Sympathetic Denervation of the Upper Limb Improves Forearm Exercise Performance and Skeletal Muscle Bioenergetics

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Background—Sympathetic activation may limit exercise performance by restraining muscle blood flow or by negatively affecting skeletal muscle metabolic behavior. To test this hypothesis, we studied the effect of thoracoscopic sympathetic trunkotomy (TST) on forearm exercise duration, blood flow, and muscle bioenergetics in 13 patients with idiopathic palmar hyperhidrosis.

Methods and Results—Heart rate and beat-by-beat mean arterial pressure were recorded at rest and during right and left rhythmic handgrip before and 4 to 7 weeks after right TST. Forearm blood flow was measured bilaterally at rest and on the right during exercise. Right forearm muscle phosphocreatine content and intracellular pH were assessed by $^{31}$P magnetic resonance spectroscopy. After right TST, exercise duration increased from 8.9 ± 1.4 to 13.4 ± 1.8 minutes ($P<0.0001$) with the right forearm and from 5.7 ± 0.4 to 7.6 ± 0.9 minutes ($P<0.05$) with the left ($P<0.05$ for the interaction between treatment and side). Right forearm blood flow at rest was 66% higher ($P<0.01$) after right TST, but this difference decreased as the exercise progressed. After right TST, a significant reduction occurred in muscle acidification and phosphocreatine depletion during ipsilateral forearm exercise. This was associated with a significantly reduced mean arterial pressure response to right handgrip, whereas the pressor response to left handgrip did not change.

Conclusions—Sympathetic denervation of the upper limb significantly improves forearm skeletal muscle bioenergetics and exercise performance in patients with idiopathic palmar hyperhidrosis. (Circulation. 2000;101:2716-2720.)

Key Words: nervous system, autonomic ★ muscles ★ metabolism ★ blood flow ★ exercise

Whether exercise-induced reflex sympathetic activation can limit skeletal muscle exercise performance has been a matter of considerable debate. This could occur through the following 2 mechanisms: (1) a sympathetically induced vasoconstriction limiting oxygen and other substrate delivery to the working muscle or (2) a direct effect on muscle bioenergetics.

In support of the first mechanism, data show that reflex adrenergic stimulation causes a reduction in blood flow and oxygen uptake in the working muscle, although other studies have indicated that the vasodilating action of local metabolites can largely offset neurogenic vasoconstriction during exercise (so-called metabolic sympatholysis). The second mechanism is supported by data indicating that both $\alpha$- and $\beta$-adrenergic stimulation could adversely affect muscle efficiency and impair performance by stimulating glycogenolysis and lactate production.

The recent introduction of thoracoscopic sympathetic trunkotomy (TST) for the treatment of idiopathic hyperhidrosis has provided a unique model to test the importance of sympathetic neural activity in regulating skeletal muscle performance and bioenergetics in humans. Idiopathic hyperhidrosis of the hands or axillae has been attributed to overactivity of the sympathetic fibers that pass through the upper thoracic sympathetic ganglia. Transection of the sympathetic trunk between the first and second thoracic sympathetic ganglia, with diathermy coagulation of the lower end of the divided trunk, produces long-lasting ipsilateral sympathetic denervation of the upper limb, resulting in inhibition of eccrine sweat gland activity and an increase in forearm blood flow in 95% of patients. We studied the effect of TST on forearm exercise performance, blood flow, and muscle bioenergetics (which were evaluated by $^{31}$P magnetic resonance spectroscopy [$^{31}$P MRS]).

Methods

A total of 13 patients (mean age, 30 ± 2 years; 8 women) took part in this study. No patient was taking medication. Apart from hyperhidrosis of the palms (n=5), the axillae (n=2), or both (n=6), their
past medical history and physical examination were unremarkable. In patients with palmar hyperhidrosis, the sympathetic trunk was divided between the first and second thoracic sympathetic ganglia, whereas in patients with axillary hyperhidrosis, the additional procedure of removing the second and third thoracic sympathetic ganglia was attempted (usually successfully). TST was performed first on the right side and, 5 to 16 weeks later, on the left. All patients were studied before and after right TST and before left TST.

