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Abstract
Background Erythromelalgia (EM) is a chronic disorder characterized by intermittent pain, warmth and erythema of the extremities. Symptoms can be precipitated by increasing the temperature of the affected limb and can be partially relieved by direct cooling.

Materials and methods Microvascular assessment was conducted under `hot' (28°C) environmental conditions in 61 EM (EMI) patients and 30 control subjects. Twenty patients with many of the symptoms of EM were enrolled as an active control group (EMII). Using laser Doppler flowmetry, basal skin erythrocyte flux (SkEF) and the hyperaemic response to local heating (44°C) were measured.

Results Compared with control subjects, basal SkEF was reduced at the toe (P<0·001), index finger (P<0·05), dorsal and plantar aspects. of the foot (P<0·01) in both patient groups and at the medial mid-calf (P<0·05) in EMI patients. Both EM groups also had a significantly reduced maximum SkEF at the dorsum of foot and medial mid-calf (all P<0·001) compared with control values. In a subset of patients and control subjects, transcutaneous carbon dioxide levels were raised in EMI patients (P < 0·02) compared with levels in control subjects. Toe temperature was significantly reduced in both EM groups compared with control subjects (both P<0·001).

Conclusion Our study indicates for the first time that there is a vasoconstrictor tendency in patients with EM, which may be related to functional or structural changes in skin microvessels. Thus, the previous hypothesis that the pathophysiology of EM relates to vasodilatation is not supported in our patients. We believe that, in EM, vasoconstriction precedes reactive hyperaemia, similar to that seen in Raynaud's phenomenon.

Keywords Erythromelalgia, laser Doppler flowmetry, skin blood flow, vasoconstriction. Eur J Clin Invest 1999; 29 (7): 588-593

Introduction

Erythromelalgia (EM) is a chronic disorder characterized by intermittent pain, warmth and erythema of the extremities, usually the feet and lower legs. The pain is often described as being of a burning nature that can limit and, in extreme cases, prevent walking. The symptoms can be precipitated by exercise, placing the limb in a dependent position and by increasing the temperature of the affected limb directly or by central body warming. Partial relief is obtained by elevation of the affected limb or by direct cooling.

Confusion surrounds not only the nomenclature of EM but also its pathophysiology. The first reported case of EM was documented by Graves [1] in 1834, and the syndrome itself by Mitchell in 1878 [2]. He used a combination of the Greek words erythros (red), melos (extremities) and algos (pain) to illustrate the presenting symptoms of the disease. In 1938, Smith & Allen [3] proposed the use of the term erythermalgia to emphasize the associated increase in skin temperature. We use the term EM as described by Mitchell [2].

EM can present in a primary form, with no associated disease, or in a form secondary to a variety of disorders, particularly those in which there is an increase in platelet count (e.g. thrombocythaemia Ref. 4) and hyperviscosity syndromes such as polycythemia rubra vera [5]. Drenth & Michiels [6] restrict the use

of the term EM to the condition when it is associated with essential thrombocythaemia. They report that EM in this form is responsive to treatment with acetylsalicylic acid (aspirin), whereas all other forms, which are refractory to aspirin therapy, they name erythermalgia [6]. Interestingly, as with Raynaud's phenomenon (RP), the symptoms of EM can predate the development of an associated disease by over 12-16 years [4,5], and some patients initially documented as having primary EM may in fact have an early secondary form of the disorder.

The pathophysiology of the erythema in EM is unclear, and the only available data are from small studies or single case reports. One theory is that the erythema may result from impaired cutaneous peripheral vasoconstriction, owing to sympathetic neural dysregulation [7,8]. Alternatively, the vasodilatation may result from reactive hyperemia after a period of ischemia [9], similar to that seen during re-warming in patients with Raynaud's phenomenon [10]. A common feature of the secondary forms of EM is microvascular ischaemia. We hypothesize that microvascular ischaemia may be involved in the pathophysiology of EM.

