Erythromelalgia: Vasculopathy, Neuropathy, or Both?

A Prospective Study of Vascular and Neurophysiologic Studies in Erythromelalgia

Mark D. P. Davis, MD; Paola Sandroni, MD, PhD; Thom W. Rooke, MD; Phillip A. Low, MD

Objective: To assess the frequency and type of vascular changes and neurologic abnormalities in patients with erythromelalgia.

Design: Prospective study of patients with no spontaneous symptoms at the time of their visit and with provoked symptoms.

Setting: Tertiary referral center.


Interventions: Testing nerve and vascular function in patients without symptoms present; testing vascular function after provoking symptoms with exercise or by increasing ambient temperature.

Main Outcome Measures: In patients in whom symptoms could be elicited, vascular function with and without symptoms was assessed by measurement of local skin temperature, laser Doppler flow, and transcutaneous oximetry. Neurologic assessment included electromyography, nerve conduction studies, and autonomic reflex screening (using the quantitative sudomotor axon reflex test, adrenergic function testing, heart rate response to deep breathing, and the Valsalva ratio).

Results: Autonomic reflex screening was performed on 57 (85%) of the 67 patients. Of these 57 patients, 46 (81%) had abnormal quantitative sudomotor axon reflex test results; 14 (25%) had abnormal adrenergic function; and 15 (26%) had abnormal cardioadrenergic function. Put in another way, results were abnormal for 49 (86%) of the 57 patients who had autonomic reflex screening. Severe sudomotor abnormalities (ie, absent or markedly reduced sweat production) were present in 46 (94%) of these 49 patients; 14 (29%) had abnormal adrenergic function, and 15 (31%) had a cardioadrenergic abnormality. Electromyography and nerve conduction studies were performed in 24 (36%) of the 67 patients. Of these 24 patients, 14 (58%) had abnormal electromyographic results and 10 (42%) had abnormal nerve conduction study results. Vascular function studies, with and without symptoms present, were performed in 13 of the 67 patients. During symptoms, the mean temperature of the toe skin increased by 7.8°C, and blood flow increased 10.2-fold. Paradoxically, mean transcutaneous oximetry measurements did not change.

Conclusion: This prospective study extends and confirms our previous observation that, in addition to other forms of neuropathy, most patients with erythromelalgia have small-fiber neuropathy.

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nomic function in patients with erythromelalgia.4 We noted that during symptoms, an increase in blood flow (from a mean of 6.8 mL/min per 100 g of tissue to a mean of 76.5 mL/min per 100 g of tissue) and temperature (mean increase, 11.6°C) is accompanied paradoxically by a decrease in oxygenation (mean decrease in transcutaneous oximetry pressure [TcPO2], 6.7 mm Hg) in the affected area. We noted that a high proportion of patients (17 of 27) had severe postganglionic sudomotor impairment, and that 5 of these 17 had additional peripheral adrenergic dysfunction.

Subsequently, we prospectively studied patients presenting to our institution with erythromelalgia. We report our findings in this article.

### METHODS

#### PATIENT SELECTION

Patients presenting to Mayo Clinic from 1999 through 2001 who met the clinical criteria for a diagnosis of erythromelalgia were evaluated according to the protocol outlined in Table 1. The study population comprised all patients with a diagnosis of primary erythromelalgia referred to Mayo Clinic from 1999 through 2001 for evaluation of their symptoms, and who could be tested. They had been referred to the following specialty areas of Mayo Clinic: internal medicine, neurology, vascular medicine, and pediatrics. The only factor that characterized the patients not following the protocol in Table 1 was that it was not possible, for various practical reasons, to complete the tests specified.

#### DEFINITION OF ERYTHROMELALGIA

Erythromelalgia was defined as the occurrence of erythema, heat (observed both subjectively and objectively), and associated discomfort (variably described as pain, burning, tingling, or a similar sensation) in the extremities.

