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# Attenuated vascular responsiveness to noradrenaline release during dynamic exercise in dogs

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**During dynamic exercise, there is reduced responsiveness to $\alpha_1$- and $\alpha_2$-adrenergic receptor agonists in skeletal muscle vasculature. However, it is desirable to examine the sympathetic responsiveness to endogenous release of neurotransmitter, since exogenous sympathomimetic agents are dependent upon their ability to reach the abluminal receptor. Therefore, to further our understanding of sympathetic control of vasomotor tone during exercise, we employed a technique that would elicit the release of endogenous noradrenaline (norepinephrine) during dynamic exercise. Mongrel dogs ($n$ = 8, 19–24 kg) were instrumented chronically with transit time ultrasound flow probes on both external iliac arteries. A catheter was placed in a side branch of the femoral artery for intra-arterial administration of tyramine, an agent which displaces noradrenaline from the nerve terminal. Doses of 0.5, 1.0 and 3.0 $\mu$g ml$^{-1}$ min$^{-1}$ of iliac blood flow were infused for 1 min at rest and during graded intensities of exercise. Dose-related decreases in iliac vascular conductance were achieved with these concentrations of tyramine. The reductions in iliac vascular conductance (means ± S.E.M.) were 45 ± 6 %, 30 ± 4 %, 26 ± 3 % and 17 ± 2 %, for the 1.0 $\mu$g ml$^{-1}$ min$^{-1}$ dose at rest, 3.0 miles h$^{-1}$, 6.0 miles h$^{-1}$ and 6.0 miles h$^{-1}$, 10 % gradient, respectively. At all doses, the magnitude of vasoconstriction caused by administration of tyramine was inversely related to workload. We conclude that there is a reduced vascular responsiveness to sympathoactivation in dynamically exercising skeletal muscle.**

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At the onset of exercise, vascular conductance and blood flow increase in active skeletal muscle. The magnitude of increase is determined by the relative degree of vasoconstrictor and vasodilator influences (Kjellmer, 1965). Direct measurements reveal a prompt increase in sympathetic efferent nerve activity to muscle at the onset of dynamic exercise, with further increments as intensity increases (Hajduczok *et al.* 1991; DiCarlo *et al.* 1996; Hill *et al.* 1996). That this sympathetic activity evokes tonic vasoconstriction in exercising skeletal muscle has been established by observations of an increase in vascular conductance following blockade of adrenergic receptors (Buckwalter *et al.* 1997; O'Leary *et al.* 1997; Buckwalter & Clifford, 1999). However, there is substantial evidence that the magnitude of sympathetic vasoconstriction in the skeletal muscle vasculature is attenuated by muscle contractions (Remensnyder *et al.* 1962; Burcher & Garlick, 1973; Howard & DiCarlo, 1992; Thomas *et al.* 1994, 1997; Daly & Cook, 1999; Hansen *et al.* 1999; Buckwalter *et al.* 2001). This reduced vascular responsiveness has been termed sympatholysis (Remensnyder *et al.* 1962). Noradrenaline release, reuptake, and receptor binding may be altered by metabolic by-products released during muscle contraction (Vanhoutte *et al.* 1981) with the net effect being less vasoconstriction in response to sympathoactivation. Production of nitric oxide (Patil *et al.* 1993; Thomas & Victor, 1997), adenosine (Nishigaki *et al.* 1991), prostaglandins (Gottlieb *et al.* 1980), and local metabolic disturbances such as acidosis (Medgett *et al.* 1987; McGillivray-Anderson & Faber, 1990; Tateishi & Faber, 1995) and hypoxia (Tateishi & Faber, 1995) have been shown to attenuate $\alpha$-adrenergic vasoconstriction. Increases in temperature have also been shown to alter adrenergic receptor sensitivity (Cooke *et al.* 1984; Masset *et al.* 1998). Thus, exercise may create conditions within the contracting muscles which blunt the vascular responses to elevated sympathetic outflow.