To test this hypothesis, the present large-scale study has concentrated on the assessment of cutaneous microvascular function using the non-invasive techniques of infrared thermography, laser Doppler flowmetry and transcutaneous oximetry. As the symptoms of EM can be precipitated by heat, we performed our assessments in a `hot' (28°C) temperature-controlled environment.

Methods

Patient and subjects

Investigations were performed after approval had been obtained from the local ethics committee. All participants gave written, informed consent.

Eighty-one patients were referred to our vascular laboratory by doctors who had failed to determine the cause of the patient's symptoms. A symptom history was obtained from all patients (Table 1). The patients were divided into two groups based on their symptoms. Sixty-one patients reported burning pain of the extremities on warming and/or limb dependency that improved with cooling and/or limb elevation. This group is referred to as type I EM (EMI). The specific diagnostic criteria for inclusion as EMI patients were attacks of burning pain in their hands and/or feet; the attacks were initiated or aggravated by standing, exercise or exposure to heat; relief was obtained by elevation and exposure to cold; during attacks the affected parts became flushed, congested and exhibited an increase in local skin temperature; the condition was refractory to treatment.

The remaining 20 patients reported many of the criteria necessary for the diagnosis of EM, with the exception of burning pain. They reported acroparaesthesias including tingling, formication and pins and needles (Table 1), symptoms normally experienced by EM sufferers preceding the burning distress. This second group is referred to as type II EM (EMII) and were included in the study as an ‚active' control group. Well before microvascular investigation, all patients had been given acetylsalicylic acid therapy (aspirin 500-1000 mg per day), from which no benefit was obtained. Thirty healthy age and sex-matched control subjects were enrolled.

The 61 EMI patients (10 men, 51 women) had a median (interquartile range, IQR) age of 53 (30-66) years and the 20 EMII patients (two men, 18 women) a median age of 52 (45-67) years. Control subjects (five men, 25 women) were aged 47 (40-64) years and were enrolled from the University staff, their relatives and participants in a retired persons' keep-fit class.

Assessment of macrovessels To exclude peripheral arterial occlusive disease (PROD), arterial systolic pressures were measured at the brachial and posterior tibial arteries using a continuous wave bidirectional Doppler ultrasound probe (Model 306, Parks Electronics, USA). Values below 0-9 for the ankle brachial pressure index (ABPI) were considered abnormal [11].

Table 1 Duration, nature and location of pain/discomfort in EMI and EMII patients

	EMI ($n = 61$)	EMII ($n = 20$)
Duration of pain (median, IQR) years	3 (2–6)	3 (2–6)
Nature of pain/discomfort (number of patients)		
Burning	61	0
Pins and needles	10	13
Formication	12	5
Tingling sensations	0	2
Affected areas (number of patients)		
Toes and feet only	51	1
Ankles and knees only	3	3
Calves	0	11
Upper leg and arms	7	3
Arms	0	2
Symmetry of pain/discomfort (number)		
Bilateral	57	9
Unilateral	4	11

IQR, interquartile range.

Assessment of skin microvascular function

Measurements were carried out with subjects in a semi-reclining position after a 30-min equilibration period in a temperature-controlled room set to 28 ± 1°C. This was combined with indirect body warming by immersing the subject's left arm up to the elbow in a 44°C water bath. The combination of these thermal conditions maintains peripheral vasodilatation and stabilizes skin blood flow [12]. Infrared thermography (Agema Infrared Thermovision 880, Sweden) was used to measure the temperature of the toes, feet and lower limbs and to observe thermal asymmetries between limbs, defined as a temperature difference greater than 2°C [13].

A laser Doppler flowmeter (LDF, PF2b, Perimed, Sweden) was used to measure skin erythrocyte flux (SkEF) in arbitrary units of volts (V). All measurements were standardized to x10 gain with the time constant and cut-off frequency set to 0·2 s and 12 kHz respectively. The output signal was continuously monitored on a pen recorder (BBC Servoger SE120).

Baseline SkEF was measured at the big toe pulp, dorsal and plantar aspects of the mid-foot and medial mid-calf. SkEF was recorded until stable values were obtained. Vasodilator ability was assessed at the dorsum of the foot and the medial mid-calf by heating the skin locally to 44°C [14,15] using an integral heating probe.

