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Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value

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Summary

Complex regional pain syndrome type I (CRPS I, formerly known as reflex sympathetic dystrophy) is a painful neuropathic disorder that develops after trauma affecting the limbs without overt nerve injury. Clinical features are spontaneous pain, hyperalgesia, impairment of motor function, swelling, changes in sweating, and vascular abnormalities. In this study, the pathophysiological mechanisms of vascular abnormalities were investigated. Furthermore, the incidence, sensitivity and specificity of side differences in skin temperature were defined in order to distinguish patients with definite CRPS I from patients with extremity pain of other origin. In 25 CRPS I patients and two control groups (20 healthy subjects and 15 patients with other types of extremity pain), cutaneous sympathetic vasoconstrictor activity was altered tonically by the use of controlled thermoregulation. Whole-body temperature changes were induced with a thermal suit in which cold or hot water circulated. The vascular reflex response (skin blood flow, laser Doppler flowmetry, skin temperature, infrared thermometry) was analysed to quantify sympathetic outflow. Measurements were performed during a complete thermoregulatory cycle, i.e. during the entire spectrum of sympathetic vasoconstrictor activity from high (whole-body cooling) to low sympathetic activity (whole-body warming). Venous noradrenalin levels were determined bilaterally in five CRPS patients. (i) Three distinct vascular regulation patterns were identified related to the duration of the disorder. In the 'warm' (acute) type of regulation, the affected limb was warmer and perfusion values were higher than in the contralateral limb during the entire spectrum of sympathetic activity. In the 'intermediate' type of regulation the limb was either warmer or colder. In the 'cold' (chronic) type of regulation, skin temperature and perfusion values were lower on the affected side during the entire spectrum of sympathetic vasoconstrictor activity. (ii) Noradrenalin levels were lower on the affected side, even in chronic patients with considerable cutaneous vasoconstriction. (iii) Temperature and blood flow differences between the two sides were dynamic and most prominent at a high to medium level of vasoconstrictor activity. (iv) In both control groups, there were only minor side differences in flow and temperature. In conclusion, it is suggested that, in CRPS I, unilateral inhibition of sympathetic vasoconstrictor neurones leads to a warmer affected limb in the acute stage. Secondary changes in neurovascular transmission may lead to vasoconstriction and cold skin in chronic CRPS I, whereas sympathetic activity is still depressed. Vascular abnormalities are dynamic. The maximal skin temperature difference that occurs during the thermoregulatory cycle distinguishes CRPS I from other extremity pain syndromes with high sensitivity and specificity.

Keywords: sympathetic vasocontrictor neurones; thermoregulation; neuropathic; complex regional pain syndrome

Abbreviation: CRPS I = complex regional pain syndrome type I

Introduction

Complex regional pain syndrome type I (CRPS I, reflex sympathetic dystrophy) is a painful disorder that may develop as a disproportionate consequence of a minor trauma affecting the limbs or of bone fracture, or as a consequence of a remote process such as stroke and myocardial infarction (Wasner *et al*., 1998). The clinical features are spontaneous pain, hyperalgesia, impairment of motor function, swelling and autonomic abnormalities. An overt nerve lesion is not detectable (Schwartzman and McLellan, 1987; Baron *et al*., 1996). Regardless of the site of the precipitating event, the

abnormalities show a spreading tendency with a generalized distal distribution that is not confined to the innervation territories of peripheral nerves or roots. CRPS I is distinguished from CRPS II (causalgia), in which a partial lesion of a peripheral nerve is necessary for the diagnosis (Merskey and Bogduk, 1995; Stanton-Hicks *et al*., 1995). Besides pain, autonomic (sympathetic) disturbances are characteristic clinical symptoms (Baron and Maier, 1996). These include regional abnormalities of cutaneous vascular and sudomotor function.

At present, CRPS I is a pure clinical diagnosis and no objective test procedure exists to diagnose this entity with high sensitivity and specificity. Patients with poorly defined extremity pain of unknown origin may meet some of the clinical criteria and may be included under the umbrella category of CRPS I. In fact, several recent studies determined the validity of the clinical CRPS criteria and found that CRPS is currently overdiagnosed (Galer *et al*., 1998; Baron *et al*., 1999). Therefore, it is of utmost importance to find objective laboratory tests to define CRPS unequivocally and to distinguish this entity from similar pain syndromes of different causation.

The present investigation had two aims. First, the pathophysiological mechanisms of vascular abnormalities in CRPS I were investigated. In order to assess the function of cutaneous sympathetic vasoconstrictor neurones quantitatively, thermoregulatory reflexes were analysed under controlled conditions. Secondly, the incidence, sensitivity, specificity and diagnostic value of vascular abnormalities that occur under controlled thermoregulatory conditions were defined by comparing patients with definite CRPS I with healthy controls and a group of patients with extremity pain of other origin.

Methods

Patients and healthy volunteers

Patients with CRPS I

The study was performed on 25 patients (18 women and seven men; mean age 47 years, range 27–66 years) with the diagnosis of unilateral CRPS I who were referred to the Interdisciplinary Pain Center of the University Clinic of Kiel between 1995 and 2000 (Table 1). The upper extremity was affected in 17 cases and the lower in eight cases. Reflex sympathetic dystrophy (CRPS I) was diagnosed according to the criteria defined by Evans (Evans, 1946) and to the novel clinical criteria defined by the International Association for the Study of Pain (Merskey and Bogduk, 1995; Stanton-Hicks *et al*., 1995). All patients were characterized clinically by spontaneous pain (at least in their medical history) and evoked pains (e.g. deep hyperalgesia, mechanical allodynia) that were generalized distally and were not restricted to an innervation territory of any peripheral nerve. In all cases, pain was increased by movement of the affected limb and patients had at least one symptom of motor dysfunction, such as impairment of muscle strength, tremor or dystonia. Furthermore, there was or had been evidence of at least one autonomic involvement, such as oedema, skin temperature asymmetries or sweating abnormalities.

By using these criteria the incidence of false-positive diagnoses was minimized. The patients underwent a general physical and neurological examination, and additional investigations (radiography, three phase bone scan) were performed.