Previous attempts to examine the changes in vascular conductance with sympathetic activation have used direct nerve stimulation (Remensnyder *et al.* 1962; Rowlands & Donald, 1968; Burcher & Garlick, 1973; Thompson & Mohrman, 1983; Klabunde, 1986; Thomas *et al.* 1994, 1997; Thomas & Victor, 1997;), reflex activation (Rein, 1930; Remensnyder *et al.* 1962; O'Leary *et al.* 1991; Daly & Cook, 1999;) and exogenous sympathomimetic agents

(Burcher & Garlick, 1973; Howard & DiCarlo, 1992; Patil *et al.* 1993; Thomas *et al.* 1994, 1997, 1998; Buckwalter *et al.* 1998, 2001; Hansen *et al.* 1999). Noradrenaline released endogenously is preferred to administration of exogenous agonists because it is the physiologically active neurotransmitter and endogenous release occurs at the site of adrenergic receptors on the abluminal surface of the vessels. In one of the few attempts to investigate this question in conscious dynamically exercising animals, sympathetic activity was elevated by eliciting a baroreflex response via carotid artery occlusion (O'Leary *et al.* 1991). Unfortunately, it is not known if this manoeuvre produced identical sympathetic responses at rest and during graded levels of exercise.

The aim of this study was to examine the relationship between increasing exercise intensities and sympathetically mediated vasoconstriction caused by pharmacological stimulation of endogenous noradrenaline release. We hypothesized that with increasing exercise intensities, endogenous release of noradrenaline would produce progressively smaller changes in iliac vascular conductance.

## METHODS

All experimental procedures were approved by the Institutional Animal Care and Use Committees at the Medical College of Wisconsin and VA Medical Center and were conducted in accordance with the American Physiological Society's 'Guiding Principles in the Care and Use of Animals'. Mongrel dogs ($n = 8$) were selected for their willingness to run on a motorized treadmill. A series of sterile surgeries was performed for chronic instrumentation of the animals. Anaesthesia was induced with thiopental sodium (15–30 mg kg$^{-1}$; Gensia Pharmaceuticals, Irvine, CA, USA). After intubation with a cuffed endotracheal tube, a surgical level of anaesthesia was maintained with 1.5 % halothane (Halocarbon Laboratories, River Edge, NJ, USA) and 98.5 % oxygen. Postoperatively, animals were given an analgesic for pain management (buprenorphine hydrochlorine, 0.3 mg; Reckitt and Coleman, Kingston-upon-Hull, UK) and treated with antibiotics for 10 days (cefazoline sodium, 1 mg; Apothecon, Princeton, NJ, USA). Carotid arteries were exposed and placed into neck skin tubes for percutaneous cannulation and measurement of arterial blood pressure. After a 2 week recovery period, a second surgery was performed. A midline abdominal incision was made to allow placement of flow probes (4 mm ultrasonic transit-time flow probes; Transonic Systems, Ithaca, NY, USA) around the external iliac artery in each hindlimb to measure hindlimb blood flow. Flow probe cables and connectors were then tunnelled under the skin to the back and externalized for access. After a 2 week recovery period, the final surgery was performed, at which time a heparinized catheter (0.045 inch o.d., 0.015 inch i.d., 60 cm long; Data Science International, St Paul, MN, USA) was implanted through a side branch into the femoral artery, tunnelled to the back of the dog, and used for drug infusion. The catheters were flushed daily with saline and filled with a heparin lock (100 i.u. heparin ml$^{-1}$ in 50 % dextrose solution) to maintain patency. At least 2 days elapsed between the final surgery and any experiments. All the dogs were humanely killed at the end of the series of experiments.

