Acute sympathetic vasoconstriction at rest and during dynamic exercise in cyclists and sedentary humans

D. Walter Wray, Anthony J. Donato, Steven K. Nishiyama, and Russell S. Richardson

Department of Medicine, University of California San Diego, La Jolla, California

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Wray DW, Donato AJ, Nishiyama SK, Richardson RS. Acute sympathetic vasoconstriction at rest and during dynamic exercise in cyclists and sedentary humans. J Appl Physiol 102: 704–712, 2007. First published November 2, 2006; doi:10.1152/japplphysiol.00984.2006.—The impact of exercise training on sympathetic activation is not well understood, especially across untrained and trained limbs in athletes. Therefore, in eight sedentary subjects (maximal oxygen consumption = 40 ± 2 ml·kg⁻¹·min⁻¹) and eight competitive cyclists (maximal oxygen consumption = 64 ± 2 ml·kg⁻¹·min⁻¹), we evaluated heart rate, blood pressure, blood flow, vascular conductance, and vascular resistance in the leg and arm during acute sympathetic stimulation [cold pressor test (CPT)]. The CPT was also performed during dynamic leg (knee extensor) or arm (handgrip) exercise at 50% of maximal work rate (WRmax) with measurements in the exercising limb. At rest, the CPT decreased vascular conductance similarly in the leg and arm of sedentary subjects (−33 ± 8% leg, −38 ± 6% arm) and cyclists (−34 ± 4% leg, −31 ± 9% arm), and during exercise CPT-induced vasoconstriction was blunted (i.e., sympatholysis) in both the leg and arm of both groups. However, the magnitude of sympatholysis was significantly different between the arm and leg of the sedentary group (−47 ± 11% arm, −25 ± 8% leg), and it was less in the arm of cyclists (−28 ± 11%) than sedentary controls. Taken together, these data provide evidence that sympathetically mediated vasoconstriction in exercising skeletal muscle (52), a phenomenon known as “functional sympatholysis” (39). Although it has been demonstrated that sympathetic outflow to resting muscle (36, 37) and resting norepinephrine levels (54) are largely unchanged following aerobic exercise training, limb- and training-specific end-organ responses to sympathetic activation during acute exercise remain uncertain. Considering the array of metabolic and hemodynamic adaptations that occur as a consequence of training, it indeed seems possible that the degree of sympatholysis may differ between exercise-trained and sedentary individuals.

Therefore, we applied a cold-stress stimulus to examine whether sympathetically mediated vasoconstriction at rest and during acute exercise would differ between sedentary and exercise-trained subjects, and whether these differences would be global or limb specific. Specifically, we hypothesized that 1) sympathetic vasoconstriction in response to the CPT at rest would be attenuated in both the arms and legs of exercise-trained subjects compared with sedentary controls; 2) in sedentary subjects, acute exercise would attenuate sympathetically mediated vasoconstriction equally in the arms and legs; and 3) in the exercise-trained subjects, sympatholysis would be limb specific, such that acute exercise would attenuate sympathetically mediated vasoconstriction to a greater degree in the trained legs compared with the relatively untrained arms.

METHODS

Subjects and General Procedures

Sixteen young, healthy men [8 exercise-trained cyclists, maximal oxygen consumption (V̇O₂max) = 64 ± 2 ml·kg⁻¹·min⁻¹; 8 sedentary controls, V̇O₂max = 40 ± 2 ml·kg⁻¹·min⁻¹] participated in the present study. The present study was reviewed and approved by the Institutional Review Board committee of the University of California, San Diego, and informed consent was obtained according to the University of California, San Diego, Human Subjects Protection Program requirements. All subjects reported to the laboratory on three separate occasions, a preliminary visit and 2 experimental days. On the preliminary screening day, health history and activity questionnaires were completed, maximal handgrip and maximal knee-extensor exercise capacities were determined, and subjects performed a maximal exercise test on a cycle ergometer to volitional exhaustion to evaluate (V̇O₂max). On experimental days, subjects reported to the laboratory at 0900 in the fasted state for the CPT trials. Recognizing the variability of cardiovascular responses to the CPT (27) and the possibility of adaptation to the cold stimulus, four CPT trials...
were performed over 2 experimental days (2 trials each day) with a counterbalanced design: 1) CPT at rest with blood flow measurements made in the right arm, 2) CPT during handgrip exercise with blood flow measurements made in the right (exercising) arm, 3) CPT at rest with measurements made in the left leg, and 4) CPT during knee-extensor exercise with measurements made in the left (exercising) leg. Each CPT was preceded by at least 30 min of supine rest. For all CPT trials, sympathetic activation was accomplished through immersion of the foot in an ice-water slurry (1°C), which has been well documented as a potent reflex stimulus capable of increasing muscle sympathetic nerve activity (31, 44, 45) and plasma norepinephrine levels in both arm and leg (18) without significantly elevating plasma epinephrine (2, 20, 28).