#### VASCULAR STUDIES

First, measurements were taken when patients were not experiencing symptoms. Patients were then directed to engage in an activity that elicited their symptoms (some walked, some climbed stairs, and some put their feet in warm water). Because the duration and intensity of the stimulus provoking symptoms (exercise or increase in ambient temperature) varied from patient to patient, the provocation was not standardized. Patients returned for further testing when their symptoms had occurred. Only 13 of 67 patients were able to elicit symptoms. Studies of local vasculature before and during the occurrence of symptoms included measurement of temperature, laser Doppler flowmetry, and transcutaneous oximetry. The environmental conditions were standardized for this testing. These techniques have been demonstrated to be reliable and accurate.5,6

#### Temperature

The temperature of the limbs, including digital skin temperature, was measured without symptoms and then during symptoms if symptoms could be elicited. A handheld infrared temperature scanner (DermaTemp DT-1000; Exergen Corporation, Watertown, Mass) was used to measure the various digital and limb temperatures according to a standardized protocol. The mean temperature of the foot for each patient was calculated from the mean of 4 temperature readings on each foot, an area that was consistently involved.

#### Upper and Lower Extremity Arterial Study

Pneumatic occlusion cuffs of appropriate size were wrapped snugly around the upper arms, thighs, calves, and ankles of the supine patients. A Doppler probe (Perimed PeriFlux System 5000/5020 and 5010 [with and without heat, respectively]; Perimed Inc, Royalton, Ohio) was positioned over the radial or posterior tibial pulse, and each cuff was separately inflated to a pressure of approximately 20 mm Hg above the brachial systolic pressure. The occluding cuff was slowly deflated and the pressure on the aneroid gauge was noted when the Doppler sound returned. This represented the systolic pressure at the site of cuff occlusion. Systolic blood pressure for each ankle was measured again from the dorsalis pedal pulse. Systolic blood pressure for each arm was likewise measured from the brachial arterial pulse. Systolic and diastolic blood pressures were measured in both arms and an ankle-brachial index was calculated from the higher of the 2 systolic arm pressures.

Digital blood pressures were obtained using Doppler technique and a digital occluding cuff. Blood flow (in milliliters of blood per minute per 100 g of tissue) was measured using a laser Doppler apparatus as part of the arterial studies. Laser Doppler flowmetry measures Doppler-shifted quantities of reflected laser light to determine the cutaneous microcirculatory flux of erythrocytes.7 The blood flow in the affected extremities was examined with patients supine, with and without symptoms present.

#### Transcutaneous Oximetry

With the patient supine, oxygen-sensing electrodes with a surface temperature of 45°C (to eliminate vasospasm, if present) were attached to the skin. One reference electrode was attached to the chest. The remaining 4 electrodes were placed on the dorsum of each foot over the metatarsal region, 1 to 2 cm apart, at proximal and distal sites. The electrodes remained in place until steady-state surface oxygen measurements were made (approximately 15 minutes). The TcPO2 was recorded using Perimed PeriFlux System 5000/5040 (Perimed Inc), and the regional perfusion index (RPI) was calculated as TcPO2 foot/TcPO2 chest. The feet were elevated by 30° for 3 minutes, the TcPO2 measurements were repeated, and the RPI was recalculated. No disease or mild disease was considered to be

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**Table 1. Protocol of Investigation for Patients Presenting With Erythromelalgia**

<table>
<thead>
<tr>
<th>Clinical evaluation</th>
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<tbody>
<tr>
<td>History</td>
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<tr>
<td>Physical examination</td>
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<tr>
<td>Vascular evaluation</td>
</tr>
<tr>
<td>Studies of the following parameters in the affected extremities with and without symptoms</td>
</tr>
<tr>
<td>Color change</td>
</tr>
<tr>
<td>Skin temperature and core temperature</td>
</tr>
<tr>
<td>Blood flow (laser Doppler flowmetry)</td>
</tr>
<tr>
<td>Oxygen saturation (transcutaneous oximetry)</td>
</tr>
<tr>
<td>Ankle-brachial indices</td>
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<tr>
<td>Neurologic evaluation</td>
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<tr>
<td>Electromyography</td>
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<tr>
<td>Autonomic reflex screening</td>
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<tr>
<td>Quantitative sudomotor axon reflex test (QSART)</td>
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<tr>
<td>Heart rate response to deep breathing and Valsalva ratio (cardiovagal functioning)</td>
</tr>
<tr>
<td>Adrenergic function testing</td>
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<tr>
<td>Consultation with neurologist specializing in autonomic nerve studies if results of the above tests are abnormal</td>
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present if the resting TcPO₂ was greater than 40 mm Hg and the resting RPI was greater than 0.6. Moderate disease was considered to be present if the resting TcPO₂ was greater than 40 mm Hg; the resting RPI was greater than 0.6; and the decrease with elevation was less than 10 mm Hg for TcPO₂ or less than 0.2 for the RPI. Severe disease was considered to be present if the resting TcPO₂ was less than 20 mm Hg or if it was 20 to 40 mm Hg and the decrease with elevation was greater than 10 mm Hg for TcPO₂ or greater than 0.2 for the RPI. The mean TcPO₂ was then calculated from the mean of 2 readings on each foot, an area that was involved in each patient.