On the day of an experiment, animals were brought into the laboratory and placed in a sling where they rested for at least 5 min. Ambient temperature of the laboratory was maintained below 20 °C. The flow probes were connected to a transit-time flow meter (Transonic Systems) and a 20 gauge intravascular catheter (Insyte, Becton-Dickinson, Sandy, UT, USA) was inserted retrogradely into the lumen of the carotid artery for measurement of arterial pressure after attaching it to a solid-state pressure transducer (Ohmeda, Madison, WI, USA). Experiments were performed in random order and in duplicate during rest and under three conditions of exercise on a motorized treadmill: 3.0 miles h$^{-1}$, 6.0 miles h$^{-1}$, and 6.0 miles h$^{-1}$ with a 10 % gradient, representing mild, moderate and heavy exercise intensities. Release of noradrenaline from the sympathetic nerve terminals in the hindlimb was accomplished by infusion of tyramine (Sigma Chemical, St Louis, MO, USA) through the femoral artery catheter at doses of 0.5, 1.0 and 3.0 $\mu$g ml$^{-1}$ min$^{-1}$ of blood flow. Adjusting tyramine dosage for iliac blood flow ensured that the effective concentration of the drug was similar under all exercise intensities. The doses were selected from pilot experiments showing their ability to elicit graded degrees of vasoconstriction within a physiological range. Constant infusions of tyramine were accomplished with an infusion pump (Harvard Apparatus, Nattick, MA, USA) during the fifth minute of steady-state exercise. On a given day, all three doses were administered at a single workload in random order, with 30 min of rest separating each infusion. At least 24 h separated each workload and all resting infusions were performed prior to any exercise.

Arterial blood pressure and external iliac blood flow were recorded at 100 Hz directly to a computer (Apple G3 Power PC) using a MacLab system (ADInstruments, Castle Hill, Australia). Data were analysed off-line using the MacLab software to calculate mean arterial pressure, heart rate, iliac blood flow, and iliac vascular conductance (iliac blood flow/mean arterial pressure). Control measurements were averaged over the 1 min immediately prior to infusion of tyramine. The final 10 s of infusion was averaged and represented the maximum response to tyramine. The duplicate trials were averaged to yield a single value for each dose and intensity.

Heart rate, mean arterial blood pressure, iliac blood flow (experimental and control limb) and iliac vascular conductance (experimental and control limb) were analysed using a two-way (drug × exercise intensity) repeated measures analysis of variance. The percentage change from the baseline for iliac vascular conductance and iliac blood flow were also analysed with a two-way repeated measures analysis of variance (drug × exercise intensity) for both the experimental and the control limb. Where significant $F$ ratios were found, a Tukey's *post hoc* test was performed. All data are expressed as means ± S.E.M.

## RESULTS

Intraarterial infusion of tyramine produced vasoconstriction at all doses at rest and during exercise. Figure 1 is an original trace from an individual dog during exercise at 6.0 miles h$^{-1}$. The trace shows that tyramine infusion (1.0 $\mu$g ml$^{-1}$ min$^{-1}$ blood flow) resulted in a substantial reduction in iliac vascular conductance in the experimental limb without affecting blood flow or conductance in the contralateral limb, or mean arterial pressure.

**Table 1. Haemodynamic values before (baseline) and after (response) intra-arterial infusion of tyramine for each dose and workload in the limb with the femoral catheter**