Patients with chronic extremity pain of other origin

Fifteen patients (eight women and seven men; mean age 42 years, range 18–57 years) with chronic pain of one limb of origin other than CRPS (the patients did not meet the criteria described above) served as one of two control groups (Table 2). Although the patients were suffering from different diseases, the following reasons argue against the possibility that they had early CRPS I or II. (i) In all patients with nerve injury the pain was restricted to the affected nerves with no tendency to spread beyond the innervation territory. Therefore, they were classified as having post-traumatic neuralgia (Baron *et al*., 1999). (ii) The clinical picture was stable for several months in the control patients, and it was therefore unlikely that symptoms had begun to generalize, as would be expected in early CRPS II. (iii) No control patient demonstrated trophic disturbances. (iv) None of the patients suffered from oedema and there was no history of autonomic abnormalities.

Healthy controls

Twenty healthy subjects (11 women and nine men; mean age 27 years, range 23–45 years) served as the second control group.

General procedure

All neurophysiological tests were performed between 15.00 and 18.00 hours. The subjects were tested in supine position (room temperature 24°C). None of the control subjects or patients were on drugs affecting vascular function. Patients suffering from cardiovascular disorders were excluded from the study. The aims and procedures of the study were explained to all subjects according to the Declaration of Helsinki. All individuals gave their informed consent to participation in the study, which was approved by the local ethics committee. The procedures followed were in accordance with institutional guidelines.

Measurement of skin perfusion and skin temperature at the extremities

Cutaneous blood flow in glabrous skin (tip of second finger or first toe) was measured bilaterally by continuous laser

Table 1 *Clinical characteristics of CRPS patients*

Patient	Age (years)/ sex	Location	Precipitating event	Duration of disease (months)	Type of regulation
1	62/F	L upper limb	Wrist fracture	1.5	Warm
2	62/M	R upper limb	Wrist fracture	2.5	Warm
3	43/F	L upper limb	Metacarpal fracture	20	Intermediate
4	44/F	L upper limb	Colles fracture	12	Intermediate
5	49/F	L lower limb	Ankle joint distortion	35	Cold
6	51/F	R upper limb	No obvious trauma	48	Intermediate
7	55/M	L lower limb	Strain	5	Warm
8	56/F	L upper limb	Colles fracture	14	Cold
9	27/F	R lower limb	No obvious trauma	48	Cold
10	34/F	R upper limb	Post-elbow surgery	48	Cold
11	40/F	R upper limb	Strain	3	Warm
12	50/F	L lower limb	Lower leg fracture	25	Cold
13	66/M	L upper limb	Colles fracture	2	Intermediate
14	63/F	R upper limb	Tendovaginitis	5	Warm
15	57/M	R upper limb	Shoulder torn tendon	2	Warm
16	40/M	R upper limb	No obvious trauma	10	Intermediate
17	52/F	R upper limb	Colles fracture	0.5	Warm
18	64/F	R upper limb	Elbow dislocation	3.5	Warm
19	34/F	R upper limb	Tendosynovitis	18	Cold
20	49/F	R lower limb	No obvious trauma	4.5	Warm
21	33/F	R upper limb	Post-tenosynovitis	7	Intermediate
22	30/M	R lower limb	Metacarpal fracture	10	Cold
23	39/F	L upper limb	No obvious trauma	15	Warm
24	43/F	R lower limb	Ankle joint fracture	7	Intermediate
25	27/M	L lower limb	Sprain	2	Warm

M = male; F = female; L = left; R = right.

Table 2 *Clinical characteristics of patients with extremity pain of other origin*

Patient	Age (years)/ sex	Location	Disease	Duration (months)
1	38/M	L upper limb	Traumatic neuralgia of ulnar nerve and internal cutaneous nerve	33
2	47/M	R upper limb	Lunatomalacia	0.5
3	39/F	R lower limb	Radiculopathy	18
4	57/M	L upper limb	Central pain after thalamic infarction	6
5	49/F	R lower limb	Achillodynia	103
6	56/M	L upper limb	Ischaemic nerve lesion at wrist and dorsal hand	12
7	38/M	L upper limb	Pseudoarthrosis in the wrist	10
8	42/F	R lower limb	Traumatic neuralgia of peroneal nerve	17
9	32/F	L upper limb	Carpal tunnel syndrome	6
10	18/F	R upper limb	Traumatic nerve lesion at wrist and ulnar hand	48
11	53/F	R upper limb	Traumatic neuralgia of radial nerve	25
12	49/M	L upper limb	Neuralgia of ulnar nerve	23
13	42/M	L upper limb	Severe shoulder trauma with lesion of brachial plexus	7
14	36/F	R upper limb	Brachial plexopathy	38
15	50/F	L upper limb	Traumatic nerve lesion at thumb	6

M = male; F = female; L = left; R = right.

Doppler flowmetry (Periflux PF 4001, integrating probes PF 413; Perimed, Stockholm, Sweden). The tips of the digits were selected for investigation because the abundant arteriovenous anastomoses of this area are under strict sympathetic vasoconstrictor control, and thus changes mediated by cutaneous vasoconstrictor activity are prominent and vasomotor reflexes are extensive (Wasner *et al*., 1999). Simultaneously, skin temperature was measured bilaterally at all finger or toe tips at 5-min intervals with infrared thermometers.

Assessment of cutaneous vascular regulation

Controlled alteration of sympathetic vasoconstrictor activity

The sympathetic vasoconstrictor activity of the skin is under thermoregulatory control. Controlled thermoregulatory reflexes were performed to induce a physiological tonic change in sympathetic nerve activity in the skin. This was achieved by changing the environmental temperature by means of a thermal suit. The subject lay in a cotton suit containing tubes in which water at 12°C or 50°C (inflow temperature) circulated, in order to cool and warm the whole body, respectively. Neither the hands nor the feet were covered by the suit. Whole-body cooling is the most effective way to induce massive tonic activation of cutaneous vasoconstrictor neurones, as has been demonstrated in microneurographical recordings (Bini *et al*., 1980); warming leads to complete inhibition of this activity. Degeneration or dysfunction of vasoconstrictor neurones results in attenuation of the cooling response. Alteration of sympathetic activity was assessed indirectly by measuring skin blood flow and skin temperature at the hands or feet as described above (Fig. 1). In order to assess central effects of the whole-body temperature changes, tympanic membrane temperature (close to body core temperature) was measured with an infrared thermometer at 10-min intervals, and blood pressure was documented continuously with a non-invasive Finapress device (Ohmeda, Englewood, Col., USA).

