Endothelin-1-mediated vasoconstriction at rest and during dynamic exercise in healthy humans

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ENDOTHELIN-1-MEDIATED VASOCONSTRICTION AT REST AND DURING DYNAMIC EXERCISE, METABOLIC BYPRODUCTS PRODUCED BY THE ACTIVE TISSUE PROMOTE VASODILATION AND ENSURE ADEQUATE PERFUSION IN THE EXERCISING MUSCLE (25). ALTHOUGH THE MECHANISMS THAT GOVERN EXERCISE HYPEREMIA REMAIN INCOMPLETELY UNDERSTOOD, RECENT WORK HAS PROVIDED EVIDENCE THAT THIS METABOLIC VASODILATION IS ACCOMPLISHED AT LEAST IN PART THROUGH THE INHIBITION OF VASOCONSTRICTOR PATHWAYS. PRIOR STUDIES IN BOTH ANIMALS AND HUMANS HAVE DEMONSTRATED AN INHIBITION TO VASOCONSTRICTION EVOKED BY 2-ADRENERGIC AGONISTS (7, 38, 51), ANGII (5), TYRAMINE (15, 39, 48), AND NEUROPEPTIDE Y (6) WHEN INFUSED INTRA-ARTERIALLY INTO THE EXERCISING LIMB. THESE STUDIES HAVE IDENTIFIED AN EXERCISE INTENSITY-DEPENDENT INHIBITION OF THESE PHARMACOLOGICAL AGONISTS WITH THE IMPETUS THAT THE RESPECTIVE VASOCONSTRICTOR MECHANISMS BECOME LESS EFFECTIVE DURING EXERCISE.

METHODS

SUBJECTS AND GENERAL PROCEDURES. EIGHT HEALTHY SUBJECTS (23 ± 1 yr; 7 men, 1 woman) PARTICIPATED IN THE CURRENT STUDY. ALL SUBJECTS

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were nonsmokers, normotensive (<140/90 mmHg), normally active, and free of overt cardiovascular disease. Protocol approval and informed consent was obtained according to the University of California San Diego Human Subjects Protection Program requirements. Subjects reported to the laboratory on a preliminary day to complete health histories, physical examinations, and perform a graded single leg knee-extensor (KE) test to determine maximal work rate (WRmax).

Experimental protocols. Subjects reported to the laboratory at 0800 on the experimental day. After 30 min of supine rest, two catheters [common femoral artery (CFA) and antecubital vein] were placed using sterile technique as previously reported (3). After catheter placement, subjects rested for ~30 min, and then underwent the protocol as outlined in Fig. 1. All data collection took place with subjects in a semirecumbent position (~60° reclined), and all studies were performed in a theroneutral environment.

On a separate day within 2 wk of the drug infusion study day, four of the eight volunteers returned to the laboratory to undergo a time control study. For this visit, catheters were not placed, and no drugs were administered. Apart from these differences, the time line for this study was identical to the drug infusion day, with the addition of leg blood flow measurements immediately before and after a light meal to examine possible postprandial hemodynamic effects.

Drug infusions. PE (Sigma-Aldrich, St. Louis, MO) was administered as a selective α1-adrenergic agonist. PE was prepared at a concentration of 2.5 μg/ml 0.9% sterile saline and infused for 2.5 min at a blood flow-adjusted rate of 8.3 ng/ml leg blood flow. We (51) have previously identified the dose-response relationship of PE in the human leg, and for the present study, we selected a dose that would elicit significant vasoconstriction but limit the risk of systemic spillover during the higher infusion rates that occurred during KE exercise.

ET-1 (Clinalfa; Merck Biosciences, La¨ufelfingen, Switzerland) was prepared at a concentration of 12.5 ng/ml 0.9% sterile saline and infused for 2.5 min at a blood flow-adjusted rate of 10 μg/ml 0.9% sterile saline and added to the PE infuse to block potential β2-mediated vasodilation during PE infusion (47).

ET-1 (Clinalfa; Merck Biosciences, L¨aufelfingen, Switzerland) was administered as a nonspecific ETα1 and ETβ1 receptor agonist. Previous studies have demonstrated that the constrictor response to ET-1 is principally mediated by the ETβ1 receptor subtype (14, 35), promoting vasoconstriction through vascular smooth muscle activation. ET-1 was prepared at a concentration of 12.5 ng/ml 0.9% sterile saline and infused at a blood flow-adjusted rate of 40 pg/ml leg blood flow. The vascular effects of ET-1 vary widely according to dose and duration of drug administration (20), making dose-response curves difficult to characterize. Thus, for the present study, we selected a dose of ET-1 previously reported to promote significant vasoconstriction without systemic effects (10, 43).