| | Dose ($\mu$g ml$^{-1}$ min$^{-1}$ iliac blood flow) | Workload (miles h$^{-1}$/% gradient) | Mean arterial pressure (mmHg) | Heart rate (beats min$^{-1}$) | Iliac blood flow (ml min$^{-1}$) | Iliac conductance (ml min$^{-1}$ mmHg$^{-1}$) |
|---|---|---|---|---|---|---|
| Baseline | 0.5 | Rest | 107 ± 4 | 96 ± 8 | 114 ± 11 | 1.1 ± 0.1 |
| | | 3 | 112 ± 4 | 142 ± 5‡ | 486 ± 28‡ | 4.2 ± 0.4‡ |
| | | 6 | 112 ± 3 | 175 ± 4‡ | 684 ± 48‡ | 6.2 ± 0.5‡ |
| | | 6/10% | 119 ± 4 | 207 ± 4 ‡ | 1045 ± 59‡ | 9.0 ± 0.6‡ |
| | 1.0 | Rest | 107 ± 4 | 88 ± 10 | 108 ± 9 | 1.0 ± 0.1 |
| | | 3 | 109 ± 3 | 142 ± 4‡ | 497 ± 35‡ | 4.6 ± 0.4‡ |
| | | 6 | 118 ± 4 | 175 ± 4‡ | 691 ± 47‡ | 6.2 ± 0.6‡ |
| | | 6/10% | 115 ± 3 | 212 ± 5‡ | 1094 ± 59‡ | 9.6 ± 0.7‡ |
| | 3.0 | Rest | 114 ± 4 | 94 ± 8 | 116 ± 3 | 1.1 ± 0.1 |
| | | 3 | 108 ± 3 | 145 ± 4‡ | 500 ± 41‡ | 4.7 ± 0.4‡ |
| | | 6 | 112 ± 4 | 173 ± 3‡ | 667 ± 48‡ | 6.1 ± 0.6‡ |
| | | 6/10% | 117 ± 3 | 213 ± 6‡ | 1045 ± 52‡ | 9.1 ± 0.6‡ |
| Response | 0.5 | Rest | 107 ± 8 | 94 ± 11 | 82 ± 8† | 0.8 ± 0.1† |
| | | 3 | 111 ± 17 | 135 ± 5 | 371 ± 13† | 3.3 ± 0.2† |
| | | 6 | 111 ± 6 | 173 ± 6 | 530 ± 20† | 4.9 ± 0.3† |
| | | 6/10% | 119 ± 6 | 211 ± 7 | 899 ± 47† | 7.5 ± 0.4† |
| | 1.0 | Rest | 111 ± 6 | 89 ± 13 | 63 ± 6† | 0.6 ± 0.1† |
| | | 3 | 109 ± 5 | 139 ± 6 | 342 ± 14† | 3.2 ± 0.2† |
| | | 6 | 117 ± 7 | 167 ± 5 | 481 ± 26† | 4.2 ± 0.3† |
| | | 6/10% | 118 ± 6 | 205 ± 6 | 869 ± 43† | 7.3 ± 0.4† |
| | 3.0 | Rest | 114 ± 8 | 88 ± 11 | 59 ± 6† | 0.5 ± 0.1† |
| | | 3 | 114 ± 5 | 140 ± 7 | 277 ± 18† | 2.5 ± 0.2† |
| | | 6 | 116 ± 7 | 161 ± 7 | 412 ± 24† | 3.7 ± 0.3† |
| | | 6/10% | 124 ± 7* | 186 ± 6* | 800 ± 46† | 6.4 ± 0.5† |

Values are means ± S.E.M. * $P < 0.05$ compared to baseline. † $P < 0.01$ compared to baseline. ‡ $P < 0.01$ compared to rest.

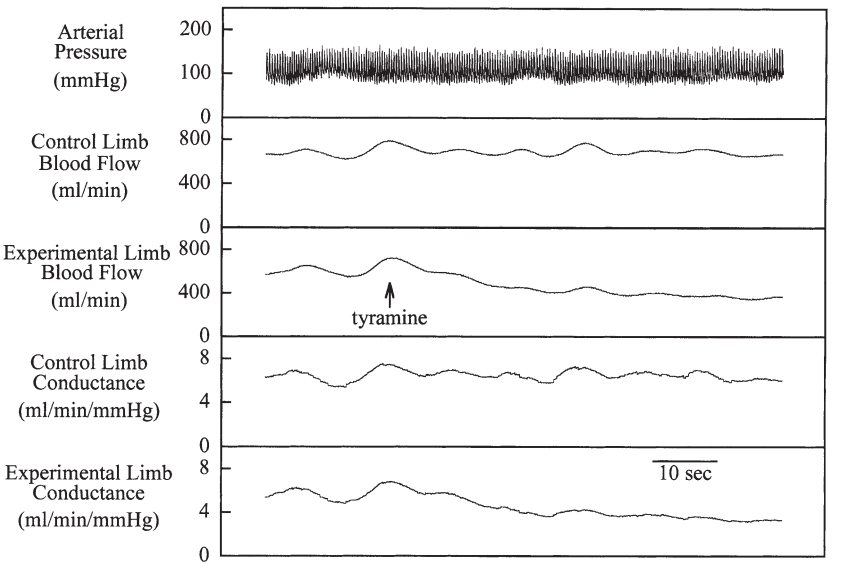


**Figure 1. Original record from a dog exercising on a treadmill at 6 miles h$^{-1}$**

Infusion of tyramine (1 $\mu$g ml$^{-1}$ of blood flow) for 1 min into the femoral artery of the experimental limb produced a substantial decrease in iliac vascular conductance. Note that there were no changes in the control (contralateral) limb blood flow or arterial blood pressure.