In a sub-sample of subjects (10 control subjects, 17 EMI and 10 EMII patients), oxygen and carbon dioxide pressures were measured transcutaneously at the dorsum of the foot using a transcutaneous oximeter (TCM3, Radiometer, Denmark) set to a sensor temperature of 44°C.

Statistical analysis

Results are expressed as medians and interquartile ranges. Data were analysed using the Wilcoxon test for non-parametric data. The null hypothesis was rejected at P<0-05. Statistical analyses were performed using Statgraphics software (Statistical Graphics Corporation, Mangistics).

Results

Left and right limbs were assessed, but only left limb data are presented because values were similar.

Assessment of macrovessels

The ABPIs were similar in the three groups: EMI = 1 -0
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(0·9-1·1), EMII = 1·0 (0·9-1·1) and control subjects = 1·0 (1·0-1·1).

Assessment of skin microvascular function

Skin temperature

No thermal asymmetry was noted between the limbs. Toe temperatures, however, were significantly lower in both patient groups than in control subjects. Control subjects had a toe temperature of 35.7°C (35.0-36.0°C) compared with 34.5°C (33.5-35.0°C) and 35.0°C (34.1-35.4°C) in EMI and EMII respectively (both $P < 0·001$).

Basal skin erythrocyte flux

Basal SkEF was lower in EM patients than in control subjects. The EMI group had a significantly lower SkEF at the toe pulp, dorsum of the foot, medial mid-calf (all $P<0·001$) and plantar aspect of the foot ($P<0·05$) compared with values in control subjects (Table 2). The EMII group had significantly reduced basal SkEF values at the toe pulp ($P<0·001$) and the dorsum of the foot ($P<0·01$) compared with control values (Table 2). There was also a trend for lower SkEF values at the plantar aspect of foot and medial mid-calf in the EMII compared with control values (both $P=0·07$). EMI and EMII patients had lower basal SkEF values at the index finger pulp compared with values in control subjects (both $P<0·05$, Table 2). There were no significant differences in basal SkEF between EMI and EMII patients.

Skin microvascular response to local (44°C) heating

Local heating produced skin vasodilatation in all groups at the measured sites. The maximum SkEF was significantly reduced at the dorsum of the foot and medial mid-calf in EMI and EMII patients (all $P<0·001$) compared with responses in control subjects (Table 3).

Transcutaneous oximetey

Transcutaneous oxygen levels were not significantly different in the three groups: 72 (54-84)mmHg, 68 (6175)mmHg and 71 (67-78) mmHg in control subjects, EMI and EMII patients respectively. Compared with control subjects, transcutaneous carbon

dioxide levels were not significantly different in EMII patients, 33 (28-37) and 36 (34-41)mmHg (control and EMII respectively), but were raised significantly in EMI patients, 39 (35-42) mmHg, (P<0-02).

Table 2 Basal skin erythrocyte flux (SkEF) in a hot environment (27°C) in control subjects and EMI and EMII patients. Values are medians and interquartile ranges

Parameter	Control ($n = 30$)	EMII ($n = 20$)	EMI ($n = 61$)
Basal SkEF (V)			
Toe pulp	16.2 (13.3–20.0)	10.3 (7.4–14.6)	12.3 (8.6–17.4)
	$P < 0.001$	$P < 0.001$	
Dorsum of the foot	2.5 (1.5–3.0)	1.5(1.1–2.1)	1.5 (1.0–1.6)
	$P < 0.001$	$P < 0.001$	
Plantar aspect of the foot	4.5 (2.0–11.6)	3.3 (1.5–5.0)	2.6 (1.7–4.4)
	$P < 0.05$	$P < 0.05$	
Medial mid-calf	1.5 (1.2–2.5)	1.3 (1.2–1.5)	1.1 (0.8–1.5)
	$P < 0.001$	$P < 0.001$	
Index finger	14.6 (13.2–23.3)	13.8 (9.0–16.6)	14.4 (10.6–16.7)
	$P < 0.05$	$P < 0.05$	