Exercise Modalities

Single-leg knee-extensor exercise was performed as described previously (1, 40, 56). Briefly, the ergometer was adjusted so that contraction of the quadriceps muscles turned a flywheel producing an "90°–170° arc of the lower leg, and tension was incremented by increasing friction on a belt surrounding the flywheel. Each subject completed a one-leg maximal work rate (WRmax) test to volitional exhaustion on the preliminary visit, and this WRmax value was used to calculate an individual work rate of 50% WRmax for dynamic (1 Hz) knee-extensor exercise.

Handgrip exercise was also performed, as described previously (10, 57). The handgrip exercise protocol was designed with a concerted effort to modify the traditional static handgrip model to be more dynamic (including pilot work assessing perceived effort) to facilitate matching of arm and leg exercise modalities. A single maximal voluntary contraction (MVC) was established for each subject using a hydraulic handgrip dynamometer with an analog output (Rolyan Ability One, Germantown, WI), and this MVC value was used to calculate an individual work rate of 50% MVC for dynamic (0.5 Hz) handgrip exercise. During the handgrip exercise, subjects were instructed to squeeze the dynamometer as quickly as possible, which limited the isometric contraction phase to <20% of the 2-s duty cycle.

Both arm and leg exercise was performed for 5–6 min to achieve steady-state blood flow conditions before the CPT commenced.

Measurements

Ultrasound Doppler. The ultrasound Doppler system (Logiq 7, GE Medical Systems, Milwaukee, WI) was equipped with two linear array transducers operating at an imaging frequency of 7–8 MHz (leg) and 10 MHz (arm). Vessel diameter was determined at a perpendicular angle to the central axis of the scanned area, where the best spatial resolution was achieved. The common femoral artery of the leg was imaged at the S–T3 cm proximal to the bifurcation. The brachial artery of the right arm was imaged at the S–T3 cm proximal to the biceps brachii muscle. The blood velocity profile was obtained using the same transducers with a Doppler frequency of 4.0–5.0 MHz, operated in the high-pulsed repetition-frequency mode (2–25 kHz) with a sample volume depth of 1.5–3.5 cm. In duplex mode, real-time ultrasound imaging and pulse-wave velocity profile were viewed simultaneously. All blood velocity measurements were obtained with the probe appropriately positioned to maintain an insonation angle of 60° or less. The sample volume was maximized according to vessel size and centered, verified by real-time ultrasound visualization of the vessel. Using artery diameter and mean blood velocity (Vmean), blood flow was calculated as:

\[ \text{Blood flow (ml/min)} = V_{\text{mean}} \pi \cdot (\text{vessel diameter}/2)^2 \cdot 60 \]

At all sample points, arterial diameter and angle-corrected, time- and space-averaged, and intensity-weighted Vmean values were calculated using commercially available software (Logiq 7, GE Medical Systems). Two digital ultrasound recordings and velocity spectra segments of 20–30 s were recorded at rest and during minutes 1, 2, and 3 of the CPT and saved to the GE Logiq 7 hard drive for offline image and waveform analysis.

Arterial blood pressure and heart rate. Arterial blood pressure was measured on the left wrist using automated radial tonometry (Medwave Vasotrac APM205A, BioPac Systems, Goleta, CA), with one measurement every 10–15 s. Heart rate was recorded from a standard three-lead ECG, an integral component of the Doppler system (Logiq 7, GE Medical Systems).

