Vascular Abnormalities in Acute Reflex Sympathetic Dystrophy (CRPS I)

Complete Inhibition of Sympathetic Nerve Activity With Recovery

Gunnar Wasner, MD; Klaus Heckmann; Christoph Maier, MD; Ralf Baron, MD

Background: Reflex sympathetic dystrophy/complex regional pain syndrome type I (RSD/CRPS I) is a painful neuropathic disorder that may develop as a disproportionate consequence of a 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.

Objective: To investigate pathophysiological mechanisms of vascular abnormalities in RSD/CRPS I.

Design: Case study.

Setting: Autonomic test laboratory at a university hospital.

Participants: A patient with an early stage of RSD/CRPS I of the upper limb and 2 healthy control subjects.

Interventions: Cutaneous sympathetic vasoconstrictor innervation was assessed by measuring cutaneous blood flow (laser Doppler flowmetry) and skin temperature (infrared thermometry). To quantify sympathetic vasoconstrictor function, phasic (induced by deep inspiration) and tonic (induced by controlled thermoregulation) sympathetic reflexes were analyzed. Venous norepinephrine levels were determined bilaterally. The same tests were performed in the controls after induction of cutaneous antidromic vasodilation produced by histamine dihydrochloride application.

Main Outcome Measure: Sympathetic cutaneous vasoconstrictor function in RSD/CRPS I.

Results: Two weeks after the onset of RSD/CRPS I, skin temperature on the affected side was higher (close to core body temperature) than on the contralateral side at room temperature and during controlled thermoregulation, indicating maximal vasodilation. Phasic and tonic stimulation of cutaneous vasoconstrictor neurons did not induce a decrease of skin blood flow or temperature on the affected side but were normal on the contralateral side. Venous norepinephrine levels were lower on the affected side. Parallel to clinical improvement, loss of vasoconstrictor function completely recovered within weeks. Results of investigations in healthy subjects ruled out the possibility that antidromic vasodilation caused by activation of nociceptive afferents is responsible for the complete depression of sympathetic vasoconstrictor reflexes.

Conclusions: Demonstrated for the first time is a complete functional loss of cutaneous sympathetic vasoconstrictor activity in an early stage of RSD/CRPS I with recovery. The origin of this autonomic dysfunction is in the central nervous system.

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SUBJECTS AND METHODS

SUBJECTS

The patient was a 52-year-old woman seen at the Pain Clinic of the Neurological, Anaesthesiological, and Orthopedic Clinics in Kiel, Germany, with acute RSD (CRPS I) after having fractured the right distal radius. Two healthy volunteers served as control subjects. The patient and the controls were asked to refrain from coffee and food intake and from smoking for at least 3 hours before being tested. They were not taking drugs affecting vascular function. The aim of the study and the nature of the tests were explained to the patient and the controls according to the Helsinki Declaration. The study was approved by the local ethics committee. The patient and the controls gave informed consent after the nature of the procedures had been fully explained. The procedures followed were in accordance with institutional guidelines.

MATERIALS AND PROCEDURE

All neurophysiological tests were performed between 3 and 6 PM. The patient and the controls were tested while in the supine position (room temperature of 24°C). In the patient, the first set of experiments was performed during the early phase of the disease, i.e., 24 days after the fracture and 2 weeks after the onset of typical CRPS I symptoms (week 2). Five weeks later the experiments were repeated (week 7).

Measurement of Skin Perfusion and Skin Temperature in Both Hands

Cutaneous blood flow in the glabrous skin (of the index fingertip) was measured bilaterally using a laser Doppler flowmeter (Periflux pf 4001 and integrating probe pf 413; Perimed, Stockholm, Sweden). The fingertips were selected for investigation because the abundant arteriovenous anastomoses of this area are under strict sympathetic vasoconstrictor control; thus, changes mediated by cutaneous vasoconstrictor activity are prominent, and vasomotor reflexes are extensive. Simultaneously, skin temperature was measured bilaterally in the dorsum of the hand (continuously) and in all fingers at 3-minute intervals with infrared thermometers.

During all the experiments described below, laser Doppler and continuous thermometer signals were recorded online (IBM-compatible computer) with an analog digital converter and counter interface (Burr-Brown Co, Tucson, Ariz, data acquisition software CARDS by Stefan Tiedemann, Department of Physiology, University of Kiel) for subsequent analysis.

Neurophysiological Assessment of Cutaneous Vascular Regulation

Phasic Alteration of Sympathetic Vasoconstrictor Activity During Forced Breathing. To assess phasic modulation in sympathetic activity, respiratory reflexes were examined. Deep inspiration induces a phasic activation of cutaneous vasoconstrictor neurons that is followed by a marked short-lasting decrease of blood flow through the skin. Degeneration or dysfunction of these neurons results in an attenuation of the vasoconstrictor response.

