Sympathetic Drive to Liver and Nonhepatic Splanchnic Tissue During Prolonged Exercise Is Increased in Diabetes

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This study was conducted to assess whether nonhepatic splanchnic (NHS) and hepatic tissues contribute to the increase in circulating norepinephrine during prolonged exercise, and to determine whether such a response is exaggerated during exercise in the poorly controlled diabetic when the arterial norepinephrine response is excessive. Chronically catheterized (carotid artery, portal vein, and hepatic vein) and instrumented (Doppler flow probes on hepatic artery and portal vein) normal (n = 6) and alloxan-diabetic (n = 5) dogs were studied during rest (30 minutes) and moderate treadmill exercise (150 minutes). Basal plasma glucose of diabetic dogs was threefold that of control dogs. Since epinephrine is not released by splanchnic tissues, NHS and hepatic epinephrine fractional extraction (FX) can be accurately measured. Because epinephrine FX = norepinephrine FX, norepinephrine spillover can be calculated. NHS and hepatic epinephrine FX remained stable during rest and exercise in both control and diabetic dogs. Although basal NHS norepinephrine spillover was not different between the two groups, basal hepatic norepinephrine spillover was lower in the controls (1.1 ± 0.3 ng/kg · min) compared with the diabetics (3.6 ± 1.1 ng/kg · min). Although NHS norepinephrine spillover increased with exercise in the normal dog (3.1 ± 0.6 ng/kg · min at t = 150 minutes), there was no increase in hepatic norepinephrine spillover (1.1 ± 0.3 ng/kg · min at t = 150 minutes). In contrast, NHS (8.8 ± 1.6 ng/kg · min at t = 150 minutes) and hepatic (6.9 ± 1.8 ng/kg · min at t = 150 minutes) norepinephrine spillover were both markedly increased in the diabetic dog to rates approximately threefold and sixfold higher than in the normal dog. These data show that an increase in NHS but not hepatic norepinephrine spillover is a component of the normal response to prolonged exercise. The exaggerated increase in arterial norepinephrine during exercise in the diabetic state is due, in part, to both increased sympathetic drive to the gut and liver. This increase in sympathetic drive to the splanchnic bed may contribute to the deleterious effects of exercise in poorly controlled diabetes.

ARTERIAL NOREPINEPHRINE levels are increased during prolonged exercise in healthy subjects, and this increase can be amplified by a metabolic stress such as diabetes.[1] However, the exact importance of the norepinephrine response to exercise is difficult to assess, since the specific sites of sympathetic nerve endings that release the norepinephrine have not been defined. This is particularly relevant, because sympathetic drive may be a controller of the metabolic events that provide fuel for working muscle and may contribute to some of the undesirable effects of exercise in diabetes.[1] Identifying sites of increased sympathetic drive in people with diabetes may also be important, since they may be more sensitive to adrenergic stimulation than nondiabetics.[2-5]

The present study was conducted to assess the potential contribution of sympathetic nervous and vascular catecholamine delivery to nonhepatic splanchnic (NHS) and hepatic tissue during prolonged moderate exercise in healthy and poorly controlled alloxan-diabetic dogs. This problem was addressed by assessing norepinephrine spillover and vascular catecholamine delivery to the splanchnic tissues of chronically catheterized dogs at rest and during treadmill exercise.

