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

D. Walter Wray,1 Steven K. Nishiyama,1 Anthony J. Donato,3 Mikael Sander,4 Peter D. Wagner,1 and Russell S. Richardson1,2,5

1Department of Medicine, University of California San Diego, La Jolla, California; 2Departments of Medicine and Exercise and Sport Science, University of Utah, Salt Lake City, Utah; 3Department of Integrative Physiology, University of Colorado, Boulder, Colorado; 4Aviation Medicine and Copenhagen Muscle Research Centre, Department of Cardiology, National Hospital, Copenhagen, Denmark; and 5Geriatric Research Education and Clinical Center, Salt Lake City VAMC, Salt Lake City, Utah

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Wray DW, Nishiyama SK, Donato AJ, Sander M, Wagner PD, Richardson RS. Endothelin-1-mediated vasoconstriction at rest and during dynamic exercise in healthy humans. Am J Physiol Heart Circ Physiol 293: H2550–H2556, 2007. First published August 10, 2007; doi:10.1152/ajpheart.00867.2007.—It is now generally accepted that α-adrenoreceptor-mediated vasoconstriction is attenuated during exercise, but the efficacy of nonadrenergic vasoconstrictor pathways during exercise remains unclear. Thus, in eight young (23 ± 1 yr), healthy volunteers, we contrasted changes in leg blood flow (ultrasound Doppler) before and during intra-arterial infusion of the α1-adrenoreceptor agonist phenylephrine (PE) with that of the nonadrenergic endothelin A (ETA)/ETB receptor agonist ET-1. Heart rate, arterial blood pressure, common femoral artery diameter, and mean blood velocity were measured at rest and during knee-extensor exercise at 20%, 40%, and 60% of maximal work rate (WRmax). Drug infusion rates were adjusted for blood flow to maintain comparable vascular conductance evoked by changes in leg blood flow at rest, but ET-1 would do so with much slower kinetics than PE. Therefore, the current study sought to evaluate the magnitude and time course of ET-1-mediated vasoconstriction (indicated by changes in leg blood flow and vascular conductance) when infused intra-arterially into the exercising limb. These studies have identified an exercise intensity-dependent inhibition of these pharmacological agonists with the implication 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

endothelial; α-adrenoreceptor; exercise hyperemia; ultrasound Doppler

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 α-adrenergic agonists (7, 38, 51), angiotensin II (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 implication that the respective vasoconstrictor mechanisms become less effective during exercise.

Therefore, the current study sought to evaluate the magnitude and time course of ET-1-mediated vasoconstriction (indicated by changes in leg blood flow and vascular conductance) when infused intra-arterially into the exercising limb at rest and during exercise compared with vasoconstriction evoked by the α1-adrenergic agonist phenylephrine (PE). At rest and during exercise, the doses of these two vasoconstrictors were blood flow-adjusted dependent on the hyperemic condition. We hypothesized: 1) intra-arterial, nonsystemic doses of ET-1 and PE would provoke a similar degree of vasoconstriction in the leg at rest, but ET-1 would do so with much slower kinetics than PE; 2) PE-induced vasoconstriction would be attenuated during exercise in an intensity-dependent manner; and 3) ET-1-mediated vasoconstriction would persist during all exercise intensities with no attenuation in the vasoconstrictor efficacy of the drug.

Address for reprint requests and other correspondence: D. W. Wray, Dept. of Medicine, 9500 Gilman Dr., Univ. of California San Diego, La Jolla, CA 92039-0623 (e-mail: dwray@ucsd.edu).

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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 thermonutral 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 spill-over during the higher infusion rates that occurred during KE exercise. The nonspecific β-adrenergic antagonist propranolol (Sigma-Aldrich) was prepared at a concentration of 10 μg/ml 0.9% sterile saline and added to the PE infusion to block potential β2-mediated vasodilatation during PE infusion (47).

ET-1 (Clinalfa; Merck Biosciences, Läufelfingen, Switzerland) was administered as a nonselective ETa and ETb receptor agonist. Previous studies have demonstrated that the constrictor response to ET-1 is principally mediated by the ETA 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 ET-1 infusion (22), exercising blood flow measurements made 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) and as an integral part of the Doppler system (Logiq 7, GE Medical Systems).

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![Fig. 1. Experimental protocol](http://ajpheart.physiology.org/) for April 4, 2017
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 variable was significant. 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\(^{-1} \)·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\(^{-1} \)·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. 1). 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 vasconstrictor 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 significantly reduced within 5 min and reached a maximal vasoconstriction after 28 ± 1 min of continuous infusion (Table 1, Figs. 3 and 4). 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).