Study Protocol
The study was approved by the Central Oxford Research Ethics Committee, and written informed consent was obtained from each participant.

After 30 minutes of rest in the supine position in a quiet room with a controlled temperature of 22°C to 24°C, 11 patients performed rhythmic handgrip exercise (using a hydraulic dynamometer modified from Grip dynamometer TK-1201) at 30% of their maximal voluntary contraction at 40 pulls/min until exhaustion. Maximal voluntary contraction of both forearms was assessed 3 times before and after sympathetic denervation. Right and left handgrip exercises, in rhythm order, were performed twice before and twice 4 to 7 weeks after right TST. At least 30 minutes of rest were allowed between right and left handgrip exercises, and a minimum of 48 hours elapsed between each exercise session. Approximately 90 minutes after the completion of these tests, patients underwent $^{31}$P MRS of the right flexor digitorum superficialis muscle at rest and during rhythmic handgrip exercise (as described above), once before and once after right TST. Two additional patients had $^{31}$P MRS studies before and after the operation but no other laboratory investigations.

Measurements
Lead II of the ECG and beat-by-beat arterial blood pressure were recorded for 5 minutes at rest, during rhythmic handgrip, and for 5 minutes after exercise.

Toe blood pressure was measured continuously by a Finapres 2300 BP Monitor (Ohmeda), and mean arterial blood pressure (MAP) was obtained by averaging the blood pressure waveform. We compared MAP measurements (by Finapres) obtained in the toe with those simultaneously recorded in the finger at rest and during rhythmic handgrip exercise (as described above), once before and once after right TST. Two additional patients had $^{31}$P MRS studies before and after the operation but no other laboratory investigations.

Forearm blood flow (FFB; mL·100 mL$^{-1}$·min$^{-1}$) at rest was obtained every 20 s for 5 minutes by venous occlusion plethysmography (model EC4, DE Hokanson). On a separate visit, FFB was also measured in the exercising right forearm of 5 patients during a 6-s pause at the end of each minute of exercise. All signals were simultaneously acquired at a sampling rate of 500 Hz (AcqKnowledge 3.01, BIOPAC System).

$^{31}$P MRS studies were performed using a Fourier transform spectrometer (Oxford Research Systems) interfaced with a 1.9-Tesla, 30-cm bore superconducting magnet (Oxford Instruments). Patients were studied in the supine position with the arm abducted to 90° and positioned in the bore of the magnet. The 2.5-cm diameter surface coil, tuned to the $^{31}$P resonance frequency of 32.54 MHz, was placed over the flexor digitorum superficialis muscle at the midforearm. A pulse width of 20 μs and an interpulse delay of 2 s were used to maximize the signal obtained. Immediately before the beginning of exercise, a spectrum consisting of an average of 128 scans (256 s) was collected to provide a baseline for exercise and recovery. Throughout exercise, spectra consisting of 16 scans (32 s) each were acquired. Data from the postexercise recovery period consisted of 4 spectra of 16 scans each, followed by 4 of 32 scans and 2 of 64.

Data Analysis
Homodyemic data are expressed as 5-minute averages at rest and as the average of the last 30 s of each minute during exercise and recovery. Forearm vascular resistance (FVR) was calculated by dividing MAP by FBF, and it is expressed in arbitrary units. Because no difference existed in the duration of the left or right handgrip exercises performed before and after the surgical procedure, we compared the average duration of 3 exercise tests (2 in the laboratory and 1 during $^{31}$P MRS) with the right arm and 2 with the left before and after right TST. $^{31}$P MRS data were processed with 6-Hz line-broadening and Fourier transformation. Peak heights and areas were calculated using manual triangulation of the peaks corrected for line shape and magnetic saturation to estimate relative changes in the intracellular concentrations of phosphocreatine (PCr), inorganic phosphate (Pi) and ATP. Cytoplasmic concentrations of PCr and Pi were calculated from the PCr/ATP and Pi/ATP ratios, assuming an intracellular concentration of ATP in the resting muscle of 8.2 mmol/L of intracellular water. Phosphocreatine was expressed as the ratio of PCr/(PCr+Pi) to correct for changes in signal intensity due to movement artifacts. Free ADP was calculated as described in Arnold et al. The intracellular muscle pH (pHi) was determined from the chemical shift of the Pi peak relative to the PCr peak, and it was used as an index of anaerobic glycolysis.