NEUROPHYSIOLOGY TESTING

Neurophysiologic studies included nerve conduction studies and needle electromyography (EMG). The autonomic reflex screen (ARS) included the quantitative sudomotor axon reflex test (QSART), determination of heart rate response to deep breathing and the Valsalva ratio, and adrenergic function testing. The ARS became available at our institution in 1983 and is described extensively elsewhere.8,9

Nerve Conduction Studies and Needle EMG

Nerve conduction studies were performed in 54 patients with standard techniques using surface electrodes for stimulation and recording. Limb temperature was monitored and maintained at 32°C or warmer. In the lower extremities, peroneal and tibial motor and either sural or medial planar sensory nerve conduction studies were performed. Peroneal and tibial F waves were recorded. If abnormal values were obtained in the lower extremities, median motor and ulnar sensory nerve conduction studies were performed. Values for amplitude, distal latency, conduction velocities, and F-wave latencies were compared with reference ranges established in the Mayo Clinic EMG laboratory. The extent of needle examination varied depending on the nerve conduction and findings on the muscles tested, but distal lower limb muscles were examined in all patients. Insertional and spontaneous activity, recruitment, and morphologic changes in motor unit potential were assessed in each muscle. Peripheral neuropathy was considered to be predominantly axonal when motor or sensory responses were reduced in amplitude and conduction velocities, or when distal latencies varied from normal limits by 30% or less. A substantial demyelinating component was considered to be present if conduction velocities and distal latencies varied between 30% and 50% from normal limits when amplitudes were normal, or by more than 50% when amplitudes were reduced.

AUTONOMIC REFLEX SCREEN

Quantitative Sudomotor Axon Reflex Test

The QSART quantitatively evaluates the postganglionic sympathetic sudomotor axon reflex.10-13 As usual, the QSART was recorded from the forearm, the proximal lateral and medial distal regions of the leg, and the proximal region of the foot over the extensor digitorum brevis muscle. Acetylcholine was applied iontophoretically, and the responses were recorded in a compartment of a multicompartmenal sweat cell different from the stimulus compartment. Control values were derived from studies in 223 control subjects aged 10 to 83 years.13

Heart Rate Response to Deep Breathing and the Valsalva Ratio

Heart rate response to deep breathing and the Valsalva ratio were determined as previously described.10,11,13 Heart rate response to deep breathing was the change in heart rate in response to forced respiratory sinus arrhythmia, with the patient breathing 6 breaths per minute. For the Valsalva maneuver, the patient, rested and recumbent, was asked to generate an expiratory effort sufficient to maintain a column of mercury at 40 mm Hg for 15 seconds. The Valsalva ratio is the ratio of the maximal heart rate to the minimal heart rate. Control values were from 157 healthy subjects aged 10 to 83 years.13

Adrenergic Function Testing

Beat-to-beat blood pressure was monitored using a continuous noninvasive blood pressure monitor (Finapres Monitor; Ohmeda, Englewood, Colo) with input into a computer console that displays systolic, diastolic, and mean blood pressures continuously.14 Blood pressure was also recorded using a sphygmomanometer cuff and mercury manometer over the brachial artery. The autonomic stresses consisted of a series of Valsalva maneuvers and a tilt study, in which the patient was tilted to an angle of 80° for 5 minutes. An autonomic function was evaluated from the responses of the blood pressure to the tilting and the Valsalva maneuvers.13

STATISTICS

Appropriate summary statistics were used to describe the data. Descriptive statistics were used for the vascular and neurophysiologic studies.

RESULTS

The results of nerve and vascular function tests are summarized in Table 2 and Table 3.

Of the 67 patients with clinical criteria consistent with erythromelalgia, 57 (85%) had ARS performed. Among them, 46 (81%) had abnormal QSART results, 14 (25%) had normal adrenergic function, and 15 (26%) had abnormal cardiovagal function.
Put in another way, severe sudomotor abnormalities (ie, absent or markedly reduced sweat production on QSART) accounted for most of the ARS abnormalities (46/49 [94%]). Abnormal adrenergic function (14 [29%]) and cardiovascualr abnormality (15 [31%]) were less common.

