Effects of chronic sympathectomy on vascular function in the human forearm

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To determine whether endothelial function is altered by chronic surgical sympathectomy, we infused ACh, isoproterenol, nitroprusside (NTP), and the nitric oxide synthase inhibitor N\(^\text{\text{-}}\)mono-methyl-L-arginine (\(^\text{\text{-}}\)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 to lower body controls were also studied. Forearm blood flow (FBF) was increased because of a normal vasoconstrictor response to tyramine indicates that major disruptions in vascular function in the forearm. The normal forearm vasodilator response to mental stress and other sympathoexcitatory maneuvers were NO dependent since the forearm dilator responses to mental stress and other sympathoexcitatory maneuvers were NO dependent but probably not caused by vasodilator nerves, suggesting an important role for the vascular endothelium (7, 8, 11, 20, 25). When the older data are viewed in light of the newer findings, the implication is that endothelial function in the human forearm is impaired after surgery (1, 16, 17). With this information as background, the purpose of our study was to test the hypothesis that endothelium-mediated vasodilation in the forearm will be blunted in patients who have undergone surgical sympathectomy.
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 from 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 within 12 h before participation. All sympathectomy patients –

**Gender, male/female** 7/1 8/1 1.0

**Age, yr** 32.6 ± 3.3 32.7 ± 3.2 0.99

**Height, cm** 179.4 ± 2.9 179.8 ± 2.6 0.92

**Weight, kg** 75.7 ± 1.9 88.7 ± 5.2 0.04

**Systolic blood pressure, mmHg** 119 ± 6 131 ± 7 0.20

**Diastolic blood pressure, mmHg** 73 ± 3 80 ± 3 0.06

**Mean arterial pressure, mmHg** 88 ± 3 97 ± 4 0.09

**Baseline forearm blood flow, ml·min⁻¹** 2.5 ± 0.3 2.5 ± 0.4 0.95

**Baseline forearm vascular conductance, units** 2.6 ± 0.3 2.4 ± 0.4 0.74

**Months after sympathectomy** 29.6 ± 8.14

*Values are means ± SE. The 2 groups were compared by using the 2-sample *t*-test for all variables except gender, which was compared by using Fisher’s exact test.*

**Table 1. Subject characteristics**
four different drug infusion conditions (tyramine, NTP, isoproterenol, and ACh). For these analyses, either FVC or FBF was the dependent variable, sympathectomy was an independent cross-classification variable, and dose was the repeated factor. In addition, for NTP, isoproterenol, and ACh, additional repeated-measures models were used in which the presence or absence of L-NMMA was included as a second repeated factor. In all cases, data are reported as means ± SE. Significance was set at the P < 0.05 level.

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.

Vasocoonstrictor 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. To supplement the repeated-measures analysis, the paired t-test was used for each group to compare FVC to baseline at each dose level. *Significantly different (P < 0.05) from baseline.

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⁻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.
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, $P = 0.942$ for sympathectomy, and $P = 0.913$ for the main effect of sympathectomy and the sympathectomy-by-dose interaction). Before $L$-NMMA, at the highest NTP dose ($2.0 \mu g\cdot dl^{-1}\cdot min^{-1}$), FBF was $18.8 \pm 3.3 ml\cdot dl^{-1}\cdot min^{-1}$ in the sympathectomy group vs. $20.2 \pm 1.4 ml\cdot dl^{-1}\cdot min^{-1}$ in the control group. After $L$-NMMA, there was no change in maximal FBF to NTP both within and between the sympathectomy patients ($19.9 \pm 2.3 ml\cdot dl^{-1}\cdot min^{-1}$) and controls ($23.8 \pm 1.6 ml\cdot dl^{-1}\cdot min^{-1}$).

**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, $\beta$-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
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 during 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 \(\beta_2\)-mediated vasodilation in the patients as a result of upregulation of \(\beta_2\)-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 var-
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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