	2	3	4	5
Hb, g/100 ml						
Control	7.6 ± 0.3	7.5 ± 0.3	8.0 ± 0.3*	8.1 ± 0.3*	8.1 ± 0.3*	8.1 ± 0.3*
Saline	7.5 ± 0.2	7.8 ± 0.2*	7.9 ± 0.2*	8.1 ± 0.2*	8.1 ± 0.2*	8.3 ± 0.2*
Art pH						
Control	7.44 ± 0.01	7.47 ± 0.01*	7.47 ± 0.01*	7.47 ± 0.01*	7.47 ± 0.01*	7.47 ± 0.01*
Saline	7.45 ± 0.01	7.45 ± 0.01	7.46 ± 0.01	7.48 ± 0.01*	7.48 ± 0.01*	7.49 ± 0.01*
Art P_{CO_2}, mmHg						
Control	44 ± 2	42 ± 1*	42 ± 1*	41 ± 1*	41 ± 1*	40 ± 1*
Saline	44 ± 1	43 ± 1	42 ± 1	41 ± 1*	39 ± 1*	38 ± 1*
Art P_{O_2}, mmHg						
Control	103 ± 2	107 ± 2	105 ± 2	106 ± 3	104 ± 3	107 ± 3
Saline	100 ± 2	102 ± 3	104 ± 2	106 ± 3	102 ± 2	105 ± 3
MV pH						
Control	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 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
MV P_{CO_2}, mmHg						
Control	53 ± 1	54 ± 1	54 ± 1	56 ± 1*	56 ± 1*	58 ± 1*
Saline	53 ± 1	54 ± 1	54 ± 1	54 ± 1	53 ± 1†	54 ± 1†
MV P_{O_2}, mmHg						
Control	41 ± 1	34 ± 1*	33 ± 1*	30 ± 1*	28 ± 1*	25 ± 1*
Saline	40 ± 1	34 ± 1*	33 ± 1*	31 ± 1*	27 ± 1	26 ± 1*
CV pH						
Control	7.37 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.38 ± 0.01	7.38 ± 0.00	7.38 ± 0.01
Saline	7.39 ± 0.01	7.38 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.39 ± 0.01	7.38 ± 0.01
CV P_{CO_2}, mmHg						
Control	59 ± 2	56 ± 2	57 ± 2	56 ± 2	56 ± 1	58 ± 1
Saline	56 ± 2	54 ± 2	54 ± 2	54 ± 1	54 ± 1	55 ± 1
CV P_{O_2}, mmHg						
Control	25 ± 1	25 ± 1	25 ± 1	24 ± 1	24 ± 1	22 ± 1
Saline	25 ± 1	25 ± 1	25 ± 1	24 ± 1	24 ± 1	23 ± 1

Values are means ± SE; $n = 9$ pigs. *$P < 0.05$ vs. Rest (lying); †$P < 0.05$ vs. Control.

during exercise, which compensate for the loss of K^+_{ATP} channel activity (10).

The decrease in systemic vascular conductance produced by glibenclamide impeded O_2 delivery within the systemic bed necessitating an increase in whole body O_2 extraction to maintain BVO_2, reflected in the decrease in mixed venous P_{O_2}. The impediment of O_2 delivery was associated with a widening of the arterio-mixed venous pH gap, which could be interpreted to suggest anaerobic metabolism. However, the increased pH difference was principally due to a widening of the arterio-mixed venous P_{CO_2} difference. The latter probably resulted from a maintained whole body CO_2 production in the face of a reduced cardiac output.

Pulmonary Circulation

Evidence for K^+_{ATP} channels in the pulmonary vascular bed has been obtained in a variety of species such as rats (13), cats (20), pigs (24, and present study), and dogs (28) by demonstrating pulmonary vasodilator responses to K^+_{ATP} channel agonists in vivo. However, under basal conditions, K^+_{ATP} channel activity appears to contribute minimally to regulation of vasomotor tone in the intact lung of anesthetized rats (13) and cats (6). Only in anesthetized newborn piglets was a decrease in pulmonary vascular conductance observed after exposure of a lung lobar arterial system to 10 μM of glibenclamide (24). However, glibenclamide at a dose higher than 5 μM may produce blockade of other K^+ channels (14, 26), including Ca^{2+}-sensitive channels, which are abundantly present in the pulmonary bed and active under basal conditions (13). This may also explain why Kadowitz and co-workers (6, 20) observed that glibenclamide, in a dose of 20 mg/kg but not at 5 mg/kg, produced a transient increase in pulmonary artery pressure in anesthetized cats. Thus 20 mg/kg in a 3-kg cat with an approximate blood volume of 300 ml corresponds to a concentration of free glibenclamide of 8 μM, whereas 5 mg/kg corresponds to 2 μM. Another concern is that in most previous in vivo studies anesthesia was employed, which can produce K^+_{ATP} channel blockade (28). However, because in awake dogs glibenclamide (3 mg/kg iv) had no effect on pulmonary vascular conductance (28), and in the present study, glibenclamide (3 mg/kg iv, a dose that produced a systemic vasoconstrictor response) had also no effect on pulmonary vascular conductance, the weight of evidence suggests that K^+_{ATP} channel activity is minimal under basal conditions in the pulmonary vascular bed.