The data displayed in Table 1 show the baseline values (before drug infusion) at rest and during exercise for heart rate, mean arterial pressure, iliac blood flow and iliac vascular conductance. As expected, there were increases in heart rate, mean arterial pressure, iliac blood flow and iliac vascular conductance from rest to exercise that were graded according to the intensity of exercise. Also shown are the responses of these variables to infusion of tyramine. Heart rate and mean arterial pressure did not increase significantly as a result of tyramine infusion at rest or during exercise at 3 miles $h^{-1}$ and 6 miles $h^{-1}$. At the highest intensity, infusion of 3.0 $\mu$g $ml^{-1}$ $min^{-1}$ tyramine was associated with a significant increase in mean arterial pressure and significant decrease in heart rate.

Iliac blood flow and iliac vascular conductance in the experimental limb decreased in a dose-dependent manner in response to tyramine infusion for each exercise condition. For the control limb, there were no changes in iliac blood flow or vascular conductance for the two lower doses of tyramine (data not shown), but infusion at a rate of 3.0 $\mu$g $ml^{-1}$ $min^{-1}$ caused significant decreases in iliac vascular conductance at 6 miles $h^{-1}$ (0.53 ± 0.13 ml $min^{-1}$ $mmHg^{-1}$) and 6 miles $h^{-1}$,10 % gradient (0.94 ± 0.20 ml $min^{-1}$ $mmHg^{-1}$).

When expressed as a percentage change from the baseline, experimental limb iliac blood flow (Fig. 2) and iliac vascular conductance (Fig. 3) were reduced less by tyramine during exercise than at rest. In addition, there was a significant dose × exercise intensity interaction ($P < 0.01$). That is, as exercise intensity increased, the decreases in iliac vascular conductance and iliac blood flow were attenuated for each dose. Figure 4 displays the tyramine dose–response curves for rest and each exercise workload. There was a progressive upward shift in the dose–response curve with increasing exercise intensity.

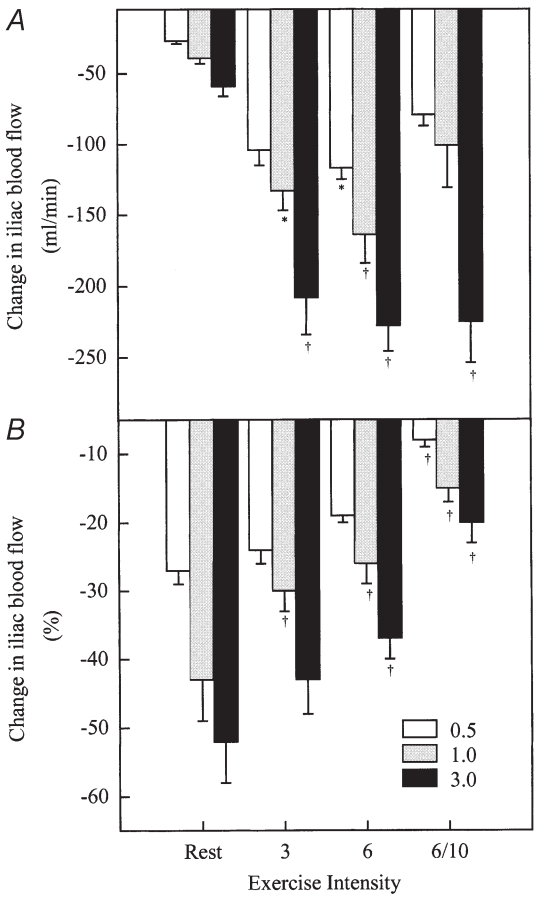


**Figure 2. Absolute change in iliac blood flow (*A*) and percentage change in iliac blood flow (*B*) in the experimental limb for each workload and tyramine dose**

Tyramine dose is shown in $\mu$g $ml^{-1}$ $min^{-1}$. There was an inverse relationship between exercise intensity and the percentage change in iliac blood flow. Values are means ± S.E.M. * $P < 0.05$ compared to rest. † $P < 0.01$ compared to rest.

