Effects of chronic sympathectomy on vascular function in the human forearm

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Effects of chronic sympathectomy on vascular function in the human forearm. J Appl Physiol 92(6): 2019–2025, 2002.—To determine whether endothelial function is altered by chronic surgical sympathectomy, we infused ACh, isoprotenerol, nitroprusside (NTP), and the nitric oxide synthase inhibitor N\(_{\text{G}}\)-mono-methyl-L-arginine (l-NMMA) into the brachial arteries of nine patients 5–64 mo after thoracic sympathectomy for hyperhidrosis. Age- and gender-matched controls were also studied. Forearm blood flow (FBF) was measured by venous occlusion plethysmography. Lower body negative pressure was used to assess reflex vasoconstrictor responses. Tyramine, which acts locally and causes norepinephrine release from sympathetic nerves, was also administered via the brachial artery. FBF at rest was 2.5 ± 0.4 ml·dl\(^{-1}\)·min\(^{-1}\) in the patients and 2.5 ± 0.3 ml·dl\(^{-1}\)·min\(^{-1}\) in the controls (\(P = 0.95\)). The normal vasoconstrictor responses to lower body negative pressure were abolished in the patients. By contrast, tyramine produced dose-dependent vasoconstriction in the patients that was identical to that of controls. The dose-response curves to ACh were similar in patients and controls, with maximum values of 19.3 ± 4.4 vs. 25.5 ± 2.8 ml·dl\(^{-1}\)·min\(^{-1}\), respectively. l-NMMA reduced baseline FBF similarly and reduced the maximal FBF response to ACh in both groups (patients 8.9 ± 3.5 vs. controls 9.7 ± 2.5 ml·dl\(^{-1}\)·min\(^{-1}\)). The vasodilation to isoprotenerol was similar and blunted to the same extent in both groups by l-NMMA. The responses to NTP in patients and controls were similar and not affected by l-NMMA. We conclude that, in humans, chronic surgical sympathectomy does not cause major disruptions in vascular function in the forearm. The normal vasoconstrictor responses to tyramine indicate that there were viable sympathetic nerves in the forearm that were not engaged by LBNP.

forearm blood flow; endothelium; vasodilation; nitric oxide; tyramine

IMMEDIATELY AFTER SURGICAL sympathectomy, forearm blood flow (FBF) increases dramatically because of a lack of sympathetic vasoconstriction. However, after a few weeks, resting blood flow returns to pre sympathetec-
To test this hypothesis, we performed pharmacological studies of endothelial function in the forearms of sympathectomized patients and control subjects.

MATERIALS AND METHODS

Subjects. Nine patients (8 men, 1 woman, ages 25–45 yr) were studied 5–64 mo after bilateral endoscopic thoracic sympathectomy for palmar hyperhidrosis (26). They were compared with age- and gender-matched controls. Both groups were studied in the same laboratory environment January through March of 2001. The protocols were approved by the Institutional Human Subjects Committee, and each patient and subject gave written informed consent. Subject characteristics are shown in Table 1. The female patient and control had negative serum pregnancy tests within 12 h before participation. All sympathectomy patients reported anhidrosis of the upper extremities. One patient was on low-dose amitriptyline (discontinued 24 h before the study) for bothersome hyperhidrosis of the lower extremities. Another patient with mild narcolepsy was taking pemoline, withdrawn 3 days before the study. One patient and one control subject with hypertension were taking atenolol, which was discontinued 24 h before the study.

Subject instrumentation. Heart rate was monitored by use of a five-lead electrocardiogram. A 20-gauge, 5-cm catheter was placed in the brachial artery of the nondominant arm under aseptic conditions after local anesthesia (1% lidocaine). A three-port connector was placed in series with a catheter-transducer system so that drugs could be infused simultaneously (7).

FBF. FBF was measured by use of venous occlusion plethysmography with a mercury-in-Silastic strain gauge placed around the nondominant forearm at its greatest circumference (10). During recording, a wrist cuff was continuously inflated to suprasystolic pressure (250 mmHg) to occlude arterial blood flow to the hand while a venous occlusion cuff around the upper arm was inflated to 50 mmHg for 7.5 of every 15 s, providing one blood flow measurement every 15 s. FBF values were expressed as ml/100 ml tissue−1 min−1.

