Sympathetic Innervation and Function in Reflex Sympathetic Dystrophy

David S. Goldstein, MD, PhD,* Cees Tack, MD,† and Sheng-Ting Li, MD*

Patients with reflex sympathetic dystrophy have posttraumatic pain disproportionate to the injury and spreading beyond the distribution of any single peripheral nerve. We examined sympathetic neurocirculatory function and the role of sympathetic postganglionic nerve traffic in maintaining the pain in 30 patients with reflex sympathetic dystrophy. Most had had the condition for more than 1 year, and 14 had undergone sympathectomy for the pain. Positron emission tomographic scanning after administration of $^{13}$N-ammonia was used to assess local perfusion, and $6^{-[18]}$fluorodopamine was used to assess sympathetic innervation. Rates of entry of norepinephrine in the regional venous drainage (spillovers) and regional plasma levels of L-dihydroxyphenylalanine (the immediate product of the rate-limiting enzymatic step in norepinephrine biosynthesis) and dihydroxyphenylglycol (the main neuronal metabolite of norepinephrine) were measured with and without intravenous trimethaparn for ganglion blockade. $^{13}$N-Ammonia–derived radioactivity was less on the affected side than on the unaffected side, whereas $6^{-[18]}$fluorodopamine–derived radioactivity was symmetrical. Thus, perfusion-adjusted $6^{-[18]}$fluorodopamine–derived radioactivity was higher on the affected side. Norepinephrine spillover and arteriovenous increments in plasma levels of L-dihydroxyphenylalanine and dihydroxyphenylglycol did not differ significantly between affected and unaffected limbs, although 4 patients had noticeably less norepinephrine spillover and smaller arteriovenous increments in plasma dihydroxyphenylglycol on the affected side. Trimethaparn decreased the pain in only 2 of 12 nonsympathectomized patients. The results indicate that patients with chronic unilateral reflex sympathetic dystrophy have decreased perfusion of the affected limb, symmetrical sympathetic innervation and norepinephrine synthesis, decreased release and turnover of norepinephrine in the affected limb, and failure of ganglion blockade to improve the pain in most cases. These findings suggest augmented vasoconstriction, intact sympathetic terminal innervation, possibly impaired sympathetic neurotransmission, and pain usually independent of sympathetic neurocirculatory outflows.


Reflex sympathetic dystrophy, renamed complex regional pain syndrome type I, 1 refers to posttraumatic pain that spreads from the site of injury; exceeds in magnitude and duration the expected clinical course of the inciting event; progresses variably over time; is associated with nonspecific symptoms and signs such as altered skin color, altered skin temperature, altered sudomotor activity, allodynia, disuse atrophy, or edema; and, in contrast to complex regional pain syndrome type II (formerly called causalgia), occurs in a distribution different than that resulting from injury to a single peripheral nerve.

The pathogenetic basis of reflex sympathetic dystrophy has been and remains controversial and unclear. As the name of the condition implies, investigators often view reflex sympathetic dystrophy as a disorder of the sympathetic nervous system. Neurophysiological and neurochemical studies have failed to support increased postganglionic sympathetic nerve traffic in reflex sympathetic dystrophy, 2,3 and a disappointingly large proportion of patients with chronic reflex sympathetic dystrophy have recurrence of pain after surgical or chemical sympathectomy. 4,5 Alternatively, partial sympathetic denervation might contribute to the pathogenetic process. 6 Thus, animal models of neuropathic pain based on chronic constriction injury to peripheral or spinal nerves often feature physiological, histological, or neurochemical evidence of local denervation. 6–8 Studies in both humans and animals have reported lower concentrations of the sympathetic neurotransmitter norepinephrine or of its neuronal metabolite dihydroxyphenylglycol in venous plasma from the affected side than from the opposite unaffected side. 2,3,9 These findings are consistent with the denervation hypothesis.

Damage to sympathetic effector fibers might secondarily increase expression of nerve growth factor or other

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Address correspondence to Dr Goldstein, NINDS, NIH, Building 10, Room 6N252, 10 Center Drive, MSC-1620, Bethesda, MD 20892–1620.

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neurotrophic factors, which could enhance pain transmission by a variety of mechanisms.\textsuperscript{10–15} Denervation supersensitivity of vascular smooth muscle cells might also develop, augmenting vasoconstrictor responses to norepinephrine released from nearby terminals or to circulating catecholamines. Consistent with this view, patients with upper extremity reflex sympathetic dystrophy have augmented constriction of cutaneous veins in response to locally administered norepinephrine in the affected limb.\textsuperscript{16}

