Sympathetic Nerves in the Tarsal Tunnel: Implications for Blood Flow in the Diabetic Foot

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Digital sympathectomy is a well-known and established treatment for medically refractory Raynaud's disease, a vasospastic disorder thought to result from an overactive sympathetic nervous system. Morgan et al. first localized the sympathetic nerves in the hands and fingers.[1] Subsequent prospective and retrospective studies showed that digital sympathectomy is effective for ulcer healing, and for ulcer and amputation prevention.[2–4] Demonstrating sympathetic fibers within the tarsal tunnel would be a first step in providing a basis for applying these upper extremity concepts to the lower extremity.

Lower extremity peripheral neuropathy with superimposed nerve compression has been treated successfully by decompression surgery.[5–7] Aszmann et al. also demonstrated that tarsal tunnel decompression can change the natural history of lower extremity peripheral neuropathy by reducing the incidence of future ulceration and amputation. In their 50-patient cohort who had lower extremity nerves decompressed on only one extremity, none of the decompressed extremities went on to have any wound complications, whereas 12 ulcerations and three amputations occurred in 15 different patients in the contralateral limb over a 4.5-year follow-up period.[8] These patients also had documented improvement in sensation to the feet of their operated legs; thus, one reason for this lack of wound problems is increased protective sensation. Other possibilities that have yet to be evaluated are enhanced blood flow sresulting from vessel dilatation, such as might occur with a "sympathectomy" performed with epineurectomy during decompression. To elucidate this potential mechanism, we first attempted to identify sympathetic nerve fibers in the tarsal tunnel using immunohistochemical methods.

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PATIENTS AND METHODS

Seven consecutive patients evaluated at our clinic were enrolled in this pilot study, which was approved by the institutional review board of our university. All patients had neuropathy as documented by their clinical history, physical examination, and use of the Pressure-Specified Sensory Device (Sensory Management Services, Baltimore, Md.), a valid and reliable measuring tool for peripheral neuropathy.[9–11] Five of the patients were men and three were diabetic. The mean age of our patients was 62 years. During tarsal tunnel decompression, all of which took place between March of 2007 and May of 2007, all patients had a partial epineurectomy of the tibial nerve, a portion of which was sent as a specimen. In addition, we normally dissect and remove the connective tissue between the tibial nerve and vessels, as this tissue is often thickened, much like the proliferative sy-

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novium in a rheumatoid patient with carpal tunnel syndrome (Fig. 1). This tissue was also harvested as a specimen.

Specimens were fixed in 10% neutral buffered formalin for 3 to 4 hours and then embedded in paraffin. Three-micron sections were obtained from the block and used for immunohistochemistry, which was performed using a mouse monoclonal antibody against tyrosine hydroxylase (MO20001; Neuromics, Edina, Minn.) diluted 1:50 in Discovery Diluent (Ventana Medical Systems, Inc., Tucson, Ariz.) on a Discovery XT Automated Immunostainer (Ventana Medical Systems). Deparaffinization, cell conditioning (antigen retrieval), primary antibody staining, detection with biotinylated-streptavidin-horseradish peroxidase and diaminobenzidine, and hematoxylin counterstaining were performed on this instrument using Ventana Medical Systems–validated reagents. After staining, slides were dehydrated through graded alcohols, cleared by xylene, and cover slipped with Pro-Texx mounting medium (Baxter Diagnostics, Deerfield, Ill.). Images were captured using a Nikon Labophoto-2 Paxcam digital camera (Nikon, Tokyo, Japan) and PaxIt imaging software (MIS, Villa Park, Ill.). Images were standardized for light intensity. Tyrosine hydroxylase antibody is well known to be specific for noradrenergic neurons and was therefore used to evaluate for the presence of sympathetic nerves.[12] As a positive control, an adrenal gland biopsy specimen was obtained from the University of Arizona Pathology Department and processed with tyrosine hydroxylase antibody in a similar manner.

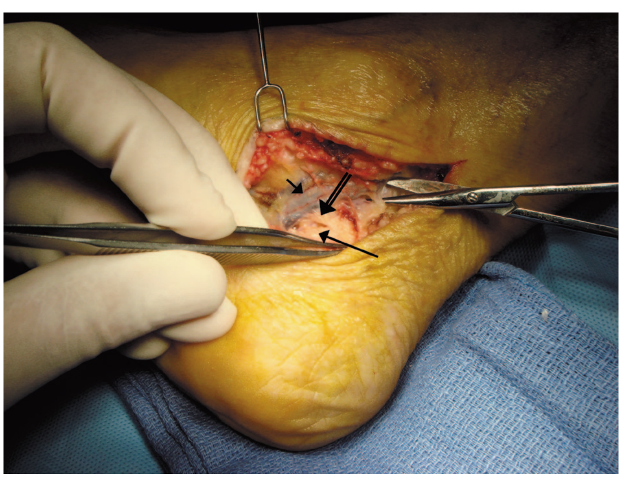

Fig. 1. Representative photograph of a patient undergoing tarsal tunnel decompression. The *small arrow* points to the tibial vessels. The *long arrow* points to the tibial nerve, which branches distally into medial and lateral plantar nerves and which has been subjected to epineurectomy. The *double arrow* points to the thickened connective tissue between the tibial nerve and vasculature that is sent as a specimen.