Thermoregulatory cycle

Skin blood flow and temperature measurements were performed during a complete thermoregulatory cycle, i.e. during the entire spectrum of sympathetic vasoconstrictor activity. After the patients had put on the thermal suit and had then had a period of rest, whole-body cooling was performed to induce maximal vasoconstrictor activity. The cooling session was continued until the skin temperature on the unaffected side (the right side in healthy controls) was close to room temperature (25°C). Thereafter, whole-body warming was performed until the skin temperature on the unaffected side (the right side in healthy controls) was close to body core temperature (i.e. 35°C) in order to induce maximal inhibition of sympathetic activity (Fig. 1).

Side differences in skin blood flow and temperature during the thermoregulatory cycle

In order to analyse unilateral abnormalities in cutaneous vascular regulation, we determined side differences in skin blood flow and skin temperature at regular intervals during the thermoregulatory cycle. In order to compare the measurements between patients, the level of the overall cutaneous sympathetic vasoconstrictor activity was estimated indirectly from skin temperature on the unaffected side (or the right side in healthy controls) as a reference value. A skin temperature on the healthy side of $\leqslant$25°C indicates a high level of sympathetic vasoconstrictor activity in the skin, a temperature of ~30°C an intermediate level and a temperature of $\geqslant$35°C the absence of such activity. This spectrum of sympathetic activity (from high to low) was used for further analyses (Fig. 4).

Skin temperature differences at regular intervals. For individual comparisons, only the absolute values of skin temperature differences were used, independently of the sign of the difference (colder or warmer) with the following formulae. The side difference in skin temperature in CRPS patients and patients with other extremity pain was calculated as ΔT = skin temperature on affected side – skin temperature on unaffected side. The side difference in skin temperature in healthy controls was calculated as ΔT = skin temperature on right side – skin temperature on left side.

Skin perfusion differences at regular intervals. The side comparison of skin perfusion in CRPS patients and patients with other extremity pain was calculated as cp = $\log_2$ perfusion on affected side/perfusion on unaffected side. The side comparison of skin perfusion in healthy controls was calculated as $cp = \log_2$ perfusion on right side/perfusion on left side. A value of $cp = 1$ means that the blood flow on the affected (or right) side is either twice or half that on the healthy (or left) side.

Maximal side difference in skin temperature during the thermoregulatory cycle. The absolute maximal side difference in skin temperature that occurred during the whole thermoregulatory cycle was determined with the following formulae. The maximal side difference in skin temperature in CRPS patients and patients with extremity pain of other origin was calculated as ΔT_{max} = skin temperature on affected side – skin temperature on unaffected side. The maximal side difference in skin temperature in healthy controls was calculated as ΔT_{max} = skin temperature on right side – skin temperature on left side.

Noradrenalin measurements

In order to quantify sympathetic activity further, plasma levels of noradrenalin from the venous effluent of the area of autonomic dysfunction were examined in five of the CRPS

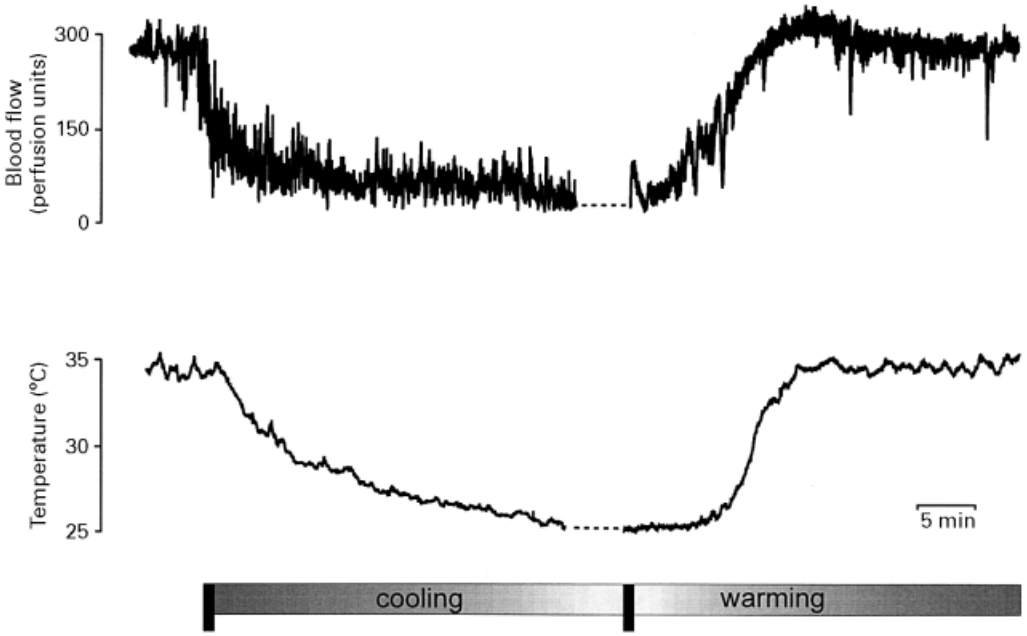

Fig. 1 On-line measurements of skin perfusion in the right index finger and of skin temperature of the right middle finger during activation of cutaneous sympathetic vasoconstrictor activity by whole-body cooling and during inhibition of cutaneous sympathetic vasoconstrictor activity by whole-body warming in a healthy control subject. Whole-body cooling led to a rapid, sustained fall in skin blood flow measured by laser Doppler flowmetry (relative perfusion units) and skin temperature in healthy skin, indicating massive tonic activation of cutaneous sympathetic vasoconstrictor activity. Whole-body warming induced inhibition of sympathetic vasoconstrictor activity followed by an increase in blood flow and temperature.

patients. About 80% of this value reflects secretion by sympathetic postganglionic vasoconstrictor terminals to muscle and (mainly) skin. Venous blood samples were taken from veins at the dorsum of both hands under resting conditions. Noradrenalin was measured by high-pressure liquid chromatography with electrochemical detection (Bio-Rad, Hercules, Calif., USA).

Statistical analysis

The *U* test was used to compare side differences in temperature and perfusion between CRPS patients and controls. Spearman's correlation was calculated for the comparison of maximal side differences in temperature and the duration of the disorder. A P value of <0.05 was regarded as statistically significant.