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

<table>
<thead>
<tr>
<th></th>
<th>PE</th>
<th>ET-1</th>
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<tr>
<td></td>
<td>Preinfusion</td>
<td>End Infusion</td>
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<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>62 ± 4</td>
<td>61 ± 3</td>
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<tr>
<td>MAP, mmHg</td>
<td>108 ± 3</td>
<td>108 ± 2</td>
</tr>
<tr>
<td>LBF, ml/min</td>
<td>285 ± 12</td>
<td>149 ± 23*</td>
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<tr>
<td>LVC, ml·min(^{-1})·mmHg(^{-1})</td>
<td>2.6 ± 0.1</td>
<td>1.3 ± 0.1*</td>
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<tr>
<td>FAD, cm</td>
<td>0.91 ± 0.02</td>
<td>0.84 ± 0.02*</td>
</tr>
<tr>
<td><strong>20% WR(_{\text{max}})</strong></td>
<td></td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>80 ± 4</td>
<td>77 ± 4</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>111 ± 4</td>
<td>113 ± 3</td>
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<tr>
<td>LBF, ml/min</td>
<td>2,283 ± 176</td>
<td>1,855 ± 117*</td>
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<tr>
<td>LVC, ml·min(^{-1})·mmHg(^{-1})</td>
<td>21 ± 2</td>
<td>17 ± 1*</td>
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<tr>
<td>FAD, cm</td>
<td>0.90 ± 0.01</td>
<td>0.85 ± 0.01*</td>
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<tr>
<td><strong>40% WR(_{\text{max}})</strong></td>
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<tr>
<td>HR, beats/min</td>
<td>90 ± 5</td>
<td>88 ± 5</td>
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<tr>
<td>MAP, mmHg</td>
<td>117 ± 3</td>
<td>116 ± 3</td>
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<tr>
<td>LBF, ml/min</td>
<td>2,883 ± 130</td>
<td>2,672 ± 146*</td>
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<tr>
<td>LVC, ml·min(^{-1})·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><strong>60% WR(_{\text{max}})</strong></td>
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<tr>
<td>HR, beats/min</td>
<td>99 ± 5</td>
<td>97 ± 5</td>
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<tr>
<td>MAP, mmHg</td>
<td>123 ± 4</td>
<td>121 ± 6</td>
</tr>
<tr>
<td>LBF, ml/min</td>
<td>3,172 ± 152</td>
<td>3,119 ± 147</td>
</tr>
<tr>
<td>LVC, ml·min(^{-1})·mmHg(^{-1})</td>
<td>26 ± 1</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>FAD, cm</td>
<td>0.90 ± 0.01</td>
<td>0.89 ± 0.02</td>
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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 \( /H9251\)-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.

**ET-1- 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 \( /H9251\)-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, McEnery 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
Experiments and ET-1. Because of the invasive nature of catheter-based studies, the present study was designed to administer two different vasoconstrictor drugs on the same study day (Fig. 1). However, due to the slow kinetics of ET-1 binding and clearance and also the suggestion that ET-1 may potentiate α-adrenergic vasoconstriction (55, 56), the study was ordered so that PE administration always preceded ET-1. We acknowledge that resting blood flow differed between PE and ET-1 trials, which was addressed through appropriate adjustment of drug infusion rate. Additionally, due to the need for continual ET-1 infusion during exercise, preinfusion exercising blood flow values were not possible during the ET-1 trials. However, time control studies demonstrated highly reproducible measurements of leg blood flow during repeated bouts of KE exercise (Fig. 5), providing confidence in the comparison of both PE- and ET-1-mediated vasoconstriction to a single, preinfusion value for each work rate. It should be noted that calculation of drug infusion rate according to blood flow, although providing a comparable intra-arterial drug concentration across varied levels of hyperemia, does not guarantee similar receptor occupancy at the vascular smooth muscle.

Finally, we acknowledge that the doses of PE and ET-1 were not equipotent and that a dose-response relationship was not undertaken for these drugs. Rather, doses were chosen based on previous studies that have identified the highest attainable dose that may be administered while minimizing the risk of drug spillover into the systemic circulation (10, 43, 51). With this approach, there remains uncertainty as to the maximal effect of exogenous ET-1, although the lack of additional vasoconstriction following a 5-min doubling dose (Fig. 2, bottom) is suggestive of a near-maximal response to exogenous ET-1 in this experimental paradigm.

GRANTS

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REFERENCES


EXERCISE AND ET-1