The present study applied neuroimaging, neurochemical, and neuropharmacological approaches to address whether abnormalities of local sympathetic innervation or function occur in reflex sympathetic dystrophy. We carried out positron emission tomographic (PET) scanning of affected and opposite unaffected limbs of patients with reflex sympathetic dystrophy after administration of \textsuperscript{13}N-ammonia,\textsuperscript{17} which is a perfusion imaging agent, and then after injection of the sympathetic imaging agent 6-[\textsuperscript{18}F]fluorodopamine.\textsuperscript{18} In the same patients, we also estimated rates of entry of endogenous norepinephrine in the regional venous drainage (norepinephrine spillover) during intravenous infusion of \textsuperscript{3}H-norepinephrine.\textsuperscript{19,20} Norepinephrine spillover indicates the rate of entry into the extracellular fluid of norepinephrine that has been released from the nerve terminals and has escaped neuronal reuptake by the membrane norepinephrine transporter.\textsuperscript{21} Arteriovenous increments in plasma levels of dihydroxyphenylglycol, the main neuronal metabolite of norepinephrine, were used to examine local norepinephrine turnover.\textsuperscript{22,23} Turnover is total loss from the tissue, and under resting conditions, norepinephrine turnover depends mainly on net leakage and metabolism of norepinephrine from vesicular stores and not from norepinephrine release. Arteriovenous increments in plasma levels of L-dihydroxyphenylalanine, the immediate product of the enzymatic rate-limiting step in norepinephrine biosynthesis, were used to examine local norepinephrine synthesis.\textsuperscript{24,25} Under steady state conditions, norepinephrine turnover matches norepinephrine synthesis, with both far exceeding norepinephrine spillover.

To determine whether sympathetic nerve traffic maintains the pain in reflex sympathetic dystrophy, we studied the effects of inhibiting ganglionic neurotransmission acutely, using intravenous infusion of trimethaphan.

For comparison, we included patients who had undergone a surgical sympathectomy for reflex sympathetic dystrophy. All the sympathectomized patients had had recurrence of the pain after the operation. We also culled previously reported normal data\textsuperscript{26–30} about forearm blood flow and norepinephrine kinetics and obtained new data about foot blood flow and norepinephrine kinetics in age-matched normal volunteers.

Patients and Methods

The study protocol was approved by the Clinical Research Subpanel of the National Institute of Neurological Disorders and Stroke. Each subject gave informed written consent.

Patients

Data were obtained from a total of 30 patients (mean age, 40 years; range, 25–55 years; 9 men, 21 women) referred to the Clinical Neurosciences Program in the Division of Intramural Research of the National Institute of Neurological Disorders and Stroke for evaluation of reflex sympathetic dystrophy, usually of one limb. Nineteen patients had an affected hand, including 10 who had undergone thoracic sympathectomy. Fifteen patients had an affected foot, including 4 who had undergone a lumbar sympathectomy. The mean duration of disease was 5.2 years (range, 3 months to >20 years). Six patients had had reflex sympathetic dystrophy for 1 year or less.

Reflex sympathetic dystrophy was diagnosed from pain that (1) was posttraumatic; (2) had persisted and spread distally after the injury; (3) had a distribution different from that of any single peripheral nerve; and (4) was associated with swelling, altered skin color, altered skin temperature, altered sweating, alopecia, hair loss, trophic skin or nail changes, or disuse atrophy of skeletal muscle.

Twenty-eight of the 30 patients were taking one or more drugs for reflex sympathetic dystrophy, including codeine or a codeine-like drug (14 patients, with acetaminophen in 9 patients), a benzodiazepine (12 patients), a selective serotonin reuptake blocker (9 patients), an opiate or opiate-receptor agonist (9 patients), a nonsteroidal anti-inflammatory agent (8 patients), a muscle relaxant (7 patients), a nonbenzodiazepine sedative (5 patients), acetaminophen with propoxyphene (4 patients), gabapentin (4 patients), an \(\alpha\)-adrenoceptor blocker (3 patients), a calcium channel blocker (3 patients), an anticonvulsant (3 patients), a tricyclic antidepressant (3 patients), tramadol (3 patients), an "herbal" or "alternative" remedy (3 patients), an \(\alpha\)-adrenoceptor agonist (2 patients), or sumatriptan (2 patients). Medications for other conditions included an antihypertensive agent (5 patients: an angiotensin-converting enzyme inhibitor for hypertension in 3, a \(\beta\)-adrenoceptor blocker in 1, and a diuretic in 1), a thyroid supplement (4 patients), an estrogen supplement (4 patients), an antacid (3 patients), an antihistamine (2 patients), an oral hypoglycemic agent (2 patients), a phenothiazine for nausea (2 patients), an anticholinergic (1 patient), a cholesterol-lowering drug (1 patient), an anticoagulant (1 patient), a bronchodilator (1 patient), and an antiarrhythmic (1 patient). Patients were allowed to continue their drugs for reflex sympathetic dystrophy and their other medications, except that they tapered and stopped adrenoceptor-active drugs and tricyclic antidepressants before admission. Two patients were untreated at the time of evaluation.

PET Scanning Procedures

The subject reported to the PET scanning area in the Nuclear Medicine Department of the National Institutes of Health Clinical Center at about 7:30 AM after an overnight fast. Room temperature was held constant at 71°F.
An arm venous catheter was inserted for drug infusion. The subject was placed in a PET scanner (GE Advance, Milwaukee, WI), with the hands or feet in the scanner so as to scan one affected and one unaffected limb. The limbs in the scanner were held in position with loosely applied tape and foam pads. $^{15}$N-Ammonia (usual dose, 20 mCi) was injected intravenously over 1 minute, with data averaged across the interval from 5 to 20 minutes. The subject was then removed from the scanner and allowed to take a light or clear liquid breakfast.

