Role of hepatic α- and β-adrenergic receptor stimulation on hepatic glucose production during heavy exercise

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Coker, Robert H., Mahesh G. Krishna, D. Brooks Lacy, Deanna P. Bracy, and David H. Wasserman. Role of hepatic α- and β-adrenergic receptor stimulation on hepatic glucose production during heavy exercise. Am. J. Physiol. 273 (Endocrinol. Metab. 36): E831–E838, 1997.—The role of catecholamines in the control of hepatic glucose production was studied during heavy exercise in dogs, using a technique to selectively block hepatic α- and β-adrenergic receptors. Surgery was done >16 days before the study, at which time catheters were implanted in the carotid artery, portal vein, and hepatic vein for sampling and the portal vein and vena cava for infusions. In addition, flow probes were implanted on the portal vein and hepatic artery. Each study consisted of a 100-min equilibration, a 30-min basal, a 20-min heavy exercise (−85% of maximum heart rate), a 30-min recovery, and a 30-min adrenergic blockade test period. Either saline (control; n = 7) or α (phenolamine)- and β (propranolol)-adrenergic blockers (Blk; n = 6) were infused in the portal vein. In both groups, epinephrine (Epi) and norepinephrine (NE) were infused in the portal vein during the blockade test period to create supraphysiological levels at the liver. Isotope ([3-3H]glucose) dilution and arteriovenous differences were used to assess hepatic function. Arterial Epi, NE, glucagon, and insulin levels were similar during exercise in both groups. Endogenous glucose production (Ra) rose similarly during exercise to 7.9 ± 1.2 and 7.5 ± 2.0 mg·kg⁻¹·min⁻¹ in control and Blk groups at time = 20 min. Net hepatic glucose output also rose to a similar rate in control and Blk groups with exercise. During the blockade test period, arterial plasma glucose and Ra rose to 164 ± 5 mg/dl and 12.0 ± 1.4 mg·kg⁻¹·min⁻¹, respectively, but were essentially unchanged in Blk. The attenuated response to catecholamine infusion in Blk substantiates the effectiveness of the hepatic adrenergic blockade. In conclusion, these results show that direct hepatic adrenergic stimulation does not participate in the increase in Ra during the exaggerated sympathetic response to heavy exercise.

catecholamine; adrenergic blockade; endogenous glucose production

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Most investigations into the regulation of hepatic function during exercise have addressed mechanisms that are operative at moderate intensities (~50% maximum oxygen uptake). Under these conditions, hepatic glucose production (Ra) is controlled by the exercise-induced changes in plasma glucagon and insulin (25). Glucoregulation during heavy exercise may be much different. It has been postulated that catecholamines are the primary regulators of the increase in Ra during heavy exercise. This is based on the fact that during heavy exercise, catecholamines may increase to 10- to 15-fold, while arterial glucagon may increase, remain the same, or even decrease, and arterial insulin levels may be unchanged (6, 16). Although this correlation analysis is consistent with the possibility that catecholamines may be important during heavy exercise, studies attempting to establish causality have been uniformly negative. Attenuation of sympathetic nerve activity to the liver and adrenal medulla, using anesthesia of the celiac ganglion, does not affect Ra during high-intensity exercise (~75% maximum oxygen uptake) (11). A second study showed that liver transplant patients (presumably free of hepatic innervation) have a normal glucose production response to high-intensity exercise (~82% maximum oxygen uptake) (12). Finally, β-adrenergic blockade actually results in an exaggerated increase in Ra during exercise at 100% maximum oxygen uptake in healthy subjects (24). These studies were informative and added greatly to our knowledge but were complicated by the use of a patient population or by the nonspecific effects of the methods used to study catecholamine action.

The aim of this study was to examine the effect of the catecholamines on Ra during heavy exercise, using a selective hepatic adrenergic receptor blockade technique that produces only minimal extrahepatic effects. This method utilizes the infusions of the α- and β-adrenergic blockers, phentolamine and propranolol, respectively, into the hepatic portal vein of chronically catheterized and instrumented conscious dogs exercising at a high intensity.