Vascular resistance and conductance. Vascular resistance and conductance were calculated as:

\[ \text{Resistance (mmHg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1}) = \frac{\text{mean arterial pressure}}{\text{blood flow}} \]

\[ \text{Conductance (ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}) = \frac{\text{blood flow}}{\text{mean arterial pressure}} \]

Both vascular resistance and conductance were calculated to allow the most comprehensive evaluation of the degree of vasoconstriction under various conditions. Others have concluded that resistance is the more appropriate calculation when changes in blood pressure are greater than changes in blood flow (such as the resting CPT), whereas conductance best describes vasoconstriction when blood flow changes dramatically (such as rest vs. exercise comparisons) (3, 24). The magnitude of sympatholysis was calculated as:

\[ \text{Vascular conductance at rest [percent change (\%\Delta)]} \]

\[ = \frac{\text{vascular conductance during exercise (\%\Delta))}}{\text{vascular conductance at rest (\%\Delta)}} \]

This index of functional sympatholysis reflects the ability of muscle contractions to blunt the vasoconstrictor response observed under resting and exercise conditions (9).

Tissue volume measurements. Forearm and thigh circumferences (at three sites: distal end, proximal end, and one-third distal-to-proximal end) and length were measured to calculate tissue volume (19). Additionally, central and dorsal skinfold measurements were taken to assess subcutaneous fat and allow an estimation of muscle volume for the thigh and forearm (19). Muscle mass of the complete forearm was then calculated from this anthropometrically measured muscle volume by multiplying by the density of muscle (1.06 g/cm³). On the basis of both an excellent agreement (±5%) and a high correlation (r² = 0.83) between this method and dual-energy X-ray absorptiometry (Explorer, Hologic, Waltham, MA) documented in our laboratory (10), we applied the following regression equation:

\[ \text{Forearm muscle mass (kg)} = 1.155 \cdot 0.24 \]

\[ = \text{forearm muscle mass (kg)} \]

Thigh muscle volume was converted to quadriceps muscle mass with the use of the following equation:

\[ \text{Thigh muscle volume (liters)} \cdot 0.307 + 0.353 = \text{thigh muscle mass.} \]

This anthropometrically determined quadriceps muscle mass, previously revealed to correlate highly with muscle mass assessed by computer tomography (r² = 0.86), was then corrected on the basis of this relationship with the following equation (35):

\[ \text{Muscle mass (anthropometric; kg)} \cdot 0.924 - 0.292 \]

\[ = \text{quadriceps muscle mass (kg)} \]

It should be noted that these calculations do not remove the volume occupied by bone.

Data Analyses and Statistics

For each ultrasound Doppler segment, Vmean was averaged across the first and last half of the recorded clip (20 s), and diameter measurements (1–3 per segment) were evaluated during diastole and during the relaxation phase of the duty cycle during exercise, as
Table 1. Subject characteristics at rest

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Cyclists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>22 ± 1</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175 ± 2</td>
<td>179 ± 2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74 ± 3</td>
<td>71 ± 3</td>
</tr>
<tr>
<td>Maximal O₂ consumption, ml·kg⁻¹·min⁻¹</td>
<td>40 ± 2</td>
<td>64 ± 2*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>61 ± 2</td>
<td>54 ± 2*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>118 ± 4</td>
<td>131 ± 4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>69 ± 4</td>
<td>64 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>86 ± 3</td>
<td>80 ± 4</td>
</tr>
<tr>
<td>Branchial artery diameter, cm</td>
<td>0.44 ± 0.01</td>
<td>0.46 ± 0.01</td>
</tr>
<tr>
<td>Common femoral artery diameter, cm</td>
<td>0.93 ± 0.01</td>
<td>1.00 ± 0.02*</td>
</tr>
<tr>
<td>Maximal handgrip, kg</td>
<td>52 ± 3</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>Maximal knee extensor, W</td>
<td>45 ± 4</td>
<td>82 ± 7*</td>
</tr>
<tr>
<td>Handgrip 50% WRmax, kg</td>
<td>26 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Knee extensor 50% WRmax, W</td>
<td>23 ± 2</td>
<td>40 ± 3*</td>
</tr>
<tr>
<td>Forearm muscle mass, kg</td>
<td>0.81 ± 0.04</td>
<td>0.86 ± 0.04</td>
</tr>
<tr>
<td>Quadriceps muscle mass, kg</td>
<td>2.19 ± 0.1</td>
<td>2.46 ± 0.1*</td>
</tr>
</tbody>
</table>