The present study is the first to investigate the role of K^+_{ATP} channel activity in regulation of pulmonary vascular conductance during exercise. The rationale for this investigation was that we previously observed that β-adrenoceptor activation contributes to exercise-induced pulmonary vasodilation in pigs (30). Because pharmacological β-adrenocep-

tor stimulation produces vasodilation in pulmonary arteries (29), as well as other vascular beds (3, 22), that is in part mediated by K^+_{ATP} channel activation, we hypothesized that the exercise-induced pulmonary vasodilation could also be mediated via K^+_{ATP} channel opening. However, the results clearly demonstrate that K^+_{ATP} channels are not mandatory for maintaining pulmonary vascular conductance in awake pigs either at rest or during treadmill exercise.

Coronary Circulation

Coronary blood flow is tightly regulated to maintain a consistently high level of myocardial O_2 extraction. Consequently, any increase in myocardial O_2 demand must be met by an equivalent increase in coronary blood flow. In dogs the exercise-induced increase in coronary blood flow does not fully match the increased myocardial O_2 demand, so that even during light exercise (<60% of maximum heart rate) myocardial O_2 extraction increases and coronary venous P_{O_2} decreases (18). In humans, myocardial O_2 extraction changes minimally during light-to-moderate exercise, but myocardial O_2 extraction increases and coronary venous P_{O_2} decreases during strenuous exercise (>85% of maximum heart rate) (18). Up to moderate exercise, pigs resemble humans more closely than dogs but, in contrast to dogs and humans, pigs also maintain a constant level of myocardial O_2 extraction and coronary venous P_{O_2} during strenuous exercise, implying that the exercise-induced increases in O_2 delivery match the increases in MV_{O_2} (7, 18). A decrease in coronary venous P_{O_2} could represent an error signal needed for negative feedback metabolic control (18), but data in pigs indicate that a decrease in coronary venous P_{O_2} is not mandatory for the increase in coronary blood flow during heavy exercise due to increased importance of β-adrenergic feedforward vasodilation (7). In awake dogs, glibenclamide decreased coronary blood flow at rest and during treadmill exercise but did not blunt the exercise-induced increase in coronary blood flow (9, 10). On the other hand, Narishige et al. (22) reported that coronary vasodilation in the dog heart that was produced by pharmacological β-adrenoceptor stimulation was markedly blunted by K^+_{ATP} channel blockade. In view of the increased importance of β-adrenergic feedforward vasodilation in the porcine coronary circulation during exercise (7), we hypothesized that β-adrenoceptor-mediated K^+_{ATP} channel activation would have increased importance in the coronary circulation of exercising pigs. Although K^+_{ATP} channel activity exerted a vasodilator influence both at rest and during exercise, contrary to our hypothesis it was not mandatory for the exercise-induced vasodilation in the porcine heart. It is possible that under normal conditions opening of these channels does contribute but that after K^+_{ATP} channel blockade other vasodilator mechanisms are recruited during exercise, which compensate for the loss of K^+_{ATP} channel activity (10).

The decrease in coronary vascular conductance produced by glibenclamide restricted MD_{O_2} at each level of MV_{O_2}, resulting in an increase in myocardial O_2 extraction and hence a decrease in coronary venous P_{O_2}. The impediment of MD_{O_2} was associated with a widening of the arteriocoronary venous pH gap, suggestive of anaerobic metabolism (i.e., ischemia). However, the increased pH difference was entirely the result of an increased arteriocoronary venous P_{CO_2} difference; the latter likely resulted from a maintained CO_2 production in the face of reduced coronary arterial inflow.

In conclusion, the opening of K^+_{ATP} channels contributes to a state of vasodilation in the systemic and coronary circulation of pigs at rest and during exercise, although K^+_{ATP} channels are not mandatory for the exercise-induced systemic and coronary vasodilation. In contrast, K^+_{ATP} channels are not mandatory for regulation of pulmonary vasomotor tone either at rest or during exercise.

The authors thank Rob H. van Bremen for technical assistance.

D. Duncker's work was supported by a Research Fellowship from the Royal Netherlands Academy of Arts and Sciences.

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