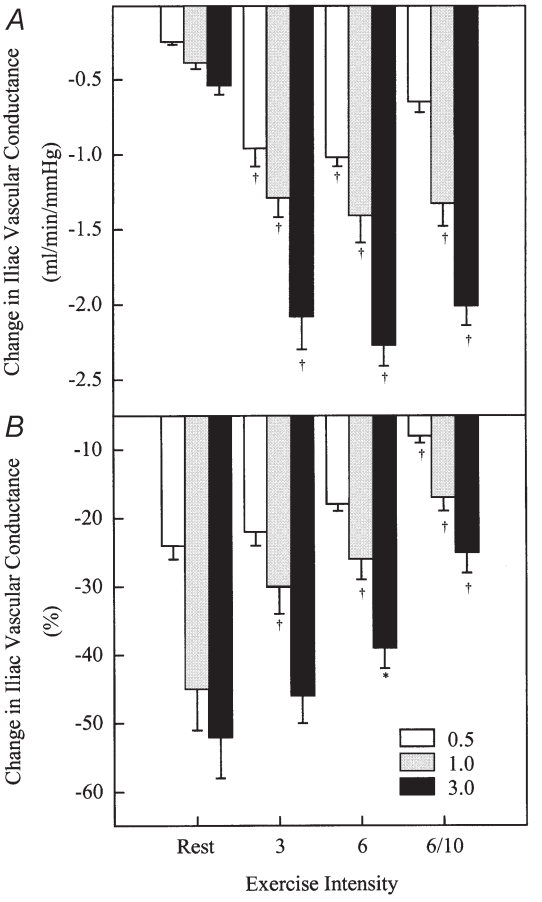


**Figure 3. Absolute change in iliac vascular conductance (*A*) and percentage change in iliac vascular conductance (*B*) in the experimental limb for each workload and tyramine dose**

Tyramine dose is shown in $\mu$g $ml^{-1}$ $min^{-1}$. With increasing exercise intensities there was a significant attenuation in the percentage reduction in iliac vascular conductance with tyramine infusion. Values are means ± S.E.M. * $P < 0.05$ compared to rest. † $P < 0.01$ compared to rest.

## DISCUSSION

The purpose of this study was to examine the effect of endogenous release of noradrenaline on skeletal muscle vasculature at rest and during dynamic exercise. The new findings of this study are: (1) intra-arterial infusion of tyramine produced dose-related decreases in blood flow and conductance at rest and during exercise; (2) tyramine infusion caused less vasoconstriction during exercise than at rest; and (3) there was an intensity effect such that increasing exercise intensity further attenuated the decrease in iliac vascular conductance associated with noradrenaline release.

Previous techniques for examining the vasomotor consequences of sympathetic activation during muscle contractions include direct nerve stimulation (Remensnyder *et al.* 1962; Rowlands & Donald, 1968; Burcher & Garlick, 1973; Klabunde, 1986; Thomas *et al.* 1994, 1997; Thomas & Victor, 1997; Thompson & Mohrman, 1983), reflex activation of sympathetic nerve activity (Rein, 1930; Remensnyder *et al.* 1962; O'Leary *et al.* 1991; Daly & Cook, 1999) and infusion of $\alpha$-adrenergic agonists (Burcher & Garlick, 1973; Howard & DiCarlo, 1992; Patil *et al.* 1993; Thomas *et al.* 1994, 1997, 1998; Buckwalter *et al.* 1998, 2001; Hansen *et al.* 1999). Most of these studies were performed in anaesthetized animals and provide limited information because of the non-physiological nature of electrically stimulated muscle contractions and the confounding cardiovascular effects of anaesthesia. Studies in conscious animals and humans have employed intra-arterial infusion of $\alpha$-adrenergic agonists (Howard & DiCarlo, 1992; Patil *et al.* 1993; Hansen *et al.* 1999; Buckwalter *et al.* 2001), but do not answer the question of vascular responsiveness to endogenous release of noradrenaline. Endogenous release of noradrenaline is preferred to exogenous agonists because it is the physiologically active neurotransmitter and is released on the abluminal surface of the vessels. The use of tyramine, which displaces noradrenaline from the nerve terminal, represents a unique approach to examining vascular responsiveness to sympathetic stimulation. The identical approach has been used in a companion study in human volunteers (Tschakovsky *et al.* 2002). The results of both studies show a diminished vascular responsiveness to sympathoactivation during exercise. This extends the findings of previous studies using other experimental approaches and supports the concept of functional sympatholysis.