Erythema and burning pain of the extremities, precipitated by heat and limb dependency, are characteristic symptoms in patients who have the condition known as erythromelalgia. The findings of the present investigation are the first from a large-scale study conducted under controlled environmental conditions. The results show that compared with normal healthy subjects, patients with EM have reduced toe temperatures and reduced basal and maximum hyperaemic skin blood flows to local heating in a `hot' environment. Collectively, these results suggest that in spite of reproducing local thermal conditions that are thought to be above the threshold for inducing erythema and burning pain [5], patients with EM have a paradoxical vasoconstrictor tendency. Basal SkEF was reduced at all measured sites, and although data are only presented for the left lower extremity, a decreased SkEF was seen equally on the right side, indicating bilateral abnormalities. EM patients also had a reduced basal finger SkEF, suggesting that reductions in skin perfusion are not limited to the lower extremities, where the symptoms are most frequently experienced. This is similar to findings in RP where vasospasm is ubiquitous but symptoms may be localized. Interestingly, EMII patients, who had all the symptoms classical of EM, except burning pain, showed similar microvascular abnormalities to those in EMI patients. These findings suggest that EMII patients may have a milder form of EM or be in a 'pre-EM' phase that may develop into classical EM.

Cutaneous blood vessels are under sympathetic neural innervation [16], and thus a reduction in blood flow could result from increased sympathetic neural activity. However, histological evidence suggests that there is an actual reduction in sympathetic innervation [7,17,18]. A reduced number of acetylcholinesterase and catecholamine-containing nerve terminals in the peri-arterial and sweat gland plexuses has been observed in skin biopsies taken from the dorsum of the foot in three EM patients [7,17,18]. Furthermore, our pilot work shows a decrease in sympathetically mediated vasoconstrictor ability in response to cold challenge and inspiratory gasp in EM patients (R. C. Littleford et al., unpublished observations).

The combination of increased vasoconstrictor tone and a decrease in sympathetic neural activity seems paradoxical, but Wakisaka and colleagues [19] have provided an animal model of abnormal skin temperature and sympathetic vasomotor innervation in

surgically induced neuropathies in the rat hind paw. They found abnormal skin temperature regulation after the induced nerve injury and showed that as a group the temperature of the rat's paw evolved from abnormally hot post-operatively to abnormally cold after 30 days. Individually however, the paw temperature could alternate from abnormally hot to abnormally cold and vice versa within days or hours. Similar to the histopathological reports in EM patients [7,17,18], Wakisaka and colleagues [19] found a decrease in the number of sympathetic effector nerves in the affected limb but normal sympathetic nerve innervation in the normal contralateral limb. Moreover, there was no typical sympathetic nerve pattern associated with the observed temperature change of the hind paws. Many of the cold limbs had no noradrenaline-containing nerves, whereas many of the abnormally hot limbs had normal neural innervation. Therefore, temperature abnormalities that accompany neuropathies do not necessarily reflect sympathetic vasomotor dysfunction. This situation is not too dissimilar to the symptoms reported by EM patients. They often seek medical advice after experiencing an acute period of `hot, burning feet', but on examination in our vascular laboratory their limb temperatures are often abnormally low.

Table 3. Maximum skin erythrocyte flux (SkEF) during local 44°C heating in a hot environment (27°C) in control subjects and EMI and EMII patients. Values are in median and interquartile ranges

	Control ($n = 30$)	EMII ($n = 20$)	EMI ($n = 61$)
Maximum SkEF (V)			
		$P < 0.001$	
Dorsum of the foot	9.2 (6.0–11.6)	4.7 (3.2–6.0)	4.7 (3.3–6.4)
			$P < 0.001$
		$P < 0.001$	
Medial mid-calf	8.2 (6.0–11.6)	3.7 (2.5–5.0)	4.1 (3.1–6.5)
			$P < 0.001$