Values are means ± SE. WRmax, maximal work rate. *Significant difference between sedentary and cyclist groups, P < 0.05.

described previously (10, 56). Data during the CPT were analyzed both in 1-min segments and averaged across the 3-min of the test. Two-way ANOVA and repeated-measures ANOVA were used to compare differences between limbs and groups, 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

Subject characteristics for both groups are presented in Table 1, and hemodynamic responses to the CPT at rest and during exercise are provided in Table 2. The physiological response to the CPT over time is inherently variable. Thus, to most accurately describe the measured responses, data are presented in 10-s intervals (Fig. 1, n = 1), 1-min segment (Figs. 2–5, all subjects), and the 3-min average response (text, Table 2, Figs. 2–5, all subjects).

CPT Responses at Rest

During the resting CPT with measurements in the arm, increases in heart rate and blood pressure were observed in both groups (Table 2). Arm blood flow decreased significantly only in the sedentary group (Fig. 2, Table 2), although vascular conductance was reduced (Fig. 3, Table 2) and resistance increased (Fig. 4, Table 2) to a similar degree in both cyclists and sedentary subjects. During the resting CPT with measurements in the leg, heart rate, blood pressure, and vascular resistance increased in both groups, while blood flow and vascular conductance decreased to a similar degree in both groups (Figs. 2, 3, 4, Table 2).

CPT Responses During Exercise

During handgrip exercise, heart rate increased similarly in both groups, but remained significantly lower in cyclists than sedentary controls during steady-state exercise (Table 2). Exercising arm blood flow, vascular conductance, and vascular resistance were similar between groups (Table 2). When the CPT was applied during arm exercise, increased heart rate and blood pressure were observed in both groups, arm blood flow increased significantly (~31%) in the sedentary group, and arm blood flow in the cyclist was unchanged (Table 2).