Results

Pain intensity in CRPS patients and patients with extremity pain of other origin

In CRPS, 20 patients had resting pain (numerical analogue scale of 0–10; average pain intensity 3.3, range 1.5–7). Five patients had no resting pain during the investigations, but suffered from evoked pains (e.g. deep hyperalgesia and mechanical allodynia). Furthermore, all these patients reported resting pain at some point during their disease, but at the time of the investigation with the thermal suit they were free of spontaneous pain because of conservative treatment or medication that did not interfere with skin perfusion or the autonomic nervous system. The control patients with extremity pain of other origin suffered from unilateral resting pain (numerical analogue scale of 1–10; average intensity 5.0, range 3.5–7). Five patients had no resting pain, but had evoked pain during the investigations. However, these patients also reported resting pain during the course of their disease.

Cutaneous vascular regulation

Healthy controls and patients with extremity pain of other origin

Whole-body cooling induced symmetrical vasoconstriction in both limbs due to maximal tonic activation of cutaneous sympathetic vasoconstrictor neurones paralleled by a bilateral decrease in skin temperature (Figs 1 and 2). Thereafter, whole-body warming was performed in order to inhibit cutaneous sympathetic vasoconstrictor activity completely. As a result, skin blood flow and temperature increased symmetrically (Figs 1 and 2). The regulation pattern was identical in the healthy control group (Fig. 2A and B) and in the group of patients with extremity pain of other origin (Fig. 2C and D). Only small side differences in skin blood

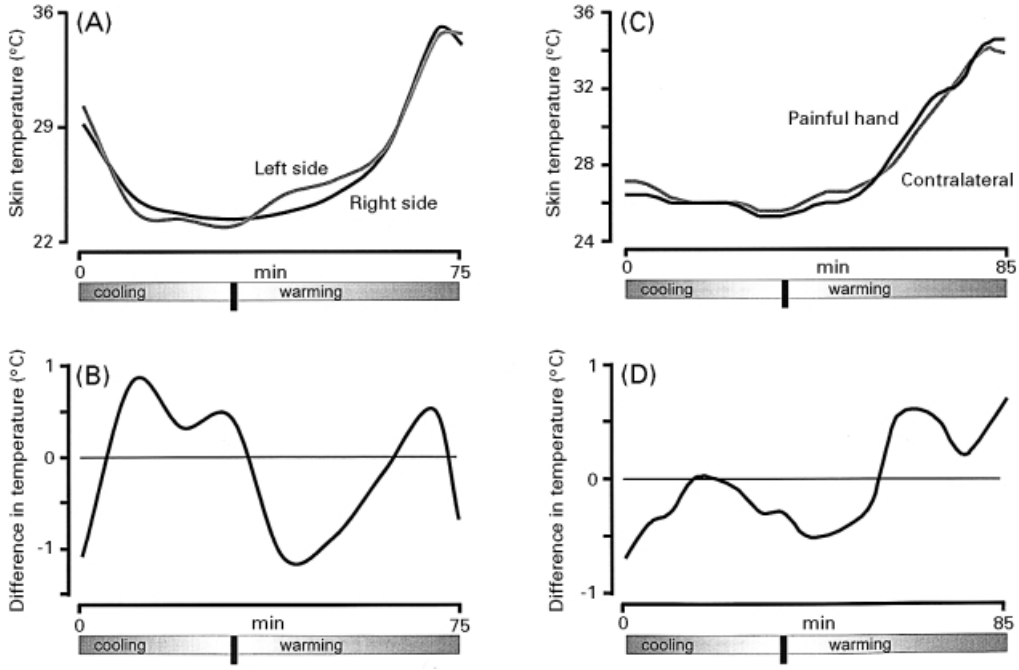

Fig. 2 Characteristics of skin temperature as a measure of cutaneous sympathetic vasoconstrictor activity in the fingers of both hands in one healthy control subject (**A**) and in a patient with extremity pain with origin other than CRPS (Patient 1 in Table 2) (**C**) during a controlled thermoregulatory cycle (controlled alteration in cutaneous sympathetic activity). Controlled thermoregulatory changes (whole-body cooling and warming) were produced by means of a thermal suit to change the environmental temperature in a standardized way and at the same time to alter the sympathetic vasoconstrictor activity of the skin by reflex action. The subject lay in a suit containing tubes supplied with running water at 12 and 50°C (inflow temperature) to cool and warm, respectively, the whole body. During the experiment, the skin temperature of the fingers of both hands was monitored at regular intervals. The healthy side is indicated by the label 'contralateral' and the affected side by the label 'painful hand'. Side differences in skin temperature of the fingers of both hands are shown for one healthy control subject (**B**) and a patient with extremity pain of other origin than CRPS (Patient 1 in Table 2) (**D**) during a controlled thermoregulatory cycle (controlled alteration in cutaneous sympathetic activity). Same subjects as in **A** and **C**.

flow and temperature occurred during the cycle (Fig. 2B and D; see below).

Patients with CRPS I

Characteristic abnormalities in cutaneous vascular regulation were found in patients with CRPS I. Whole-body cooling led to an immediate sustained decrease in skin blood flow and temperature on the unaffected distal extremities, which was very similar to the situation in healthy controls. On the affected side, three patterns of regulation were observed (Fig. 3), as described below.

Warm regulation. Patients with the 'warm' type of regulation showed higher cutaneous temperature and perfusion values in the affected limb than contralaterally during the entire spectrum of sympathetic vasoconstrictor activity (Fig. 3A–C). Almost the same temperatures occurred on the two sides only after intense warming. This type of regulation was present in 11 patients.

In one patient of this group, no modulation of skin temperature and blood flow could be induced. The temperature values were stable and close to body core temperature during the entire warming and cooling periods (Fig. 3A). No vasoconstriction could be induced even by intense whole-body cooling. This patient was examined at a very early stage of the disease (2 weeks after the onset of CRPS I symptoms) and may represent an extreme of the spectrum of patients with the warm type of regulation.

Intermediate regulation. In patients with the 'intermediate' type of regulation (Fig. 3D and E), the direction of the temperature side difference changed during the thermoregulatory cycle. The affected side was either warmer and vasodilated during a high level of sympathetic activity and colder and vasoconstricted during a low level of sympathetic activity, or vice versa. After intense warming, nearly the same temperature values were present on both sides. This type of regulation was found in seven patients.