Maximal phasic activation of sympathetic neurons was achieved by performing forced breathing. The desired respiratory frequencies and inspiration-expiration ratios were visualized graphically by a moving vertical mark on a computer screen. The actual breathing parameters were monitored by a specially designed electronic device: a small plastic tube (14 cm long) with 1 end in 1 nostril. Air movement through the tube was detected by a sensitive thermistor within the tube. The persons were asked to breathe at a low frequency of 5/min with a high tidal volume. The inspiration-

Characteristically, patients with CRPS I demonstrate a warm and vasodilated affected extremity in the early stages and cold and pale skin in the late stages. The cause of these vascular abnormalities is unknown, and it is still under debate whether the sympathetic nervous system is involved in the generation of these changes.

Animal studies have addressed the cause of vascular disturbances in neuropathic pain syndromes using experimental partial nerve lesions. Within the innervation zone of the affected nerve, changes in neurovascular transmission (i.e., sympathetic denervation of cutaneous vessels resulting in vasodilation and subsequent development of supersensitivity to circulating catecholamines leading to vasoconstriction) were demonstrated as the cause of secondary blood flow abnormalities. Moreover, after a partial nerve lesion, excessive antidromic activation of undamaged afferent C fibers and neuropeptide release leading to acute vasodilation within the innervation zone of the affected nerve were shown.

These models may apply to CRPS II (causalgia), in which a peripheral nerve lesion is by definition present. However, CRPS I (RSD) characteristically develops after a bone fracture or even a minor tissue lesion without any overt damage of peripheral nerves or major nerve branches. The autonomic symptoms spread to skin territories away from the originating injury. Therefore, interruption of sympathetic fibers and denervation of blood vessels cannot account for vascular changes in these patients. The question arises, “What alternative mechanisms might be responsible for autonomic abnormalities in CRPS I?”

Cutaneous sympathetic nerves mainly consist of vasoconstrictor fibers involved in thermoregulation. To assess their function quantitatively, sympathetic thermoregulatory and respiratory reflexes were induced under controlled conditions. Using these neurophysiological techniques, we demonstrated that acute RSD/CRPS I is characterized by complete functional inhibition of cutaneous sympathetic vasoconstrictor activity on the affected extremity. This abnormality is capable of recovering within weeks.

RESULTS

CLINICAL CHARACTERISTICS OF PATIENT WITH CRPS I

A 52-year-old woman was seen with a fracture of the right distal radius in January 1997. No other injuries were detectable, in particular no peripheral nerve lesions. Ten
To address this problem, the following control experiment was performed. Histamine, a potent stimulator of afferent C fibers, was iontophoresed into the glabrous skin (thenar) of 2 controls. Cutaneous application of histamine induces an intense axon reflex vasodilatation (antidromic vasodilatation or flare reaction) within an area of several centimeters around the application site caused by the release of calcitonin gene-related peptide and substance P from axon collaterals in the skin. Within the area of axon reflex vasodilatation (1 cm from the application site), laser Doppler measurements were performed during simultaneous activation of cutaneous sympathetic vasoconstrictor neurons using the same protocol as described above (forced breathing and controlled thermoregulation).

Histamine was applied 3 times during each experiment. After acclimatization in the laboratory (low sympathetic activity), the first application was performed to induce neurogenic inflammation and axon reflex vasodilatation. To maximize the vasodilatory effect, a second application was performed at the same site 10 minutes later. Five minutes after this stimulus, whole-body cooling was started to induce activation of cutaneous vasoconstrictor fibers. During whole-body cooling (high sympathetic activity), the third application of histamine was performed at the same site as previously.

Norepinephrine Measurements

To further assess sympathetic function, plasma levels of norepinephrine from the venous effluent were examined. About 80% of this value reflects secretion by sympathetic post-ganglionic vasoconstrictor terminals to muscle and mainly to skin. Two weeks after the onset of CRPS I symptoms (week 2), venous blood samples were taken from veins bilaterally at the dorsum of the hands under resting conditions. Norepinephrine was measured by high-pressure liquid chromatography with electrochemical detection (Biorad Laboratories, Hercules, Calif).

days after immediate reduction of the fracture under plexus anesthesia and plaster, the patient reported a change in symptoms. She complained of a marked generalized swelling of the hand, a feeling of heat, and increasing pain in the right forearm and hand that was now of burning character.