Twenty-seven patients had abnormal sudomotor function only; 13 had abnormal sudomotor function and either cardiovascualr (7) or adrenergic vasomotor (6) impair-ment; and 6 had abnormalities in all 3 tests. Only 3 patients had preserved sudomotor function but abnormal results for the cardiovascualr (1) or adrenergic (1) tests, or for both tests (1).

Of the 67 patients, 24 (36%) had EMG and nerve conduction studies performed. Among them, 14 (58%) had abnormal EMG results and 10 (42%) had abnormal results from nerve conduction studies. Four had abnormal EMG results only, but all patients with abnormal results from nerve conduction studies also had abnormal EMG results. The group who had EMG and nerve conduction studies and the group who had autonomic studies did not overlap completely. Of the 24 patients who had EMG and nerve conduction studies, only 15 also had autonomic studies. However, all patients who had both evaluations and who had abnormal EMG results had abnormal results from autonomic studies as well (8 of 14), and 6 patients with normal EMG results also had abnormal autonomic studies results.

Forty-nine patients had a neurologic examination performed by a neurologist specializing in autonomic neuropathy. Among them, 25 had abnormal results, with reduced ankle jerks and decreased sensation in a length-dependent pattern typical of peripheral neuropathies. These clinical signs were subtle. Findings in the remain-

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>ABI</th>
<th>Without Symptoms</th>
<th>Without Symptoms</th>
<th>Laser Doppler Flow, mL Blood/min per 100 g of Tissue</th>
<th>TcPO2, mm Hg</th>
<th>Regional Perfusion Index</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Core</td>
<td>Skin†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/F/56</td>
<td>Normal</td>
<td>36.7</td>
<td>22.5</td>
<td>32.93</td>
<td>40.1</td>
<td>443.3</td>
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<tr>
<td>2/F/39</td>
<td>Normal</td>
<td>36.6</td>
<td>23</td>
<td>33.7</td>
<td>2</td>
<td>35.3</td>
</tr>
<tr>
<td>3/M/70</td>
<td>Normal</td>
<td>36.4</td>
<td>28.4</td>
<td>32.9</td>
<td>9.4</td>
<td>53.9</td>
</tr>
<tr>
<td>4/F/21</td>
<td>Slightly low</td>
<td>37</td>
<td>22.9</td>
<td>30.4</td>
<td>1</td>
<td>63.4 (30-109)</td>
</tr>
<tr>
<td>5/M/52</td>
<td>Normal</td>
<td>37</td>
<td>21.46</td>
<td>31.6</td>
<td>1</td>
<td>10.8</td>
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<tr>
<td>6/F/28</td>
<td>Normal</td>
<td>36.7</td>
<td>24.4</td>
<td>31.7</td>
<td>1</td>
<td>8.6</td>
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<tr>
<td>7/F/52</td>
<td>Normal</td>
<td>36</td>
<td>23.2</td>
<td>31.44</td>
<td>4.4</td>
<td>2.5</td>
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<td>8/F/65</td>
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<td>37.4</td>
<td>21.3</td>
<td>30.01</td>
<td>1</td>
<td>46.2</td>
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<tr>
<td>9/F/49</td>
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<td>24.7</td>
<td>32.48</td>
<td>1.9</td>
<td>50.3</td>
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<tr>
<td>10/F/39</td>
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<td>36.4</td>
<td>20.39</td>
<td>29.58</td>
<td>3.2</td>
<td>11.8</td>
</tr>
<tr>
<td>11/F/39</td>
<td>Slightly low</td>
<td>Not measured</td>
<td>27.3</td>
<td>30</td>
<td>3.6</td>
<td>24</td>
</tr>
<tr>
<td>12/M/16</td>
<td>Normal</td>
<td>36.5</td>
<td>25</td>
<td>30.2</td>
<td>31.5</td>
<td>301</td>
</tr>
<tr>
<td>13/F/18</td>
<td>Normal</td>
<td>37.6</td>
<td>21</td>
<td>30.2</td>
<td>15.1</td>
<td>126.8</td>
</tr>
<tr>
<td>Median 39.0</td>
<td>Normal</td>
<td>Mean 41.8</td>
<td>23.5</td>
<td>31.3</td>
<td>8.9</td>
<td>90.7</td>
</tr>
</tbody>
</table>

Abbreviations: ABI, ankle-brachial index; TcPO2, transcutaneous oximetry measurement.
*With symptoms, local redness associated with discomfort was observed.
†Significantly different without symptoms vs with symptoms (P<.001).
‡Temperatures are the mean of 4 readings at each foot.
§Transcutaneous oximetry measurement at toes.
|Regional perfusion index is TcPO2 foot/TcPO2 chest.