Both drugs were infused intra-arterially at infusion rates of 0.5–15 ml/min using a constant speed infusion pump (Harvard Apparatus, Holliston, MA). Immediately before infusion, real-time blood flow was determined using the ultrasound Doppler, and infusion rate was blood flow-adjusted according to these “on the fly” blood flow values to ensure similar effective concentration of infused drugs both at rest and during exercise.

Because of the long-lasting effects of intra-arterial ET-1 infusion (8) and the known effect of ET-1 to potentiate adrenergic vasoconstriction (55, 56), the administration of PE always preceded ET-1, as illustrated in Fig. 1. Because of the slow kinetics of ET-1 clearance following infusion (22), exercising blood flow measurements made before PE infusion served as the “preinfusion” values for both PE and ET-1. The validity of this approach was confirmed by the similarity in exercising blood flow observed during the time control protocol (Fig. 5).

Exercise model. The KE paradigm implemented in this study has been described previously (1, 26, 37, 52). Briefly, subjects were seated on an adjustable chair with a cycle ergometer (model 828E; Monark Exercise AB, Vansbro, Sweden) placed behind them. Resistance was provided by friction on the flywheel, which was turned by the subject via a metal bar connected to the crank of the ergometer and a boot attached to the ankle of the subject. Sixty contractions per minute were maintained at each work rate. Subjects exercised at 20%, 40%, and 60% of their WRmax determined on the preliminary visit, with 10 min at each exercise intensity (Fig. 1).

Measurements. Leg blood flow was evaluated using an ultrasound Doppler device (Logiq 7; GE Medical Systems, Milwaukee, WI) equipped with a linear array transducer operating at an imaging frequency of 10 MHz. The CFA was insonated 2–3 cm proximal to the bifurcation of the CFA into the superficial and deep branches. The blood velocity profile was obtained using the same transducer with a Doppler frequency of 4.0–5.0 MHz, operated in the high-pulsed repetition frequency mode (2–25 kHz), and the sample volume was placed at a depth of 1.5–3.5 cm. Care was taken to avoid aliasing using scale adjustments, especially during exercise. All blood velocity measurements were obtained with the probe appropriately positioned to maintain an insonation angle of 60° or less (28). The sample volume was maximized according to vessel size, centered, and verified by real-time ultrasound visualization of the vessel. At all sample points, arterial diameter and angle-corrected, time-averaged, and intensity-weighted mean blood velocity (Vmean) values were calculated using commercially available software (Logiq 7, GE Medical Systems). Using measured artery diameter and Vmean, blood flow (ml/ min) was calculated as Vmean × π × (vessel diameter/2)² × 60.

Arterial blood pressure measurements were collected continually from within the femoral artery with the pressure transducer placed at the level of the catheter (Transpac IV, Abbot Laboratories). Mean arterial pressure (mmHg) was calculated as diastolic arterial pressure + (arterial pulse pressure × 0.33). Leg vascular conductance (LVC; ml·min⁻¹·mmHg⁻¹) was calculated as leg blood flow divided by mean arterial pressure. Heart rate was monitored from a standard three-lead ECG recorded in duplicate on the data acquisition device (BIOPAC) as an integral part of the Doppler system (Logiq 7, GE Medical Systems).

Fig. 1. Experimental protocol is shown. Arrows indicate points at which leg blood flow was recorded. Because of the long-lasting binding characteristics of endothelin-1 (ET-1), the administration of the α-agonist phenylephrine (PE) always preceded ET-1. KE, knee-extensor; WRmax, maximal work rate; Dbl dose, doubling dose of ET-1 (to challenge the plateau in leg blood flow response); PRE-INF, preinfusion; PE INF, PE infusion.
Data analysis and statistics. Ultrasound images and Doppler velocity waveforms were measured continuously with repeated 45-s segments recorded before and during drug infusions. For each 45-s ultrasound Doppler segment, \( V_{\text{mean}} \) was averaged across 15-s intervals of each recorded clip with intima-to-intima diameter measurements evaluated during diastole as described previously (17, 52).