At least 1 hour after $^{15}$N-ammonia administration, the subject was placed back in the scanner. 6-[18F]Fluorodopamine (usual dose, 4 mCi) was infused intravenously over 3 minutes, with data acquired from 0 to 30 minutes.

**Observation Room Procedures**

The subject reported to a Patient Observation Room on the morning after an overnight fast. Room temperature was not controlled and ranged from 77° to 80°F. A brachial arterial catheter was placed percutaneously for obtaining blood samples and for hemodynamic monitoring. Venous catheters were placed in the affected and unaffected limbs for blood sampling, and another venous catheter was placed in an unaffected limb for infusion of drugs. A brachial inflatable cuff and mercury-in-silastic strain gauge were applied for measurements of local blood flow by impedance plethysmography, without the use of a wrist or ankle cuff.

$^{3}$H-Norepinephrine (levo-[2,5,6]-$^{3}$H-norepinephrine; New England Nuclear, Boston, MA) was infused intravenously at a rate of 0.75 µCi/min (0.75 ml/min). After at least 20 minutes, local blood flow in the affected and unaffected limbs was measured at least five times. Blood (approximately 6 ml per sample) was obtained from the arterial catheter and the venous sampling catheters.

In 12 nonsympathectomized and 8 sympathectomized patients, trimethaphan camsylate (1 or 2 mg/ml) was infused intravenously at an initial rate of 0.5 mg/min. The dose was increased until symptoms and signs of ganglionic blockade were obtained. These included dry mouth, conjunctival vasodilation, increased heart rate, loss of respiratory sinus arrhythmia, and decreased pulse pressure. On attainment of adequate ganglionic blockade (usual trimethaphan infusion rate, 2–4 mg/min), local blood flows were measured, and blood was obtained again. Hemodynamic and neurochemical data during trimethaphan infusion were also obtained in 23 unaffected limbs of patients with reflex sympathetic dystrophy and in a total of 22 limbs of normal volunteers.

Before trimethaphan infusion and on attainment of ganglionic blockade, the patients rated the severity of their pain verbally on a scale from 0 (no pain whatsoever) to 10 (worst pain ever).

**Neurochemical Assays**

Arterial and venous plasma was assayed for catechols (including norepinephrine, dihydroxyphenylglycol, and L-dihydroxyphenylalanine) and $^{3}$H-norepinephrine by batch alumina extraction followed by liquid chromatography with electrochemical detection and liquid scintillation spectrometry.

**Data Analysis and Statistics**

Local norepinephrine spillover was quantified from the arterial and venous concentrations of total norepinephrine and $^{3}$H-norepinephrine as well as from local plasma flow. Positron emission tomographic images of the affected and unaffected limbs were analyzed as described previously for images of the heart. Briefly, decay-corrected radioactivity concentrations (measured in nCi/cm$^3$) were adjusted for the dose of radioactive drug per kilogram of body mass (measured in mCi/kg) and expressed in units of nCi-kg/cm$^3$-mCi. Time-averaged (1–30 minutes for 6-[18F]fluorodopamine, 5–20 minutes for $^{15}$N-ammonia) images of the same single slices (4.25 mm thick) were obtained at four different levels in the two limbs. Radioactivity concentrations in each of the four transsectional slices were averaged, and the mean radioactivity concentration among the four slices was then calculated. To provide an index of perfusion-adjusted 6-[18F]fluorodopamine–derived radioactivity, 6-[18F]fluorodopamine–derived radioactivity was divided by $^{15}$N-ammonia–derived radioactivity (18F/$^{15}$N ratio).

Differences between affected and unaffected limbs in values for hemodynamic variables, limb norepinephrine spillover, arteriovenous increments in plasma dihydroxyphenylglycol and L-dihydroxyphenylalanine, and 6-[18F]fluorodopamine–derived radioactivity at baseline and during trimethaphan infusion were quantified by calculating affected/unaffected ratios in individual patients.

For comparisons with normal volunteers, we culled an ongoing database about normal limb blood flow and norepinephrine kinetics, with elimination of data from the youngest subjects, to obtain normal values from a group matched for age with the group of patients with reflex sympathetic dystrophy.

Mean values were compared using dependent-means t tests and repeated-measures ANOVAs (StatViewSE+Graphics; Abacus Concepts, Berkeley, CA). A probability value less than 0.05 defined statistical significance.

**Results**

Patients with affected limbs, unaffected limbs, or sympathectomized limbs had similar baseline mean values for heart rate and mean arterial pressure (Table 1).

**$^{15}$N-Ammonia PET Scanning**

Twenty nonsympathectomized patients and 10 sympathectomized patients underwent $^{15}$N-ammonia scanning. Outlying data from one patient with recent onset of disease were excluded. The mean values for $^{15}$N-ammonia–derived radioactivity were similar in the hands and feet.