MATERIALS AND METHODS

Animal Care and Surgical Procedures

Experiments were performed on six normal dogs (24.0 ± 1.0 kg) and five alloxan-diabetic dogs (25.0 ± 1.0 kg) that had been fed a standard diet (Pedigree beef dinner [Waltham, Vernon, CA] and Wayne Lab Blox [Allied Mills, Chicago, IL]: 51% carbohydrate, 31% protein, 11% fat, and 7% fiber based on dry weight). 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 Committee. At least 16 days before each experiment, a laparotomy was performed under general anesthesia (0.04 mg/kg atropine and 15 mg/kg pentothal sodium presurgery and 1.0% isofluorene inhalation during surgery). Silastic catheters (0.04 in ID) were inserted into the portal vein and common hepatic vein. In addition, an incision in the neck region allowed isolation of the carotid artery, into which a silastic catheter (0.04 in ID) was inserted and advanced to the aortic arch. After insertion, catheters were filled with saline containing heparin (200 U/mL; Abbott Laboratories, North Chicago, IL), and the free ends were knotted. Ultrasonic transit-time flow probes (Transonic Systems, Ithaca, NY) were fitted and secured to the portal vein (1.0 mL/min resolution; relative accuracy, ±2%) and hepatic artery (0.2 mL/min resolution; relative accuracy, ±2%) for blood flow measurements.

Approximately 4 days after surgery, dogs that were to be made diabetic were administered a 65-mg/kg intravenous dose of alloxan (BDH Chemicals, Poole, UK). After glycosuria was detected, the dogs were treated with regular and isophane (NPH) pork insulin (Eli Lilly, Indianapolis, IN) to maintain glycosuria less than 1%. The last injection of intermediate-acting insulin was given 48 hours before study, with the last injection of short-acting insulin given 18 hours before study. This regimen of insulin dosage ensures that diabetic dogs are free of subcutaneous insulin the day of the study.[6]

At least 7 days after surgery, the dogs were acclimatized to running on a motorized treadmill. They were not exercised 48 hours before the experiment. Only animals that consumed all of the daily food ration and had a leukocyte count less than 18,000/μL 3 days before experimentation were used.

Experimental Procedures

All studies were conducted in dogs following an 18-hour fast. The catheter ends and Doppler leads were accessed through small skin

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incisions made under local anesthesia (2% lidocaine; Astra Pharmaceutical Products, Worcester, MA) immediately before experimentation; the exposed catheters were then aspirated, flushed with saline, connected to silastic tubing, and secured to the back of the dog with quick-drying glue. The protocol consisted of a basal period (−30 to 0 minutes) and a moderate exercise period (0 to 150 minutes). Exercise was performed on a motorized treadmill at a speed of 4 mph with a 12% grade.

Blood Sample Collection and Analysis

Blood samples were drawn from the carotid artery, hepatic vein, and portal vein at −30 and 0 minutes during the basal period and at 50, 100, and 150 minutes during the exercise period to assess NHS and liver catecholamine loads and balances. Blood samples were collected in tubes containing EGTA and glutathione and centrifuged at 4°C. Plasma samples were then stored at −70°C for subsequent analysis of epinephrine and norepinephrine using high-performance liquid chromatography.[7] Catecholamine concentrations were calculated based on linear regression using dihydroxybenzylamine as an internal standard. The coefficients of variation using this method in our laboratory were 5% and 7% for norepinephrine and epinephrine, respectively. The level of immunoreactive insulin was measured using a double-antibody system.[8] The coefficient of variation using this method in our laboratory was 10%. Plasma glucose concentrations were measured using a Glucose Autoanalyzer II (Beckman Instruments, Fullerton, CA).

Calculations

The equations described below were used to calculate catecholamine balance, load, fractional extraction (FX), uptake, and output (spillover) across NHS and hepatic tissue. Net NHS norepinephrine balance was calculated using the equation,

$$\text{net NHS norepinephrine balance} = ([Np] - [Na]) \cdot Pf, \quad \text{Eq 1}$$

where [Np] is the portal vein plasma norepinephrine concentration, [Na] is the arterial plasma norepinephrine concentration, and Pf is the portal vein plasma flow normalized for body weight. Net hepatic norepinephrine balance was calculated using the equation,

$$\text{net hepatic norepinephrine balance} = ([Nh] - [Na]) \cdot Af + ([Nh] - [Np]) \cdot Pf, \quad \text{Eq2}$$

where [Nh] represents the hepatic vein plasma norepinephrine concentration and Af is hepatic artery plasma flow normalized for body weight. NHS and hepatic norepinephrine loads were calculated using the following equations:

$$\text{NHS norepinephrine load} = [Na] \cdot Pf \quad \text{Eq 3}$$

and

$$\text{hepatic norepinephrine load} = ([Na] \cdot Af) + ([Np] \cdot Pf). \quad \text{Eq 4}$$