Two weeks after the onset of these symptoms (week 2), the patient was clinically examined and the neurophysiological tests were performed. At that time she complained of spontaneous pain that she rated from 5 to 8 on a numerical rating scale (NRS: 0 indicates no pain; 10, the maximum of imaginable pain). Local warming and orthostatic load increased the pain, whereas moderate cooling and lifting reduced it. The right hand was warmer, but no side difference in sweating was observed. The hand was swollen, but there were no trophic changes. Voluntary movements of all fingers were markedly reduced, and hand grip force was extremely weak. The patient reported an increase of these motor disturbances during the previous 2 weeks. A distally gen-
Phasic Alteration of Sympathetic Vasoconstrictor Activity. The first set of experiments was performed 2 weeks after the onset of CRPS I symptoms. Under forced breathing conditions (5/min), a rhythmic variation in cutaneous blood flow occurred in the finger of the unaffected side, indicating intact vasoconstrictor activity.17 The inspiratory phase was followed by considerable vasoconstriction, with a latency of several seconds between inspiration and decrease in blood flow (Figure 1). The mean relative decrease in blood flow was 58%.

On the affected side, almost no variation in blood flow was detectable (Figure 1). A small oscillation that is phase shifted in comparison with the respiratory rhythm on the unaffected side is generally thought to be passively induced by changes in blood pressure and venous tone during respiration.17 These data indicate that, on the affected side, no vasoconstriction could be induced by forced breathing.

Tonic Alteration of Sympathetic Vasoconstrictor Activity. After acclimatization in the laboratory (room temperature of 24°C, supine position, and thermal suit on), the skin temperature at the dorsum of the hand was 36°C on both sides (Figure 2). The finger skin temperature on the affected side was slightly higher than on the unaffected side (35.4°C vs 34.6°C, Figure 3). Thereafter, controlled whole-body cooling was performed to achieve tonic activation of sympathetic vasoconstrictor neurons innervating the skin. Skin blood flow and skin temperature on the unaffected side showed a normal pattern of regulation (Figures 2 and 3). Whole-body cooling immediately produced a massive activation of vasoconstrictor neurons leading to a considerable and prolonged drop in skin blood flow that reached a minimum of 19% of baseline flux before cooling. After a short latency, skin temperature slowly decreased, reaching a minimum of 24.2°C in the fingers and 29.0°C in the dorsum of the hand (Figures 2 and 3). After having switched to whole-body warming, the thermoregulatory cycle reversed...
At week 7, vasoconstrictor responses induced by forced breathing were the same in both hands and not significantly different from the controls. The mean relative decrease in blood flow was 70% on the affected side and 63% on the unaffected side (Figure 4). The shape and time course of the respiratory reflexes were normal. These results indicate that vasoconstriction induced by respiratory reflexes had completely recovered within 7 weeks of disease onset. Tonic sympathetic reflexes were not performed at week 7.

**Controls: Sympathetic Vasoconstrictor Reflexes in Neurogenic Inflamed Skin**

To test whether an intense antidromic vasodilation may be capable of mimicking the loss of sympathetic vasoconstrictor reflexes observed in the patient, control experiments were performed. Histamine iontophoresis was used to induce an axon reflex vasodilation in the glabrous skin of the hand. During this vasodilation, phasic and tonic activation of cutaneous sympathetic vasoconstrictor neurons was performed (forced breathing and controlled thermoregulation) using the same protocol as in the patient.

**Phasic Alteration of Sympathetic Vasoconstrictor Activity**

After acclimatization in the laboratory (room temperature of 24°C, supine position, thermal suit on, and low sympathetic activity), histamine application at the thenar skin induced an intense antidromic vasodilation caused by afferent C fiber axon reflex activation and neuropeptide release. The increase in blood flow was 60% (Figure 5). Furthermore, the blood flow signal was stabilized so that transient sympathetic reflexes induced by arousal stimuli extensively present in 1 control before histamine application were absent after histamine application (Figure 5). This observation indicates that antidromic vasodilation can override sympathetic vasoconstriction caused by phasic arousal reflexes. Moreover, vasoconstriction evoked by forced breathing that...
pathetic reflexes can override antidromic vasodilation. That sympathetic vasoconstriction caused by tonic sympathetic vasoconstrictor activity (Figure 5). These results show that sympathetic vasoconstriction causes by phasic respiratory reflexes.