Cold regulation. In patients with the 'cold' type of regulation, vasoconstriction was more pronounced, with lower skin temperature and perfusion values on the affected limb during the entire thermoregulatory cycle (Fig. 3F). Only after

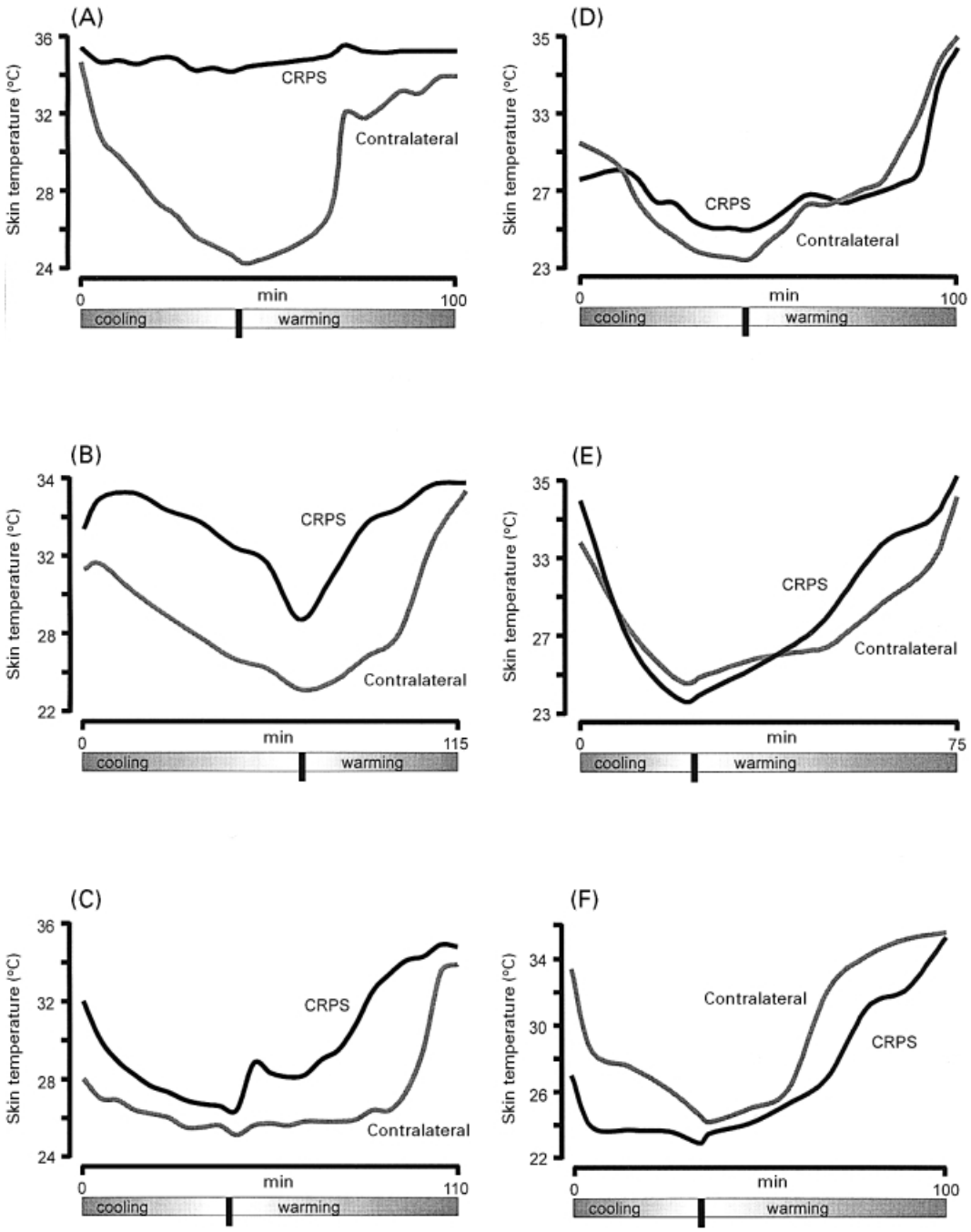

Fig. 3 Characteristics of skin temperature as a measure of cutaneous sympathetic vasoconstrictor activity in the fingers (toes) of both hands (feet) in patients with CRPS during a controlled thermoregulatory cycle (controlled alteration in cutaneous sympathetic activity). The experimental set-up was the same as in Fig. 2. The healthy side is indicated by the label 'contralateral' and the affected side by the label 'CRPS'. Three distinct patterns of vascular regulation were identified. (**A–C**) Patients with the 'warm' type of regulation showed higher cutaneous temperature and perfusion values in the affected limb than in the contralateral limb during the whole thermoregulatory cycle (entire spectrum of sympathetic vasoconstrictor activity). (**D** and **E**) In patients with the 'intermediate' type of regulation, the direction of the temperature side difference changed during the thermoregulatory cycle. In some patients the affected side was warmer during the period of high sympathetic activity and colder during inhibition of sympathetic activity (**D**). Vasoconstriction during cooling and vasodilatation during warming were less intense in the affected limb than in the contralateral limb. In other patients, the affected side was colder during the period of high sympathetic activity and warmer during inhibition of sympathetic outflow (**E**). (**F**) Patients with the 'cold' type of regulation had lower skin temperature and perfusion values on the affected side during the entire spectrum of sympathetic vasoconstrictor activity. (**A**) Patient 17; (B) Patient 15; (**C**) Patient 20; (**D**) Patient 6; (**E**) Patient 3; (**F**) Patient 8 in Table 1.

prolonged whole-body warming was the side difference almost absent. This type of regulation was found in seven patients.

Side differences in skin temperature and perfusion

CRPS I patients

The differences in skin temperature and perfusion were not static but depended critically on the thermoregulatory state (Fig. 3). During inhibition of sympathetic vasoconstrictor activity (intense whole-body warming), minimal side differences were detected in all patients. The largest side differences were found at a high to intermediate level of sympathetic activity.

The level of sympathetic activity was estimated indirectly from the skin temperature of the healthy limb. A temperature of ⩽25°C indicated a high level, a temperature of ~30°C an intermediate level and a temperature of ⩾35°C the complete absence of sympathetic vasoconstrictor activity to the skin. In order to average the skin temperature and perfusion values of all subjects in a group, this measure (skin temperature on the healthy side) was used as a reference value for the level of activity (Fig. 4); the absolute value of the difference independently of the sign (colder or warmer) was used.

Skin perfusion. The highest average difference ($cp = 0.8$) was present at a contralateral skin temperature of 27°C (Fig. 4A).

Skin temperature. The highest average difference ($\Delta T \approx 2.9$°C; Fig. 4B) was present at a contralateral skin temperature of 29°C.

