Impaired skin vasomotor reflexes in patients with erythromelalgia.

Impaired Skin Vasomotor Reflexes In Patients With Erythromelalgia by Roberta C. LITTLEFORD, Faisel KHAN and Jill J. F. BELCH

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Abbreviations: CC, cold challenge; EM, erythromelalgia; IG, inspiratory gasp; p.u., perfusion units; SkEF, skin erythrocyte flux; $SkEF_B$, baseline SkEF; $SkEF_{MIN}$ minimal SkEF.
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ABSTRACT

Erythromelalgia (EM) is a chronic disorder characterized by intermittent burning pain, warmth and erythema of the extremities. Increasing the local temperature and dependency of the affected limb(s) precipitates the symptoms, whereas direct cooling and elevation of the limb(s) can provide partial relief. Our previous findings showed that patients with EM have enhanced cutaneous vascular tone at rest and during stimulation, which may be due to an increase in sympathetic neural activity. To test this, we measured skin vasoconstrictor responses to contralateral arm cold challenge (CC) and inspiratory gasp (IG) using laser Doppler flowmetry at the toe pulp and fingertip. These areas were chosen because of their dense sympathetic innervation. An index of the vasoconstrictor response (between 0 and 1) was calculated from the change in skin perfusion from baseline following CC and IG. In control subjects, vasoconstrictor responses to CC at the toe and fingertip were both 0.70 ± 0.02 (mean+S.E.M.), which were significantly greater ($P< 0.001$) than corresponding values in patients with EM (0.37 ± 0.04 and 0.45 ± 0.04 respectively). Similarly, vasoconstrictor responses to IG were significantly greater ($P< 0.001$) at the toe and fingertip in control subjects (0.70 ± 0.03 and 0.70 ± 0.02 respectively) compared with values in EM patients (0.27 ± 0.03 and 0.45 ± 0.15 respectively). These data show that, in contrast with control subjects, patients with EM have diminished sympathetic vasoconstrictor responses to both CC and IG. Denervation super sensitivity may play a part by increasing vasoconstrictor responses to circulating catecholamines, leading to a reduction in skin blood flow. Therefore an interplay between neural and vasoactive agents may be involved in the pathophysiology of EM.

INTRODUCTION

Erythromelalgia (EM) presents with, episodic attacks, which are heralded by a prickling or itching sensation. This sensation can develop into burning pain, which is often of a severe and distressing nature. The attacks are associated with erythema, warmth and occasionally swelling of the affected part. Mitchell [1] was the first to identify EM as a syndrome in 1878, and he used combination of three Greek words, erythros (red), melos (limb) and algos (pain), to illustrate the presenting characteristics of the disease. The symptoms often present when the skin temperature of the affected area is in the critical range 32-36.°C [2,3]. The attacks can last for variable lengths, of time ranging from. minutes to days, and often extreme measures are undertaken by the patient to obtain symptomatic relief [4]. These include sleeping with their feet out of a window and putting their feet in a refrigerator.

EM can present as a primary, idiopathic form or secondary to a number of diseases and conditions, such as mellitus [5], systemic lupus erythematosus [6], hypertension [7] and Raynaud's phenomenon [8]. A common feature underlying these secondary causes of EM is microvascular ischemia. It has been postulated that the erythema seen in patients with EM may be a result of reactive hyperemia, following a period of ischemia [6]. This supposition is in keeping with our own work, in which FM patients showed enhanced cutaneous, vasoconstrictor tendency [9]. They had a bilateral reduction in toe skin temperature, decreased basal blood flow in both their upper and lower extremities and reduced hyperemic responses to local heating (44°C). In our previous study, we did not examine the possible underlying mechanisms responsible for a reduction in skin perfusion, which may be the result of one or a combination of four factors: vasospasm, vessel occlusion (e.g. due to thrombocythemia) [10], increased blood viscosity (e.g. due to polycythemia ruba vera) [2], or an increase in sympathetic neural activity.

Our previously studied EM patients had no evidence of hemorheological abnormalities, and so the aim of the present study was to examine specifically another possibility, i.e. an increase in sympathetic neural activity, as a candidate cause of the observed vasoconstrictor tendency. We therefore assessed focal sympathetic neural activity by measuring vasomotor reflexes at the toe and fingertip pulps to cold challenge (CC) and inspiratory gasp (IG) [11] in control subjects and patients with EM. These acral areas were chosen due to their abundance of arteriovenous anastomoses, which have dense sympathetic innervation [12].

