The Effects of Norepinephrine on Active Hyperemia in the Canine Gracilis Muscle

STEPHEN F. FLAIM, WILLIAM CREDE, ANTHONY BEECH, STEPHEN H. NELLIS, AND ROBERT ZELIS

SUMMARY We studied the effects of intra-arterial norepinephrine (NE) on skeletal muscle blood flow (BF), oxygen consumption (V02), and arteriovenous oxygen difference (A-V02) at rest and during exercise in an autoperfused canine gracilis muscle preparation. Static continuous exercise at a fixed level of maximal developed tension (P0) was induced by gracilis nerve stimulation; developed tension was monitored and used to control stimulation intensity. In one group of dogs (n = 10), data were collected before (rest) and at the end of each of a series of four 2-minute periods of exercise (10% P0) in each preparation. During both the rest and the exercise phases, continuous intra-arterial infusions of isotonic saline alone (control) and saline plus NE (0.11, 0.22, and 0.44 ng/min) were made. Control resting data were: BF = 5.90 ml/min; A-V02 = 5.30 vol %; V02 = 0.31 ml/min. NE during rest reduced BF by 30-69%, increased A-V02 by 79-91%, and reduced V02 by an average of 41.9%. Control exercise data were: BF = 17.2 ml/min; A-V02 = 11.2 vol %; V02 = 1.06 ml/min. NE during exercise attenuated BF by 7-85% and widened A-V02 by 22-35%. V02 was maintained at control exercise levels during lower NE infusion levels but was attenuated by 59% at the highest NE level. In the second group of dogs (n = 8), data were collected at rest and at four times during a 10-minute exercise period (2.5% P0). NE (0.089, 0.17, and 0.34 ng/min) or saline (control saline) was infused for 2 minutes each during the final 7 minutes of exercise. At the lower NE doses, no significant difference was observed relative to the control-saline experiment. At the highest NE dose BF and V02 were attenuated (BF: -22%, V02: -20%), and A-V02 was unchanged compared to control. The NE-induced attenuation in BF and V02 during exercise may in part result from a mechanism similar to that which occurs in congestive heart failure in which an exaggerated sympathoadrenal response during exercise and an attenuated exercise-induced rise in forearm V02 occurs. Circ Res 44: 660-666, 1979

THE MAJOR DETERMINANTS of blood flow to exercising skeletal muscle appear related to locally reduced oxygen tension and increased metabolite concentration (Skinner, 1975). However, a number of other factors such as the type and severity of exercise and the physical condition of the subject may affect flow to muscle. Congestive heart failure also may be a factor. Patients in this state appear to have an increased vascular stiffness as well as an excessive sympathoadrenal response to exercise (Chidsey et al., 1965; Higgins et al., 1972; Zelis et al., 1969) as evidenced by elevated circulating levels of catecholamines. This may explain partially the failure of oxygen consumption to rise normally when patients with heart failure exercise (Zelis et al., 1974; Longhurst et al., 1976). Although it is assumed that metabolic vasodilator stimuli can override the vasoconstrictor action of a-adrenergic vascular receptor stimulation, there is considerable experimental evidence to suggest that a nearly complete "functional sympatholysis" occurs only during a maximal metabolic stimulus (Remensnyder et al., 1962; Kjellmer, 1965; Strandell and Shepherd, 1967; Costin and Skinner, 1971; Burcher and Garlick, 1973). With submaximal exercise, metabolites only attenuate sympathetic a-adrenergic constriction, and this attenuation is more pronounced for neuronally released than for humorally delivered norepinephrine (NE) (Burcher and Garlick, 1973). Vascular a-adrenergic receptor stimulation in resting skeletal muscle causes a reduction in capillary surface area by closure of precapillary sphincters and a rerouting of arterial blood through shorter vascular channels. This "physiological shunting" of blood leads to a narrowing of the arteriovenous oxygen difference or a reduction in the calculated oxygen uptake of resting skeletal muscle (Nakamura, 1921; Rein and Schneider, 1938; Pappenheimer, 1941; Renkin and Rosell, 1962a; Bolme and Gagnon, 1972; Takehata et al., 1976). During exercise, there is opening of precapillary sphincters in skeletal muscle and an increased capillary surface area. This leads to an increased oxygen consumption, which varies with the magnitude of developed tension and the duration of contraction (Renkin and Rosell, 1962b; Kjellmer, 1964; Renkin et al., 1966; Stainsby and Fales, 1973). However, at low venous oxygen tensions, the control of microvascular perfusion shifts from the precapillary...
sphincters to the resistance vessels, which are able to escape less effectively from adrenergic vasoconstrictor control than can the precapillary sphincters (Granger et al., 1976). Thus it is difficult to predict what metabolic consequences are to be expected in the exercising muscle of patients with heart failure where a-adrenergic stimulation is excessive and venous oxygen saturation is low. Prediction is further complicated by lack of knowledge regarding which vessels are most altered by vascular stiffness in heart failure.