LBNP. To confirm that the patients were effectively sympathectomized, lower body negative pressure (LBNP) was used to cause graded venous pooling and activate the sympathetic nervous system (14, 24). Each subject was placed in a LBNP box before arterial cannulation. Arterial catheter placement was followed by 15 min of rest. Blood flow was then measured for 2 min at rest, followed by 2 min at 10, 20, and 30 mmHg of negative pressure.

Drug infusion protocol and drug doses. To normalize drug doses, each subject’s forearm volume was measured by water displacement. All study drugs were administered at rates of 2–3 ml/min. After LBNP, a cumulative FBF dose-response curve to intraarterial tyramine was performed. After this, incremental infusions of sodium nitroprusside (NTP), isoprenaline, and Ach were administered before and after NO1-mono-methyl-L-arginine (L-NMMA; Fig. 1). Each dose of each drug was administered for 2–3 min, and the dose-response determinations were separated by 20 min of quiet rest. Tyramine was used to test for residual sympathetic function because it evokes norepinephrine "leakage" from neuronal vesicles and consequent diffusion of norepinephrine out of the nerve terminal (9, 31). Tyramine also has no intrinsic vasodilating properties (5). It was infused for 3 min at 3, 6, and 12 μg·dl−1 tissue−1·min−1 (9). To test NO-mediated endothelium-independent vasorelaxation, the NO donor sodium nitroprusside was infused for 2 min at 0.25, 0.5, 1.0, and 2.0 μg·dl−1 tissue−1·min−1 (7, 8). To test β-adrenergic receptor-mediated vasodilation, isoprenaline was infused for 2 min at 1.0, 3.0, 6.0, and 12.0 ng·dl−1 tissue−1·min−1 (6). To test endothelium-dependent vasodilation, Ach was infused for 2 min at 1.0, 2.0, 4.0, and 8.0 μg·dl−1 tissue−1·min−1 (32).

After the initial drug infusions and return of forearm flow to baseline levels, the wrist cuff was reinflated and the eNOS inhibitor L-NMMA (50 mg) was infused over 10 min while FBF was measured (7, 8, 32). This was followed by a "maintenance" dose of L-NMMA (1 mg/min) throughout the remainder of the protocol. Administration of the three vasodilating drugs was then repeated in reverse order (ACh, isoprenaline, and NTP). We reasoned that if any differences between the patients and controls were due to NO production, then the responses after L-NMMA would be similar. The order of drug administration was not randomized so that the repeat doses of Ach could be given immediately after L-NMMA, so that we could immediately assess the magnitude of the NOS inhibition.

Data analysis. Data were digitized at 200 Hz and stored on computer. Data were analyzed off-line with signal processing software (Windaq; Dataq Instruments, Akron, OH). FBF was determined from the derivative of the forearm plethysmogram during the last 2 min of each increment of LBNP and during the last minute of each drug dose. Heart rate was derived from the electrocardiogram waveform. Mean arterial pressure (MAP) was derived from the arterial pressure waveform. Forearm vascular conductance (FVC) was calculated as ([FBF/MAP] × 100) and expressed as arbitrary units. These units were used because they are quantitatively similar to standard FBF values (25). For the LBNP data, FVC was reported because it accounts for the modest decreases in MAP during LBNP. For the remainder of the study, FBF was reported because it was the primary measured variable in the pharmacological dose-response curves and because there were negligible changes in MAP during the isolated forearm drug infusions.

Statistics. For subject characteristics (Table 1), the two groups were compared by using the two-sample t-test for all variables except gender, which was compared by using Fisher’s exact test. Repeated measures analysis of variance (ANOVA) was used to assess differences between sympathectomy and control subjects at various doses of LBNP and the
were similar between the two groups. At the highest ACh dose (8.0 μg·dl tissue⁻¹·min⁻¹), maximal FBF response was 19.3 ± 4.4 ml·dl⁻¹·min⁻¹ in the patients vs. 25.5 ± 2.8 ml·dl⁻¹·min⁻¹ in the controls. L-NMMA reduced resting FBF from 3.6 ± 0.3 to 1.8 ± 0.2 ml·dl⁻¹·min⁻¹ in the sympathectomy patients and 3.2 ± 0.3 to 1.9 ± 0.3 ml·dl⁻¹·min⁻¹ in controls with no differences observed between groups. Furthermore, maximal FBF response to ACh was reduced to 8.9 ± 3.5 in patients vs. 9.7 ± 2.5 ml·dl⁻¹·min⁻¹ in controls. The effect of L-NMMA was not significantly different between patients and controls.