METHODS

Animals and surgical procedures. Experiments were performed on a total of 13 overnight-fasted mongrel dogs (mean wt 21.5 ± 0.5 kg) of either sex that had been fed a standard diet (Pedigree beef dinner and Wayne Lab Blox; 51% carbohydrate, 31% protein, 11% fat, and 7% fiber based on dry wt). The dogs were housed in a facility that met American Association for the Accreditation of Laboratory Animal Care guidelines, and the protocols were approved by the Vanderbilt University Animal Care Subcommittee. At least 16 days before each experiment, a laparotomy was performed under general anesthesia (0.04 mg/kg atropine and 15 mg/kg pentobarbital sodium presurgery; 1.0% isoflurane inhalation anesthetic during surgery). An incision in the neck region allowed the isolation of the carotid artery, into which a Silastic catheter (0.04 in. ID) was inserted and advanced to the aortic arch for sampling and hemodynamic measurements during experiments. Silastic catheters (0.03 in. ID) were inserted into the vena cava for infusion of indocyanine green and [3-3H]glucose. Last, a Silastic catheter (0.03 in. ID) was inserted into the splenic vein and positioned so that the catheter tip rested just beyond the point where the splenic and portal veins coalesce. This catheter was used for the intraportal infusions of phentolamine and propranolol and the infusion of catecholamines during the final period of the

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experiment. Catheters were inserted into the portal vein and hepatic vein for blood sampling purposes. Ultrasonic transit time flow probes were fitted and secured to the portal vein and hepatic artery (Transonic Systems, Ithaca, NY). The knotted catheter ends and Transonic probe leads were stored in a subcutaneous pocket in the abdominal region (except for the carotid artery catheter, which was stored in a pocket under the skin of the neck) so that the complete closure of the skin incisions was possible.

At 7 days after surgery, dogs were acclimatized to running on a motorized treadmill, with the intensity of the exercise progressively increased. Each animal underwent a treadmill test to determine the work rate at which ~85% of maximum heart rate was achieved. Dogs were not exercised 48 h before the experiment. Maximum heart rate was assumed to equal 270 beats/min, based on the work of Musch et al. (18) and Ordway et al. (20). Blood samples were drawn 3 days before the experiment to determine the leucocyte count and the hematocrit of the animal. Only animals with 1) a leucocyte count below 18,000/mm³, 2) a hematocrit above 36%, 3) a good appetite (consumption of daily food ration), and 4) normal stools were used.

All studies were conducted in dogs after an 18-h fast. The free catheter ends and flow probe leads were accessed through small skin incisions made under local anesthesia (2% lidocaine; Astra Pharmaceutical Products, Worcester, MA) in the abdominal and neck regions on the morning of the experiment. Catheters were then aspirated and flushed with saline. The exposed catheters were connected to Silastic tubing, which was secured to the back of the dog with quick-drying glue.

Experimental procedures. Experiments consisted of a tracer and dye equilibration period (−130 to −30 min), basal period (−30 to 0 min), heavy exercise period (0 to 20 min), recovery period (20 to 50 min), and catecholamine infusion period (50 to 80 min). A primed (50 µCi) infusion (0.30 µCi/min) of [3-3H]glucose was initiated at time (t”) = −130 min and continued throughout the study. The tracer infusion rate was increased by 2.5-fold during the heavy exercise period to minimize changes in glucose specific activity in the non-steady state. After completion of the exercise period, the [3-3H]glucose infusion rate was returned to the basal rate, at which point it remained for the remainder of the study. A constant-rate indocyanine green infusion (0.1 mg·m⁻²·min⁻¹) was also started at t = −130 min and continued throughout the study. Indocyanine green was used as a backup method of blood flow measurement if the Doppler probes did not provide a clear signal and as confirmation of hepatic vein catheter placement. There was no Doppler flow probe failure in these studies. Two protocols were performed (Fig. 1). In the blockade protocol, the α- and β-adrenergic receptor blockers, phentolamine and propranolol, were infused intraportally from t = −50 to 80 min at rates of 2 and 1 µg·kg⁻¹·min⁻¹, respectively. To test the effectiveness of the blockade, norepinephrine and epinephrine were infused at rates of 0.40 and 0.20 µg·kg⁻¹·min⁻¹, respectively, from t = 50 to 80 min. In the control protocol, animals were handled and prepared identically except that vehicle alone (saline and ascorbate) was infused. Heart rates were monitored by a transducer connected to the carotid arterial catheter.

Blood sample collection and processing. Arterial blood samples were drawn every 5 min during the basal period and at 1- and 2.5-min intervals during the first 5 and the last 15 min of heavy exercise, respectively. Arterial blood samples were drawn every 5 min during the recovery and blockade test periods. Portal vein and hepatic vein blood samples were drawn every 10 min during the basal period, every 5 min during the exercise period, at 10 and 30 min of the recovery period, and every 10 min during the blockade test period.