Depending on the infusion rate of the drug at rest (range 0.75–1.25 ml/min), it is estimated that ~60 s were required for the drug to reach the vessel (tubing and catheter volume were ~0.8 ml). Thus hemodynamic changes in response to PE and ET-1 were evaluated after 60 s had elapsed, during which time saline that occupied the tubing “dead space” was delivered to the vessel. The time to maximal vasoconstriction produced by the current ET-1 dose was defined as the time interval after which an additional 5 min of infusion did not cause further vasoconstriction.

Statistics were performed with the use of commercially available software (SigmaStat 3.10; Systat Software, Point Richmond, CA). Repeated measure analysis of variance, analysis of variance, and Student’s \( t \)-tests were used to identify significant changes in measured variables within and between drug groups and across exercise intensities, with the Bonferroni test used for post hoc analysis when a significant main effect was found. All group data are expressed as means ± SE. Significance was established at \( P < 0.05 \).

RESULTS

Subjects. All subjects (7 men, 1 woman) were young and in good overall health (23 ± 1 yr; height 158 ± 11 cm; weight 69 ± 1 kg) and had a similar KE exercise capacity (KE WR\(_{\text{max}}\) = 51 ± 6 W).

PE administration. At rest, infusion of the \( \alpha_1 \)-adrenergic agonist PE (8.3 ng·ml\(^{-1} \cdot \text{min}^{-1} \)) did not significantly change heart rate or mean arterial blood pressure after 2.5 min (Table 1). However, this infusion did provoke a significant and marked reduction in CFA diameter, LVC, and leg blood flow (Table 1, Figs. 2 and 4). During exercise, even with the increase in PE infusion rate to match the dose to exercising blood flow, no changes in heart rate or mean arterial blood pressure were observed after infusion (Table 1). However, PE significantly decreased CFA diameter, leg blood flow, and LVC at the lower (20% and 40% WR\(_{\text{max}}\)) exercise intensities, with no effect during the highest intensity (Table 1, Figs. 3 and 4).

ET-1 administration. In contrast to PE, ET-1 was infused constantly for 60–90 min across both rest and exercise (Fig. 1). At rest, ET-1 infusion (40 pg·ml\(^{-1} \cdot \text{min}^{-1} \)) for 30 min did not significantly change heart rate, mean arterial blood pressure, or CFA diameter (Table 1). However, leg blood flow and vascular conductance were significantly reduced within 5 min and reached a maximal vasoconstriction after 28 ± 1 min of continuous infusion (Table 1, Fig. 2). As with PE, ET-1-mediated vasoconstriction was attenuated in an exercise intensity-dependent manner. ET-1 infusion significantly decreased leg blood flow and vascular conductance at the lowest (20% WR\(_{\text{max}}\)) intensity but was ineffective at 40% and 60% WR\(_{\text{max}}\) (Figs. 3 and 4). No changes in heart rate or mean arterial blood pressure were observed during the ET-1 infusion compared with preinfusion values (Table 1).

Time control study. In four of the eight volunteers who participated in the drug infusion protocol, a time control protocol was also performed. This additional protocol allowed assessment of leg blood flow during multiple exercise bouts and the consequence of food consumption without the influence of catheter insertion and drug infusions. Measurements were highly reproducible, with no significant difference in CFA diameter, heart rate, or leg blood flow across time between resting measurements or during exercise at each intensity level (Fig. 5).

DISCUSSION

The present study has identified for the first time a significant vasoconstriction in the leg of young, healthy humans following intra-arterial infusion of the potent vasoconstrictor ET-1. A robust reduction in resting leg blood flow occurred with no significant decrease in CFA diameter, providing functional evidence that vascular ET (ET\(_A\)/ET\(_B\)) receptors are