### RESULTS

Selected subject characteristics are shown in Table 1. Baseline FBF and FVC were similar in both groups. Body weight was higher and blood pressure tended to be higher in patients vs. controls.

**Vasoconstrictor responses.** In the sympathectomy patients, FBF was 2.5 ± 0.4 ml·dl⁻¹·min⁻¹ at baseline and 2.3 ± 0.3 ml·dl⁻¹·min⁻¹ at −30 mmHg LBNP. In control subjects, FBF was 2.5 ± 0.3 ml·dl⁻¹·min⁻¹ at baseline and decreased to 1.3 ± 0.2 ml·dl⁻¹·min⁻¹ at −30 mmHg LBNP. In the patients, MAP was 105 ± 4.4 mmHg at baseline and 99 ± 3.5 mmHg at −30 mmHg LBNP. In control subjects, MAP was 99 ± 3.7 mmHg at baseline and 94 ± 3.7 mmHg at −30 mmHg LBNP. Figure 2 displays the percent change from baseline FVC in response to changes in LBNP. A decline in FVC was observed with increasing LBNP for the control group whereas FVC remained unchanged in the sympathectomy group (P < 0.001 for the main effects of dose and sympathectomy, and P = 0.007 for the sympathectomy-by-dose interaction). By contrast, tyramine reduced FBF equally in both groups at every dose as shown in Fig. 3 (P < 0.001 for dose, P = 0.618 for sympathectomy, and P = 0.699 for the dose-by-sympathectomy interaction). At maximal concentration of tyramine (12 μg·dl tissue⁻¹·min⁻¹), FBF fell to 1.2 ± 0.1 ml·dl⁻¹·min⁻¹ in patients and 1.2 ± 0.2 ml·dl⁻¹·min⁻¹ in controls.

**Vasodilator responses.** There were no significant differences between patients and controls in the endothelium-dependent forearm vasodilation to ACh (P < 0.001 for dose, P = 0.523 for sympathectomy, and P = 0.348 for the dose-by-sympathectomy interaction). As can be seen in Fig. 4, the dose-response relationships were similar between the two groups. At the highest ACh dose (8.0 μg·dl tissue⁻¹·min⁻¹), maximal FBF response was 19.3 ± 4.4 ml·dl⁻¹·min⁻¹ in the patients vs. 25.5 ± 2.8 ml·dl⁻¹·min⁻¹ in the controls. L-NMMA reduced resting FBF from 3.6 ± 0.3 to 1.8 ± 0.2 ml·dl⁻¹·min⁻¹ in the sympathectomy patients and 3.2 ± 0.3 to 1.9 ± 0.3 ml·dl⁻¹·min⁻¹ in controls with no differences observed between groups. Furthermore, maximal FBF response to ACh was reduced to 8.9 ± 3.5 in patients vs. 9.7 ± 2.5 ml·dl⁻¹·min⁻¹ in controls. The effect of L-NMMA was not significantly different.

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**Table 1**

<table>
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<th>Sympathectomy</th>
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<th>LBNP</th>
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**Fig. 1.** Timeline of protocol for sympathectomized patients and controls. After tyramine, 3 vasodilators (sodium nitroprusside (NTP), isoproterenol, and ACh) were individually administered and then given in reverse order after a bolus and continuous infusion of Nω-mono-methyl-L-arginine (L-NMMA). FBF, forearm blood flow; t, time.

**Fig. 2.** Average forearm vascular responses to lower body negative pressure (LBNP) in sympathectomized individuals and control subjects. A decline in forearm vascular conductance (FVC) was observed with increasing LBNP for the control group, whereas FVC remained unchanged in the sympathectomy group. To supplement the repeated-measures analysis, the paired t-test was used for each group to compare FVC to baseline at each dose level. *Significant (P < 0.05) differences from baseline.
controls throughout. FBF was similar in the patients and controls. After L-NMMA, the peak vasodilator response to tyramine was 18.8 ± 0.6 ml·dl⁻¹·min⁻¹, whereas the controls had 19.9 ± 0.5 ml·dl⁻¹·min⁻¹. There were no differences between groups in the responses to isoproterenol, which was reduced to the same extent in the sympathectomy group vs. 20.2 ± 1.6 ml·dl⁻¹·min⁻¹ in the controls. There was no difference in endothelial nitric oxide synthase inhibition by intravenous L-NMMA in sympathectomy patients and controls. There was no evidence to suggest that this effect differed for sympathectomy vs. control.