Plasma glucose concentrations were determined by the glucose oxidase method, using a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA). For the determination of plasma glucose radioactivity, samples were deproteinized with barium hydroxide and zinc sulfate and centrifuged. The supernatant was then evaporated to remove 3H₂O and reconstituted in 1 ml water and 10 ml scintillation fluid [Ecolite (±) ICN Biomedicals, Irvine, CA]. Radioactivity was determined on a Beckman liquid scintillation counter. Blood samples were deproteinized (0.5 ml blood in 1.5 ml of 4% perchloric acid), and whole blood lactate, alanine, and glyceral concentrations were determined, using standard enzymatic methods (13), on a Monarch 2000 Centrifugal Analyzer (Lexington, MA). Free fatty acids (FFA) were measured with the use of the Wako FFA C test kit (Wako Chemicals, Richmond, VA) on the centrifugal analyzer. Immunoreactive insulin was measured, using a double-antibody procedure (interassay coefficient of variation of 16%) (17). Immunoreactive glucagon (3,500 mol wt) was measured in plasma samples containing 500 kalikrein inhibitory units (KIU)/ml Trasylol (FBA Pharmaceuticals, New York, NY), using a double-antibody system modified from the method developed by Morgan and Lazarow (17) for insulin. Plasma samples for norepinephrine and epinephrine were collected into tubes containing ethylene glycol-bis-(β-aminoethyl ether)-N,N,N’,N’-tetraacetic acid and glutathione, centrifuged at 4°C, and stored at −70°C for subsequent analysis, using high-performance liquid chromatography. Catecholamine concentrations were calculated based on linear regression, using dihydroxybenzylamine as an internal standard. With the use of this method, the coefficients of variation were 5 and 7% for norepinephrine and epinephrine, respectively. Plasma cortisoll was measured, using the Clinical Assays Gamma Coat radioimmunoassay kit (Travenol-Genet Tech Diagnostics, Cambridge, MA) with an interassay coefficient of variation of 6%.

Materials. [3-3H]Glucose was obtained from NEN (Boston, MA). Glucagon and [125I]-labeled glucagon were obtained from Novo Research Institute (Copenhagen, Denmark). Standard insulin and [125I]-labeled insulin were obtained from Linco Research (St. Louis, MO). Indocyanine green was purchased from Hynson, Westcott, and Dunning (Baltimore, MD). Enzymes and coenzymes for metabolite analyses were obtained from Boehringer Mannheim Biochemicals and Sigma Chemical.

![Figure 1](http://ajpendo.physiology.org/) Heavy exercise protocol utilizing hepatic adrenergic blockade and control groups. **Epinephrine and norepinephrine were infused into the portal vein at rates of 0.20 and 0.40 µg·kg⁻¹·min⁻¹, respectively. **Isotope infusion was increased 2.5-fold during exercise [time (t”) = 0–20 min]. ***Phentolamine and propranolol were infused into the portal vein at rates of 2 and 1 µg·kg⁻¹·min⁻¹, respectively, from t = −50 to 80 min.
Calculations. Net hepatic lactate balance (NHLB), net hepatic alanine uptake (NHMAU), and net hepatic glucose output (NHGO) were determined according to the formula HAF × ([A] - [H]) + PVF × ([P] - [H]), such that [A], [P], and [H] are the arterial, portal vein, and hepatic vein substrate concentrations, and HAF and PVF are the hepatic artery and portal vein blood flows. Hematocrits were measured at each multiple catheter sampling point to correct for changes in red cell volume. The sign was reversed for the calculation of NHGO so that net output would be a positive number. Endogenous Ra was calculated, using the two-compartment approach described by Mari (14). Changes in specific activity were minimized during the exercise period by increasing the infusion rate of [3-3H]glucose by 2.5-fold to increase the accuracy of the Ra calculation (19).

Statistical analysis. Superanova (Abacus Concepts, Berkeley, CA) software installed on a Macintosh Power PC was used to perform statistical analysis. Statistical comparisons between groups and over time were made, using analysis of variance designed to account for repeated measures. Time points were specifically examined for significance, using contrasts solved by univariate repeated measures. Statistics are reported in the corresponding table or figure legend for each variable. Data are presented as means ± SE for seven control and six hepatic adrenergic blockade dogs. Statistical significance was defined as P < 0.05.