To study the interrelationship between dilator and constrictor stimuli during exercise, steady state conditions must exist. Therefore, it is preferable to study "static" (without external shortening) rather than "dynamic" (with external shortening) exercise. Even in studies employing the static exercise mode, steady state conditions cannot be assured unless muscle tension is measured directly and the exercise is less than 10–15 percent of maximal developed tension (P₀) (Donald et al., 1967; Mottram, 1973). Under these conditions, a steady state can be achieved and accurate metabolic measurements are obtainable.

The purpose of the present studies was to evaluate the effects of NE infusion in the autoperfused canine gracilis muscle both at rest and during static exercise.

**Methods**

Eighteen male mongrel dogs (19–25 kg) were studied (gracilis muscle weight = 63–86 g). In the first series, 10 dogs were anesthetized with intravenous sodium thiamylal (25 mg/kg), following which anesthesia was maintained with a chloralose-urethane mixture (chloralose = 60 mg/kg; urethane = 100 mg/kg). In the second series, eight dogs were anesthetized with sodium pentobarbital (30 mg/kg). This agent is a peripheral vasodilator which could neutralize the effects of NE infusion in the autoperfused gracilis muscle measured in the second series. All dogs were ventilated with room air through a cuffed endotracheal tube with a respirator (Harvard Apparatus Company) at a tidal volume of 15–20 ml/kg and a rate of 20 cycles/min. Rectal temperature was measured with a Yellow Springs thermistor and maintained between 37–39°C with a thermal pad. The left femoral artery was cannulated to measure systemic arterial pressure (Statham P23db pressure transducer) and to sample arterial blood for gas and pH analysis (Radiometer Blood Microsystem MK2). Arterial blood gas and pH analyses were performed at a minimum of 30-minute intervals, and respiratory rate, the rate of oxygen delivery, or bicarbonate levels were adjusted to maintain P₀₂, Pco₂, and pH within the normal ranges and arterial O₂ saturation above 96%. To increase oxygen delivery, 100% O₂ was added to the inspired air at the respirator. Heart rate was monitored using standard ECG limb leads.

**Preparation of Gracilis Muscle**

The left gracilis muscle was exposed from the pubis to the tibia and was vascularly isolated except for the main gracilis artery and vein. The left femoral artery proximal to the gracilis artery was isolated, ligated, and cannulated to allow distal perfusion of the gracilis bed via a cannula from the right femoral artery after iv administration of heparin (300 U/kg). The left femoral vessels distal to the origin of the gracilis artery and vein were ligated and a cannula was inserted connecting the distal ends of the left femoral vein and the gracilis vein to allow venous sampling. For the first series of studies [10% maximal developed tension (P₀)], blood flow to the gracilis muscle was measured directly by an electromagnetic flowmeter (Statham model SP 2202) positioned on the gracilis artery (Fig. 1). In the second series of studies (2.5% P₀), gracilis muscle blood flow was determined by passing total gracilis muscle venous outflow through a rotameter (Shipley and Wilson, 1961) before returning it to the systemic circulation via the left femoral vein.

The distal aponoeurosis of the gracilis muscle was detached from its insertion into the tibia, and the muscle was fixed to an isometric tension rack via clamps placed at the origin and insertion. The clamp attached to the distal aponoeurosis was connected to a tension transducer (Statham UC-3, 60 g) with a Statham UL-4 load cell accessory adaptor (50 pounds) to measure tension.