DISCUSSION

There are four main findings of our study. First, endothelium-dependent forearm vasodilation was neither augmented or attenuated in humans months or years after endoscopic thoracic sympathectomy. Nitric oxide synthase inhibition by intra-arterial L-NMMA also decreased basal FBF and markedly inhibited the response to ACh to a similar extent in both patients and controls. This indicates that endothelial function was not altered in a major way by surgical sympathectomy. Second, β-adrenergic vasodilation was also similar in the patients and controls, and L-NMMA partially inhibited the dilator response to isoproterenol. Third, vascular smooth muscle responsiveness to NTP (and hence NO) was preserved after sympathectomy. Fourth, sympathectomy patients showed a normal (and puzzling) vasoconstrictor response to tyramine in spite of the fact that they do not report sweating and do not demonstrate vasoconstriction during LBNP. The physiological implications of these findings and the limitations associated with our experimental design will now be discussed in detail.

Sympathectomy and endothelial function. Our patients’ normal responses to both ACh and L-NMMA are at odds with the animal studies that showed either nearly undetectable levels of eNOS after chemical sympathectomy with guanethidine or blunted vasorelaxation to endothelial stimulation after surgical sympathectomy (1, 16, 17). One possible explanation is that the sympathectomies generated in the models were

for sympathectomy patients compared with controls (i.e., no significant interactions were detected). The sympathectomy patients who were taking pemoline and amitriptyline did not differ qualitatively from the other patients or controls.

There also were no differences between groups in the forearm vasodilation responses to isoproterenol (P < 0.001 for dose, P = 0.913 for the dose-by-sympathectomy interaction; see Fig. 5). In the absence of L-NMMA, maximal FBF in response to isoproterenol was 14.0 ± 2.4 ml·dl⁻¹·min⁻¹ in the patients vs. 13.8 ± 1.3 ml·dl⁻¹·min⁻¹ in the controls. After L-NMMA, the peak vasodilator response to isoproterenol was reduced to the same extent in the patients (10.3 ± 1.4 ml·dl⁻¹·min⁻¹) and in the controls (10.1 ± 0.9 ml·dl⁻¹·min⁻¹).

Figure 6 shows the FBF responses to sodium NTP in patients and controls. There was no difference in endothelium-independent forearm vasodilation (P < 0.001 for dose, P = 0.444 for sympathectomy, and P = 0.516 for the dose-by-sympathectomy interaction). Before L-NMMA, at the highest NTP dose (2.0 μg·dl⁻¹·min⁻¹), FBF was 18.8 ± 3.3 ml·dl⁻¹·min⁻¹ in the sympathectomy group vs. 20.2 ± 1.4 ml·dl⁻¹·min⁻¹ in the control group. After L-NMMA, there was no change in maximal FBF to NTP both within and between the sympathectomy patients (19.9 ± 2.3 ml·dl⁻¹·min⁻¹) and controls (23.8 ± 1.6 ml·dl⁻¹·min⁻¹).

J Appl Physiol • VOL 92 • MAY 2002 • www.jap.org
more "complete" than in the patients. In view of the absent constrictor responses to LBNP but the preserved constrictor responses to tyramine, it seems reasonable to speculate that the patients retained or regenerated some functional postganglionic sympathetic nerves in their forearms. However, it appears that these nerves could not be activated by normal baroreflex (or thermoregulatory) mechanisms. This possibility was raised in the 1940s, but, in contrast to our patients, the patients studied earlier had physiological signs (sweating) consistent with the reinnervation (4). In view of our findings with tyramine, we speculate that the "normal" trophic interactions between the sympathetic nerves and endothelium were still present in the patients we studied.