Healthy controls and patients with extremity pain of other origin

In these patients there were no differences or only moderate differences in skin perfusion and temperature between the two sides during the whole thermoregulatory cycle (Fig. 4).

Maximal skin temperature side differences in CRPS I and controls

The maximal skin temperature difference between the two sides (absolute values) that occurred during the thermoregulatory cycle was determined for each patient and for the controls. In CRPS patients this was $\Delta T_{max} = 4.5 \pm 0.6$°C (mean ± SEM, range 1.1–10.4°C). In contrast, patients with limb pain of other origin showed a maximal side difference of $\Delta T_{max} = 1.0 \pm 0.2$°C (range 0–2.5°C) and the healthy controls had $\Delta T_{max} = 1.3 \pm 0.1$°C (range 0.2–2.2°C).

The question arises whether these values can be used as a diagnostic tool to differentiate CRPS from limb pain of other

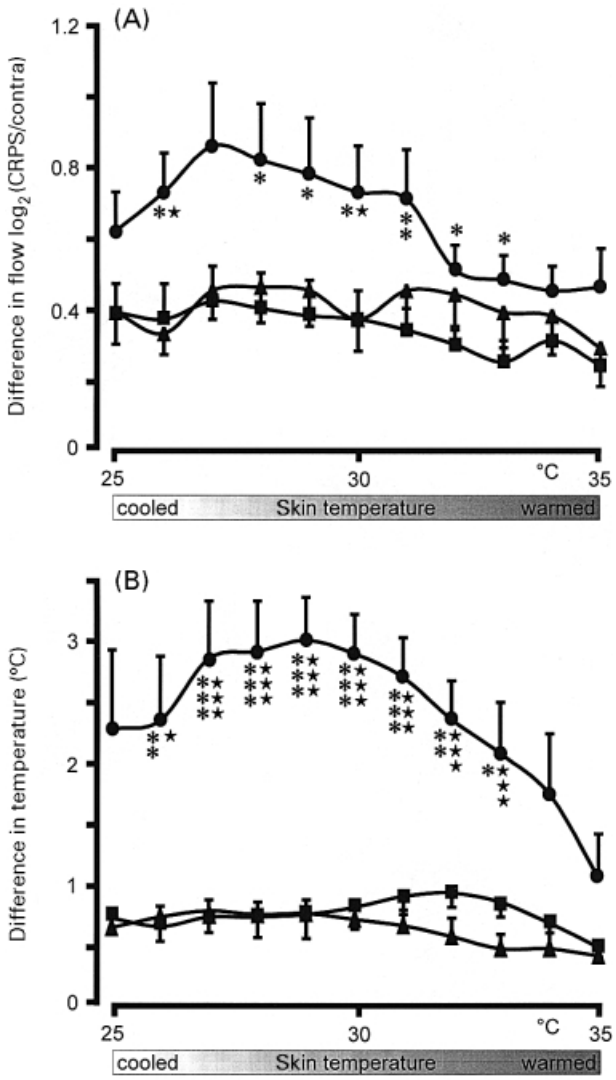

Fig. 4 Average absolute side differences in skin perfusion (**A**) and in skin temperature (**B**) of the fingers (toes) of both hands (feet) in 25 patients with CRPS (circles) in 20 healthy controls (squares) and in 15 control patients with extremity pain of other origin (triangles) during a controlled thermoregulatory cycle (controlled alteration in cutaneous sympathetic activity). The level of overall cutaneous sympathetic vasoconstrictor activity was estimated indirectly from the skin temperature on the unaffected side (the right side in healthy controls) as reference value. A skin temperature of 25°C on the healthy side indicates a high level, a temperature of 30°C an intermediate level and a temperature of 35°C complete inhibition of sympathetic vasoconstrictor activity to the skin. Mean ± standard error of the mean. Asterisks show CRPS compared with healthy controls, stars show CRPS compared with control patients with extremity pain of other origin. One symbol, $P < 0.05$; two symbols, $P < 0.01$; three symbols, $P < 0.001$.

origin. Data from the healthy control group ($n = 20$) were used to calculate normal values (95% confidence interval) for this criterion. Accordingly, maximal temperature differences of $\Delta T_{max} < 2.2$°C were considered to be normal. None of the healthy group was false-positive. On the basis of these normal values, six out of 25 CRPS patients were

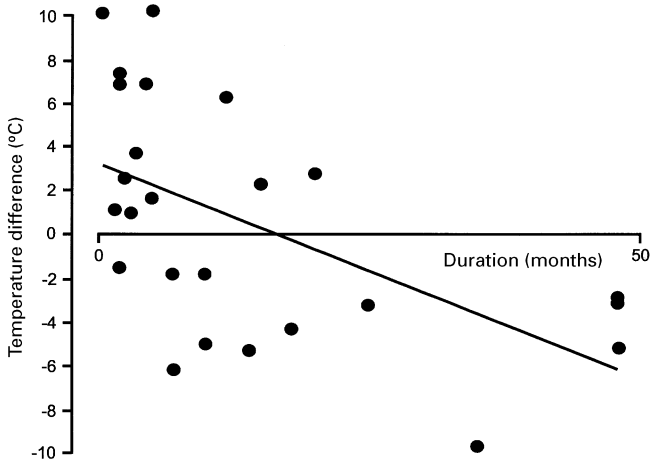

Fig. 5 Relationship between vascular abnormalities and duration of CRPS I. Asymmetries in individual maximal skin temperature are plotted against individual duration of CRPS. There was a significant negative correlation ($P < 0.001$) between the maximal temperature difference between the affected and unaffected sides (no absolute values) achieved during the thermoregulatory cycle and the duration of the disease in months.

false-negative. In the control group with limb pain of other origin, only one patient was false-positive. In summary, the maximal skin temperature difference between the two sides seemed to be a useful diagnostic test for CRPS, with high sensitivity and specificity.

Relationship between vascular abnormalities and duration of CRPS I

There was a significant relationship ($P < 0.05$) between the type of vascular regulation and the duration of the disease. Patients with the warm type of regulation suffered from CRPS I on average for 4 months (range 2 weeks to 15 months). In patients with the intermediate type of regulation the disorder lasted 15 months (2–48 months) and in patients with the cold type of regulation it lasted 28 months (14–48 months). Furthermore, the duration of the disease showed a significant negative correlation ($P < 0.001$) with the maximal temperature difference between the affected and unaffected sides (not absolute values) achieved during the thermoregulatory cycle (Fig. 5). These results were still significant when the patients without ongoing pain were excluded. However, it must be kept in mind that there were some CRPS patients who showed the cold type of regulation at a very early stage of the disease (after 2 months), whereas others had the warm type of regulation for 15 months or more.