The gracilis nerve was ligated, divided, and attached to bipolar hook electrodes. Before the beginning of the experiment, optimal length (Lo) and maximal developed tension (P₀) were determined for each muscle preparation. For the determination of Lo, we obtained a length-tension curve by stimulating the gracilis nerve, using a square-wave impulse generator (Grass model S44), with a single impulse (duration = 8 msec, voltage = 2–5 V) at each length setting while measuring tension. Lo was chosen at the apex of the length-tension curve. P₀ then was determined by setting the muscle to L₀ and stimulating the nerve with a single brief (less than 3 seconds) train of stimuli (frequency = 20 Hz, duration = 8 msec, voltage = 2–5 V) while measuring tension. It should be noted that the voltages described here refer to stimulator settings, and that the actual voltages stimulating the nerve across a saline resistance were much less. For the muscles used in these studies, P₀ averaged 15.9 ± 1.1 kg (mean ± SEM). For the studies described below, voltage to the gracilis nerve was automatically regulated by an analog feedback system controlled by gracilis muscle tension. The feedback system produced a voltage inversely proportional to the input voltage from the tension transducer and resulted in a constant static gracilis muscle contraction at the predetermined level of P₀ (2.5% or 10%). The actual voltage ranges required to generate these tension levels were measured and were as follows: 2.5% P₀, 10% P₀.
FIGURE 1 The gracilis muscle preparation used to evaluate the effects of norepinephrine infusion on static exercise. The autoperfused canine gracilis muscle is held in a rack between two clamps (A, B). Muscle tension (1) is measured from a tension transducer attached to the clamp holding the distal tendon (A). Also measured are mean gracilis arterial flow (2) or mean venous flow with a rotameter (not shown) and systemic arterial perfusion pressure (3). Syringes note the points of sampling of blood for gas analysis. Also shown are the perfusion pump for intra-arterial infusions (C), electrodes for stimulating the gracilis muscle nerve (D), thermistors for measuring gracilis muscle and rectal temperatures (E), and heat lamp for controlling gracilis muscle temperature (F).

0.08-0.15 V; 10% Po, 0.15-0.3 V. To generate exercise at 2.5% and 10% Po, nerve stimulation at the appropriate voltage was continuous over the period of exercise (frequency = 20 Hz, duration = 8 msec).

Gracilis muscle temperature was measured with a Yellow Springs needle thermistor, and a heat lamp was used to maintain tissue temperature at 34-36°C. The muscle was wrapped with Saran wrap to prevent drying and heat loss.

Experimental Protocols

Recordings of muscle tension, mean systemic arterial pressure, and arterial or venous flow were made with an optical recorder (Electronics for Medicine DR-12) with rapid writer. Arterial and gracilis venous oxygen contents were determined with a LEX O2 CON total oxygen content analyzer. Infusions of saline or NE far upstream from the gracilis artery (to ensure adequate mixing) were performed with a constant infusion pump (Harvard model 907).

Series I

In this group of dogs, four experimental tests were conducted on each gracilis muscle preparation (n = 10). In each test, values for gracilis muscle blood flow (BF), arteriovenous oxygen difference (A-Vo2), and oxygen consumption (Vo2) were obtained at two data collection points. Data collection points for each test occurred before and at the end of a 2-minute period of exercise (10% Po). The four experimental tests consisted of the continuous intra-arterial infusion (0.11 ml/min) of isotonic saline alone (control) and saline plus NE at each of three doses (0.11, 0.22, and 0.44 µg/min) delivered throughout the rest-exercise protocol. Infusion rates for all NE dosages were equal to the control-saline infusion rate. Between all experimental tests, preparations underwent a 40-minute rest-recovery period.