Norepinephrine is concurrently taken up and released from tissue beds. As a consequence, tissue norepinephrine release and removal cannot be distinguished from measurements of norepinephrine arteriovenous differences alone. Epinephrine is not produced and released from splanchnic tissues. Furthermore, the rate of re-release of epinephrine taken up by sympathetic nerve terminals is low, comprising only 1% to 2% of total norepinephrine spillover.[9] Therefore, the unidirectional uptake of epinephrine can be calculated. Since epinephrine FX equals norepinephrine FX independent of plasma catecholamine concentration,[10-13] determination of unidirectional tissue norepinephrine uptake and spillover is also possible. NHS epinephrine FX was calculated using the equation,

$$\text{NHS epinephrine FX} = ([Ea] - [Ep])/[Ea], \quad \text{Eq 5}$$

where [Ea] and [Ep] represent the arterial and portal vein plasma concentrations of epinephrine, respectively. Hepatic epinephrine FX is calculated by the equation,

$$\text{hepatic epinephrine FX} = [([Ea] \times Af/(Af + Pf) + [Ep] \times Pf)(Af + Pf) - [Eh])]/[([Ea] \times Af/(Af + Pf) + [Ep] \times Pf/(Af + Pf))], \quad \text{Eq 6}$$

where [Eh] represents hepatic vein plasma epinephrine concentration. NHS and hepatic norepinephrine uptake were calculated using the following equations:

$$\text{NHS norepinephrine uptake} = \text{Eq 3} \cdot \text{Eq 5 and} \quad \text{Eq 7}$$

$$\text{hepatic norepinephrine uptake} = \text{Eq 4} \cdot \text{Eq 6.} \quad \text{Eq 8}$$

NHS and hepatic norepinephrine spillover were calculated by the equations,

$$\text{NHS norepinephrine spillover} = \text{Eq 1} + \text{Eq 7 and} \quad \text{Eq 9}$$

$$\text{hepatic norepinephrine spillover} = \text{Eq 2} + \text{Eq 8.} \quad \text{Eq 10}$$

Statistical Analysis

Superanova (Abacus Concepts, Berkeley, CA) software installed on a Macintosh Power PC (Apple Computer, Cupertino, CA) was used to perform statistical analysis. Statistical comparisons between groups and over time were made using ANOVA for repeated measures. Time points were specifically examined for significance using contrasts solved by univariate repeated-measures analysis. Statistics are reported in the corresponding table or figure for each variable. Data are presented as the mean ± SEM for six normal and five diabetic dogs. Statistical significance was defined as P less than .05.

RESULTS

Arterial Plasma Glucose and Insulin Levels

Basal arterial glucose was lower ($P < .05$) in the control group (108 ± 2 mg/dL) compared with the diabetic group (277 ± 55 mg/dL). Arterial glucose decreased ($P < .05$) to 98 ± 1 mg/dL at 150 minutes of exercise in the control group, whereas it remained stable (301 ± 73 mg/dL) in the diabetic group (Table 1). Basal arterial insulin was higher ($P < .05$) in the control group (13 ± 2 μU/mL) than in the diabetic group (5 ± 1 μU/mL). During the exercise period, arterial insulin decreased ($P < .05$) to 6 ± 0 and 4 ± 0 μU/mL in the control and diabetic groups, respectively (Table 1).