Of 9 patients with chronic unilateral reflex sympathetic dystrophy of the foot, where the opposite foot was unaffected, 7 had less $^{15}$N-ammonia–derived radioactivity on the affected side (Fig 1), and of 7 patients with chronic unilateral reflex sympathetic dystrophy of the hand, where the opposite hand was unaffected, all 7 had less $^{15}$N-ammonia–derived radioactivity on the affected side. Across the 16 pairs of limbs, the affected/unaffected ratio of $^{15}$N-ammonia-
Table 1. Hemodynamic Values at Baseline and during Trimethaphan Infusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart Rate (bpm)</th>
<th>Mean Pressure (mm Hg)</th>
<th>Blood Flow (ml/min/dl of tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>TRI</td>
<td>BL</td>
</tr>
<tr>
<td>RSD affected hand</td>
<td>72 ± 5 (9)</td>
<td>83 ± 7 (4)</td>
<td>93 ± 3 (9)</td>
</tr>
<tr>
<td>RSD unaffected hand</td>
<td>71 ± 4 (17)</td>
<td>77 ± 4 (10)</td>
<td>92 ± 3 (17)</td>
</tr>
<tr>
<td>SNS-x hand</td>
<td>71 ± 5 (10)</td>
<td>79 ± 8 (5)</td>
<td>83 ± 5 (10)</td>
</tr>
<tr>
<td>Normal hand</td>
<td>63 ± 2 (20)</td>
<td>70 ± 5 (8)</td>
<td>89 ± 2 (21)</td>
</tr>
<tr>
<td>RSD affected foot</td>
<td>71 ± 2 (10)</td>
<td>87 ± 3 (5)</td>
<td>88 ± 4 (10)</td>
</tr>
<tr>
<td>RSD unaffected foot</td>
<td>70 ± 4 (15)</td>
<td>81 ± 6 (9)</td>
<td>92 ± 5 (15)</td>
</tr>
<tr>
<td>SNS-x foot</td>
<td>76 ± 9 (4)</td>
<td>90 ± 8 (2)</td>
<td>90 ± 8 (4)</td>
</tr>
<tr>
<td>Normal foot</td>
<td>66 ± 2 (12)</td>
<td>83 ± 2 (16)</td>
<td>96 ± 3 (12)</td>
</tr>
</tbody>
</table>

*Mean values expressed ± 1 SEM.
*Numbers in parentheses are numbers of limbs.

bpm = beats per minute; BL = baseline; TRI = trimethaphan; SNS-x = sympathectomy; RSD = reflex sympathetic dystrophy.

derived radioactivity was significantly less than 1.0 ($t = 2.8$, $p = 0.01$; Fig 2).

The mean $^{13}$N-ammonia-derived radioactivity was higher in sympathectomized feet (261 ± 40 nCi-kg/cm$^2$-Ci, $n = 5$) and hands (273 ± 48 nCi-kg/cm$^2$-Ci, $n = 8$) than in affected or unaffected feet and hands.

6-[$^{18}$F]Fluorodopamine PET Scanning

In all subjects tested, 6-[$^{18}$F]fluorodopamine-derived radioactivity was detected in both affected and unaffected limbs (see Figs 1 and 2). The mean values for 6-[$^{18}$F]fluorodopamine-derived radioactivity did not differ between affected and unaffected limbs even in sympathectomized patients (see Fig 2).

The 6-[$^{18}$F]fluorodopamine-derived radioactivity: $^{13}$N-ammonia-derived radioactivity ($^{18}$F:$^{13}$N) ratio, used as a measure of perfusion-adjusted 6-[$^{18}$F]fluorodopamine-derived radioactivity, increased progressively during the 30-minute interval of scanning (Fig 3). Trends in the $^{18}$F:$^{13}$N ratio did not differ between the patient groups.

Values for $^{18}$F:$^{13}$N ratios in the affected versus unaffected limbs and in the sympathectomized versus unaffected limbs were compared using the data for the last 10-minute interval of PET scanning. Of 16 patients with an affected limb and an unaffected opposite limb, 15 had an affected:unaffected ratio of at least 0.95 for perfusion-adjusted 6-[$^{18}$F]fluorodopamine-derived radioactivity, with the mean ratio significantly exceeding 1.0 ($t = 2.4$, $p = 0.03$; see Fig 2). In contrast, of 9 patients with a sympathectomized limb and an unaffected opposite limb, all 9 had a sympathectomized:unaffected limb ratio of less than 0.95 ($t = 5.0$, $p = 0.001$). In other words, whereas in sympathectomized limbs, the amount of 6-[$^{18}$F]fluorodopamine-derived radioactivity was significantly less than that predicted from any asymmetry in perfusion, in the affected limbs, the amount of 6-[$^{18}$F]fluorodopamine-derived radioactivity was significantly more than that predicted from asymmetry in perfusion.