Tonic Alteration of Sympathetic Vasoconstrictor Activity. Using tonic, long-lasting sympathetic vasoconstrictor reflexes, the situation was different. Sympathetic vasoconstrictor activity induced by whole-body cooling performed during the presence of antidromic vasodilation in the hand induced a sustained vasoconstriction. Additional application of histamine produced only a small increase in blood flow, indicating that axon reflex vasodilation was sufficiently depressed by ongoing sympathetic vasoconstrictor activity (Figure 5). These results show that sympathetic vasodilation caused by tonic sympathetic reflexes can override antidromic vasodilation.

Comment

Vascular abnormalities, often abnormal vasodilation and skin warming in the early phase and vasoconstriction in later stages, are characteristic symptoms of RSD/CRPS I. We present for the first time evidence that a complete inhibition of sympathetic activity may be responsible for the skin warming and vasodilation observed during the early phase of CRPS I. Several findings can be summarized: (1) Ten days after the inciting trauma, ie, a distal radius fracture, typical clinical symptoms of CRPS I developed at the distal extremity, ie, swelling, pain, impairment of movement, and vascular abnormalities. (2) Skin temperature was higher on the affected side compared with the unaffected side in normal room temperature and during controlled thermoregulation. (3) Phasic and tonic stimulation of cutaneous vasoconstrictor neurons evoked by sympathetic respiratory and thermoregulatory reflexes did not induce a decrease in skin blood flow and temperature on the affected side (Figures 1, 2, and 3). (4) Venous noradrenaline levels were lower on the affected side. (5) In relation to clinical improvement, loss in vasoconstrictor function completely recovered within weeks (Figure 4).

Cause of the Loss of Vasoconstrictor Function in Acute CRPS I

Besides the bone fracture, no skin or deep tissue lesions, in particular no nerve lesions, were present. At the time of the accident, results of a thorough neurologic examination did not reveal any neurologic abnormalities. Therefore, the loss of vasoconstrictor responses observed 2 weeks after the onset of CRPS I is unlikely to be explained as a consequence of a peripheral lesion of sympathetic fibers. These findings are supported by results of histological examinations of skin biopsy samples in patients with CRPS I. No differences in distribution of cutaneous sympathetic or nociceptor fibers was demonstrated. Another observation that challenges peripheral nerve damage as a causative factor is that the sympathetic reflex abnormalities observed in the present study were reversible within 5 weeks (Figure 4).

Alternatively, changes in the neurovascular transmission may lead to a lack of vessel responsiveness to sympathetic stimulation. However, it seems unlikely that such changes occur without the presence of a structural lesion of sympathetic postganglionic fibers. Furthermore, an ongoing C nociceptor barrage and profound antidromic vasodilation within the symptomatic skin may interfere with sympathetic outflow and therefore mimic the loss of vasoconstrictor response. Such
neurogenic inflammation has been suggested to be the source of skin warming and vasodilation in CRPS.\textsuperscript{13,21,22} In fact, results of the control experiments performed in this study show that intense antidromic vasodilation in the glabrous skin induced by histamine iontophoresis overrides vasoconstriction evoked by phasic sympathetic reflexes such as short-lasting arousal stimuli or respiratory reflexes (Figure 6). However, tonic sympathetic thermoregulatory reflexes, ie, sympathetic activation caused by whole-body cooling, can overcome antidromic vasodilation (Figure 5). Comparable results have been obtained by Hornyak et al,\textsuperscript{23} who used transcutaneous electrical stimulation to induce antidromic vasodilation in the glabrous skin and whole-body cooling to change sympathetic activity. During high sympathetic activity, vasodilation was markedly diminished and in some experiments even totally abolished. Accordingly, vasoconstriction in the hand achieved by intraneural microstimulation was found to override the antidromic vasodilator effect induced by intraneural stimulation of C nociceptors.\textsuperscript{24} This was confirmed in animal experiments investigating the interaction between sympathetic vasoconstriction and antidromic vasodilation. Electrical stimulation of the sympathetic chain with high frequencies significantly reduced axon reflex vasodilation induced by dorsal root stimulation.\textsuperscript{25} Furthermore, in a patient with a neuropathic pain syndrome after burn injury, abnormal C nociceptor sensitization was identified microneurographically, suggesting that antidromic vasodilation was the source of local skin warming. In this case, sympathetic vasconstrictor reflexes were normal.\textsuperscript{26} Taking these results together, it is unlikely that afferent antidromic mechanisms are involved in the skin warming, vasodilation, and loss of vasconstrictor responses in the patient with CRPS I described herein.

However, other vasodilatory mechanisms not tested in the present investigation may be more powerful than histamine-evoked antidromic vasodilation. Endothelium-derived nitric oxide and prostacyclins are known to induce a profound relaxation of blood vessels. Therefore, vasodilation caused by an abnormally high release of these substances might interfere with sympathetic vasoconstriction.