Table 3. Summary of Vascular Studies in Patients With Erythromelalgia, With and Without Symptoms*
In the asymptomatic state, the mean transcutaneous oximetry measurement at the toes was 60.7 mm Hg (range, 49.5-83.8 mm Hg). During symptoms, the mean transcutaneous oximetry measurement decreased minimally, by 0.1 mm Hg (range, 39-74.3 mm Hg). The mean RPI (TcPO2, toes/TcPO2, chest) without symptoms was 0.86 (range, 0.7-1.3), and with symptoms it was 0.81 (range, 0.5-1.1).

COMMENT

NEUROLOGIC STUDIES

We present the first prospective study of neurologic testing in patients with erythromelalgia. The study clearly demonstrates a consistent relationship between erythromelalgia and small-fiber neuropathy.

Analysis of autonomic and neurophysiologic studies revealed 2 major findings. First, most patients with erythromelalgia had evidence of postganglionic sudomotor failure, often with severe deficit. The finding of peripheral, especially distal, denervation, without evidence of more generalized autonomic failure, suggests the presence of a distal small-fiber neuropathy. Second, evidence from nerve conduction studies and EMG of large-fiber neuropathy was relatively common. Together, these observations support the notion that a neuropathy underlies most cases of erythromelalgia, and that it involves mainly small nerve fibers, with lesser involvement of large nerve fibers.

Among the patients who had ARS performed, 49 (98%) of 52 had an abnormal result, most consistently with the QSART (in 46 [94%] of those 49 patients). The results are striking and confirm our previous findings of a high prevalence of QSART abnormalities in patients with erythromelalgia. In that retrospective study we reported that 17 (63%) of the 27 patients who had ARS performed had normal results from QSART studies. The QSART quantitatively evaluates the postganglionic sympathetic sudomotor axon reflex. Thus, the autonomic studies indicate much more severe involvement of postganglionic sudomotor function than of adrenergic function.

It is possible that some adrenergic function abnormalities were not detected with ARS—the adrenergic tests evaluated systemic and not local vasomotor control. Evaluation of adrenergic function in the autonomic laboratory relies on changes in the systemic circulation and is therefore relatively insensitive to local changes. Adrenergic failure is detected by changes in systemic blood pressure in response to head-up tilt or to the Valsalva maneuver. These adrenergic indices detect changes when more widespread autonomic neuropathy develops. Skin vasomotor reflexes were not performed because there is too much variability in skin vasomotor reflexes to permit accurate interpretation.

Two hypotheses, the effector hypothesis and the distal neural hypothesis, have been advanced to explain erythromelalgia-associated neuropathy. Sugiyama et al used microneurographic recordings, done by inserting a tungsten microelectrode into a nerve trunk at a relatively proximal site, and reported the presence of normal skin sympathetic traffic and a normal somatoautonomic reflex arc but the absence of vasoconstrictor response. They interpreted their findings as suggesting an abnormal response of smooth muscle effectors to humoral factors in the microenvironment. This effector hypothesis has not been studied in detail and does not distinguish between a primary abnormality of effectors and a secondary effect from changes in the skin microenvironment. Changes could affect many structures, including receptors, sweat glands, and cutaneous smooth muscle endothelial cells. Uno and Parker reported reduced density of catecholamine-containing nerve endings in the periarterial plexus. This distal neural hypothesis requires distal sympathetic nerve involvement, which would not have been detected with microneurography. Our findings involving both vascular and sudomotor function are in closer agreement with the mechanism suggested by Uno and Parker. Our results could reflect the involvement of distal sympathetic fibers to the skin.

The possibility of an interplay between neural and vasoactive agents in the pathophysiology of erythromelalgia has been implicated by Littleford et al, who observed enhanced cutaneous vascular tone at rest and during stimulation. In a separate observation, Littleford et al demonstrated that patients with erythromelalgia have diminished sympathetic vasoconstrictor responses in contrast with control subjects under 2 different types of stress.