METHODS

Patient and subject characteristics

The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and

Table 1: Duration, nature and location of pain/discomfort in EM1 and EM2 patients.		
Parameter	EM1 (n=61)	EM2 (n=20)
Duration of pain [median (interquartile range) years]	3 (2-6)	3 (2-6)
Nature of pain/discomfort (no. of patients)		
Burning	61	0
Pins and needles	10	13
Formication	12	5
Tingling sensation	5	2
Other	35	14
Affected areas (no. of patients)		
Toes/feet	55	15
Lower leg	30	12
Upper leg	11	8
Fingers/hand	4	0
Arm	3	3

investigations were performed after approval had been obtained from the local ethics committee. All participants gave written informed consent. A total of 81 patients were referred to the Vascular Laboratory at Ninewells Hospital., Dundee, by physicians who were unable to determine the cause of the patients' distressing symptoms. The patient cohort as divided into two groups according to their reported symptoms (Table 1). The 61 patients who reported burning pain in their extremities on warming and/or limb dependency, which was improved by cooling and/or limb elevation, were enrolled and referred to as type I EM (EM1). The remaining 20 patients reported many of the criteria necessary for the diagnosis of EM, but their pain was not of a burning nature. They reported acroparesthesias, including tingling, formication and pins and needles (Table 1), which are the symptoms normally experienced by EM sufferers preceding the burning distress. This second group was termed type II EM (EM2), and were included in the study as an active control group. In addition, 30 healthy, age- and sex-matched control subjects were enrolled.

Of the EM patients, 26 EM1 and 5 EM2 patients had primary (idiopathic) EM, i.e. no associated disorder. Thus 35 EM1 and 15 EM2 patients had an associated disorder (secondary EM), including Raynaud's phenomenon, diabetes mellitus, hypertension and rheumatoid arthritis.

None of the patients or control subjects were taking; any analgesics or vasoactive drugs at the time of investigation.

The 61 EM1 patients (10 male, 51 female) had a median age of 53 rears (interquartile range 30-66 years), and the 20 EM2 patients (2 male, 18 female) had a median age of 52 years (interquartile range 45-67 years). The control group of 30 subjects (5 male, 25 female) had a median age of 47 years (interquartile range 40-64 years), and were enrolled from the University staff and their relative, and friends.

Assessment of vasoconstrictor responses to CC and IG

Vasoconstrictor responses were assessed in a quiet, temperature-controlled laboratory set at $28 \pm 1°C$ and with a relative humidity of $55 \pm 15\%$. Subjects and patients were encouraged to relax. They were clothed lightly and allowed a 30 min equilibration period. Measurements were carried out with subjects in a semi-reclining position. In addition, indirect body warming was used by immersing the subject's left arm up to the elbow in a water bath set at 44°C. As cutaneous blood flow can be highly variable, the combination of these thermal conditions maintains peripheral vasodilatation and limits fluctuations in skin blood flow which may complicate the interpretation of the measurements [11].
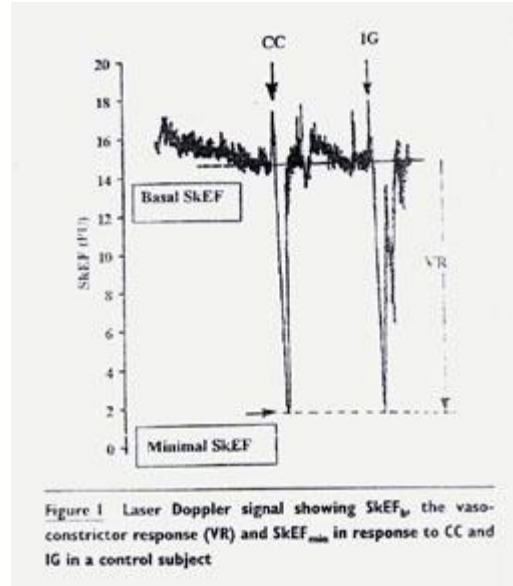

Figure 1 Laser Doppler signal showing $SkEF_b$, the vasoconstrictor response (VR) and $SkEF_{min}$ in response to CC and IG in a control subject

A laser Doppler flowmeter (Perimed PF2b) was used to measure skin erythrocyte flux (SkEF) in arbitrary perfusion units (p.u.), with the time constant and cut-off frequency set to 0.2 s and 12 kHz respectively. The output signal was monitored continuously on a pen recorder (BBC Servoger SE120; Goetz, Metrawart, Austria).

After 30 min of equilibration, baseline SkEF (SkEF-b) was measured at left and right toe pulp and right index fingertip. Transferring the left arm (contralateral arm) from the warm water (44°C) into a cold water bath (15°C) produces a reflex vasoconstrictor response which is mediated via afferent impulses in the 'cold' sensory fibers of the peripheral nerves and a sympathetic efferent pathway [13,14].