Blood Flow and Vascular Resistance

Mean blood flow in the hands consistently exceeded that in the feet ($F = 6.2$, $p < 0.001$) but did not between affected, unaffected, and sympathectomized limbs (see Table 1). Overall, affected:unaffected ratios for blood flow and vascular resistance did not differ significantly from 1.0 even in patients with a history of sympathectomy (data not shown).

Norepinephrine Kinetics

Values for mean norepinephrine spillover in the hand exceeded those in the foot in all groups, although the difference was statistically significant only for unaffected limbs ($F = 5.2$, $p = 0.03$; Table 2). In nonsympathectomized patients, norepinephrine spillover was approximately symmetrical; thus, mean values for norepinephrine spillover were similar in the affected and unaffected limbs (see Table 2).

In 5 of 15 nonsympathectomized patients, norepinephrine spillover was clearly less in the affected limb than in the unaffected limb (Fig 4). Of these 5 patients, 4 also had a decreased affected:unaffected ratio for the arteriovenous increment in plasma dihydroxyphenylglycol. Only 1 of the 5 had decreased 6-[$^{18}$F]fluorodopamine-derived radioactivity, however, and even in this patient, perfusion-adjusted 6-[$^{18}$F]fluorodopamine-derived radioactivity was approximately symmetrical (data not shown).

Although 5 sympathectomized patients also had a clearly decreased sympathectomized:unaffected ratio for norepinephrine spillover, the group mean affected:unaffected ratio in sympathectomized patients did not differ significantly from that in nonsympathectomized patients. Venous levels of norepinephrine, however, were significantly lower in the sympathectomized limb.

52 Annals of Neurology Vol 48 No 1 July 2000
than in the opposite unaffected limb ($t = 2.8, p = 0.03$).

**Plasma Catechols**

Mean values for arteriovenous increments in concentrations of norepinephrine did not differ between affected (0.09 ± 0.10 nmol/L) and unaffected (0.16 ± 0.08 nmol/L) hands or between affected (0.53 ± 0.22 nmol/L) and unaffected (0.46 ± 0.21 nmol/L) feet of patients with reflex sympathetic dystrophy.

The mean values for arteriovenous increments in plasma levels of dihydroxyphenylglycol and L-dihydroxyphenylalanine also did not differ between the affected and unaffected limbs of nonsympathectomized patients in either the hands or feet (data not shown). Patients with a history of sympathectomy usually had low values for arteriovenous increments in both catechols; the differences from the corresponding increments in unaffected limbs were not statistically significant.

**Trimethaphan**

Infusion of trimethaphan increased mean heart rate, decreased mean arterial pressure, and increased local blood flow ($F = 44.0, p = 0.0001$; $F = 43.0, p = 0.0001$; $F = 6.6, p = 0.02$, respectively). Local vascular resistance only tended to decrease ($F = 2.8, p = 0.10$), mainly because the blood flow did not increase in some patients. The extent of increase in blood flow did not differ between affected and unaffected limbs; however, the extent of decrease in vascular resistance tended to be larger in affected limbs than in unaffected limbs ($F = 3.2, p = 0.08$). In sympathectomized patients, trimethaphan did not significantly affect blood flow but did decrease vascular resistance ($F = 5.1, p < 0.001$).

Across all groups, trimethaphan decreased local norepinephrine spillover ($F = 7.6, p = 0.008$). The effect of trimethaphan on local norepinephrine spillover depended significantly on the group. In affected hands...
Fig 2. Mean (± SEM) affected/unaffected ratios for $^{13}$N-ammonia–derived radioactivity (top), 6-[$^{18}$F]fluorodopamine–derived radioactivity (middle), and the 6-[$^{18}$F]fluorodopamine: $^{13}$N-ammonia–derived radioactivity ($[^{18}$F/$^{13}$N]) ratio (bottom) in patients with reflex sympathetic dystrophy, without or with sympathectomy (SNS-x). Whereas $^{13}$N-ammonia–derived radioactivity was less in the affected limb than in the opposite unaffected limb, $^{13}$N-ammonia–derived radioactivity was greater in the sympathectomized limb than in the opposite unaffected limb. Whereas $[^{18}$F/$^{13}$N] was higher in the affected limb than in the opposite unaffected limb, $[^{18}$F/$^{13}$N] was lower in the sympathectomized limb than in the opposite unaffected limb.

Fig 3. Mean (± SEM) concentrations of perfusion-adjusted 6-[$^{18}$F]fluorodopamine–derived radioactivity in affected and unaffected limbs as a function of time after a 3-minute intravenous injection of 6-[$^{18}$F]fluorodopamine.

and feet, norepinephrine spillover did not change during trimethaphan infusion. In contrast, in unaffected hands and feet of patients with reflex sympathetic dystrophy as well as in normal volunteers, norepinephrine spillover decreased significantly during trimethaphan infusion ($t = 2.7, p = 0.02$; $t = 3.1, p = 0.01$; $t = 4.2, p = 0.001$, respectively). Responses of norepinephrine spillover to trimethaphan infusion did not differ significantly between affected and unaffected hands or between unaffected limbs.