We evaluated the reproducibility of these measurements in 8 healthy subjects who performed rhythmic handgrip tests until exhaustion; these tests were done 1 week apart. The mean difference between the first and second test at rest, at matched workloads (see below), and peak exercise were, respectively, $-0.02\pm 0.02, 0.03\pm 0.26$, and $-0.03\pm 0.22$ for pHi, $-0.02\pm 0.02, 0.00\pm 0.23$, and $-0.02\pm 0.22$ for PCr/(PCr+Pi), and $0.27, -9.38$, and $-6.35\mu mol/L$ for ADP ($P=NS$ for all).

Statistical Analysis
ANOVA (SuperANOVA, Abacus Concept Inc) was used to test the interaction between side (left versus right handgrip) and treatment (before versus after right TST). Post hoc testing was performed with Fisher’s protected least SD procedure. Data obtained at peak exercise before right TST were compared both with peak exercise data after TST and with data recorded at the same absolute workload after TST (matched workload). FBF and FVR during exercise before and after TST were compared by using the Wilcoxon signed rank test. Statistical significance was set at $P<0.05$. Values are presented as mean±SEM or as geometric means, where indicated.

Results
Right TST abolished ipsilateral sweating of the hands in all subjects and improved axillary hyperhidrosis in 6 of 7 patients with this complaint. Maximal voluntary contraction was unaffected by surgery (2.5±0.2 versus 2.4±0.2 bars for the right arm and 2.3±0.3 versus 2.4±0.2 bars for the left arm) in all patients except one who developed neuropaaxia of the right ulnar nerve. Data from this patient have been excluded from analysis.

Exercise Performance
Exercise duration increased in both the right and left forearms after right TST. The magnitude of the increase, however, was significantly larger in the right arm (from 8.9±1.4 to 13.4±1.8 minutes with the right arm, $P<0.0001$, and from 5.7±0.4 to 7.6±0.9 minutes, $P<0.05$, with the left arm; $P<0.05$ for the effect of the interaction between treatment and side). In addition, the increase in MAP in response to right handgrip was significantly reduced after right TST, whereas the pressor response to left handgrip did not change (Figure 1). Because TST causes partial cardiac adrenergic denervation, heart rate at rest and during exercise was significantly lower after the operation (Figure 1). However,
no difference existed between the chronotropic response to right or left handgrip before and after right TST (Figure 1).

**Forearm Blood Flow**

Right TST significantly increased resting FBF and decreased FVR in the right forearm but not in the left (Table 1). In 5 patients, right FBF was also determined at the end of each minute of rhythmic handgrip. Right forearm exercise duration in this subgroup increased from 7.8 ± 1.7 to 17.0 ± 4.2 minutes after right TST (P < 0.001). FBF at peak exercise was significantly higher after TST, and FVR was lower (Figure 2). Differences, however, failed to reach statistical significance at the fourth minute of exercise and at matched workloads.

**Muscle Bioenergetics**

Sympathetic denervation did not change intracellular PCr and ADP concentrations at rest, but it was associated with a modest reduction in muscle pH (Table 2).

During rhythmic handgrip, muscle pH and PCr gradually decreased and ADP increased (Table 2). As illustrated in Figure 3, muscle pH and PCr were similar during the first few minutes of handgrip before and after TST, but differences developed as the exercise progressed (Figure 3 and Table 2 for mean values). Significantly less ipsilateral muscle acidification and PCr depletion occurred at matched workloads after right TST, and the combined effect of these changes resulted in a lower muscle ADP content (Table 2). Muscle PCr and pH at peak exercise were significantly higher after sympathetic denervation, the PCr depletion at the end of exercise was often not great enough to allow for a reliable measurement of recovery rates.