Arterial, Portal Vein, and Hepatic Vein Plasma Epinephrine and Norepinephrine Concentrations

Basal arterial, portal vein, and hepatic vein epinephrine were similar for the control (128 ± 34, 61 ± 10, and 12 ± 7 pg/mL) and diabetic (71 ± 24, 38 ± 6, and 10 ± 6 pg/mL) groups. In addition, there were no differences ($P > .05$) between the

Table 1. Arterial Plasma Glucose and Insulin During the Basal and Exercise Periods

Variable	Basal	Moderate Exercise (min) 50	100	150
Glucose (mg/dL)				
Control	108 ± 2	103 ± 2	98 ± 4	98 ± 1
Diabetic	277 ± 55*	283 ± 64*	275 ± 65*	301 ± 73*
Insulin (μU/mL)				
Control	13 ± 2	9 ± 1	7 ± 1	6 ± 0
Diabetic	5 ± 1*	5 ± 1*	4 ± 1*	4 ± 0*

NOTE. Values are the mean ± SE; n = 6 control and 5 alloxan-diabetic dogs.

*$P < .05$ *v* control value at corresponding times.

control and diabetic groups during the exercise period (Fig 1). Basal arterial, portal vein, and hepatic vein norepinephrine were not different ($P > .05$) between the control (177 ± 36, 226 ± 37, and 86 ± 24 pg/mL) and diabetic (192 ± 19, 210 ± 18, and 106 ± 20 pg/mL) groups. Arterial norepinephrine increased ($P < .05$) to 402 ± 71 and 670 ± 113 pg/mL in the control and diabetic groups, respectively, at 150 minutes of exercise. Arterial norepinephrine increased to higher ($P < .05$) levels in diabetic dogs during exercise. Portal vein norepinephrine increased ($P < .05$) to 459 ± 50 and 1,101 ± 308 pg/mL in the control and diabetic groups, respectively, at 150 minutes of exercise. The exercise-induced increase in portal vein norepinephrine was significantly greater ($P < .05$) in the diabetic group. Hepatic vein norepinephrine was increased ($P < .05$) in the control (164 ± 37 pg/mL at $t = 150$ minutes) and diabetic (218 ± 80 pg/mL at $t = 150$ minutes) groups, but was not different ($P > .05$) between groups (Fig 2).

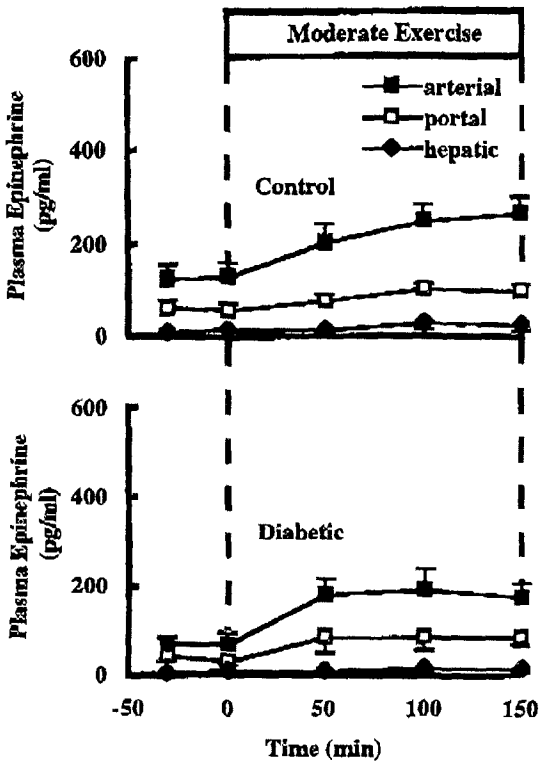

Fig 1. Arterial, portal vein, and hepatic vein plasma epinephrine in the basal state and during moderate exercise in normal control (n = 6) and diabetic (n = 5) dogs. Data are the mean ± SE.

NHS and Hepatic Epinephrine FX

NHS epinephrine FX was similar in the control and diabetic groups during the basal and exercise periods. Hepatic epinephrine FX was also similar in the control and diabetic groups during the basal and exercise periods (Fig 3).