An index of the magnitude of the vasoconstrictor reflex, described by Khan et al. [11], was obtained from SkEF-b and the minimum blood SkEF (SkEF-min) induced by the stimulus, using the term:

(SkEF-b - SkEF-min) / SkEF-b

Figure I shows the phases of the response and indicates how the measurements were made from the trace recording.

For the IG studies, subjects were asked to take a deep breath, which they held until being instructed to return to normal breathing. Usually between seven and eight heartbeats were sufficient for the laser Doppler flowmeter to reach a minimum value due

to the induced transient vasoconstriction. This vasoconstriction is mediated by a spinal reflex with unknown efferent and sympathetic afferent pathways [15]. The response was quantified as above.

Statistical analysis

All blood flow results are expressed as means ± S.E.M. Data were analyzed using the Wilcoxon test for nonparametric data. The Spearman Rank Correlation was used to analyze the relationship between vasoconstrictor responses in CC and IG within each group. The null hypothesis was rejected at P<0.05. Statistical analyses, were performed using Statgraphics software (Statistical Graphics Corp.)

RESULTS

Both left and right toe vasoconstrictor reflex responses to CC and IG were assessed, but only data for the right toe are presented, since the values were similar for both. Right index finger vasoconsrictor responses to CC and IG are presented.

SkEF-b

SkEF-b at the toe pulp was significantly lower in EM1 (P< 0.01) and EM2 (P< 0.001) patients compared with values in control subjects (12.9 ± 0.1 p.u., 11.7 ± 0.1 p.u. and 16.9 ± 0.1 p.u. respectively). Fingertip SkEF-b was similar in the two EM groups, but was significantly reduced (P< 0.05) in comparison with values in control subjects (14.8 ± 0.7 p.u., 14.2 ± 1.1 p.u. and 17.8 ±1.2 p.u. in EM1, EM2 patients and control subjects respectively).

Table –2: SkEF-min after CC and IG at the right toe pulp and index fingertip in control subjects (n = 30), EM2 (n = 20) and EM1 (n =61) patients.

Location	Control	EM2	EM1
CC			
Toe pulp	4.9+0.5	6.1 ± 1.0	9.2 -0 1.**
Index fingertip	4.9+03	7.6 ± 1.2*	8.0 ± 0.7***
IG			
Toe pulp	4.9±0.5	7.4±1.1**	10.2±0.9****
Index fingertip	4.9±0.5	9.9±0.2****	9.9±0.7****

Values are means ± S.E.M. Significance of differences compared, with controls: *P < 0.05; **P < 0.01; ***P < 0.005; ****P < 0.001.

SkEF-min after CC and IG

SkEF-min achieved at the toe pulp after CC was significantly higher in EM1 patients compared with values in. the control group (P< 0.01; Table 2). EM1 and EM2 patients achieved similar fingertip SkEF-min values in response to CC, and these were significantly higher than values in control subjects (EM1 P< 0.005, EM2 P< 0.05; Table 2).

IG resulted in significantly higher SkEF-min values at the toe pulp in EM1 (P< 0.001) and EM2 (P< 0.01) patients compared with values in the control group (Table 2). Fingertip SkFF-min values were similar in the two EM groups, but were significantly higher than values in control subjects (both P<0.001 : Table 2).

Vasoconstrictor Responses to CC and IG

Vasoconstrictor responses to CC were significantly reduced at the toe pulp and fingertip in both EM groups compared with values in control subjects (both P< 0.001; Figure 2). Vasoconstrictor responses at the toe were 0.70 ± 0.02, 0.47 ± 0.31, and 0.37 ± 0.04 (on a scale of 0-1) in control subjects, EW2 and EM1 patients respectively (Figure 2); corresponding values at the fingertip were 0.70 ± 0.02, 0.45 ± 0.06 and 0.45 ± 0.04 respectively (Figure 2).
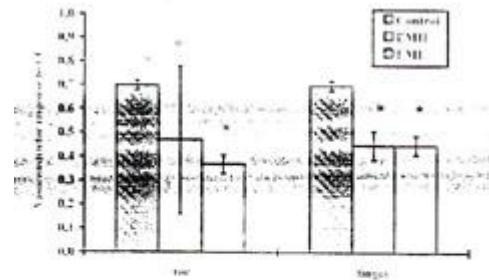

Figure 2 Vasoconstrictor responses to CC at the toe pulp and fingertip in control subjects (n = 30), EMII (n = 20) and EMI (n = 61) patients

Values are means ± S.E.M. *P < 0.001 compared with controls (Wilcoxon test).