Noradrenalin measurements in CRPS I patients

It was possible to measure venous noradrenalin levels in five patients (Table 3). Two of these were classified as having regulation of the warm type, one as having intermediate regulation and two as having cold regulation. The two patients with warm regulation demonstrated lower levels of noradrenalin on the affected side than on the healthy side, indicating a decreased level of sympathetic vasoconstrictor activity (Table 3). Interestingly, those patients with cold regulation and intense cutaneous vasoconstriction also had lower noradrenalin values on the affected side than on the healthy side. Only one patient (intermediate type) demonstrated higher noradrenalin values on the affected side than on the healthy side.

Discussion

Vascular abnormalities are a characteristic feature of patients with CRPS I. The sympathetic nervous system is suggested to be involved in these disturbances. In the present study, we analysed the function of sympathetic cutaneous vasoconstrictor neurones and their effect on the skin vasculature. The technique of controlled thermoregulation was used to assess quantitatively abnormalities in the sympathetic vasoconstrictor system and vascular regulation. Furthermore, plasma levels of noradrenalin in venous effluent from the area of autonomic dysfunction were examined in five of these cases. The results can be summarized as follows. (i) Three distinct vascular regulation patterns were identified: (a) patients with a 'warm' type of regulation showed higher cutaneous temperature and perfusion values in the affected limb compared with the contralateral side during the thermoregulatory cycle, i.e. during the entire spectrum of sympathetic vasoconstrictor activity; (b) in patients with an 'intermediate' type of regulation, the affected limb was sometimes colder and sometimes warmer during the cycle; (c) patients with a 'cold' type of regulation had lower skin temperature and perfusion values on the affected side during the entire thermoregulatory cycle. (ii) These patterns of regulation were correlated with the duration of the disorder. In acute cases of CRPS I the affected limb was warm, whereas in chronic CRPS I the affected limb was cold. (iii) Temperature differences between the two sides were dynamic values that were greatest at a high to medium level of vasoconstrictor activity. (iv) The maximal side difference in temperature that occurs during the thermoregulatory cycle can be used as a diagnostic tool to distinguish CRPS I from other extremity pain syndromes. (v) Noradrenalin levels were mostly lower on the affected side, even in chronic patients with the cold type of regulation.

Pathophysiological mechanisms of vascular abnormalities in CRPS

Vascular regulation in acute CRPS: warm regulation

Whole-body cooling during controlled thermoregulation is the most effective stimulus to activate cutaneous vasoconstrictor neurones tonically, as demonstrated in microneurographic recordings (Bini *et al*., 1980). However, in patients with the warm type of regulation, whole-body cooling induced a much

Table 3 *Venous noradrenalin levels in five CRPS patients*

Patient	Duration of disease (months)	Type of regulation	Concentration on healthy side (pg/ml)	Concentration on affected side (pg/ml)
17	0.5	Warm	527	314
11	3	Warm	282	194
4	12	Intermediate	299	391
5	35	Cold	295	184
10	48	Cold	332	100

lower level of vasoconstriction in the affected limb than on the healthy side. In fact, in one very acute patient (2 weeks after onset of symptoms) the vasoconstrictor response to cooling was completely abolished (Wasner *et al*., 1999). In accordance with these findings, several recent studies have shown increased cutaneous perfusion and diminished phasic sympathetic vasoconstrictor reflexes in the affected limb in early-stage CRPS patients (Kurvers *et al*., 1995; Birklein *et al*., 1998; Schürmann *et al*., 1999).

Because no major nerve damage was detectable in the patients of the present series (CRPS I), it is unlikely that the loss of vasoconstrictor responses can be explained as a consequence of a peripheral lesion of sympathetic fibres. In support of this, histological examination of skin biopsies in patients with CRPS I did not show any differences in the distribution of cutaneous sympathetic or nociceptor fibres (Drummond *et al*., 1996*a*).

An ongoing C-nociceptor barrage and profound antidromic vasodilation within the symptomatic skin may interfere with sympathetic outflow and mimic the observed loss of vasoconstrictor response. Such neurogenic inflammation has been suggested to be the source of skin warming and vasodilatation in CRPS (Oyen *et al*., 1993; Moriwaki *et al*., 1997; Daemen *et al*., 1998). However, several studies of the interaction of sympathetic vasoconstriction with antidromic vasodilatation have shown that intense tonic vasoconstrictor activity overrides vasodilatation (Cline *et al*., 1989; Hornyak *et al*., 1990; Ochoa *et al*., 1993; Häbler *et al*., 1997*b*). Other vasodilatory substances, such as endothelium-derived nitric oxide and prostacyclins, may also be involved in skin warming in CRPS. Nitric oxide induces profound relaxation of the blood vessels and is known to interact with sympathetic nerve activity under physiological conditions (Häbler *et al*., 1997*a*). Moreover, it may play a role in vascular abnormalities in diabetic neuropathy (Pitei *et al*., 1997; Veves *et al*., 1998). However, the role of these substances under pathophysiological conditions is unclear.

In summary, anatomical damage of sympathetic fibres and excessive antidromic vasodilatation due to neurogenic inflammation is unlikely to be responsible for the skin warming, vasodilatation and attenuation of vasoconstrictor responses observed in acute CRPS patients with the warm type of regulation. Therefore, it seems reasonable to conclude that profound inhibition and, in some cases, complete functional loss of cutaneous sympathetic vasoconstrictor activity is the underlying mechanism. This inhibition of sympathetic outflow is confined to the extremity in which the inciting trauma occurred. In accordance with this, patients with warm regulation had lower venous noradrenalin levels and reduced levels of its intracellular metabolite 3,4-dihydroxyphenylethyleneglycol, as well as of neuropeptide Y (Drummond *et al*., 1991, 1994; Harden *et al*., 1994), indicating a substantial decrease in transmitter release from postganglionic sympathetic vasoconstrictor fibres on the affected side.