NHS Norepinephrine Uptake and Spillover

Basal NHS norepinephrine uptake was lower ($P < .05$) in the control group (1.1 ± 0.1 ng/kg · min) compared with the diabetic group (2.2 ± 0.3 ng/kg · min). Although NHS norepinephrine uptake increased ($P < .05$) in both groups during exercise, it was still lower ($P < .05$) in the control group (2.6 ± 0.6 ng/kg · min at $t = 150$ minutes) compared with the diabetic group (4.4 ± 0.7 ng/kg · min at $t = 150$ minutes) (Table 2). Basal NHS norepinephrine spillover was similar in the control (1.8 ± 0.4 ng/kg · min) and diabetic (2.6 ± 0.3 ng/kg · min) groups. NHS norepinephrine spillover increased ($P < .05$) with exercise in both the control (3.1 ± 0.6 ng/kg · min at $t = 150$ minutes) and the diabetic (8.8 ± 1.6 ng/kg · min at $t = 150$ minutes) groups. The increase was considerably greater ($P < .05$) in diabetic dogs (Fig 4).

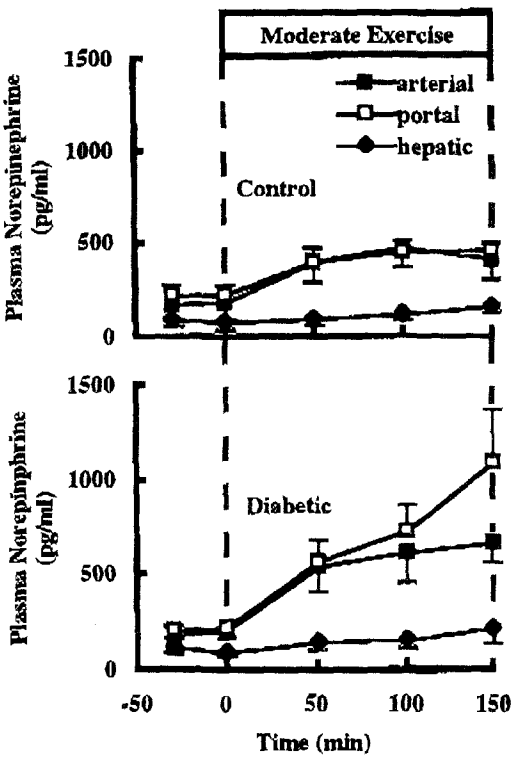

Fig 2. Arterial, portal vein, and hepatic vein plasma norepinephrine in the basal state and during moderate exercise in normal control (n = 6) and diabetic (n = 5) dogs. Arterial and portal vein norepinephrine levels were significantly higher in the diabetic group at $t = 100$ and 150 minutes of exercise *v* the control group ($P < .05$). Data are the mean ± SE.

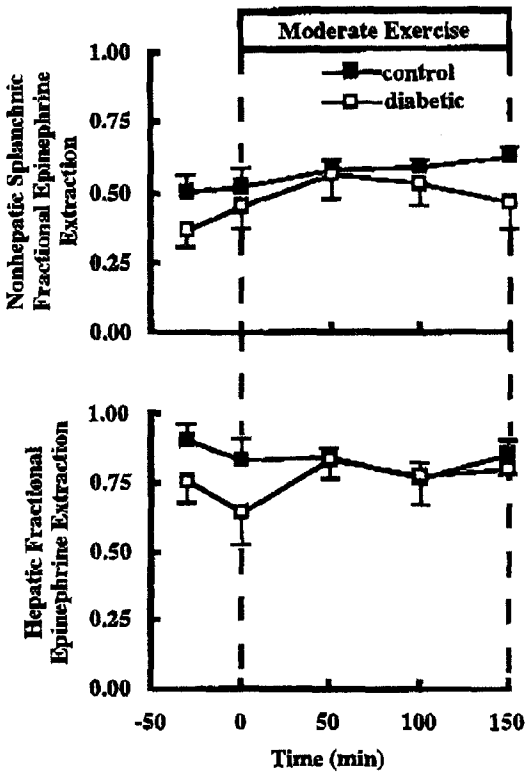

Fig 3. Nonhepatic splanchnic and hepatic fractional epinephrine extraction in the basal state and during moderate exercise in normal control (n = 6) and diabetic (n = 5) dogs. Data are the mean ± SE.