One of the assumptions of this experimental approach is that tyramine at the specified doses and under the various conditions produced equal noradrenaline release. To verify this assumption, we considered determining hindlimb noradrenaline spillover, one measure that has been traditionally employed to quantify sympathetic activity. However, careful studies (Chang *et al.* 1991; Grossman *et al.* 1991) have shown that measurements of regional noradrenaline spillover are invalid under conditions where blood flow changes. Thus, in the present study, it would have been impossible to distinguish between increased noradrenaline spillover caused by an elevated blood flow and that caused by infusion of tyramine. We assume that intra-arterial infusion of tyramine caused release of noradrenaline which was proportional to the dose delivered. This is supported by the fact that tyramine elicited dose-dependent vascular responses at rest and at each exercise workload. To maintain the same effective concentration of tyramine across conditions, the dose was adjusted to the prevailing iliac blood flow.

Can elevated flow, by itself, blunt sympathetic vasoconstriction? There are strong data to show that this is not the case. Thomas *et al.* (1994) infused hydralizine into the rat hindlimb to elevate flow and found no attenuation of the decrease in femoral blood flow or vascular conductance in response to lumbar sympathetic nerve stimulation when compared to rest. In a separate set of experiments (Thomas *et al.* 1997), reactive hyperaemia and isoproterenol infusion also failed to attenuate the decrease in vascular conductance in response to lumbar sympathetic stimulation. Finally, Tschakovsky *et al.* (2002) report similar findings in a companion manuscript. In fact, forearm infusion of tyramine during elevation of blood flow with adenosine resulted in a much greater reduction (no attenuation) in vascular conductance compared to rest. Functional sympatholysis cannot be

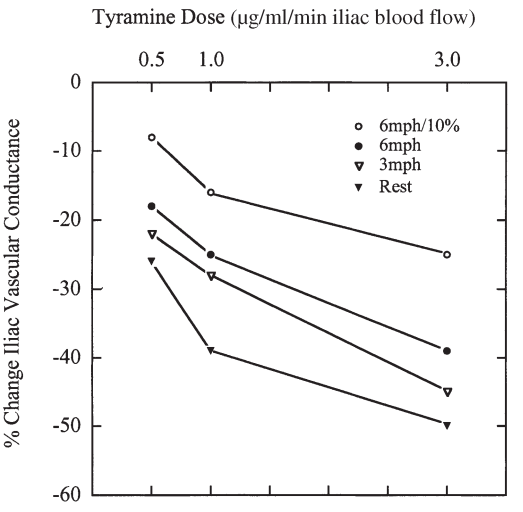


**Figure 4. Dose–response curve for tyramine at rest and 3 exercise intensities**

Standard error bars were excluded for clarity of presentation. Increasing exercise intensity produced a progressive upward shift in the curve.

attributed to the elevation in blood flow alone, but must be due to some other factor related to exercise.

The mechanism for sympatholysis has not been clearly elucidated. There is an exercise intensity-dependent increase in sympathetic efferent nerve activity to exercising skeletal muscle (DiCarlo *et al.* 1996). In spite of this rise in nerve activity, several studies have shown a reduced vasoconstrictor response with increases in exercise intensity (Burcher & Garlick, 1973; Thompson & Mohrman, 1983; Buckwalter *et al.* 2001). Conditions prevailing in the contracting muscle may modulate presynaptic release of noradrenaline or postsynaptic responsiveness to this neurotransmitter. Local modulation of the noradrenergic neuroeffector system has been discussed thoroughly elsewhere (Vanhoutte *et al.* 1981). Although attenuated vasoconstriction in response to noradrenaline infusion during skeletal muscle contraction (Kjellmer, 1965) indicates a postsynaptic mechanism, greater attenuation of vasoconstriction by direct nerve stimulation in the same study suggests an additional presynaptic effect. Presynaptic modulation is likely to occur in response to metabolites that are released during muscle contractions. One candidate for presynaptic modulation is adenosine, a substance released during skeletal muscle contraction which has been shown to inhibit noradrenaline release (Sneddon *et al.* 1984; Rongen *et al.* 1996).