Mork et al examined skin microvascular perfusion in response to vasoconstrictory and vasodilatory stimuli by measuring laser Doppler perfusion in 14 patients with primary erythromelalgia and in healthy controls. Skin perfusion preceding provocative stimuli was significantly reduced in patients with erythromelalgia (P<.01). The laser Doppler flowmetry signal after sympathetic stimulation of reflexes mediated through the central nervous system was significantly less in patients with erythromelalgia than in healthy controls. Local neurogenic vasoconstrictor (venous cuff occlusion and dependency of the extremity) and vasodilator reflexes (local heating of the skin), as well as vascular smooth muscle and vascular endothelial function (postocclusive hyperemic response), were maintained. Mork et al postulated that postganglionic sympathetic dysfunction and denervation hypersensitivity may play a pathogenetic role in primary erythromelalgia, whereas local neurogenic function as well as endothelial function are unaffected.
Mørk et al have further proposed that erythromelalgia is not a separate disease entity, but a symptom complex, a condition caused by 1 specific pathophysiologic response, arteriovenous shunting.

Specific small-fiber dysfunction could lead to altered vascular and sudomotor function, and could also induce neurogenic inflammation and lead to the elevated limb temperature that characterizes erythromelalgia. Pathogenetic mechanisms of erythromelalgia are still open to speculation. It is plausible that different mechanisms could account for erythromelalgia symptoms. The alternative explanation for the involvement of both eccrine sweat gland and smooth muscle is possible, but it requires the simultaneous involvement of muscarinic receptor, type 3 (M3) and adrenergic receptors.

Erythromelalgia may resemble complex regional pain syndrome I (CRPS I), also known as reflex sympathetic dystrophy, and distinguishing these conditions can be difficult. For example, patients with either condition may have hot, swollen, painful limbs. However, several factors may help to distinguish the conditions. First, although there are exceptions, erythromelalgia is usually bilateral whereas CRPS I is usually unilateral. Second, most patients with CRPS I are alldynic to cold and avoid cold exposure, whereas the pain of patients with erythromelalgia is relieved by cold. Third, patients with CRPS I often have a history of injury or trigger, and usually no injury is reported before the onset of erythromelalgia. Fourth, sympathetic blocks usually provide no substantial benefit in patients with erythromelalgia, whereas they can benefit patients with CRPS I. However, there are exceptions to these guidelines: erythromelalgia can be unilateral, and patients with CRPS I may seek cold exposure or have no history of injury.

**VASCULAR STUDIES**

We previously reported a retrospective study of measurements of vascular function in 5 patients with erythromelalgia. The present study of 13 patients in whom vascular function was measured with and without symptoms present confirms our previous observation that, during symptoms, a marked increase in temperature (mean, 11.6°C in our previous study; mean, 7.8°C in the present study) is accompanied by a massive increase in blood flow as measured by laser Doppler flowmetry (mean, 11-fold in our previous study; mean, 10-fold in the present study), and, paradoxically, by a comparative lack of change in tissue oxygenation as measured by transcutaneous oximetry.

An increase in temperature in the symptomatic area is a hallmark of this condition. During symptoms, skin temperatures increased in all the patients we studied. Although symptomatic pain has been said to occur in direct relationship to the temperature of the limb, above a critical point that is typically between 32°C and 36°C and constant for each individual, many of the patients we studied were unable to provoke their symptoms during their evaluation.

Anecdotally, we have noted that during the asymptomatic state, feet are frequently cold and occasionally slightly cyanotic, which is consistent with our finding that toe temperatures varied from 20.4°C to 28.4°C (mean, 23.5°C). However, no reference values have been established for toe temperatures; and, because of the wide variability in toe temperatures in the normal population, it is not possible to establish that the temperatures we measured are abnormal. This observation is consistent with that of Littleford et al who reported lower basal skin temperatures and higher transcutaneous carbon dioxide levels between episodes.