### Table 1. Impact of drug infusions on cardiovascular parameters at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>PE Preinfusion</th>
<th>PE End Infusion</th>
<th>ET-1 Preinfusion</th>
<th>ET-1 End Infusion</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR, beats/min</td>
<td></td>
<td>HR, beats/min</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>62 ± 4</td>
<td>61 ± 3</td>
<td>65 ± 5</td>
<td>64 ± 5</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>108 ± 3</td>
<td>108 ± 2</td>
<td>106 ± 2</td>
<td>107 ± 4</td>
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<tr>
<td>LBF, ml/min</td>
<td>285 ± 12</td>
<td>149 ± 23*</td>
<td>375 ± 17†</td>
<td>248 ± 14*</td>
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<td>LVC, ml·min(^{-1} \cdot \text{mmHg}^{-1})</td>
<td>2.6 ± 0.1</td>
<td>1.3 ± 0.1*</td>
<td>3.7 ± 0.1†</td>
<td>2.2 ± 0.1*</td>
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<tr>
<td>FAD, cm</td>
<td>0.91 ± 0.02</td>
<td>0.84 ± 0.02*</td>
<td>0.91 ± 0.02</td>
<td>0.90 ± 0.02</td>
</tr>
<tr>
<td>20% WR(_{\text{max}})</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>80 ± 4</td>
<td>77 ± 4</td>
<td>84 ± 3</td>
<td></td>
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<tr>
<td>MAP, mmHg</td>
<td>111 ± 4</td>
<td>113 ± 3</td>
<td>110 ± 7</td>
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<tr>
<td>LBF, ml/min</td>
<td>2,283 ± 176</td>
<td>1,855 ± 117*</td>
<td>1,984 ± 144*</td>
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<tr>
<td>LVC, ml·min(^{-1} \cdot \text{mmHg}^{-1})</td>
<td>21 ± 2</td>
<td>17 ± 1*</td>
<td>18 ± 2*</td>
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<tr>
<td>FAD, cm</td>
<td>0.90 ± 0.01</td>
<td>0.85 ± 0.01*</td>
<td>0.91 ± 0.01</td>
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<td>40% WR(_{\text{max}})</td>
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<tr>
<td>HR, beats/min</td>
<td>90 ± 5</td>
<td>88 ± 5</td>
<td>90 ± 3</td>
<td></td>
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<tr>
<td>MAP, mmHg</td>
<td>117 ± 3</td>
<td>116 ± 3</td>
<td>120 ± 7</td>
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<tr>
<td>LBF, ml/min</td>
<td>2,883 ± 130</td>
<td>2,672 ± 146*</td>
<td>2,637 ± 186</td>
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<tr>
<td>LVC, ml·min(^{-1} \cdot \text{mmHg}^{-1})</td>
<td>25 ± 1</td>
<td>23 ± 1*</td>
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<tr>
<td>FAD, cm</td>
<td>0.90 ± 0.01</td>
<td>0.87 ± 0.02</td>
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<tr>
<td>60% WR(_{\text{max}})</td>
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<tr>
<td>HR, beats/min</td>
<td>99 ± 5</td>
<td>97 ± 5</td>
<td>99 ± 3</td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>123 ± 4</td>
<td>121 ± 6</td>
<td>122 ± 8</td>
<td></td>
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<tr>
<td>LBF, ml/min</td>
<td>3,172 ± 152</td>
<td>3,119 ± 147</td>
<td>3,218 ± 157</td>
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<tr>
<td>LVC, ml·min(^{-1} \cdot \text{mmHg}^{-1})</td>
<td>26 ± 1</td>
<td>26 ± 2</td>
<td>28 ± 3</td>
<td></td>
</tr>
<tr>
<td>FAD, cm</td>
<td>0.90 ± 0.01</td>
<td>0.89 ± 0.02</td>
<td>0.91 ± 0.02</td>
<td></td>
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</table>

PE, phenylephrine; ET-1, endothelin-1; HR, heart rate; MAP, mean arterial pressure; LBF, leg blood flow; LVC, leg vascular conductance; FAD, femoral artery diameter; WR\(_{\text{max}}\), maximal work rate. *Significant difference between pre- and end infusion; †significant difference between preinfusion groups.
located predominantly distal to this site in the vascular tree of the leg. Furthermore, we have demonstrated a significant metabolic attenuation of ET-1-mediated vasoconstriction during dynamic leg exercise and shown that this response is exercise intensity-dependent. At the selected doses, the hemodynamic responses to ET-1 at rest and during exercise exhibited a similar pattern as the α2-adrenergic agonist PE but with much slower temporal pattern. Collectively, these findings support a significant role for the ET vasoconstrictor pathway in the regulation of skeletal muscle blood flow in the resting human leg. However, the significant attenuation of ET-1-mediated vasoconstriction during leg exercise suggests a high sensitivity of vascular ETA/ETB receptors to metabolic inhibition, which may contribute to the requisite hyperemia during high-intensity leg exercise.

**ETA- vs. PE-mediated vasoconstriction at rest.** Both PE and ET-1 provoked significant hemodynamic effects at rest but did so through activation of vascular receptors with distinct patterns of distribution. PE provoked an immediate and robust reduction in CFA diameter and leg blood flow, whereas 30 min of ET-1 infusion reduced leg blood flow without a change in CFA diameter. This spatial difference between adrenergic and nonadrenergic receptors extends similar findings for the angiotensin II (5) and α2-adrenergic (51) receptors, both of which produce significant vasoconstriction to agonist infusion (ANG II and BHT 933, respectively) without changes in conduit vessel diameter. Thus the current data showing no change in CFA diameter during ET-1 infusion are indicative of a “downstream” ETA/ETB receptor distribution in the human leg vasculature.