IG also produced significantly reduced vasoconstrictor responses at the toe pulp and fingertip in both EM groups compared with responses in control subjects (both P< 0.001; Figure 3). Vasoconstrictor responses at the toe were 0.70 ± 0.03, 0.39 ± 0.07 and 0.27 ± 0.03 in control subjects, EM1 and EM2 patients respectively (Figure3); corresponding values at the fingertip were 0.70 ± 0.02, 0.45 ± 06 and 0.45 ± 0.15 respectively (Figure 3).

Vasoconstrictor responses to CC and IG at the finger and toe were significantly correlated within the EM1, EM2 and control groups (Table 3).

There were no significant differences between vasoconstrictor responses in EM1 and EM2 patients (P = O.83).

DISCUSSION

In this study, the integrity of skin vasoconstrictor responses to CC and IG has been examined in patients with EM. The main finding is that, in comparison with control subjects, EM patients have diminished sympathetic vasoconstrictor responses to both stimuli, suggesting that the previously detected enhanced skin vasoconstrictor tone in EM patients is unlikely to be due to elevated sympathetic neural activity. Diminished vasoconstrictor

Figure 3 Vasoconstrictor responses to IG at right toe pulp and right index fingertip in control subjects (n = 30), EMII (n = 20) and EMI (n = 61) patients

Values are means ± S.E.M. *P < 0.001 compared with controls (Wilcoxon test)

responses most probably result from impaired sympathetic activity, as responses to both CC and IG are dependent on sympathetic neural innervation [11]. It is not clear, however,
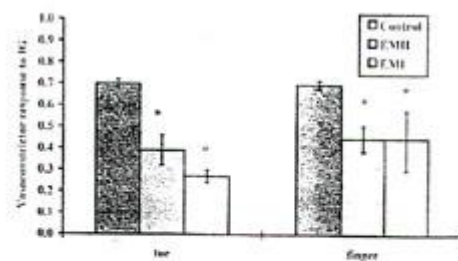
if the level of dysfunction lies along the efferent pathway and/or reflects damage to the spinal cord, where the vasomotor reflexes are coordinated Furthermore, we found no significant differences in vasoconstrictor responses between primary and secondary EM patients, and therefore the underlying condition is unlikely to have played a major role in producing reduced vasoconstrictor responses.

A possible reason for the lower calculated vasoconstrictor responses in EM patients is that they had a lower level of basal perfusion, which is consistent with our previous work [9]. The minimum blood flow achieved, however, in response to both stimuli (with the exception of the toe in response to CC in EM1 patients) was significantly higher in EM patients than in control subjects, and therefore the overall extent of vasoconstriction was reduced.

Since an increase in sympathetic neural tone appears not to be the cause of reduced

Table 3: Correlation between CC and IG at the toe and index fingertip in control subjects (n=30), EM1 (n=61) and EM2 (n=20) patients.

Group	Parameter	Toe	Fingertip
Control	r	0.61	0.46
	P	0.001	0.01
EM1	r	0.51	0.67
	P	0.001	0.001
EM2	r	0.80	0.46
	P	0.001	0.005

skin blood flow in EM patients, other factors must be involved. One possibility may be a maldistribution of blood flow between the thermoregulatory vascular bed (hyperperfusion) and the nutritive bed (hypoperfusion), as seen in some patients [16]. However, this observation was made while patients were experiencing EM symptoms; this is in contrast with our patients who were all asymptomatic at the time of investigation, and it is unlikely that maldistribution of blood flow played a major role in the present study.

A local fault in the vascular smooth muscle such as thickened blood vessel basement membranes perivascular edema or endothelial swelling,, which have been observed in primary and secondary EM parents [10,16] , may be contributory factors to the reduced skin perfusion seen in the present and previous [9] studies. However, defective vascular smooth muscle per se does not appear to affect local sympathetic-mediated regulation of blood flow in patients with Type I diabetes [17]. Thus it is reasonable to suggest that local sympathetic neural dysfunction is the most likely cause of the reduced vasoconstrictor responses seen in EM1 and EM2 patients.