RESULTS

Arterial epinephrine and norepinephrine concentrations. Catecholamine values for five of the seven control experiments have been published previously (4). Plasma epinephrine rose (P < 0.05) in control experiments from 165 ± 41 to 530 ± 100 pg/ml at 20 min of exercise. In the blockade group epinephrine levels were not different (P > 0.05) from controls, increasing from 207 ± 27 to 495 ± 85 pg/ml at 20 min of exercise (Fig. 2). Plasma norepinephrine increased (P < 0.05) from 416 ± 96 to 1,093 ± 182 pg/ml at 20 min of exercise in control experiments and from 365 ± 68 to 1,109 ± 258 pg/ml at 20 min of exercise in the blockade group (Fig. 2). There was no difference in the exercise response between groups. No significant differences were noted in plasma epinephrine or norepinephrine between the groups during recovery or the blockade test period.

Arterial insulin, glucagon, and cortisol concentrations. No significant differences in plasma insulin were noted between the two groups throughout the basal, exercise, or recovery periods. However, plasma insulin was significantly higher in the control group compared with the blockade group because of hyperglycemia during the blockade test period (Fig. 3). Plasma glucagon rose similarly in both groups during exercise and was not significantly different between groups throughout the remainder of the experiment (Fig. 3). Plasma cortisol was higher in the blockade group compared with the control group during the basal period (P < 0.05). Otherwise, there was no significant difference between protocols (Table 1).

Arterial glucose concentration and kinetics. Arterial plasma glucose was similar in both control and blockade groups during the basal, exercise, and recovery periods. During the blockade test period, arterial plasma glucose was greater (P < 0.05) in the control group (164 ± 5 mg/dl at t = 60 min) than the blockade group (126 ± 4 mg/dl at t = 60 min; Fig. 4). NHGO was also similar in both groups during the basal, exercise, and recovery periods. During the blockade test period, NHGO was greater (P < 0.05) in the control group (8.5 ± 3.3 mg·kg⁻¹·min⁻¹ at t = 60 min) compared with the blockade group (3.0 ± 0.9 mg·kg⁻¹·min⁻¹ at t = 60 min; Fig. 4). Ra rose similarly from 3.1 ± 0.2 and 3.0 ± 0.2 mg·kg⁻¹·min⁻¹ during the basal period to 7.9 ± 1.2 and 7.5 ± 2.0 mg·kg⁻¹·min⁻¹ at 20 min of exercise in the control and blockade groups, respectively. Ra was also similar during the recovery periods. However, Ra was higher (P < 0.05) during the blockade test period in the control group (10.9 ± 1.2 mg·kg⁻¹·min⁻¹ at t = 60 min) compared with the blockade group (4.1 ± 0.3 mg·kg⁻¹·min⁻¹ at t = 60 min; Fig. 5).

Arterial lactate concentrations and NHLB. Mean basal arterial lactate was less in the control group (478 ± 58 µmol/l) than in the blockade group (674 ± 150 µmol/l). Arterial lactate rose to a significantly greater level in the control group (1,315 ± 75 µmol/l at t = 20 min) than the blockade group (881 ± 84 µmol/l at t = 20 min) during the exercise period. Arterial lactate remained elevated (P < 0.05) in the control group during the recovery period. Arterial levels during the blockade test period were not different between the two groups (Fig. 6). NHLB in both control and blockade groups shifted similarly from net uptake during the basal period to net output during exercise. NHLB was similar...
during the recovery and blockade test periods in the control and blockade groups (Fig. 6).

Arterial alanine concentrations and NHAU. Arterial alanine was higher in the control group at t = 30 min and during the recovery period (P < 0.05). No significant differences were present during the blockade test period between the two groups (Fig. 7). NHAU was less (P < 0.05) in the control group (1.4 ± 0.3 µmol·kg^-1·min^-1 at t = 20 min) than the blockade group (3.6 ± 0.7 µmol·kg^-1·min^-1 at t = 20 min) during exercise. No significant differences in NHAU were seen during the recovery or blockade test periods (Fig. 7).

Arterial FFA and glycerol concentrations. Arterial FFA was significantly higher in the blockade group at t = 20 min during the exercise period. Otherwise, both FFA and glycerol levels responded similarly in the two groups (Table 1).