Across all groups, trimethaphan infusion decreased the mean arteriovenous increment in plasma dihydroxyphenylglycol levels ($F = 4.3, p = 0.04$; see Table 2). The extent of decrease in the arteriovenous increment did not differ as a function of the group. Trimethaphan infusion also highly significantly decreased the mean arteriovenous increment in plasma L-dihydroxyphenylalanine levels ($F = 7.6, p = 0.001$), with the extent of decrease similar among the groups.

Trimethaphan infusion significantly decreased the fractional extraction of $^{3}$H-norepinephrine ($F = 47, p = 0.0001$). The extent of decrease varied significantly as a function of the group ($F = 5.9, p = 0.0001$) because of different responses in the feet and hands. Thus, trimethaphan decreased the fractional extraction of $^{3}$H-norepinephrine in normal feet ($t = 6.9, p = 0.0001$) but not in normal hands, tended to decrease the fractional extraction of $^{3}$H-norepinephrine in affected feet ($t = 2.1, p = 0.10$) but not in affected hands, and decreased the fractional extraction of $^{3}$H-norepinephrine in unaffected feet ($t = 4.3, p = 0.002$) but not in unaffected hands. Among patients with re-
flex sympathetic dystrophy, the decrease in fractional extraction of $^3$H-norepinephrine in unaffected feet did not differ significantly from that in affected feet.

The mean pain score was 5.5 before and 4.7 during trimethaphan infusion. Of 12 nonsympathectomized patients, 2 had improvement in pain, 1 had worsening, and 9 had no change. Of 11 sympathectomized patients, 4 had improvement in pain and 7 had no change.

**Comparisons with Normal Controls**

Patients with reflex sympathetic dystrophy had significantly less fractional extraction of $^3$H-norepinephrine than did age-matched normal volunteers (0.57 ± 0.05; $F = 7.2, p = 0.001$) not only in the affected (0.34 ± 0.06) or sympathectomized (0.41 ± 0.04) limbs but also in the unaffected limbs (0.34 ± 0.04). In the feet, the mean value for fractional extraction of $^3$H-norepinephrine in patients with reflex sympathetic dystrophy (0.44 ± 0.12) was less than that in normal volunteers (0.60 ± 0.05), but the difference was not statistically significant. There were no significant differences in local norepinephrine spillover, the arteriovenous increment in plasma dihydroxyphenylglycol levels, or the arteriovenous increment in plasma L-dihydroxyphenylalanine levels between the affected limbs in the patients and the corresponding limbs in normal volunteers (data not shown).

The mean values for norepinephrine spillover, arteriovenous increments in plasma dihydroxyphenylglycol levels, and arteriovenous increments in plasma L-dihydroxyphenylalanine levels did not differ between sympathectomized and normal hands or feet; however, the mean extraction fraction of $^3$H-norepinephrine was significantly less in sympathectomized hands than in normal hands ($F = 5.5, p = 0.03$) and feet ($F = 11.9, p = 0.004$).

**Discussion**

In the present study, patients with chronic unilateral reflex sympathetic dystrophy had lower tissue concentrations of $^{15}$N-ammonia–derived radioactivity, as measured by PET scanning, in the affected hands or feet than in the opposite unaffected limbs. The low concentrations of $^{15}$N-ammonia–derived radioactivity indicate decreased perfusion of the affected limbs. This finding is in agreement with those of previous reports noting decreased cutaneous temperature or decreased cutaneous blood flow in the affected limbs of patients with chronic reflex sympathetic dystrophy.10,34–36 The present findings show decreased blood flow also to deeper tissues.

Because one of the patients with recent onset of reflex sympathetic dystrophy had substantially increased $^{15}$N-ammonia–derived radioactivity in the affected limb, the present results may not apply to perfusion of acutely affected limbs. Analogously, previous reports have reported increased cutaneous temperature or blood flow in this setting.9,37,38

The same patients who had decreased $^{15}$N-ammonia–derived radioactivity in the affected extremity did not have decreased blood flow as measured by impedance plethysmography. For PET scanning, the room temperature was controlled rigorously at 71°F (21.6°C), whereas for impedance plethysmography, the Patient Observation Room was much warmer, approaching 80°F (26.6°C) on some testing days. The environmental warmth probably caused local sympathoinhibition, and this could well have obscured real asymmetries in vascular function that would have been evident in a cooler room. Thus, in the warm Patient Observation Room, blood flow did not differ between sympathectomized and intact opposite limbs, whereas in the cool PET scanning room, the same patients had increased $^{15}$N-ammonia–derived radioactivity in the sympathectomized limbs. A previous report noted that

<table>
<thead>
<tr>
<th>Table 2. Neurochemical Values at Baseline and during Trimethaphan Infusion</th>
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<tbody>
<tr>
<td>Norepinephrine Spillover (pmol/min/dl of tissue)</td>
</tr>
<tr>
<td>Group</td>
</tr>
<tr>
<td>RSD affected hand</td>
</tr>
<tr>
<td>RSD unaffected hand</td>
</tr>
<tr>
<td>Normal hand</td>
</tr>
<tr>
<td>RSD affected foot</td>
</tr>
<tr>
<td>RSD unaffected foot</td>
</tr>
<tr>
<td>SNS-x foot</td>
</tr>
<tr>
<td>Normal foot</td>
</tr>
<tr>
<td>1.17 ± 0.34 (9)</td>
</tr>
</tbody>
</table>

*aMean values expressed ± 1 SEM.
*bNumbers in parentheses are numbers of limbs.