Table 2. Hemodynamic responses to the cold pressor test (3-min average) at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>Cyclists</th>
<th>% Change</th>
<th>Sedentary</th>
<th>Cyclists</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow, ml/min</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rest arm</td>
<td>93 ± 12</td>
<td>68 ± 8*</td>
<td>−23 ± 8</td>
<td>62 ± 8†</td>
<td>49 ± 5</td>
<td>−16 ± 4</td>
</tr>
<tr>
<td>Rest leg</td>
<td>386 ± 45</td>
<td>285 ± 27*</td>
<td>−20 ± 9</td>
<td>304 ± 21†</td>
<td>251 ± 50*</td>
<td>−16 ± 9</td>
</tr>
<tr>
<td>Ex arm</td>
<td>296 ± 44</td>
<td>350 ± 39*</td>
<td>+31 ± 12</td>
<td>334 ± 39</td>
<td>363 ± 62</td>
<td>+8 ± 8</td>
</tr>
<tr>
<td>Ex leg</td>
<td>1,943 ± 117</td>
<td>2,037 ± 185</td>
<td>+3 ± 4</td>
<td>2,953 ± 316†</td>
<td>2,898 ± 283</td>
<td>−2 ± 7</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest arm</td>
<td>86 ± 4</td>
<td>107 ± 6*</td>
<td>+20 ± 4</td>
<td>85 ± 3</td>
<td>104 ± 5*</td>
<td>+23 ± 3</td>
</tr>
<tr>
<td>Rest leg</td>
<td>88 ± 4</td>
<td>107 ± 7*</td>
<td>+19 ± 4</td>
<td>91 ± 5</td>
<td>117 ± 8*</td>
<td>+28 ± 5</td>
</tr>
<tr>
<td>Ex arm</td>
<td>96 ± 4</td>
<td>112 ± 3*</td>
<td>+16 ± 2</td>
<td>95 ± 6</td>
<td>109 ± 6*</td>
<td>+16 ± 3</td>
</tr>
<tr>
<td>Ex leg</td>
<td>97 ± 4</td>
<td>111 ± 4*</td>
<td>+13 ± 4</td>
<td>105 ± 5</td>
<td>121 ± 6*</td>
<td>+16 ± 3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest arm</td>
<td>59 ± 2</td>
<td>74 ± 3*</td>
<td>+27 ± 6</td>
<td>54 ± 2†</td>
<td>57 ± 2†</td>
<td>+8 ± 4</td>
</tr>
<tr>
<td>Rest leg</td>
<td>61 ± 2</td>
<td>69 ± 1*</td>
<td>+15 ± 4</td>
<td>54 ± 2†</td>
<td>61 ± 4*</td>
<td>+13 ± 8</td>
</tr>
<tr>
<td>Ex arm</td>
<td>72 ± 3</td>
<td>80 ± 4*</td>
<td>+9 ± 3</td>
<td>64 ± 3†</td>
<td>70 ± 5*</td>
<td>+11 ± 6</td>
</tr>
<tr>
<td>Ex leg</td>
<td>91 ± 2</td>
<td>98 ± 3*</td>
<td>+12 ± 3</td>
<td>89 ± 4</td>
<td>95 ± 4</td>
<td>+8 ± 5</td>
</tr>
<tr>
<td>VC, ml·min⁻¹·mmHg⁻¹</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rest arm</td>
<td>1.13 ± 0.2</td>
<td>0.65 ± 0.1*</td>
<td>−38 ± 6</td>
<td>0.76 ± 0.1</td>
<td>0.48 ± 0.1*</td>
<td>−31 ± 9</td>
</tr>
<tr>
<td>Rest leg</td>
<td>4.34 ± 0.4</td>
<td>2.79 ± 0.4*</td>
<td>−33 ± 8</td>
<td>3.42 ± 0.3</td>
<td>2.27 ± 0.3*</td>
<td>−34 ± 4</td>
</tr>
<tr>
<td>Ex arm</td>
<td>3.15 ± 0.5</td>
<td>3.15 ± 0.3</td>
<td>+13 ± 11</td>
<td>3.45 ± 0.2</td>
<td>3.24 ± 0.4</td>
<td>−7 ± 8</td>
</tr>
<tr>
<td>Ex leg</td>
<td>20 ± 1</td>
<td>18 ± 2</td>
<td>−9 ± 4</td>
<td>29 ± 4†</td>
<td>25 ± 3</td>
<td>−12 ± 7</td>
</tr>
<tr>
<td>VR, mmHg·ml⁻¹·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest arm</td>
<td>1.07 ± 0.2</td>
<td>1.99 ± 0.3*</td>
<td>+99 ± 24</td>
<td>1.50 ± 0.2</td>
<td>2.52 ± 0.4*</td>
<td>+79 ± 27</td>
</tr>
<tr>
<td>Rest leg</td>
<td>0.25 ± 0.03</td>
<td>0.47 ± 0.08*</td>
<td>+93 ± 27</td>
<td>0.31 ± 0.03</td>
<td>0.54 ± 0.1*</td>
<td>+77 ± 20</td>
</tr>
<tr>
<td>Ex arm</td>
<td>0.41 ± 0.07</td>
<td>0.36 ± 0.04</td>
<td>−3 ± 9</td>
<td>0.30 ± 0.02</td>
<td>0.35 ± 0.04</td>
<td>+15 ± 11</td>
</tr>
<tr>
<td>Ex leg</td>
<td>0.05 ± 0.01</td>
<td>0.06 ± 0.00</td>
<td>+12 ± 4</td>
<td>0.04 ± 0.01</td>
<td>0.05 ± 0.01</td>
<td>+22 ± 14</td>
</tr>
</tbody>
</table>

Values are means ± SE. CPT, cold pressor test (3-min average); MAP, mean arterial blood pressure; HR, heart rate; VC, vascular conductance; VR, vascular resistance; Ex, exercise. *Significantly different from baseline (pre-CPT), P < 0.05. †Significant difference between sedentary and cyclist groups, P < 0.05.
During leg (knee-extensor) exercise, heart rate was similar between groups, and exercising leg blood flow and leg vascular conductance were higher in the cyclists than sedentary controls, attributable to the higher absolute work rate in cyclists (Table 2). When the CPT was applied during leg exercise, increases in both heart rate and blood pressure were observed, whereas leg blood flow was unchanged in both groups (Table 2, Fig. 2).