Heart rate and blood flow. Heart rate increased by 118 ± 6 and 121 ± 3 beats/min at 20 min of exercise in the control and blockade groups, respectively (Fig. 8). Heart rate did not increase during the blockade test period in either group, indicating that splanchnic escape of the catecholamines was minimal. Blood flow measurements for five of the seven control experiments

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**Table 1. Plasma cortisol and free fatty acids**

<table>
<thead>
<tr>
<th>Time, min: Mean Basal</th>
<th>Exercise</th>
<th>Recovery</th>
<th>Blockade Test</th>
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<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td><strong>Plasma cortisol, µg/dl</strong></td>
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<td></td>
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</tr>
<tr>
<td>Control</td>
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<td>5.0 ± 0.9</td>
<td>5.6 ± 1.0</td>
</tr>
<tr>
<td>Blockade</td>
<td>4.4 ± 0.7*</td>
<td>5.1 ± 0.7</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td><strong>Plasma free fatty acids, µeq/l</strong></td>
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<td></td>
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<tr>
<td>Control</td>
<td>837 ± 128</td>
<td>658 ± 80</td>
<td>691 ± 77</td>
</tr>
<tr>
<td>Blockade</td>
<td>699 ± 95</td>
<td>559 ± 70</td>
<td>681 ± 83</td>
</tr>
<tr>
<td><strong>Blood glycerol, µmol/l</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>86 ± 10</td>
<td>147 ± 16</td>
<td>153 ± 16</td>
</tr>
<tr>
<td>Blockade</td>
<td>73 ± 11</td>
<td>122 ± 15</td>
<td>151 ± 24</td>
</tr>
</tbody>
</table>

Values are means ± SE for 7 control and 6 adrenergic blockade dogs. *Significantly different from control group (P < 0.05).
have been published previously (4). Hepatic artery blood flow was less ($P < 0.05$) in the control group (5 ± 1 ml·kg$^{-1}$·min$^{-1}$) compared with the blockade group (11 ± 1 ml·kg$^{-1}$·min$^{-1}$) during the basal period. Hepatic artery blood flow was also less ($P < 0.05$) during the recovery period in the control group. However, there was no significant difference in hepatic artery blood flow between the two groups during the exercise and blockade test periods (Table 2). In contrast, portal vein blood flow was higher ($P < 0.05$) in the control group compared with the blockade group during exercise and the blockade test period (Table 2). Total hepatic blood flow was not significantly different between the two groups during the course of the experiment.

**DISCUSSION**

The results of this study demonstrate that the exercise-induced increment in $R_a$ is not critically dependent on adrenergic receptor stimulation during heavy exercise. The use of frequent sampling, arteriovenous difference techniques, and improved tracer methods coupled with local delivery of $\alpha$- and $\beta$-adrenergic blockers to the liver permitted a more precise assessment of the role of catecholamines during exercise. These findings in the dog support studies conducted in humans that
failed to show an effect of catecholamines on $R_a$ during heavy exercise (11, 12, 24). The attenuation of sympathetic nerve activity to the liver and adrenal medulla, using celiac ganglion blockade during heavy exercise (~75% maximum oxygen uptake), did not affect $R_a$ (11).

In addition, liver transplant patients who are free of hepatic innervation have a normal $R_a$ response to heavy exercise (~82% maximum oxygen uptake) (12). Last, systemic infusion of a $\beta$-adrenergic blocker, propranolol, does not attenuate the rise in $R_a$ during exercise at 100% of maximum oxygen uptake ($V_{O2 max}$) (24). The interpretation of these previous studies was complicated by the use of a patient population or by the nonspecific nature of the methods used to prevent hepatic adrenergic stimulation. The present study provides strong support for the assertion that catecholamine actions mediated through hepatic adrenergic receptors do not play an essential role in mediating the increase in $R_a$ during heavy exercise. This conclusion is supported by a study in the adrenalectomized rat that showed that the breakdown of hepatic glycogen during high-intensity exercise was independent of epinephrine replacement (15).

Previous studies have shown that the fall in insulin and the increase in glucagon are the major determinants of the increase in $R_a$ during moderate exercise (25). In the present study, heavy exercise resulted in similar arterial glucagon and insulin levels in both the control and blockade groups. It is important to recognize that the glucagon levels in the portal vein to which the liver is mainly exposed increase considerably more than those in the artery (26). It is noteworthy, however, that $R_a$ still increases during cycling in humans in whom systemic glucagon and insulin were clamped at basal levels, using the pancreatic clamp technique (23). These investigators deduced indirectly from these studies that catecholamines must be important. This conclusion contrasts with results obtained when they tried to assess catecholamine action directly, using $\beta$-adrenergic blockade during heavy exercise.