SNS-x = sympathectomy.
Previous reports have noted lower concentrations of norepinephrine\(^2,3,9\) or its neuronal metabolite, dihydroxyphenylglycol\(^2\), in venous plasma from the affected limb than in that from the opposite unaffected limb in patients with reflex sympathetic dystrophy. As discussed below, these findings are consistent with partial sympathetic denervation of the affected limb. In the present study, affected:unaffected ratios for local norepinephrine spillover and arteriovenous increments in plasma dihydroxyphenylglycol levels did not differ significantly from 1.0. The warm room temperature could have decreased sympathetic outflows and resulted in similar values between affected and unaffected limbs, because the mean values for norepinephrine spillover and arteriovenous increments in plasma dihydroxyphenylglycol levels also did not differ between sympathectomized and normal limbs.

In 5 patients, the ratios of affected versus unaffected values for norepinephrine spillover clearly were much less than 1.0, and in 4 of the 5 patients, the ratios for the arteriovenous increment in plasma dihydroxyphenylglycol were also decreased, supporting the notion of decreased sympathetically mediated release of norepinephrine in at least some patients.

The combination of decreased local production of norepinephrine and dihydroxyphenylglycol in at least some patients raises the possibility that partial sympathetic denervation might secondarily augment sensitivity of \(\alpha\)-adrenoceptors on vascular smooth muscle cells,\(^2,11,12,36\) resulting in decreased tissue perfusion. Thus, affected hands of patients with reflex sympathetic dystrophy have augmented \(\alpha\)-adrenoceptor–mediated venous contractile responses,\(^16\) and the density of \(\alpha_1\)-adrenoceptors, as indicated by \(^{123}\)I-HEAT binding, is significantly higher in skin samples from affected limbs of patients with reflex sympathetic dystrophy than from limbs of normal control subjects.\(^39\)

Several of the present findings cast doubt on the denervation hypothesis, however. First and foremost, patients with reflex sympathetic dystrophy had symmetrical tissue concentrations of \(^6\)-\(^{18}\)F)fluorodopamine–derived radioactivity as detected by PET scanning. Indeed, taking into account the decreased perfusion, as indicated by decreased \(^13\)N-ammonia–derived radioactivity, the affected limbs had significantly increased perfusion-adjusted \(^6\)-\(^{18}\)F)fluorodopamine–derived radioactivity. In contrast, as expected, in sympathectomized patients, the concentration of perfusion-adjusted \(^6\)-\(^{18}\)F)fluorodopamine-derived radioactivity was always less in the sympathectomized limb than in the opposite unaffected limb. These findings suggest a normal amount of sympathetic terminal innervation in the affected limb.

L-Dihydroxyphenylalanine is the immediate product of the rate-limiting enzymatic step in norepinephrine biosynthesis, tyrosine hydroxylase. In the limbs, tyrosine
hydroxylation in sympathetic nerves results in local arteriovenous increments in plasma L-dihydroxyphenylalanine levels. In the present study, the similarity of mean values for arteriovenous increments in plasma L-dihydroxyphenylalanine in the affected and unaffected limbs supports the notion of symmetrical sympathetic terminal innervation. In contrast, patients with chronic pain attending diabetic neuropathy have both decreased perfusion-adjusted 6-[^18]F]fluorodopamine–derived radioactivity and small or absent arteriovenous increments in plasma L-dihydroxyphenylalanine levels in the painful limbs (C. Tack, unpublished observations), providing a positive control for the expected effects of denervation. Rats with hyperalgesia caused by chronic constriction injury also have normal arteriovenous increments in plasma L-dihydroxyphenylalanine levels despite decreased arteriovenous increments in plasma norepinephrine levels.

In agreement with the view that patients with reflex sympathetic dystrophy have generally intact sympathetic terminal innervation in the affected limb, biopsied skin from hyperalgesic regions contains a normal content and distribution of tyrosine hydroxylase staining compared with values in unaffected regions and in normal control subjects. Moreover, a histopathological study of amputated limbs from patients with reflex sympathetic dystrophy reported evidence for degeneration and loss of afferent C-fibers but did not observe abnormalities of efferent fibers.