The findings of reduced focal sympathetic activity are in keeping with histological evidence from three case reports, which showed a decrease in sympathetic innervation in EM patients [5,18,19]. Two of these patients had diabetes mellitus and reduced nerve conduction velocities [5,19]. A decreased number of acetylcholinesterase and catecholamine-containing nerve terminals in peri-arterial and sweat-gland plexi was observed in skin biopsies taken from the dorsum of the foot in these three EM patients. Uno and Parker [18] concluded that a reduction in sympathetic tone leads to a decrease in vasoconstriction, resulting in red and warm feet observed during symptomatic EM. In addition, they concluded that the decrease in sympathetic neural activity may cause the

vasculature to develop denervation supersensitivity which amplifies the microvascular response to circulating catecholamines. These authors did not, however, offer an explanation as to how an increased responsiveness to catecholamines -(which presumably -leads, to increased vasoconstriction), could promote red, warm feet. One possibility, which may also explain the findings of the present study, is that there is an increased sensitivity of the microvessels following denervation, resulting- in enhanced vasoconstriction and perhaps ischemia, which may be the forerunner of the hyperermia (red, warm, feet).

Alternatively, Zoppi and colleagues [20] suggested that the symptoms of EM are under total sympathetic control, as they found their patient population (n = 3) to benefit from reversible sympathetic blockade. Their hypothesis is that reversible sympathetic blocks cause an interruption of the `peripheral-central-peripheral' cycle of events. This cycle has also been related to the similar clinical condition of reflex sympathetic dystrophy (now known as chronic regional pain syndrome Type 1), in which an increase in internuncial neuron pool activity in the spinal cord (registered centrally as pain) might further stimulate sympathetic efferent fibers, thereby contributing to a cycle of pain and increased sympathetic activity [21]. Reversible sympathetic blockade could also lead to compensatory up- or down-regulation of the adrenoceptors, which may counterbalance the super-sensitivity and sub-sensitivity, and perhaps lead to normalization. It may be, however, that the time period between sympathetic blocks (L2-L4; one per day for 10 days) was insufficient for the compensatory mechanisms to develop. Additionally, there have been a few reports of EM patients benefiting from sympathectomy or neurolitic irreversible blocks of the lumbar sympathetic ganglia [22,23], while others have found the symptoms of EM to be aggravated by such treatment [24,25], possibly as a result of denervation supersensitivity. It would appear, therefore, that the symptoms of EM are related in part to sympathetic activity, but the mode of action and potency of neural innervation is unclear.

Not surprisingly, diminished vasoconstrictor responses, similar to the current findings, have been found in patients with sympathetic dystrophies [26], dysautomias [27], post-regional sympathectomy [28] and diabetic neuropathies [11]. Although over two-thirds of EM2 and over half of EM1 patients identified a traumatic event, neither group fully satisfied the diagnostic criteria for chronic regional pain syndrome.

Neurological impairment may result from other factors unrelated to direct physical trauma. This may be from a more intimate source, such as nerve (endoneurial) ischemia, as seen in diabetic neuropathy [29]. Factors contributing to nerve ischemia include structural defects in the endoneurial microvasculature, together with rheological abnormalities and abnormalities in the production or action of vasoactive agents which play a key role in nerve blood flow, including nitric oxide and prostaglandins. In diabetes mellitus, endoneurial ischemia is related to defects in basement membrane thickening, endothelial cell swelling and proliferation, intimal and smooth muscle swelling and occlusion of microvessels with platelet thrombi [30]. These microvascular abnormalities are also found in both primary EM (except microthrombi) [31] and myeloproliferation-related secondary EM [10]. Indeed, reduced vasoconstrictor and hyperemic responses

found in the EM1 and EM2 patients in the present study and in our previous one [9] are similar to the microvascular abnormalities seen in patients with diabetes mellitus [32].

Both EM1 and EM2 patients have an increased vasoconstrictor tendency and reduced sympathetically mediated vasomotor reflexes in both affected and unaffected areas. Previous workers [26] have also identified a bilateral dysfunction of sympathetic vasoconstrictor reflexes in patients with chronic regional pain syndrome. It is interesting; to note that the microvascular and sympathetic dysfunction identified in tile patients studied appear to be widespread, rather than being restricted to areas,, normally associated with the symptoms of EM. Therefore how the individual vascular bed is affected may depend in part on its interactions with sympathetic control, microvascular architecture and sensitivity to circulating vasoactive mediators. The lower limbs, however, were affected to a greater degree than the finger in the present study. The feet are subject to additional forces, namely increased hydrostatic pressure, which may enhance the effects of the neurovascular pathology discussed.

In conclusion, the findings of the present study suggest that reduced skin sympathetic activity may lead to denervation supersensitivity and an increase in vasoconstrictor responses to circulating catecholamines, thereby causing a reduction in skin blood flow. An interplay between neural and vasoactive agents may therefore be involved in the pathophysiology of EM.

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