The potential for the catecholamines to stimulate $R_a$ is dependent on their levels at the liver. This is determined by catecholamine delivery via the circulation and/or sympathetic nerve activity (norepinephrine). The gut extracts ~50% of the plasma catecholamine concentration delivered to it by the blood during rest and heavy exercise (4). This results in portal vein levels that are ~50% of the arterial epinephrine levels. Plasma norepinephrine concentration in the portal vein remains comparable to arterial levels, despite gut norepinephrine extraction, because of sympathetic innervation of the gut and spillover of norepinephrine into the portal vein. In addition, marked increases in hepatic norepinephrine spillover during heavy exercise show that sympathetic drive to the liver is increased (4). Even though norepinephrine levels at the liver are higher than epinephrine levels, the effectiveness of norepinephrine in stimulating $R_a$ is 30-fold less than that of epinephrine in the dog (5). Thus the reason that adrenergic stimulation is less effective in stimulating $R_a$ during heavy exercise than has previously been postulated (16) is that arterial epinephrine levels overestimate those at the liver and norepinephrine is less effective compared with epinephrine in stimulating $R_a$.

The hepatic adrenergic blockade was designed to achieve completeness and selectivity. That the hepatic adrenergic blockade was virtually complete was shown by the attenuation of the rise in $R_a$ in the blockade group during the portal vein infusion of catecholamines. $R_a$ increased approximately threefold during the catecholamine infusion in the control group. In contrast, $R_a$ was unchanged in the blockade group during the catecholamine infusion period. Other differences in the blockade and control groups (circulating glucose and insulin) are probably secondary to the higher $R_a$ during the blockade test in controls. That the hepatic adrenergic receptor blockade was largely selective to the liver was demonstrated by similar glycerol and FFA responses during exercise in the present study. Local sympathetic nervous activity elicits fat mobilization (10), whereas the blockade of sympathetic nerves attenuates glycerol and FFA responses to heavy exercise (11). In addition, catecholamines have marked effects on pancreatic hormone secretion. The similar glucagon and insulin responses in both groups further support that the extrahepatic effects of the portal vein adrenergic blocker infusion are small. Peripheral $\alpha$-adrenergic receptor blockade of the pancreas would increase insulin secretion, whereas $\beta$-adrenergic blockade would decrease insulin secretion (21, 22). In addition, an $\alpha$- and/or $\beta$-adrenergic blockade would be expected to attenuate the increase in glucagon during exercise (22). Thus the local delivery of adrenergic blockers to the liver did not seem to affect pancreatic hormone secretion. The local nature of the hepatic blockade is also seen by the equal heart rate responses

### Table 2. Hemodynamic measurements

<table>
<thead>
<tr>
<th>Time, min:</th>
<th>Mean Basal</th>
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<th>Recovery</th>
<th>Blockade Test</th>
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<td>5</td>
<td>10</td>
<td>15</td>
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<tr>
<td></td>
<td>Portal vein blood flow, ml·kg⁻¹·min⁻¹</td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>25 ± 2</td>
<td>20 ± 1</td>
<td>18 ± 0</td>
<td>20 ± 2*</td>
</tr>
<tr>
<td>Blockade</td>
<td>20 ± 2</td>
<td>16 ± 1*</td>
<td>14 ± 2*</td>
<td>14 ± 1*</td>
</tr>
<tr>
<td></td>
<td>Heparic artery blood flow, ml·kg⁻¹·min⁻¹</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
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<td>6 ± 1</td>
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<tr>
<td>Blockade</td>
<td>11 ± 1*</td>
<td>9 ± 3</td>
<td>9 ± 2</td>
<td>9 ± 3</td>
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</table>

Values are means ± SE for 7 control and 6 adrenergic blockade dogs. *Significantly different from control group (P < 0.05).
to exercise in both groups, since blockade of β-
adrenergic receptors by propranolol has been shown to
decrease heart rate during exercise by 60% (1). Portal
vein administration of adrenergic blockers localizes
their action to the liver, and their efficient extraction by
the liver reduces their systemic effects (9). In addition,
the local irrigation of the liver with adrenergic blockers
allows the infusion rate to be markedly reduced over
that utilized during peripheral infusion. Therefore, it is
likely that only small amounts of the adrenergic block-
ers are available to extrahepatic tissues.