Sympathetic inhibition in acute CRPS

Unilateral functional inhibition of sympathetic vasoconstrictor outflow seems to be a characteristic feature of acute CRPS. The present examination could not determine whether the source of sympathetic abnormalities was located in the peripheral or the central nervous system. However, there is recent evidence for a central component leading to a unilaterally disturbed sympathetic reflex pattern (Birklein *et al*., 1998; Wasner *et al*., 1999). Furthermore, there is evidence for a bilateral sympathetic dysfunction in CRPS, especially in the early stage of the disease, which indicates a spinal mechanism (Rosen *et al*., 1989; Bej and Schwartzman, 1991; Kurvers *et al*., 1996). The design of the present study was not suitable for the clarification of this aspect, but contralateral disturbances in skin blood flow cannot be excluded.

There are several other symptoms of CRPS I that might involve dysfunction of the central nervous system. (i) Hyperhidrosis, a typical feature of many CRPS I patients, must be explained by an increase in sympathetic sudomotor outflow because sweat glands, in contrast to blood vessels, do not develop denervation supersensitivity (Fleming and Westfall, 1988; Chelimsky *et al*., 1995; Birklein *et al*., 1997). However, this might also be due to pre- or postganglionic sudomotor disturbances. (ii) Impairment of muscle strength involving all muscles of the affected distal extremity that is not due to pain, oedema or severance of peripheral nerves may be the result of centrally mediated impulse abnormalities in the motor neurone pool. Alternatively, paresis might be due to decreased sympathetic activity in skeletal muscles (Orbeli effect) (Jami *et al*., 1984). (iii) A neglect-like syndrome responsible for severe motor dysfunctions (Galer *et al*., 1995) points to a central mechanism. (iv) An increased physiological tremor, present in ~50% of the patients with CRPS I, is suggested to be due to central changes (Deuschl

et al., 1991). (v) Sensory impairment and hyperalgesia in CRPS I frequently extends far beyond the area affected by spontaneous pain (Rommel *et al*., 1999), indicating changes in central afferent processing (Sieweke *et al*., 1999).

Vascular regulation in chronic CRPS: cold regulation

Increased sympathetic activity to the affected extremity in chronic CRPS patients has been suggested repeatedly. However, several observations argue against sympathetic overactivity as an underlying mechanism for skin cooling and vasoconstriction in chronic CRPS. First, in chronic CRPS patients with cold limbs, venous catecholamine values were also reduced rather than elevated in the affected limb (Drummond *et al*., 1991, 1994; Harden *et al*., 1994). Secondly, bilateral microneurographic recordings in chronic CRPS patients with marked cutaneous vasoconstriction did not show hyperactive sympathetic discharge (Casale and Elam, 1992).

What alternative mechanism might be responsible for the cold limbs in chronic CRPS patients? In animal experiments it has been demonstrated clearly that the vasculature develops adaptive supersensitivity to catecholamines due to receptor upregulation after nerve injury (Jobling *et al*., 1992). However, no overt nerve lesion is present in CRPS I. Alternatively, the profound functional inhibition of sympathetic vasoconstrictor activity that is present during acute CRPS may also induce secondary changes in neurovascular transmission (Kurvers *et al*., 1995). Supersensitivity to circulating catecholamines may lead to intense vasoconstriction that is only marginally modulated by sympathetic innervation (Baron and Maier, 1996). In support of this idea, venous vasoconstriction was increased after application of noradrenalin in the affected limb (Arnold *et al*., 1993) and the mean density of α1-adrenoceptors was significantly higher in the hyperalgesic skin of CRPS patients than in the skin of normal individuals (Drummond *et al*., 1996b).

Unilateral vascular disturbances: a diagnostic sign for CRPS I?

CRPS I is a clinical diagnosis. Patients with extremity pain of other origin may meet some of the clinical criteria and may be included under the umbrella category of CRPS I. Therefore, it is important to find objective laboratory tests to define CRPS in order to distinguish CRPS from other extremity pain syndromes (Chelimsky *et al*., 1995).

During controlled changes of environmental temperature (controlled thermoregulation with a thermal suit), side differences in skin temperature and blood flow between the affected and unaffected extremities were found to be typical features in CRPS I. However, these side differences in cutaneous regulation were not static during the thermoregulatory cycle. When sympathetic vasoconstrictor activity was low or absent (intense experimental whole-body warming or warm environmental temperature and relaxing atmosphere etc.), no significant differences were detectable; differences were most pronounced during periods of high to intermediate sympathetic activity. Therefore, the maximal skin temperature difference that occurred during the thermoregulatory cycle was used as a descriptive measure of vascular dysregulation. Using this parameter, patients with CRPS showed an average maximal side difference of $\Delta T_{max} = 4.5°C$. In contrast, in healthy controls and in patients with chronic extremity pain of similar severity but of other origin, side differences were minimal. From control data in healthy subjects, a normal value of $\Delta T_{max} < 2.2°C$ was calculated. The maximal side difference in temperature during the thermoregulatory cycle provides a novel and reliable diagnostic measure to distinguish CRPS I from other extremity pain syndromes with high sensitivity and specificity. However, the difficulty in performing the evaluation limits its clinical applicability.

Other disorders with unilateral vascular disturbances

Other clinical entities that clearly present unilateral temperature disturbances might demonstrate a vascular regulation pattern during the thermoregulatory cycle very similar to that seen in patients with CRPS. These syndromes might present a problem in differential diagnosis and may have to be excluded clinically in order to avoid false-positive test results. First, all kinds of inflammations and infections (e.g. rheumatism and phlegmones) might induce intense unilateral skin warming. Secondly, unilateral arterial or venous occlusive diseases obviously present with a unilateral cold or warm limb and high temperature differences between the affected and healthy side. Thirdly, repetitive artificial occlusion of the blood supply to one limb (as in the psychiatric artefact syndrome) might induce secondary structural changes of the blood vessels with consecutive abnormalities in perfusion.

In summary, the present paper focuses on vascular disturbances in patients with CPRS I. There is evidence of inhibition of cutaneous sympathetic vasoconstrictor neurones that is characterized clinically by a warmer affected limb in the initial stage of the disease. In chronic CRPS, sympathetic vasoconstrictor neurones are still inhibited but the temperature of the skin changes gradually to colder values caused by secondary changes of the neurovascular transmission. The individual vascular abnormalities are dynamic and depend critically on activity in sympathetic vasoconstrictor neurones. This phenomenon should be considered when defining diagnostic criteria for CRPS. However, the maximal difference in skin temperature during the thermoregulatory cycle is a reliable means of distinguishing CRPS I from other extremity pain syndromes.

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