RESULTS

All slides were reviewed by a senior pathologist. The results of these reviews are listed in Table 1. Five of seven tibial epineurial specimens stained positively with tyrosine hydroxylase, whereas in two specimens, no nervous tissue was found (Fig. 2). Five of six connective tissue specimens stained positively with tyrosine hydroxylase. One specimen was accidentally ruined during processing and one specimen contained no nervous tissue. Interestingly, tyrosine hydroxylase staining was concentrated solely around the periphery of the local microvasculature (Fig. 3).

DISCUSSION

In our present work, we have demonstrated that an epineurectomy of the tibial nerve also provides a localized sympathectomy to the posterior tibial artery. It remains to be determined whether including an epineurectomy of the tibial nerve during tarsal tunnel decompression can alter blood flow to the foot. This possibility is plausible, given the localization of sympathetic fibers along the local microvasculature in our specimens.

We were puzzled at first that some epineurial and connective tissue specimens lacked any nerve tissue. As we performed more procedures, however, we noticed that these patients had a significant degree of fibrosis within the tarsal tunnel perhaps resulting from severe and/or long-standing compression. The lack of nervous tissue in these specimens might therefore reflect the severe degree of fibroproliferation occurring around chronically compressed structures. In these patients, the primary benefit of nerve decompression surgery would be to improve sensation and decrease pain. If, however, future studies demonstrate an association between such nerve decompressions and blood flow to the foot, advanced cases such as these may represent a subpopulation of patients who might not see any change in blood flow and therefore may be at relatively higher risk for future wound problems. Finally, although past studies suggest that diabetic vessels are less compliant than those of nondiabetic patients,[13] there are also recent reports of potential imbalances in sympathetic and parasympathetic factors within the microcirculation of the diabetic foot. Specifically, Arora et al. found an impaired vasodilatory response to acetylcholine in the diabetic foot.[14] They argue that this mechanism might explain the

Table 1. Patient Demographic Information and Results of Staining with Tyrosine Hydroxylase in Epineurium and Connective Tissue Samples

	Demographic Information			Tyrosine Hydroxylase Staining	
Patient	Age (yr)	Sex	Diabetic Status	Epineurium	Connective Tissue
1	81	M	Yes	+	—*
2	65	M	No	+	+
3	58	M	Yes	+	+
4	63	F	No	No nerve found	+
5	54	F	No	+	+
6	69	M	No	No nerve found	+
7	45	M	Yes	+	No nerve found

M, male; F, female.
*Tissue lost during processing.

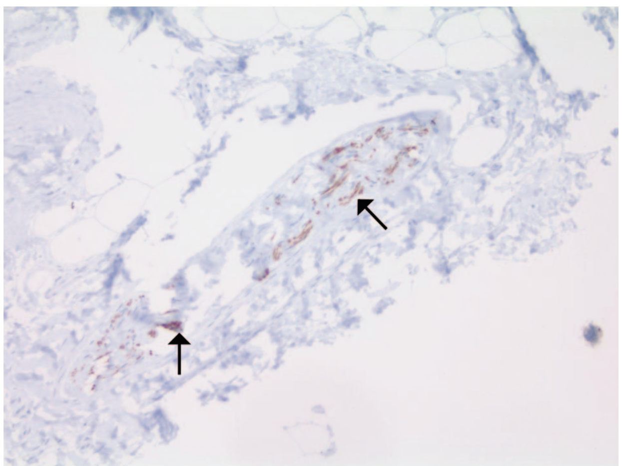

Fig. 2. Tyrosine hydroxylase immunohistochemical staining of tibial epineurium from the tarsal tunnel. Positively staining sympathetic fibers (*arrows*) are seen within a larger nerve bundle.

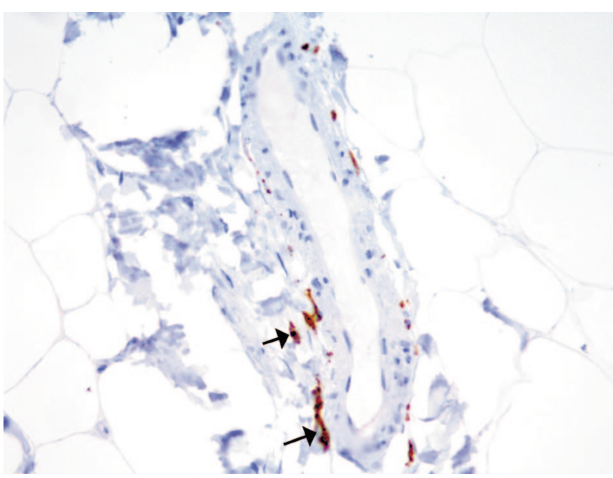

Fig. 3. Tyrosine hydroxylase immunohistochemical staining of connective tissue from the tarsal tunnel. Several positively staining sympathetic fibers (*arrows*) are seen innervating the media of a local venule.

persistence and/or development of foot ulcers in some diabetic feet despite adequate revascularization. Perhaps a sympathectomy such as we perform in our procedure might tilt the balance back in favor of vasodilatation.

Future studies will attempt to correlate similar staining results with blood flow measurements both before and after tarsal tunnel release. Direct measurements of improved capillary blood flow will more definitively demonstrate the effects of sympathectomy on the microvasculature of the foot. If blood flow were improved, perhaps our tarsal tunnel release with sympathectomy could be considered an adjunct to bypass surgery in patients with lower extremity peripheral vascular disease.

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