**Magnitude of Sympatholysis**

The percent change in vascular conductance during the resting and exercising CPT was distinct between limbs and groups (Fig. 3). To more comprehensively quantify these changes, the difference in vascular conductance between rest and exercise, or “magnitude of sympatholysis” (9), was calculated and is summarized in Fig. 5. In sedentary subjects, a greater sympatholysis (i.e., metabolic blunting of sympathetic vasoconstriction) was seen in the arm compared with the leg. The sympatholytic response was similar between limbs in the cyclists, with significantly less sympatholysis in the arm of cyclists compared with sedentary subjects.

**DISCUSSION**

The present study has provided several new findings regarding the impact of exercise training on sympathetically mediated vasoconstriction at rest, and the blunting of this response during acute exercise. Despite lower resting limb blood flow in the cyclists, a similar vasoconstriction was observed in both the arm and leg of the two groups in response to the CPT. Thus, contrary to our stated hypotheses, vasoconstriction in response to the CPT at rest was not affected by exercise training status and was not limb specific. However, during acute exercise, sympathetic vasoconstriction was blunted in the arms and legs of both groups, and the magnitude of this sympatholysis was significantly less in the arm of the cyclists compared with sedentary controls. Taken together, these data provide evidence that sympathetically mediated vasoconstriction is expressed equally and globally at rest, with a differential pattern of vasoconstriction during acute exercise according to training.
Fig. 3. Changes in calculated vascular conductance from pre-CPT values during a 3-min CPT at rest (solid black bars) and during exercise at 50% of WRmax (solid gray bars) in leg (top) and arm (bottom) trials in sedentary and cyclist groups. Also shown is the 3-min average (avg) response for the CPT at rest (hatched black bars) and exercise (hatched gray bars). For all CPT trials, sympathetic activation was accomplished through immersion of the foot in ice water. Values are means ± SE. *Significantly different from resting CPT trial, $P < 0.05$.

Fig. 4. Changes in calculated vascular resistance from pre-CPT values during a 3-min CPT at rest (solid black bars) and during exercise at 50% of WRmax (solid gray bars) in leg (top) and arm (bottom) trials in sedentary and cyclist groups. Also shown is the 3-min average response for the CPT at rest (hatched black bars) and exercise (hatched gray bars). For all CPT trials, sympathetic activation was accomplished through immersion of the foot in ice water. Values are means ± SE. *Significantly different from resting CPT trial, $P < 0.05$. 
status and perhaps training modality. This unique alteration in exercising hemodynamic control between trained and untrained limbs exemplifies the systemic impact of limb-specific exercise training, and teleologically it may represent an adaptation that optimizes the distribution of blood flow to meet limb-specific demand in these individuals during exercise.

**Limb Specificity and Sympathetic Vasoconstriction at Rest**

In the present study, the CPT was utilized to activate skin thermoreceptors, which subsequently provoked a profound reflex increase in sympathetic nerve activity (25), with subsequent changes in heart rate, arterial blood pressure, and blood flow. The typical cardiovascular response to the CPT in the resting arm of a cyclist is illustrated in Fig. 1.

Expression of sympathetic activation in response to the CPT has been well documented, with others demonstrating a robust (>300%) increase in muscle sympathetic nerve activity (32, 44) that does not differ according to fitness (45) or between limbs (42, 46). Similarly, the CPT elevates venous norepinephrine levels 40–60% to a similar degree in both arms and legs (18) and does not differ between athletes and sedentary individuals (6, 16). These similarities in sympathetic activation between limbs and fitness levels thus set the stage to explore the end-organ translation of sympathetic activation into vasoconstriction, which to our knowledge has not been investigated with ultrasound Doppler methodologies.