Whereas TcPO2 at the feet should be within 10 mm Hg of that measured at the chest, it was much lower at the feet than at the chest in our 13 patients. Thus, even when they were without symptoms, increased flow concomitant with decreased TcPO2 was noted in the affected extremities. Mørk et al also observed this apparent anomaly of a hyperperfusion state coexisting with tissue hypoxemia, even in patients at rest. They proposed that the underlying mechanism is arteriovenous shunting, with increased flow through the shunts; and that this microvascular steal leads to decreased flow through nutrient vessels. They proposed that maldistribution of skin microvascular blood flow leads to compensatory arteriolar dilation and increased maldistribution, creating a vicious cycle. Moreover, Mørk et al demonstrated a relation between clinical symptoms and increased perfusion in the region of numerous anatomical arteriovenous shunts in 8 patients after heat provocation. More recently, they noted reduced skin capillary density after heating. The investigators proposed that this locally increased perfusion supported the hypothesis of increased thermoregulatory arteriovenous shunt flow during attacks in primary erythromelalgia. Thus, a sudden large increase in flow associated with decreased oxygenation may well be the result of an increase in shunting and a reduction in nutritive flow. This finding is similar to that reported in other forms of neuropathy, eg, diabetic neuropathy.

Because transcutaneous oximetry measures TcPO2 in a large area and because we measured it on the dorsum of the feet, we may have missed areas of hypoxemia. Future studies that include measurements in the acral/palmoplantar areas of affected skin may show the presence of a steal phenomenon (maldistribution of blood from the capillaries to the arteriovenous shunts), as proposed by Mørk et al.

We postulate as an alternative or additional underlying mechanism an increase in local cellular metabolism. This would cause increased temperature and waste production from cellular metabolism as well as hypoxemia, of which the increased blood flow may be a result. If the increased blood flow is insufficient to meet metabolic needs, cumulative tissue damage may occur from the waste products, ischemia, heat, and considerable pain may then occur. In support of this theory is the finding that TcPO2 does not increase as expected in the affected extremities despite a massive increase in local blood flow.

The manifestations of neurogenic inflammation and possible sympathetic dysfunction in erythromelalgia are intriguing. One can speculate that mitochondrial dysfunction is the primary pathogenetic event, with a dissociation at the energy/heat production level inducing temperatures warmer than core temperatures, axonal damage, and end-organ dysfunction. However, the limited involvement of the body (such as involvement of only the
feet) associated with erythromelalgia makes that hypothesis difficult to explain.

Our data have limitations. First, the number of patients is not large. However, the syndrome is rare and the experience presented is a relatively large one. Second, the number of patients in whom it was possible to elicit symptoms during vascular studies was relatively small. This finding is consistent with our previous observation that patients may not be able to elicit symptoms during their visits with a physician. We conclude that erythromelalgia is associated with a neuropathy (primarily, small-fiber) and a vasculopathy (with intermittent increased blood flow and perhaps shunting), and possibly with increased local cellular metabolism. But what is the primary abnormality? Is erythromelalgia primarily a neuropathy leading to a vasculopathy, or vice versa?

Anecdotally, we and others have noted patients with inherited neuropathy in whom erythromelalgia subsequently developed. This observation supports the theory that erythromelalgia is primarily a neuropathy. Conversely, some patients in this study had erythromelalgia and no demonstrable neuropathy. Vasculopathy with hypoxia may cause neuropathy. Thus, neuropathy and vasculopathy coexist, and on the basis of the present study we cannot state which is primary and which is secondary. We can only speculate.

To which facet of erythromelalgia should therapy be directed? The answer is not apparent, but various degrees of success have been reported with medications used for both neuropathy (such as gabapentin, tricyclic antidepressants, and selective serotonin reuptake inhibitors) and vasculopathy (such as β-blockers and calcium antagonists).

Perhaps erythromelalgia is heterogeneous, and more than 1 mechanism is responsible for this syndrome. If so, identifying patients by pathophysiological subgroups may be important for targeting therapeutic strategies.

In summary, the following findings are consistently observed: (1) most patients with erythromelalgia have a predominantly small-fiber neuropathy; (2) the redness and warmer temperature of the affected limbs (usually both limbs) are accompanied by a massive increase in blood flow; and (3) the redness and warmer temperature are not accompanied by an increased oxygenation of tissue. How each of these mechanisms contributes to the syndrome deserves further study. It is intriguing to speculate that erythromelalgia may represent a neuropathy in which the neural control of vascular tone is disturbed.

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Portions of the “Methods” and “Comment” sections were published previously in Sandroni et al by permission of Lippincott Williams & Wilkins.

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