Series II

In this group of dogs, two experimental tests were conducted on each gracilis muscle preparation (n = 8). In each test, values for gracilis muscle BF, A-Vo2, and Vo2 were obtained before (control) and during a 10-minute period of static exercise (2.5% Po). Exercise data were collected immediately prior to minutes 3, 6, 8, and 10. Immediately after the 3-minute exercise data point, an intra-arterial infusion at 0.11 ml/min was instituted which continued to the end of the experimental test. The first experimental test consisted of the intra-arterial infusion of isotonic saline alone. The second experimental test consisted of the infusion of saline plus NE. NE infusion was instituted at 0.08 µg/min, increased to 0.17 µg/min immediately after the 6-minute exercise data point, and increased again to 0.34 µg/min after the 8-minute exercise data point. The different NE infusions were delivered at proportionally increased volume flow rates. Identical increases in infusion rates were instituted during the saline control ex-
periment at the appropriate time points.

Analysis of Data

In Series I, the effects of intra-arterial NE infusion at rest and during exercise were tested according to ANOVA statistical procedures. In addition, data obtained during exercise experiments were compared to corresponding data obtained during rest experiments. In Series II, values obtained during saline runs were compared to corresponding values obtained during NE runs. Statistical comparisons were made with the use of Student's t-test for grouped observations for both series of data. P values less than 0.05 were considered significant. All data are presented as means ± standard error of the mean (SEM).

Results

In all experiments, no significant changes occurred in heart rate (HR) or mean systemic arterial blood pressure (BP) (HR = 124-145/min; BP = 123-130 mm Hg). Arterial P02 (150-300 mm Hg), Pco2 (30-50 mm Hg), pH (7.35-7.45), and O2 saturation (96-98%) remained within the normal ranges throughout all experimental procedures.

Effects of NE on the Resting Muscle

Control data obtained during saline infusion in the resting muscle were: BF = 5.90 ± 0.76 ml/min; A-V02 = 5.30 ± 0.73 vol %; V02 = 0.31 ± 0.05 ml/min (n = 10). The effects of graded NE infusion on these parameters in the resting muscle are shown in Figure 2. BF was significantly reduced with NE as compared to the control level during saline infusion (Fig. 2, Panel A). A-V02 was widened significantly by NE (Fig. 2, Panel B); V02 was reduced at the highest NE level, but this change was not statistically significant (Fig. 2, Panel C). The mean values for the change in V02 during NE were not significantly different for increasing NE concentrations: change in V02 during NE at 0.11 μg/min = −0.04 ± 0.06 ml/min; change during 0.22 μg/min = −0.07 ± 0.05 ml/min; change during 0.44 μg/min = −0.12 ± 0.06 ml/min.

Effects of NE on the Muscle during Static Exercise (10% P0)

Control data obtained after 2 minutes of exercise during intra-arterial saline infusion were: BF = 17.2 ± 2.6 ml/min; A-V02 = 11.2 ± 1.0 vol %; V02 = 1.96 ± 0.36 ml/min. The effects of graded NE infusion on these parameters in the exercising muscle are shown in Figure 2. BF was significantly reduced with NE as compared to the control exercise plus saline level (Fig. 2, Panel A). Similarly, A-V02 was widened significantly with NE (Fig. 2, Panel B). V02 appeared to increase at the lower two NE levels but was attenuated significantly during the highest NE dose (Fig. 2, Panel C).

Evaluation of data obtained during exercise (10% P0) compared to the corresponding data obtained from resting muscle suggests that exercise significantly increased BF (Fig. 2, Panel A), A-V02 (Fig. 2, Panel B), and gracilis muscle V02 (Panel C) at rest (broken lines) and during static exercise (solid lines) (10% P0; 2 minutes). Data are presented as mean ± SEM (n = 10). P values indicate the level of significance (ANOVA) between norepinephrine infusion and the respective control observations (C). Asterisks indicate statistical significance (P < 0.026) between comparable rest and exercise data.

Effects of NE on the Muscle at Rest and during Static Exercise (2.5% P0)