Others have recognized vascular limb specificity in response to orthostasis (17), and sympathomimetics (34), whereas our group (56, 57) and others (29, 30, 41) have identified marked differences in vascular reactivity between limbs. In a recent study, Jacob et al. (18) evaluated adrenergic receptor sensitivity (change in vascular resistance) following sympathomimetic drug infusion (phenylephrine and isoproterenol) and the CPT in the arm and leg of younger, normally active volunteers. This study reported a similar increase in local norepinephrine spillover in the arms and legs following the CPT, but interestingly the calculated vascular resistance increased in the arm but decreased in the leg, suggesting a limb-specific end-organ response. However, during adrenergic drug infusions in the same subjects the arm demonstrated a greater sensitivity to phenylephrine and a lesser sensitivity to isoproterenol compared with the leg, suggesting that adrenergic-receptor differences cannot explain the paradoxical leg response. This study thus provides convincing evidence for similar sympathetic activation between limbs, but it provides no explanation for the dissociation between sympathetic activation and its functional correlate in the leg.

Despite these limb-specific differences in other experimental paradigms, in the present study we observed similar changes in vascular conductance and resistance in the arms and legs of both cyclists and sedentary controls in response to the CPT at rest (Table 2, Figs. 2 and 3). The reasons for the disparity between the present data and those of Jacob et al. (18) may be attributed to methodological differences (venous plethysmography vs. ultrasound Doppler in the present study) or age (24–50 yr vs. 19–22 yr in the present study). These data thus support the concept that sympathetically mediated vasoconstriction provoked by the CPT is expressed systemically at rest.
in the peripheral circulation (38), with no apparent selectivity of this response between limbs.

**Exercise Training and Sympathetic Vasoconstriction at Rest**

Although several cross-sectional (45, 51) and longitudinal (36, 47) studies have suggested that regular exercise training does not significantly change resting MSNA, we hypothesized that the actual expression of sympathetic activity would be lessened due to limb-specific, training-induced changes in end-organ (i.e., α-adrenoreceptor) function. Animal data are equivocal regarding the effect of exercise training on limb α-adrenergic responsiveness. In rats, longitudinal training studies have demonstrated decreased sensitivity to sympathometrics in the trained muscle (53) and no change (11) or decreased sensitivity (50) in isolated arterial segments. In addition, in situ studies have reported enhanced adrenergic vasoconstriction in the untrained spinotrapezius muscle of the exercise-trained rat (23). In humans, to our knowledge only two studies have assessed the effect of exercise training on α-adrenoreceptor-mediated vasoconstriction. Smith et al. (48) observed similar changes in arm blood flow (venous plethysmography) and arterial blood pressure in sedentary and endurance-trained subjects in response to both sympathomimetic infusion and orthostatic challenge. Similarly, O’Sullivan et al. (33) demonstrated a similar degree of vasoconstriction in the forearm of trained and sedentary subjects in response to a 2-min CPT. Thus, the present findings utilizing ultrasound Doppler measurements in both the arm and leg extend these earlier findings, demonstrating that chronic exercise training does not alter resting sympathetically mediated vasoconstriction to either trained or untrained limbs in young, healthy subjects (Figs. 2 and 3, Table 2).

**Sympathetic Vasoconstriction During Acute Exercise**

Although sympathetic activation is fully expressed in resting muscle, recent studies indicate that this response may be blunted in the exercising limb, an event know as functional sympatholysis (52). In further support of this concept, we observed smaller changes in both arm and leg vasoconstriction during acute exercise compared with the resting CPT (Fig. 4). These data extend recent observations by Koch et al. (22) that leg blood flow did not change when the CPT was applied to young subjects during upright cycling, although this study did not include a resting CPT trial for comparison. In another study involving cystic fibrosis patients and healthy controls, a 2-min CPT was applied at rest and during handgrip exercise at 5–15% of WRmax, but no sympatholysis was observed in the exercising forearm compared with rest (43). Again, the discrepancy between these previous findings and the current data may be due to methodological differences; for example, the present protocol utilized a higher work rate in the arm (50% WRmax), which is significant considering the suggested intensity-depandant nature of sympatholysis (4, 55). Thus, to our knowledge, this is the first report of a blunted sympathetic vasoconstriction in response to the CPT during limb-specific exercise in humans.