In summary, anatomic damage of sympathetic fibers and excessive antidromic vasodilation caused by neurogenic inflammation are not responsible for the loss of vasconstrictor responses and the skin warming observed in our patient. Therefore, it seems reasonable to suggest that the loss of vasconstrictor responses is related to a functional inhibition of sympathetic neuronal activity. The sympathetic inhibition is so intense that respiratory and thermoregulatory vasoconstrictor reflexes are completely abolished. This inhibition of sympathetic outflow is confined to the extremity where the inciting trauma occurred.

In accordance with the idea of an inhibition of sympathetic activity, the norepinephrine level in the venous blood samples from the affected side was considerably lower compared with that from the healthy side, indicating a substantial decrease of transmitter release from postganglionic sympathetic vasconstrictor fibers. In similar studies,\textsuperscript{27,28} norepinephrine, its intracellular metabolite 3,4-dihydroxyphenylethanolamine, and neuropeptide Y, which coexist with norepinephrine in sympathetic vasoconstrictor neurons, were shown to be reduced in venous blood samples from affected limbs of patients with CRPS.

**PATHOPHYSIOLOGICAL MECHANISMS WITHIN THE CENTRAL NERVOUS SYSTEM LEADING TO INHIBITION OF SYMPATHETIC ACTIVITY**

These findings support the idea that vascular abnormalities of acute CRPS I are associated with a disturbed sympathetic innervation of the affected limb. An abnormal unilateral reflex pattern of sympathetic vasoconstrictor neurons evoked by respiratory and thermoregulatory stimuli is present. The pathophysiological mechanisms underlying such disturbed sympathetic reflex activity must be located in the central nervous system.\textsuperscript{30} This interpretation is consistent with experimental findings, which show that the centrally generated reflex pattern in cutaneous vasoconstrictor neurons changes in neuropathic animals.\textsuperscript{11,31}

There are several other symptoms of CRPS I that favor a central origin of the disorder: (1) Hyperhidrosis, a typical feature of many patients with CRPS I, cannot be explained by a peripheral mechanism because, in contrast to blood vessels, sweat glands do not develop denervation supersensitivity.\textsuperscript{32} Therefore, an increase in sweating must be explained by an increase in activity in sympathetic sudomotor neurons that is of central origin.\textsuperscript{32,34} (2) Impairment of muscle strength involving all muscles of the affected distal extremity that cannot be explained by pain, edema, or severance of peripheral nerves also are the result of a centrally mediated impulse abnormality in the motor neuron pool projecting to the distal extremity. Also, a neglectlike syndrome responsible for severe motor dysfunctions described recently\textsuperscript{35} points to a central mechanism. (3) Moreover, an increased physiologic tremor, present in approximately 50% of patients with CRPS I, is caused by central changes.\textsuperscript{26}

**SYMPATHETICALLY MAINTAINED PAIN: CAN IT EXIST IN COMBINATION WITH INHIBITION OF SYMPATHETIC ACTIVITY?**

Interruption of the efferent sympathetic nerve supply to the affected extremity may relieve the pain in patients with CRPS I. The pain is therefore called “sympathetically maintained pain.” Also, in the patient presented herein, use of regional guanethidine blocks relieved the pain. This observation seems to contradict the finding that the sympathetic outflow to the affected limb is already inhibited or abolished. However, the sympathetic tests used in this study exclusively assess the function of cutaneous vasoconstrictor neurons. It is possible that although the cutaneous sympathetic outflow is inhibited, the sympathetic innervation of deeper tissues such as muscle or bone is normal or even enhanced. Results of recent animal experimental studies\textsuperscript{36} indicate that separate functional channels of the sympathetic nervous system exist that can be activated selectively and indepen-
Several conclusions can be summarized from this case of CRPS I (RSD). (1) In the early stages of CRPS I, cutaneous sympathetic vasoconstrictor reflexes may be completely abolished on the affected side. (2) This loss of response is not caused by anatomic damage of sympathetic nerve fibers. (3) Although an intense vasodilatory mechanism that mimics the loss of vasoconstrictor response cannot be ruled out completely, it is reasonable to consider a functional unilateral inhibition of sympathetic activity to be the likely cause. (4) The pathophysiological mechanism of these sympathetic abnormalities is located in the central nervous system. (5) The functional sympathetic inhibition may be reversible within weeks of the disease course, leading to complete recovery of symptoms. (6) Sympathetically maintained pain is unlikely mediated by cutaneous vasoconstrictor fibers in the early stage of CRPS I. The underlying sympathetic-afferent interaction might be located in deep tissue, ie, bone or muscle.

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