Prior to intra-arterial infusion, static exercises at 2.5% P0 increased BF, A-V02, and V02 compared to their respective levels in the resting muscle (Fig. 3, Panels A through C). Data obtained during intra-arterial infusion of the two lower NE doses were similar to comparable data obtained during saline infusion. All values through the 8-minute time point during both saline and NE infusion remained increased compared to their respective resting levels. At the highest NE dose (as compared to parallel data obtained during saline infusion), gracilis muscle BF (Fig. 3, Panel A) and V02 (Fig. 3, Panel C) were reduced significantly, but A-V02 did not
FIGURE 3 The effects of graded norepinephrine (NE) infusion on gracilis muscle blood flow (Panel A), arteriovenous (A-V) oxygen difference (Panel B), and oxygen consumption (Panel C) during continuous static exercise (2.5% P0, 10 minutes) (unfilled circles, broken lines) compared with the effects of saline infusion during a comparable period of exercise (filled circles, solid lines). The exercise period as well as NE infusion concentrations and time periods are indicated at the bottom of Panel C. Data are presented as means ± SEM (n = 8). P values refer to comparisons between parallel data points obtained during NE and saline infusion runs (exercise plus saline vs. exercise plus NE).

Discussion

In this study, intra-arterial NE reduced BF to the resting skeletal muscle while widening A-VO2 (Fig. 2). The increased extraction of oxygen allowed for the maintenance of regional oxygen consumption, which did not appear to change significantly during the resting state (Fig. 2, Panel C). This effect may be dose-dependent, because the highest concentration of NE infused in the present study produced a moderate reduction in skeletal muscle VO2. This change was not significant only because the drug induced an opposite response in one dog. It is likely that with a larger number of determinations, the reduction in VO2 caused by norepinephrine in resting muscle would be statistically significant.

Static exercise at 10% of maximal developed tension for 2 minutes resulted in an increased BF, a widened A-VO2, and an increased VO2 (Fig. 2). When NE infusion was begun prior to exercise, a significant attenuation of exercise hyperemia and a further widening of A-VO2 occurred (Fig. 2). At the two lower levels of NE infusion, an increase in the extraction of oxygen appeared to compensate for the attenuation of exercise hyperemia, and, consequently, skeletal muscle VO2 was maintained at its control level. However, during infusion of the highest NE dose, an imbalance between exercise BF and the extraction of oxygen occurred, which resulted in a fall in regional skeletal muscle VO2 during exercise (Fig. 2, Panel C).

Because the level of exercise chosen (10% P0) was close to the level at which steady state conditions may cease to exist, and because the duration of the exercise period was brief (2 minutes), a longer period of exercise was studied (10 minutes) at a lower exercise intensity (2.5% P0). When a graded NE infusion was instituted during this 10-minute exercise period, similar results were obtained. The highest NE dose resulted in an attenuation of exercise BF and exercise VO2 (Fig. 3, Panels A through C). Although the results of the two exercise studies are similar, minor differences were noted. These differences may be accounted for partially by the higher levels of BF and VO2 observed during the resting state in the latter series of studies, in which a barbiturate anesthetic was employed as opposed to the chloralose-urethane mixture used during the first series of studies. Although a true steady state was achieved during 10 minutes of exercise when saline was infused, it may not have existed during all NE infusions, and only could be achieved if the NE infusion rate were instantaneously varied as a function of gracilis muscle BF.

It is generally known that skeletal muscle VO2 in the dog as well as in humans is relatively independent of skeletal muscle BF (Honig, 1977). This relationship for the canine gracilis muscle has been described by Durán and Renkin (1974). They showed that in the majority of cases VO2 in the resting muscle remained nearly constant over a wide range of passively controlled BF levels and fell only at flows below 2 ml/min × 100 g (Durán and Renkin, 1974). Stainsby and Otis (1964), furthermore, demonstrated similar findings for the resting as well as the exercising canine gastrocnemius-plan-
tars group. In the present study, relatively small norepinephrine-induced reductions in flow to the canine gracilis muscle caused significant reductions in exercising skeletal muscle VO2. Honig (1977) states that canine skeletal muscle VO2 can be reduced by lowering the oxygen content of the muscular capillaries. Therefore, it appears that NE, at least at the highest levels, may act to reduce flow preferentially through the capillary bed by competing with or overcoming the dilator effect of local metabolites on the precapillary sphincters. This effect could contribute to the increased vascular stiffness of the larger vessels that has been noted in heart failure patients (Zelis et al., 1968). At lower concentrations, NE may reduce only resistance vessel flow, whereas the precapillary sphincters, which are less sensitive to β-adrenergic stimulation under conditions of increased local metabolism (Granger et al., 1976), can regulate intramuscular BF distribution to provide a greater oxygen supply to the more actively metabolizing fibers. Thus low concentrations of NE actually may result in an increase in oxygen consumption.