Our findings that endothelial function was not altered by sympathectomy are also at odds with Lepori et al. (19). These authors reported that forearm vasoconstrictor responses to systemic (i.e., whole body) infusion of l-NMMA were augmented (in comparison to the nonsympathectomized calf) in patients who have undergone thoracic sympathectomy. They interpreted their data to suggest enhanced NO synthesis or bioavailability after sympathectomy. However, the increase in arterial blood pressure during systemic l-NMMA could have evoked a baroreflex-mediated reduction in sympathetic outflow to the calf but not the forearm in these patients (12). This means that the constriction caused by l-NMMA was unopposed in the forearm but that it was probably offset by sympathetic withdrawal in the calf. Thus the greater forearm vasoconstriction observed by Lepori et al. was probably not due to greater NO "tone" after sympathectomy. Along these lines, our results seem most consistent with the experiments in rats and dogs that showed unchanged ACh-evoked vasodilation after either chemical or surgical sympathectomy (18, 27). Finally, because the dilator responses to the NO donor NTP were similar in the patients and controls, it is unlikely that our results could be explained by differences in how the vessels responded to NO.

**Responses to tyramine and isoproterenol.** As discussed earlier, the preserved vasoconstrictor responses to tyramine in the absence of vasoconstriction to LBNP suggest that there was at least some viable postganglionic sympathetic innervation in the forearm after sympathectomy. This conclusion is supported by the isoproterenol dose-response curves. If there had been a complete absence of sympathetic innervation, then it would have been reasonable to expect augmented β2-mediated vasodilation in the patients as a result of upregulation of β-receptors.

In this context, we can only speculate as to what mechanisms might be preserving the postganglionic sympathetic nerves. First, it is possible that T2 sympathectomy only disconnects the vasoconstrictor nerves to the forearm from cardiovascular and thermoregulatory reflexes and that the postsynaptic nerves to the forearm are sustained from another level of the sympathetic chain or from other neural structures (22, 29). If this occurs, it may take some time because there is typically marked vasodilation after sympathectomy with a return of vascular tone over several weeks (2). This may also explain why therapeutic sympathectomies for va-
ious clinical syndromes are initially effective but fail over time (21, 23, 28). A second mechanism that might sustain the postganglionic nerves after sympathectomy is the venoarteriolar axon reflex (13). This is a powerful reflex that acts locally to cause norepinephrine release when the limb veins are distended. This reflex is retained in patients with spinal cord lesions, but it is not known whether it remains active in patients similar to those we studied (13). Whatever the mechanism, it would appear that ganglionic connections that respond to baroreflex input were destroyed but that at least some postganglionic neurons that could be stimulated by tyramine remained functional.

Finally, it should be noted that in a previous study conducted many years ago, one sympathectomy patient received intra-arterial tyramine and showed no vasoconstrictor response (9). This raises the possibility that the older surgical techniques differ from the approach used in the patients we studied (26, 30). If this were the case, then any trophic interactions between the sympathetic nerves and endothelium might have been eliminated with at least one of the older techniques. This would then explain the previously noted absence of vasodilator responses now thought to be mediated by endothelial NO release (3). However, the technique used in our patients results in an almost immediate rise in finger temperature to 36°C that falls over several weeks, and this response is consistent with the earlier observations on the time course of blood flow changes after surgical sympathectomy (2).

Limitations. There are several limitations that should be noted. First, the patients had higher baseline blood pressure levels and tended to be heavier. These two factors can cause blunted vasodilator responses to ACh and might explain why the peak blood flow response to ACh tended to be lower in the patients. In this context, these differences might have reached significance had we studied more subjects, but the patients still had robust blood flow responses to ACh. The second major limitation is that the baseline flows after 1-NMMA (but before the second isoproterenol or NTP trials) tended to drift upward. This suggests that the maintenance dose of 1-NMMA was not effective. However, the blood flow responses to isoproterenol after 1-NMMA were still blunted in a manner consistent with previous reports from the literature, suggesting adequate NOS inhibition throughout the second half of the study (5). A more likely explanation for this drift is that the baseline flows did not return to their absolute minimum during the 20-min rest period between administration of the various vasodilator drugs.

In summary, our current observations suggest that loss of endothelial function is not responsible for the return of tone that occurs in the forearm weeks and months after surgical sympathectomy. Our observations also either refute the idea that there are major trophic interactions between the sympathetic nerves and vascular endothelium in humans or suggest that any trophic relationship between the sympathetic nerves and the vascular endothelium was somehow maintained in the absence of functional thermoregulatory and baroreflex-mediated connections between the CNS and forearm sympathetic nerves.

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