While leg blood flow decreased significantly during both PE and ET-1 infusions, this change exhibited a dissimilar temporal pattern. PE produced significant vasoconstriction within a few seconds and reached a plateau within 1 min, whereas 25–30 min were required before a plateau in ET-1-mediated vasoconstriction was observed (Fig. 2). The magnitude of vasoconstriction to ET-1 reached after 30 min is in agreement with previous infusion studies in the human forearm, although the time to plateau seen in the present study is faster than previously reported (60–120 min; Refs. 19, 42, 43).

Conceptually, this distinct pattern for PE- and ET-1-mediated vasoconstriction may be related to differences in receptor distribution, drug potency, or sensitivity. Smooth muscle cell culture binding studies have identified a substantially greater
number of α1-adrenergic receptors (12) compared with ET$_A$ (2), suggesting that the observed differences between PE and ET-1 may be partially attributed to differences between α1- and ET$_A$-receptor density. To compare potency between drugs, a dose-response relationship would be required for both PE and ET-1. However, the long-lasting nature of ET-1 binding precludes description of a physiological dose-response relationship for this drug in vivo (21), and thus it remains unclear whether the observed differences between PE- and ET-1-mediated vasoconstriction in the present study are related to drug potency. Cell culture studies have also demonstrated that ET-1 increases intracellular Ca$^{2+}$ within 30 s (11), suggesting that the observed delay in ET-1 effects in vivo is not due to slow receptor binding of the vascular ET$_A$ receptor for ET-1.

With this in mind, we speculate that the delay in vasoconstriction seen in the present study may be partially attributed to binding of ET-1 to ET$_B$ receptors located on the endothelial cells, which promote vasodilation through the production of nitric oxide. There is evidence both for (23) and against (20) a transient vasodilation at the onset of intra-arterial ET-1 infusion in the forearm, a disparity that is likely due to differences in methodology, drug dose, or limb specificity. Interestingly, some subjects in the present study exhibited a slight tendency to vasodilate in the first 5 min of infusion, although vasoconstriction was the prevailing response in this time frame. Thus, from these previous studies and the current data, it appears that changes in blood flow following intra-arterial ET-1 infusion may be a consequence of both ET$_A$/ET$_B$-mediated vasoconstriction and endothelial ET$_B$ receptor vasodilation, the balance of which will ultimately dictate the early (<10 min) kinetics of the hemodynamic response.

**PE- vs. ET-1-mediated vasoconstriction during exercise.**

One of the primary means of elevating blood flow to meet the metabolic demand of exercise is through the removal of restraint imposed by vasoconstrictor pathways. Experimentally, the decreased ability of exogenous sympathomimetics and ANG II to evoke vasoconstriction provides evidence that their signal transduction pathways are at least partially inhibited during exercise (5, 15, 48, 51). This has led to the suggestion that endogenous vasoconstrictors may play an important role in the “fine tuning” of skeletal muscle blood flow in an intensity-dependent manner during physical activity (9).

The current study adds to these prior pharmacological findings with intra-arterial infusion of the potent peptide ET-1 into the exercising leg vasculature at three intensities (20%, 40%, and 60% WR$_{max}$). Although the degree of vasoconstriction in response to ET-1 was blunted at all exercise intensities compared with rest, some ET$_A$/ET$_B$ receptor responsiveness was evident at lower (20% WR$_{max}$) intensities, which was then abolished as exercise intensity increased (Fig. 4). The present findings are in contrast to previous work from Krum and Katz (24), who reported that 5 min of high-dose ET-1 evoked a 20% decrease in arm blood flow at rest that was maintained during handgrip exercise. This discrepancy in findings is most likely related to the use of very large doses of ET-1 (250 mg delivered in a 5-min bolus) as well as the use of a short exercise bout and a relatively older subject population. The current study with blood flow-adjusted ET-1 doses extends this previous work, identifying a clear exercise intensity-dependent inhibition of leg ET$_A$/ET$_B$ receptors during dynamic KE exercise in young, healthy volunteers.