These studies have significant implications regarding the metabolic response to exercise in patients with heart failure. This group of subjects is known to have an exaggerated sympathoadrenal response to exercise, resulting in an increase in circulating levels of catecholamines (Chidsey et al., 1974; Longhurst et al., 1976). It is likely that increased circulating NE also may account for an attenuation of exercise hyperemia at submaximal exercise levels (Zelis et al., 1974; Longhurst et al., 1976). The attenuation of regional VO2 noted during both forearm dynamic and static exercise in patients with heart failure could be accounted for by the increased sympathoadrenal response alone. However, the role that local vascular stiffness may play in this phenomenon is yet unknown.

Thus, with heart failure, some increase in the level of circulating NE may be helpful in shunting blood preferentially from less active to more active tissue. The result would be an enhanced extraction of oxygen and the maintenance of normal levels of VO2. At higher levels of NE, the metabolic consequences would be unfavorable, and skeletal muscle VO2 during exercise would fall. At that point, inefficient anaerobic processes would be necessary to provide energy for exercise, and lactic acidosis would result.

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SUMMARY We determined the effects of direct renal intra-arterial injections of [des-Asp^1]angiotensin I (0.2-3.2 μg) and angiotensin III (0.00625-0.1 μg) on renal blood flow in 10 dogs anesthetized with pentobarbital. Both [des-Asp^1]angiotensin I and angiotensin III caused dose-dependent decreases in renal blood flow. The decreases in ipsilateral renal blood flow occurred in the absence of alterations in systemic arterial pressure and flow to the contralateral kidney, suggesting that the response was a local event. The renovascular responses to [des-Asp^1]angiotensin I were greatly attenuated during the intravenous administration of SQ 20881, a synthetic peptide that competitively inhibits angiotensin converting enzyme. SQ 20881 did not alter the vasoconstrictor responses to angiotensin II, angiotensin I, or norepinephrine. [Ile^7]Angiotensin III (an angiotensin III antagonist) abolished decreases in renal blood flow produced by [des-Asp^1]angiotensin I, angiotensin II, angiotensin III, and angiotensin I, whereas the response to norepinephrine was unchanged. These results suggest that the decrease in renal blood flow produced by [des-Asp^1]angiotensin I is due to its local enzymatic conversion to angiotensin III. About 7% of [des-Asp^1]angiotensin I is converted to angiotensin III during one transit through the kidney. Circ Res 44:666-671, 1979

IT HAS BEEN demonstrated recently that [des-Asp^1]angiotensin II (angiotensin III) is as potent as angiotensin II in decreasing renal blood flow, and it was hypothesized that the local production of angiotensin III occurs at the level of the renal arteriolar receptor (Freeman et al., 1975). Data are available to support the existence of two pathways for the generation of angiotensin III: the first from angiotensin II by the cleavage of the N-terminal aspartic acid through the action of aminopeptidases (Glenner et al., 1962; Regoli et al., 1963), and the second from the nonapeptide [des-Asp^1]angiotensin I by the cleavage of the C-terminal dipeptide histidyl-leucine through the action of angiotensin converting enzyme (Tsai et al., 1975).

The present experiments assessed the ability of the kidney to form angiotensin III by the second pathway. The effects of [des-Asp^1]angiotensin I and angiotensin III on renal blood flow were examined in the presence and absence of a synthetic nonapeptide, SQ 20881 (Pyr-Trp-Pro-Arg-Pro-Glu-Ile-Pro-Pro), that inhibits angiotensin converting enzyme (Ferreira et al., 1970a, 1970b; Cushman et al., 1971; Ondetti et al., 1971; Schaeffer et al., 1971; Yang et al., 1971). Experiments also were performed in the presence and absence of [Ile^7]angiotensin III, an angiotensin III antagonist (Peach, 1977). The results suggest that the renal vasoconstrictor effects of [des-Asp^1]angiotensin I are due to its local enzymatic conversion to angiotensin III. About 7% of [des-Asp^1]angiotensin I is converted to angiotensin III during one transit through the renal vasculature.
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