**Discussion**

The novel findings from this study are as follows. (1) Right TST increases exercise performance with the ipsilateral arm. (2) Sympathetic denervation produces important changes in the bioenergetics of the working muscle, ie, it retards exercise-induced muscle acidification and causes a significant reduction in PCr depletion and ADP concentration. These changes are associated with a significantly reduced pressor response to exercise. (3) Right FBF at rest and at the beginning of exercise is greater after sympathetic denerva-

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**TABLE 1. Hemodynamic Measurements at Rest Before and After Right TST**

<table>
<thead>
<tr>
<th></th>
<th>Right Forearm</th>
<th>Left Forearm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before TST</td>
<td>After TST</td>
</tr>
<tr>
<td>FBF, mL · 100mL⁻¹ · min⁻¹</td>
<td>4.5 ± 0.7</td>
<td>6.6 ± 1.1*</td>
</tr>
<tr>
<td>FVR, ru</td>
<td>22 ± 3</td>
<td>13 ± 1†</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>75 ± 5</td>
<td>70 ± 4</td>
</tr>
</tbody>
</table>

ru indicates resistance units.

*P < 0.05, †P < 0.01 for the effect of right TST.
tion, but at the same absolute workload, differences become smaller as the exercise progresses.

Because blood flow in working muscles increases proportionately to the intensity of dynamic exercise, it has been proposed that the vasoconstrictor effect of the exercise-induced increase in sympathetic activity must be offset by the local release of metabolites. Some experiments, however, have indicated that sympathetic activity might still be able to oppose metabolic vasodilatation in the exercising muscle. Such persistent sympathetic vasoconstriction may be required for maintaining arterial blood pressure during intense whole-body dynamic exercise. However, when the working muscle mass is small, sympathetic vasoconstriction could impair exercise performance by limiting muscle oxygenation or other substrate delivery. In our study, the difference in FBF and FVR before and after sympathetic denervation became smaller as the exercise progressed, which is consistent with animal data showing that sympathetic vasoconstriction in the exercising muscle is inversely related to the intensity of exercise. In contrast, Hansen et al demonstrated that the reduction in muscle oxygenation that accompanies a reflex increase in sympathetic activity at rest is completely abolished during both mild and severe dynamic handgrip. In addition, they showed that oxygenation in the exercising muscle is not affected by the inhibition of sympathetic neurotransmission by regional infusion of bretylium tosylate. These data suggest that mechanisms other than enhanced oxygenation might contribute to the improvement in exercise performance and muscle bioenergetics observed in our patients after TST.

Sympathetic activity could adversely affect exercise performance by its direct influence on skeletal muscle metabolism and/or fiber composition. Acute α- and β-adrenergic stimulation increases metabolic rate and glycogenolysis in the contracting muscle, whereas chronic adrenoceptor blockade causes a ubiquitous reduction in glycolytic fast-twitch (type II) fibers and a relative increase in slow-twitch (type I) fibers. The latter generate their energy largely through oxidative phosphorylation of pyruvate and fatty acids and are slow to contract and to fatigue (ie, ideal for supplying energy for sustained submaximal work).

Data on the effect of sympathetic denervation on skeletal muscle biochemical characteristics are sparse and inconsistent. Henriksson et al did not show any change in the histochemical or enzymatic properties of the rat gastrocnemius muscle 12 weeks after unilateral abdominal sympathectomy. Conversely, Karlsson and Smith showed a significant reduction in the proportion of slow-twitch fibers in the canine gracilis muscle 14 weeks after unilateral lumbar sympathectomy. In our study, forearm exercise performance increased significantly 4 to 7 weeks after surgery. This was associated with a significant reduction in PCR depletion and muscle acidification during dynamic exercise, which is consistent with decreased glycolytic activity and/or a shift from fast- to slow-twitch fiber composition in the forearm muscles after TST. Interestingly, the level of intracellular ADP (the metabolite that is thought to control the rate of oxidative metabolism) was also reduced, suggesting that sympathetic denervation may lower both glycolytic energy production and the drive to oxidative phosphorylation. This apparent contradiction is consistent with a shift in muscle fiber-type composition after TST, but it might also reflect improved perfusion at the cellular level and changes in membrane transport processes (eg, more effective lactate efflux from the muscle).