Although the hepatic adrenergic blockade was far
more selective than could be obtained by using conven-
tional approaches, there was still evidence that there
may be systemic effects of the blockers. During heavy
exercise, arterial lactate was higher in the control
group than the blockade group. Because net hepatic
balance of lactate was similar in both groups, lactate
formation must be reduced or lactate clearance must be
greater in the blockade group at an extrahepatic site.
β2-Adrenergic receptors mediate the epinephrine-
stimulated increase in glycogenolysis and, by doing so,
stimulate muscle lactate release (7). It may be that
enough propranolol is escaping from the splanchic bed
to attenuate this response.

NHAU fell during heavy exercise in controls. This
decrease may be due to a potent stimulation of hepatic
glycogenolysis and glycolytic flux during short-term
(27), high-intensity exercise. This could decrease NHAU
by causing an opposing increase in alanine efflux from
the liver. Evidence for an increase in hepatic glycolytic
flux is seen by the parallel increase in net hepatic
lactate output. It is unlikely that NHAU is decreased
because of a direct stimulation of the A transport
system, which mediates hepatic membrane alanine
transport, since glucagon, its major endocrine agonist
(2), is increased. A surprising finding was that hepatic
adrenergic blockade prevented the fall in NHAU dur-
ing heavy exercise. This implies that the fall in NHAU
is mediated, in some way, by hepatic adrenergic stimu-
lation. It is hard to relate this effect of adrenergic
stimulation to an overall effect on hepatic glycogenol-
ysis and glycolysis, since net hepatic glucose and lactate
output responses were still intact. Regardless, it is
unlikely that the greater NHAU in the blockade group
could have had a major effect on R_a by providing more
substrate for the gluconeogenic pathway. This is be-
cause the increase in R_a during short-term exercise is
due to an increase in hepatic glycogenolysis (25), and
the additional carbon due to the differences in NHAU is
small relative to the increment in R_a.

Another interesting finding was the increased basal
arterial cortisol response in the blockade group com-
pared with the control group. This difference was not
present during exercise. The stimulatory effect of in-
traportal blocker administration on basal cortisol levels
suggests that hepatic afferents may play a role in the
regulation of cortisol secretion. It is unlikely that this
increase in cortisol had a significant impact on the
interpretation of this short study, since cortisol must
remain elevated for a longer duration to have metabolic
effects (8). Even if increased cortisol levels were studied
over an extended time period, the relative importance
would probably be minor, since the hormone serves to
enhance the capacity for gluconeogenesis and glycogen
synthesis, neither of which operates at high rates
during heavy exercise. In addition to basal cortisol
levels, blood flow distribution was also altered by
intraportal blocker administration. Although the total
hepatic blood flow was the same in the two groups,
portal vein blood flow made up 82 and 63% of the total
blood flow in the control and blockade groups, re-
spectively. It is conceivable that the increased blood flow in
the hepatic artery may be due to phentolamine enter-
ing the systemic circulation and the adrenergic block-
ade of α-receptors, which cause vasoconstriction.
The decrease in portal vein blood flow may be compensatory
for the increase in hepatic artery blood flow. It is
important to recognize that the exercise-induced blood
flow responses were similar in the two groups. The
metabolic effects of this redistribution in blood flow, if
any, will require further investigation.

The present study utilizes rapid arterial sampling,
arteriovenous difference techniques, improved tracer
methodology, and a selective hepatic adrenergic recep-
tor blockade to determine the role of the catechol-
amines in control of hepatic glucose output during
heavy exercise. The effectiveness of the hepatic adrener-
getic blockade was illustrated by the demonstration that
the blockade eliminated the increases in R_a and NHGO
resulting from a combined norepinephrine and epineph-
rine challenge. Minimal extrhepatic effects of the
adrenergic blockade are supported by the similar insu-
lin, glucagon, glycerol, FFA, and heart rate responses to
heavy exercise in control and adrenergic blockade
groups. In conclusion, under conditions in which gluca-
gon, insulin, and plasma glucose levels are equal, the
R_a and NHGO responses to heavy exercise are una-
fected by hepatic adrenergic receptor blockade. This
demonstrates that the catecholamines do not play an
essential role in mediating the increase in R_a during
heavy exercise.

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