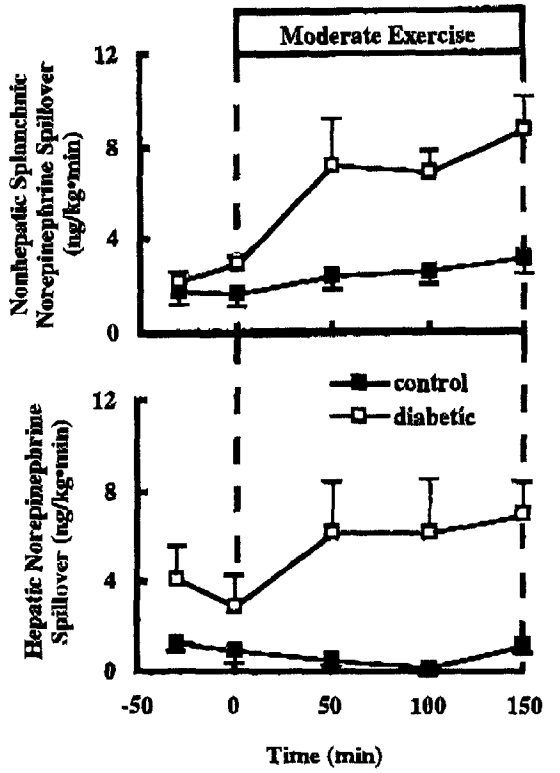

Fig 4. Nonhepatic splanchnic and hepatic norepinephrine spillover in the basal state and during moderate exercise in normal control (n = 6) and diabetic (n = 5) dogs. Nonhepatic splanchnic norepinephrine spillover was significantly greater in the diabetic group at *t* = 50, 100, and 150 minutes of exercise *v* the normal control group ($P < .05$). Hepatic norepinephrine spillover was significantly greater in the diabetic group throughout the experiment *v* the normal control group. Data are the mean ± SE.

Hepatic Norepinephrine Uptake and Spillover

Basal hepatic norepinephrine uptake was lower ($P < .05$) in the control group (3.4 ± 0.5 ng/kg · min) than in the diabetic group (5.9 ± 1.0 ng/kg · min). Although hepatic norepinephrine uptake was increased ($P < .05$) in both groups during exercise, rates remained lower ($P < .05$) in the control group throughout the exercise period, with values of 5.0 ± 0.5 and 17.2 ± 4.0 ng/kg · min in the control and diabetic groups, respectively, at t = 150 minutes (Table 2). Basal hepatic norepinephrine spillover was lower ($P < .05$) in the control group (1.1 ± 0.3 ng/kg · min) compared with the diabetic group (3.6 ± 1.1 ng/kg · min). Surprisingly, hepatic norepinephrine spillover was not increased ($P > .05$) by exercise in the control group (1.1 ± 0.3 ng/kg · min at 150 minutes). In contrast, hepatic norepinephrine spillover increased ($P < .05$) to 6.9 ± 1.8 ng/kg · min at 150 minutes of exercise in the diabetic group (Fig 4).

Blood Flow Measurements

Portal vein blood flow decreased ($P < .05$) from 23.3 ± 3 and 30 ± 3 mL/kg · min during the basal period to 18 ± 2 and 17 ± 1 mL/kg · min at 150 minutes of exercise in the control and diabetic groups, respectively. Hepatic artery blood flow was 7 ± 2 and 7 ± 2 mL/kg · min during the basal period and 5 ± 1 and 5 ± 1 mL/kg · min at 150 minutes of exercise in the control and diabetic groups, respectively (Table 3).