### Table 2. Right Forearm Muscle Bioenergetics at Rest and During Rhythmic Handgrip Before and After Right TST

<table>
<thead>
<tr>
<th></th>
<th>Before TST</th>
<th>After TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>7.05±0.01</td>
<td>7.00±0.01</td>
</tr>
<tr>
<td>Matched workload</td>
<td>6.73±0.07</td>
<td>6.90±0.05</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>6.73±0.07</td>
<td>6.83±0.07</td>
</tr>
<tr>
<td>PCr/(Pi+PCr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.90±0.01</td>
<td>0.90±0.01</td>
</tr>
<tr>
<td>Matched workload</td>
<td>0.35±0.04</td>
<td>0.55±0.05</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>0.35±0.04</td>
<td>0.49±0.06</td>
</tr>
<tr>
<td>ADP, μmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>7±1</td>
<td>6±1</td>
</tr>
<tr>
<td>Matched workload</td>
<td>61±10</td>
<td>37±6†</td>
</tr>
<tr>
<td>Peak exercise</td>
<td>61±10</td>
<td>44±8</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001 for differences before and after TST.

**Figure 3.** Right forearm muscle bioenergetics before and after TST. Top, Time course of changes in muscle pH and phosphocreatine, which is expressed as PCr/(PCr+Pi) ratio, in right flexor digitorum superficialis during rhythmic handgrip in one patient before and after right TST. Solid vertical line indicates onset of exercise, and dotted line, matched workload. Note increase in exercise duration and reduction in muscle acidification and phosphocreatine depletion after TST. Bottom, 31P MRS at rest and at matched workload in same patient, before and after right TST.
In humans, the reflex sympathetic activation elicited by rhythmic handgrip is coupled with a decrease in the intracellular pH of the working muscle, which agrees with the hypothesis that muscle biochemical events (in particular, glycolysis) play an important part in the sympathetic and pressor response to exercise. Although muscle pH at rest was slightly reduced after sympathetic denervation (consistent with a tonic control of the Na+/H+ exchanger or other membrane transport systems by sympathetic nerve activity), a significant attenuation occurred in both muscle acidification and the pressure response to right handgrip (Table 2 and Figure 3) after right TST. Further studies of 8 patients with palmar hyperhidrosis demonstrated that TST is not associated with muscle sensory deaffereation because both the pressor and pain response to ischemic cuff occlusion of the right arm at peak exercise did not change after right TST (data not shown).

Left forearm exercise duration increased slightly after the operation, probably as a result of familiarization with the exercise test or, less likely, a true influence of right TST on left forearm skeletal muscle performance. We did not perform P MRS studies in the left forearm; nevertheless, the absence of change in FBF (Table 1) and the MAP response to left handgrip after the operation (Figure 1) indicate that right TST is unlikely to affect muscle bioenergetics in the contralateral forearm. Finally, right TST was associated with a significant reduction in heart rate at rest and during exercise, but the chronotropic response to right or left handgrip did not differ after the operation (Figure 1). These findings confirm that the pressor (but not the chronotropic) response to dynamic exercise is dependent on the metabolic behavior of the working muscle.

Our study may have important implications for patients with congestive heart failure who have increased sympathetic activity and reduced exercise tolerance due to premature muscle fatigue. These patients show significantly increased intracellular acidification and PCR depletion in the working muscle and a greater proportion of glycolytic fast-twitch fibers. Acute sympathetic inhibition with clonidine in patients with CHF increases blood flow in the exercising limb, but it does not affect exercise performance, which is consistent with the idea that changes in skeletal muscle fiber composition secondary to chronic sympathetic inhibition may play an important role in the improvement in muscle bioenergetics and exercise duration seen in our subjects 4 to 7 weeks after TST. Sympathetic hyperactivity, however, is only a component of the heart failure syndrome, and further work is required to test whether chronic inhibition of adrenergic activity can reverse the skeletal muscle abnormalities of patients with congestive heart failure.

Acknowledgments

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References


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