The combination of decreased norepinephrine release and decreased dihydroxyphenylglycol production can occur in other situations besides denervation. For instance, decreased postganglionic sympathetic traffic to intact terminals not only can produce this pattern but can augment adrenoceptor-mediated vasoconstriction and increase tissue concentrations of 6-[^18]F]fluorodopamine–derived radioactivity. Loss of the radioactivity presumably depends partly on postganglionic sympathetic nerve traffic. An analogous process involving decreased transmission of sympathetic nerve traffic might occur in patients with reflex sympathetic dystrophy. Decreased nerve traffic can also help to explain the finding of trimethaphan-induced decreases in norepinephrine spillover in unaffected but not affected limbs of patients with reflex sympathetic dystrophy, since the rate of postganglionic sympathetic nerve traffic would already be decreased in the affected limbs. Because of the presumed development of postsynaptic supersensitivity, further decreases in receptor occupancy during trimethaphan infusion could have resulted in the observed trend toward augmented decreases in vascular resistance in the affected limb.

In the present study, both acute ganglion blockade and chronic sympathectomy were associated with increased limb perfusion. Decreased nerve traffic to intact sympathetic terminals does not explain reduced perfusion in the affected limbs of patients with chronic reflex sympathetic dystrophy. One may speculate that norepinephrine released in response to traffic along residual fibers binds to upregulated α-adrenoceptors on vascular smooth muscle cells. Epinephrine released in the circulation during emotional distress might also bind to upregulated α-adrenoceptors. Alternatively, augmented vasoconstrictor responses might occur independently of α-adrenoceptor numbers, for example, from the local or indirect effects of inflammatory mediators in endothelial production of vasoactive factors.

The finding of increased perfusion-adjusted 6-[^18]F]fluorodopamine–derived radioactivity in the affected limbs does not necessarily indicate decreased sympathetic nerve traffic. For instance, aberrant sprouting of sympathetic nerve terminals, resulting from production of nerve growth factor, coupled with upregulation of α-adrenoceptors on vascular smooth muscle cells could produce the same result.

Patients who had undergone sympathetic ganglionectomy for reflex sympathetic dystrophy had evidence for residual (or recrudescence) postganglionic nerve traffic, because ganglion blockade with trimethaphan decreased norepinephrine spillover, vascular resistance, and arteriovenous increments in plasma dihydroxyphenylglycol and L-dihydroxyphenylalanine levels from the already decreased baseline values in sympathectomized limbs. Sympathetic terminal innervation, as judged by perfusion-adjusted 6-[^18]F]fluorodopamine–derived radioactivity, was decreased but nevertheless present in sympathectomized patients. The findings are thus consistent with decreased but not eliminated sympathetic terminals.

All the sympathectomized patients had had recurrence of the pain after the procedure. Whether patients with long-term successful treatment by sympathectomy differ from patients in whom treatment has failed in terms of return of sympathetic neuroeffector function is unknown. The present findings do not allow conclusions about the efficacy of sympathectomy to treat pain in patients with reflex sympathetic dystrophy, because patients in whom treatment failed may have been the predominant group referred for evaluation. The findings do demonstrate, however, that sympathectomy does not reliably result in long-term improvement.

Despite clear clinical, neurochemical, and hemodynamic evidence for adequate ganglion blockade, only 2 of 12 nonsympathectomized patients had lessening of their pain during intravenous infusion of trimethaphan. These results indicate that in chronic reflex sympathetic dystrophy, mechanisms independent of postganglionic sympathetic nerve traffic probably maintained the pain. Because ganglion blockade increased local blood flow substantially, the failure to alleviate pain did not arise in any simple way from local ischemia.

In all groups, mean values for perfusion-adjusted 6-[^18]F]fluorodopamine–derived radioactivity increased
during the PET scanning. Because arterial plasma levels of the tracer itself decrease rapidly after cessation of the 3-minute infusion, the increases in 6-[18F]fluorodopamine–derived radioactivity probably reflected tissue uptake of a metabolite of 6-[18F]fluorodopamine. The finding of similar curves relating perfusion-adjusted 6-[18F]fluorodopamine–derived radioactivity with time in affected and unaffected limbs provides further support for similar sympathetic terminal function in the affected and unaffected limbs.

In summary, patients with chronic unilateral reflex sympathetic dystrophy have evidence for less perfusion in the affected limb than in the unaffected opposite limb, with generally intact sympathetic terminal innervation. The neurochemical and neuroimaging findings lead to the suggestion that at least in the chronic form of the condition, the patients have decreased postganglionic sympathetic traffic to intact sympathetic terminals. Surgical sympathectomy does not prevent recurrence of pain in reflex sympathetic dystrophy despite evidence of continuing, albeit partial, sympathectomy. Neither local hypoperfusion nor sympathetic neuronal outflows maintain the pain in most cases.

The results generally indicate independence of chronic pain from sympathetic function in this condition. Coincidental damage to sympathetic efferent fibers and nociceptor afferent fibers might lead to increased expression of neurotrophic factors that, although possibly allowing sympathetic terminal reinnervation, could also enhance pain transmission. We therefore support abandonment of the term reflex sympathetic dystrophy in favor of the more descriptive term complex regional pain syndrome.

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Goldstein et al: Sympathetic Function in Reflex Sympathetic Dystrophy 59