The complex interactions of local and central mechanisms involved in vasomotor regulation of cutaneous microvessels appear to be altered in EM. The fault in cutaneous microvessels may lie at the level of the vascular smooth muscle itself. Vascular smooth muscle function was tested in this study by heating the skin locally to. 44°C, which abolishes microvascular reflexes [20] and maximally vasodilates the microcirculation [14]. This function was impaired in EM patients. The pathophysiology of a reduced hyperaemic response is not clear, but this abnormality also occurs in insulin-dependent diabetes [21], PAOD [22,23], hypertension [24] and Raynaud's phenomenon [25], in which microvascular structural changes are common. In insulin-dependent diabetes, for example, the structural change takes the form of basement membrane thickening [21], whereas microvascular sclerosis can occur in PROD, hypertension and secondary Raynaud's phenomenon [26]. Thickened blood vessel basement membranes, perivascular oedema and endothelial swelling have been observed in affected skin lesions in three primary EM patients [27], and therefore similar structural microvascular abnormalities may be responsible for the vasoconstrictor tendencies seen in the present study [4].

Although basal and maximum SkEF were reduced in EM patients, microvascular oxygenation was normal. In contrast, transcutaneous carbon dioxide levels were significantly higher in the EMI group than the values in normal control subjects, which may be accounted for by an increase in local tissue metabolism. Kvernebo & Seem [27] found evidence of hypoxia in the presence of skin hyperperfusion in the feet of three EM

patients. These patients were investigated while experiencing acute EM symptoms, unlike our patients who experienced no EM symptoms during testing.

Additional cutaneous pathology has been noted in secondary EM associated with myloproliferative disorders [4]. Arteriolar inflammation, fibromuscular intima proliferation and thrombotic occlusions are typical skin biopsy results [4]. It has been postulated that prostaglandins derived from activated platelets may account for the local and cutaneous inflammatory symptoms seen in EM [4,28], whereas the release of platelet-derived growth factor may cause fibromuscular intimal proliferation [4]. The pharmacological action of aspirin inhibits platelet aggregation and prostaglandin synthesis by causing irreversible inactivation of the cyclooxygenase enzyme [29]. Complete abolishment of the microvascular occlusive symptoms in some forms of EM is evident after aspirin therapy, and this is thought to be in itself diagnostic of the condition [4]. In our EM patients, however, there was no evidence of myloproliferative disorders such as thrombocythaemia and their symptoms were not relieved by aspirin therapy.

Blood flow in the microcirculation is critically dependent on the integrity of the endothelium and the various properties of the liquid and cellular elements of blood. Endothelial swelling has been shown to be a pathological feature of both primary [30] and secondary [4] EM. Endothelial dysfunction could result from swelling or in response to damage induced by thrombotic occlusion leading to an imbalance in the production or activity of vasodilators (e.g. nitric oxide) and vasoconstrictors (e.g. endothelin or thromboxane A2) [31].

Our patients were tertiary referrals from fellow consultant colleagues. None had thrombocythaemia or any other myeloproliferative disease; these patients having been diagnosed and treated elsewhere. Our population, therefore, is a selected one and this could be construed as a potential limitation of the study. However, these patients came from all over the UK, all fulfilled the diagnostic criteria for EM as described in Methods and all exhibited the abnormalities documented above. We believe, therefore that our patient population is representative of the disease we call EM and that the findings have clinical and pathological relevance.

In conclusion, the findings of this study show, for the first time, that compared with normal healthy subjects, patients with EM have a vasoconstrictor tendency, and that patients in a 'pre-EM' phase (EMII) have similar microvascular abnormalities. Increased vascular tone in our patients may result from an enhanced activity of cutaneous microvessels to stimuli. In addition, structural alterations of the cutaneous microvessels may in part, or in combination with vasoactive mediators, influence vascular tone. Alternatively, the ischemic stimulus may be vasospasm [32]. Thus, the previous hypothesis that the pathophysiology of EM relates purely to vasodilatation is not supported by the present study. It could be that excessive vasoconstriction precedes reactive hyperemia, similar to that seen in patients with Raynaud's phenomenon.

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