Evidence for the ET-1 system as a potential regulator of exercising muscle blood flow has come largely from assays with evidence both for (29) and against (13, 27) increased circulating ET-1 as a consequence of exercise. However, the preferential abluminal release of ET-1 and low endogenous concentration have led to the suggestion that systemic plasma ET-1 levels may not accurately reflect local ET-1 concentration (21, 35). Recent work in animals has evaluated exercise-induced vasodilation with and without ET$_A$ and ET$_A$/ET$_B$ blockade (30, 35) and reported that the vasodilatory effects of blockade were significantly less during exercise compared with control. In contrast, McEniery et al. (33) examined the effect of ET$_A$ receptor blockade during a 15-min bout of static, intermittent handgrip exercise in hypertensive and normotensive subjects and found no difference in the vasodilator response to exercise between blocked and control trials in the normotensive group. The current data build on these previous studies through direct activation of ET$_A$/ET$_B$ receptors during exercise, showing intensity-dependent desensitization during dynamic leg exercise. Teleologically, the observed blunting of ET-1-mediated vasoconstriction may imply a need for decreased ET-1 receptor sensitivity during exercise to lessen the underlying, tonic effect of this vasoconstrictor system. However, additional studies involving ET$_A$ and ET$_B$ receptor blockade with the present exercise paradigm are required to further investigate this issue.

Prior studies from our group (5, 51) and others (15, 38, 48) have characterized α-adrenergic responsiveness during exercise in
humans. However, to our knowledge, this is the first study involving real-time, flow-adjusted doses of PE in the human leg during exercise. Rosenmeier et al. (38) assessed vasoconstriction in the arm to blood flow-adjusted doses of intra-arterial PE during low-intensity handgrip exercise and demonstrated a significant attenuation of $\alpha_1$-receptors in the exercising muscle. Our current data in the leg support these findings with the addition of multiple exercise intensities to demonstrate an intensity-dependent metabolic inhibition to intra-arterial PE infusion.

**Perspectives.** The progressive loss of vasoconstriction in response to both PE and ET-1 during exercise suggests that both of these pathways become less obligatory in regulating blood flow within the exercising muscle during high-intensity exercise. However, this inhibition of both adrenergic- and ET-mediated vasoconstriction may not necessarily indicate that these pathways are physiologically insignificant. It is well known that sympathetic nerve activity increases systemically during exercise to ensure appropriate changes in cardiac output and redistribution of blood flow to the exercising muscles (46, 50) but that this autonomic activity is translated into vasoconstriction to varying degrees depending on the tissue (45). In the active muscle tissue, a partial inhibition of sympathetic restraint due to metabolic blunting of $\alpha$-adrenergic receptors has been reported, an event termed “functional sympatholysis” (36). This response is by no means deleterious but serves to simultaneously ensure maintenance of muscle perfusion and arterial blood pressure during exercise.

In contrast, ET-1 production is not directly linked to the autonomic nervous system but is instead stimulated by direct exposure of endothelial cells to local factors including vasoactive hormones, shear stress, free radicals, and hypoxia and is inhibited by stimuli that increase cGMP such as nitric oxide and prostaglandins (21). Each of these factors may increase in both active and quiescent tissue as a consequence of exercise with the degree of change in each factor dictated in part by the duration and intensity of the exercise. This concept of heterogeneous ET-1 effects during exercise is supported by recent studies using the KE exercise model to assess arterio-venous ET-1 levels, which re-
duced ET-mediated vasoconstriction may not necessarily indicate that these pathways are physiologically insignificant. It is well known that sympathetic nerve activity increases systemically during exercise to ensure appropriate changes in cardiac output and redistribution of blood flow to the exercising muscles (46, 50) but that this autonomic activity is translated into vasoconstriction to varying degrees depending on the tissue (45). In the active muscle tissue, a partial inhibition of sympathetic restraint due to metabolic blunting of $\alpha$-adrenergic receptors has been reported, an event termed “functional sympatholysis” (36). This response is by no means deleterious but serves to simultaneously ensure maintenance of muscle perfusion and arterial blood pressure during exercise.

Clinical implications. The importance of ET-1 in the regulation of exercising skeletal muscle blood flow may be particularly relevant in populations where endogenous ET-1 levels/ sensitivity are elevated such as essential hypertension (40), heart failure (34), chronic obstructive pulmonary disease (COPD; Ref. 18), obesity (4), and even healthy aging (16, 32, 49). All of these clinical states are associated with activation of angiotensin in the cardiovascular system. Int J Biochem Cell Biol 35: 826–837, 2003.