DISCUSSION

The present study shows an elevated NHS and hepatic norepinephrine spillover response in poorly controlled alloxan-diabetic dogs during moderate exercise in comparison to healthy nondiabetic dogs. Although basal NHS norepinephrine spillover was similar in control and diabetic dogs, NHS

Table 2. NHS and Hepatic Norepinephrine Uptake

Variable	Basal	Moderate Exercise (min) 50	100	150
NHS norepinephrine uptake (ng/kg · min)				
Control	1.1 ± 0.1	2.4 ± 0.4	3.0 ± 0.5	2.6 ± 0.7
Diabetic	2.2 ± 0.3	6.5 ± 2.0*	5.8 ± 1.0*	4.4 ± 0.7*
Hepatic norepinephrine uptake (ng/kg · min)				
Control	3.4 ± 0.5	4.6 ± 1.1	4.7 ± 0.9	5.0 ± 0.5
Diabetic	5.9 ± 1.0	13.0 ± 4.8*	15.8 ± 6.0*	17.2 ± 4.0*

NOTE. Values are the mean ± SE; n = 6 control and 5 alloxan-diabetic dogs.

*$P < .05$ *v* control dog value at corresponding time.

Table 3. Blood Flow Measurements

Variable	Basal	Moderate Exercise (min) 50	100	150
Portal vein (mL/kg · min)				
Control	23 ± 2	20 ± 1*	19 ± 1*	18 ± 2*
Diabetic	30 ± 3	22 ± 3*	21 ± 3*	17 ± 1*
Hepatic artery (mL/kg · min)				
Control	7 ± 2	5 ± 1	5 ± 1	5 ± 1
Diabetic	7 ± 2	6 ± 1	5 ± 1	5 ± 1

NOTE. Values are the mean ± SE; n = 6 control and 5 alloxan-diabetic dogs.

*$P < .05$ *v* basal.

norepinephrine spillover response to exercise of the diabetic dogs was threefold greater. A surprising finding is that hepatic norepinephrine spillover was not significantly increased during exercise in the control dogs. However, this variable was elevated by diabetes in the basal state. Moreover, in contrast to control dogs, moderate exercise elicited an increase in hepatic norepinephrine spillover in alloxan-diabetic dogs. Their mean basal plasma glucose levels were 277 ± 55 mg/dL. It is possible that a better-controlled diabetic model may have a normalized splanchnic norepinephrine spillover.

NHS norepinephrine balance reflects norepinephrine spillover from the pancreas, spleen, adipose tissue, and gastrointestinal tract. This variable is measured by assessing arterial norepinephrine inflow and portal venous norepinephrine outflow. The potential for an increase in sympathetic drive to this area exists, since the splanchnic bed is extensively innervated by sympathetic nerves. Celiac and superior mesenteric ganglia provide innervation to the small intestine, while superior and mesenteric ganglia provide innervation to the colon. Sympathetic input to the pancreas and spleen is supplied by the celiac ganglion.[10] The increases in NHS norepinephrine spillover observed in the present study are consistent with physiological changes that occur in NHS tissues during prolonged exercise. For example, glucagon is increased and insulin is decreased by both prolonged exercise and sympathetic stimulation. In addition, the spleen contracts and splanchnic blood flow decreases in response to both stimuli. Although few data exist on the response of NHS tissue to exercise in the diabetic state, there is some physiological evidence consistent with a greater increase in sympathetic drive to NHS tissues. Examples of this may be the greater decrease in portal vein blood flow and a greater NHS release of alanine in exercising diabetic dogs.[6]

Previous study in our laboratory has shown significant increases in NHS and hepatic norepinephrine spillover during heavy exercise in the normal dog.[14] The present study demonstrates that while the stress of heavy exercise is sufficient to elicit an increase in sympathetic drive to NHS and hepatic tissue in normal dogs, moderate exercise of even prolonged duration stimulates only a relatively small increase in NHS norepinephrine spillover and no increase in hepatic norepinephrine spillover. In the diabetic state, NHS and hepatic norepinephrine spillover increase markedly during exercise just as in the normal dog during heavy exercise, suggesting the more stressful nature of exercise in the diabetic state.