**Sympatholysis and Exercise Training**

Others have reported that exercise training results in a reduction in muscle sympathetic nerve activity during acute knee-extensor (36) and handgrip (49) exercise, a response that appears to be limited to the trained limb (47). Thus one focus of the present study was to identify potential limb-specific responses to sympathetic vasoconstriction within both sedentary and exercise-trained subjects during acute exercise. These comparisons are made with recognition of the caveat that handgrip and knee-extensor exercise may produce different metabolic stress in the exercising tissue. However, the similar increases in mean arterial pressure from rest to exercise in the arm and leg of both groups (Table 2) suggest that these exercise modalities, although certainly not identical, may be comparable.

Although leg blood flow and vascular conductance were significantly higher in cyclists than sedentary subjects during knee-extensor exercise (due to the higher absolute work rate), the CPT during exercise did not cause significant change in absolute leg vascular conductance in either group (Table 2). These responses resulted in a similar calculated magnitude of sympatholysis between sedentary (−24 ± 8%) and cyclists (−22 ± 9%) (Fig. 5). In contrast to the leg, the magnitude of vasoconstriction in the arm during exercise compared with rest differed according to training status. In both the sedentary and cyclist groups, absolute arm vascular conductance was significantly reduced during the resting CPT and unchanged during the exercising CPT (Table 2). However, when these vascular conductance changes are expressed as percent changes, the magnitude of sympatholysis in the arm was significantly greater in the sedentary group (−47 ± 11%) than in the cyclists (−28 ± 11%) (Fig. 5).

From these results, it appears that vasoconstriction in the arm of the cyclists is somewhat less inhibited (i.e., more sympathetic vasoconstriction during exercise) than the sedentary group during exercise. We speculate that this response may be due to increased α-adrenergic sensitivity, similar to animal data demonstrating increased adrenergic vasoconstriction in the untrained (spinotrapezius) skeletal muscle of treadmill trained rats (23). Conceptually, this observed decrease in arm sympatholysis compared with the sedentary group may represent a training adaptation related to end-organ sensitivity designed to ensure optimal distribution of blood flow to the exercising legs, and it may serve to prevent possible overperfusion of the arm and potential blood flow “steal” from the legs. However, further studies with measurements at multiple exercise intensities are needed to determine the mechanism responsible for this intriguing response in the relatively untrained limb of competitive cyclists.

**Experimental Considerations**

Several limitations must be considered when evaluating the findings from the present study. The CPT is inherently variable, and it may evoke different afferent pain responses depending on the tolerance and sensitivity of the subject. In addition, the possibility exists for adaptation when multiple CPT tests are performed. To address these issues, by design each subject served as his or her own control, a lengthy recovery time was included in the protocol, and the order of the CPT trials was counterbalanced to minimize any possible ordering effect. Similar increases in mean arterial pressure between the four trials confirm that the stimulus was comparable across tests and groups (see Table 2). It is noteworthy that
the two exercise modalities (handgrip and knee extensor) require varying degrees of isometric muscle contraction, and so subsequent exercise-induced metabolic milieu may differ between arm and leg exercise. However, the use of a short isometric phase (~20% of the duty cycle) and slow cadence (0.5 Hz) during handgrip exercise ensured that this exercise was as dynamic as possible. We also recognize the possibility that central venous pressure may be elevated as a result of exercise training (26), and thus the reported calculations of vascular conductance and vascular resistance using only mean arterial pressure may be slightly over- or underestimated, respectively. Finally, we acknowledge the possibility that flow-mediated vasodilation and myogenic tone may have contributed to the overall vasomotor response to exercise and the CPT.

In summary, we have reported that sympathetically-mediated vasodilation in response to the CPT at rest is not limb-specific or affected by exercise training status, and that acute exercise effectively blunts sympathetic vasodilation (i.e., sympathetic) in both trained and untrained limbs. However, there was a reduced magnitude of sympatholysis in the arm of predominantly leg-trained individuals, exemplifying the systemic vascular effects of exercise training that may optimize blood flow distribution to meet limb-specific demand in these individuals during exercise.

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