Changes in postsynaptic responsiveness to sympathoactivation could be a function of altered receptor binding or downstream signal transduction. Three mechanisms which may be involved are: (1) metabolite production; (2) release of nitric oxide; and (3) temperature. Skeletal muscle contractions may produce acidosis (Medgett *et al.* 1987; McGillivray-Anderson & Faber, 1990; Tateishi & Faber, 1995), regional hypoxia (Tateishi & Faber, 1995), and localized ischaemia (McGillivray-Anderson & Faber, 1991) – all factors which have been shown to inhibit adrenergic vasoconstriction. There is evidence that metabolic activation of $K_{ATP}$ channels can attenuate $\alpha$-adrenergic vasoconstriction (Thomas *et al.* 1997). In addition to metabolites, there is increasing evidence for nitric oxide as a modulator of vascular responsiveness to $\alpha$-adrenergic agonists (Patil *et al.* 1993; Thomas *et al.* 1998) or sympathetic nerve stimulation (Thomas & Victor, 1997). Mice with deficiencies in neuronal or endothelial nitric oxide synthase (nNOS or eNOS) do not exhibit functional sympatholysis (Thomas *et al.* 1998), and acute inhibition of nitric oxide synthase partially restores sympathetic vasoconstriction in contracting limbs (Patil *et al.* 1993; Thomas & Victor, 1997). Finally, there is evidence that temperature influences the response to vasoconstrictor agents (Cooke *et al.* 1984; Flavahan *et al.* 1985; Faber, 1988; Masset *et al.* 1998) as supported by the fact that $\alpha_2$-receptors become less responsive as muscle temperature increases (Cooke *et al.* 1984). In the present study, as exercise intensity increased, we assume there was an increase in the heat production, which may partially account for the exercise intensity-dependent decrease in the response to tyramine.

Interpretation and expression of the data has led to some disagreement about whether sympatholysis is a real phenomenon or an artifact. Early studies on this topic (Rein, 1930; Remensnyder *et al.* 1962) have been questioned (O'Leary, 1991; O'Leary *et al.* 1991) because of the use of resistance as a measure of vasomotor tone. Both O'Leary (1991) and Lautt (1989) have pointed out the linear relationship between vascular conductance and blood flow, establishing it to be a more appropriate assessment of vasomotor tone than resistance. It must be emphasized however, that Remensnyder *et al.* (1962) did not base their conclusions solely on resistance calculations. They employed a model with constant flow perfusion in which vasoconstriction could be inferred from changes in pressure. Careful inspection of Fig. 10 in their paper reveals that carotid sinus hypotension elicited marked increases in pressure at rest, but not during contractions. This demonstration of functional sympatholysis cannot be attributed to a mathematical artifact. In the current study, the data were analysed as percentage changes in conductance because of the changing baselines from rest to different exercise intensities. When expressed as such, a given percentage change in conductance corresponds to a predictable percentage change in vessel radius. Thus, the present study confirms the original observation of functional sympatholysis as a true physiological event.

It has been argued that active skeletal muscle becomes progressively more important in the regulation of systemic blood pressure as exercise intensity increases (O'Leary *et al.* 1991; Rowell, 1993). A diminished vascular responsiveness to noradrenaline, as observed in the present study, does not imply that the skeletal muscle vasculature is unimportant for blood pressure regulation during exercise. The fact that skeletal muscle receives the bulk of the cardiac output at higher intensities of exercise permits small degrees of vasoconstriction to have a marked impact on blood pressure. Thus, skeletal muscle vascular conductance remains a major determinant of blood pressure despite a blunted sympathetic vasoconstrictor responsiveness compared to rest. Functional sympatholysis allows local regulation of blood flow to override CNS-elicited sympathetic vasoconstriction to provide adequate oxygen delivery to meet the metabolic needs of the contracting skeletal muscles.

In summary, the present study demonstrates the ability of tyramine to elicit adrenergic vasoconstriction in the arterial vasculature of skeletal muscle during exercise. There was a reduced vasoconstrictor response during exercise compared to rest and a progressive, intensity-dependent attenuation of noradrenaline-induced vasoconstriction in active

skeletal muscle. Functional sympatholysis is an important mechanism that participates in the regulation of skeletal muscle blood flow during exercise.

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