The lack of a hepatic norepinephrine spillover response to moderate exercise in the normal dog may explain why surgical hepatic denervation does not affect hepatic glucose production in normal dogs during prolonged moderate exercise.[15] Although sympathetic innervation does not act as the primary mediator of hepatic glucose production during moderate exercise in the normal dog, increased sympathetic stimulation of NHS and hepatic tissue may play a role in the exercise-induced increase in hepatic glucose production in diabetes. The insulin-deficient diabetic state during exercise is characterized by increased glucose release from the liver despite excessive circulating glucose levels. The increased sympathetic drive to the splanchnic bed, coupled with studies showing that hepatic glucose production may be more sensitive to adrenergic stimulation in individuals with insulin-dependent diabetes[2-5] and in depancreatized dogs,[6] suggests that catecholamines may be a stimulus for hepatic glucose production under these conditions.

In further support of a role for the increased sympathetic drive during exercise in diabetes is that at elevated rates of delivery, norepinephrine has rapid stimulatory effects on gluconeogenic precursor mobilization and intrahepatic gluconeogenic efficiency, independent of changes in pancreatic hormones.[17] Thus, the increase in splanchnic adrenergic drive may be important in stimulating the exaggerated rate of gluconeogenesis demonstrated in the poorly controlled diabetic dog. Poorly controlled depancreatized dogs compared with normal dogs have accelerated rates of NHS gluconeogenic precursor (lactate and alanine) release that contribute to the exaggerated gluconeogenic rates during exercise.[6] Therefore, it is possible that increased sympathetic drive may contribute to the increase in glucose production during exercise in diabetes by direct hepatic stimulation, but also indirectly, by increasing gluconeogenic precursor output from the gut.

Since portal vein blood flow is about 80% of total hepatic blood flow, the composition of this blood is critical to the regulation of the liver. Portal vein norepinephrine, and consequently, hepatic vascular norepinephrine delivery, is increased by exercise in normal dogs due to both an increase in the rate that norepinephrine enters the splanchnic bed from the systemic circulation and an increase in NHS norepinephrine spillover. Moderate exercise in diabetic dogs is characterized by a considerably greater hepatic vascular norepinephrine delivery than in normal dogs, due to exaggerated increments in both the rate that norepinephrine is derived from the systemic circulation and the rate of NHS spillover. Portal vein epinephrine is increased considerably less by exercise than norepinephrine in both control and diabetic dogs. Arterial epinephrine levels are similar during rest and exercise in the two groups. NHS tissues attentuate the amount of the epinephrine increase in the portal vein, as they extract approximately half of the epinephrine delivered to them. As a result, the rate that epinephrine is delivered to the liver via vascular channels will be much slower than might be estimated based on its arterial levels.

In summary, normal dogs show a relatively small increase in NHS norepinephrine spillover and no increase in hepatic norepinephrine spillover during prolonged exercise. In sharp

contrast, poorly controlled alloxan-diabetics show a much more substantial increase in NHS norepinephrine spillover during exercise. Moreover, hepatic norepinephrine spillover in alloxan-diabetics is greater during the basal period and increases still more with exercise. The increased NHS norepinephrine spillover response in the diabetic state may be responsible for increases in splanchnic proteolysis and lipolysis, which, in turn, can increase circulating gluconeogenic substrate and glucose production during exercise. Exaggerated NHS and hepatic norepinephrine spillover responses in alloxan-diabetic dogs are important because they may contribute to some of the deleterious effects of exercise in the diabetic state.

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