Reflex sympathetic dystrophy: result of autonomic denervation?

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1. To investigate the nature of sympathetic dysfunction in the pathogenesis of reflex sympathetic dystrophy, the microcirculatory vasoconstrictive responses to dependency were investigated in the skin of the hand of 76 reflex sympathetic dystrophy patients with unilateral disease by means of laser Doppler flowmetry (in perfusion units) and capillary microscopy. The patients were divided into three stages according to their perception of skin temperature (stage I in the case of a stationary warmth sensation, stage II in the case of an intermittent warmth and cold sensation, and stage III in the case of a stationary cold sensation). The vasoconstrictive responses were induced by lowering of the affected hand.

2. As compared to controls, the mainly sympathetically mediated vasoconstrictive response at thermoregulatory level of the skin microcirculation, as measured by laser Doppler flowmetry, was attenuated at stage I (1.82 versus 1.41, P<0.05), stage II (1.82 versus 1.09, P<0.0001) and stage III (1.82 versus 1.14, P<0.01), suggesting the involvement of sympathetic denervation at all stages of the reflex sympathetic dystrophy syndrome. This sympathetic denervation may also account for the observed increase in thermoregulatory skin blood flow at stage I as compared to controls (152 versus 81, P<0.01).

3. Since sympathetic denervation has been reported to cause increased sensitivity of vascular structures to catecholamines, the decrease in thermoregulatory skin blood flow at stages II (54 versus 81, P<0.05) and III (31 versus 81, P<0.05), both as compared to controls, may result from hypersensitivity to catecholamines of skin microvessels.

4. The sympathetically independent vasoconstrictive response at the nutritive level of skin microcirculation, as measured by capillary microscopy, was impaired only at stage III as compared to controls (1.04 versus 2.06, P<0.05). This divergence in microvascular reactivity upon dependency of the nutritive and thermoregulatory subsystems also supports the hypothesis of sympathetic dysfunction.

5. The disturbed vasoconstrictive responses to dependency may give rise to raised capillary pressures, contributing to the formation of oedema.

6. These findings suggest that sympathetic denervation and consequent hypersensitivity to catecholamines play an important role in the pathophysiology of reflex sympathetic dystrophy.

INTRODUCTION

Reflex sympathetic dystrophy (RSD), which is usually localized in the extremities, is an incompletely understood pain syndrome. It is characterized by a triad of autonomic (sympathetic), motor and sensory disturbances [1]. Generally, an increase in efferent sympathetic activity has been purported to play a pivotal role in the pathophysiology of the disorder [2–5]. Therefore, treatment of RSD has focused predominantly on interruption of the alleged increase in efferent sympathetic nerve activity by means of sympathectomy, the outcome of which has not been invariably satisfactory [6].

Microcirculatory vasoconstriction in limbs upon dependency is mediated by central and/or local (venoarteriolar or myogenic) mechanisms [7]. At the thermoregulatory level (arteriovenous anastomoses and subpapillary plexus), this postural response is predominantly controlled by a sympathetically mediated local venaarteriolar response [7]. At the nutritive level (capillaries), the vasoconstrictive response is considered to be mainly controlled by sympathetically independent local factors, such as vasoactive metabolic substances accumulating during ischaemia and tissue oxygenation [7, 8].

To investigate the role of sympathetic dysfunction in the pathogenesis of RSD, we examined the postural response, by means of laser Doppler flow-
metry (LDF) and capillary microscopy. LDF was used because arteriovenous anastomoses and the subpapillary plexus, which are richly innervated by sympathetic nerve endings [9], contribute predominantly to the flow signal recorded with this technique [10]. Therefore, disturbances in thermoregulatory flow upon dependency, if any, may reflect sympathetic dysfunction. Capillary microscopy was used to study microcirculatory vasoconstrictive responses upon dependency at the nutritive level. The responses at this level were studied because they are likely to be controlled differently to the responses at the thermoregulatory level. If sympathetic dysfunction plays a role in the pathophysiology of RSD, vasoconstrictive responses upon dependency will be disturbed more at the thermoregulatory than at the nutritive level of skin microcirculation.

MATERIALS AND METHODS

Patients

The study was performed on 76 patients with unilateral RSD of the upper extremity, who had all given informed consent. The age of the 24 males and 52 females ranged from 16 to 91 years, with a mean age of 49 years. All patients met the standards of the American Association for Hand Surgery on the definition of RSD: diffuse pain, loss of function and objective evidence of significant autonomic dysfunction [11]. In our study, the signs and symptoms had to be present in an area larger than and distal to the area of primary injury or operation. In addition, the autonomic dysfunction had to be reflected by an abnormal temperature sensation and at least one of the six following symptoms: oedema, increased sweating, abnormal hair or nail growth, atrophy of skin or subcutaneous tissues. The patients thus admitted to our study met, to a large extent, the criteria of RSD as defined by Veldman et al. [12] in a prospective study of 829 patients. Since the pathophysiology of primary cold RSD might be of a different origin than that of primary warm RSD [12], we restricted ourselves to the latter. The skin areas to be examined had to be within the area affected by RSD, with respect to both pain complaints and sensation of abnormal skin temperature.

The large number of complaints in combination with the considerable overlap of signs and symptoms between the three stages (Table 1) makes it virtually impossible to classify the patients unequivocally with the traditionally used classification systems [13, 14]. Moreover, categorization solely on the basis of duration of complaints disregards the interindividual variance with respect to the relationship between clinical stage and duration of the syndrome. Hence, for the purpose of adequate and reproducible categorization, we confined ourselves to perception of skin temperature. Patients with a stationary warmth sensation were categorized stage I (n = 15, mean duration of the RSD syndrome 3 months), patients with an intermittent warmth and cold sensation were categorized stage II (n = 47, mean duration of the RSD syndrome 8 months), and in case of stationary cold sensation, patients were categorized stage III (n = 14, mean duration of the RSD syndrome 40 months).

Additional disorders in the three patient categories, evaluated by means of patient history and physical examination, are listed in Table 1. Precipitating events are shown in Table 2, whereas smoking habits, age, and duration of the RSD syndrome per stage are displayed in Table 3.

Patients receiving cardiovascular medication, suffering from diabetes mellitus or with a history of sympathectomy within 3 months prior to the microcirculatory investigation, were excluded from the study.

A group of 16 age-matched volunteers served as controls. We did not use the contralateral non-affected upper extremity of reflex sympathetic dystrophy patients as control, because it has been shown that microvascular reactivity in this extremity may be altered [15, 16].

Experimental protocol

The experimental protocol had been approved by the ethical committee of our institution. Patients abstained from smoking and did not consume caf-
**Table 2. Causes of RSD, expressed as percentage of the whole group**

<table>
<thead>
<tr>
<th>Fracture</th>
<th>Soft tissue trauma</th>
<th>Neurovascular compression</th>
<th>Operation</th>
<th>Cerebrovascular accident</th>
<th>Whiplash trauma</th>
<th>Untraceable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger</td>
<td>Finger</td>
<td>Wrist</td>
<td>Hand</td>
<td>Shoulder</td>
<td>Wrist</td>
<td>Elbow</td>
</tr>
<tr>
<td>Carpal/metacarpal bone</td>
<td></td>
<td>Hand</td>
<td>Wrist</td>
<td>Thoracic outlet</td>
<td>Lower arm</td>
<td>Neck</td>
</tr>
<tr>
<td>Wrist</td>
<td>Lower arm</td>
<td>Elbow</td>
<td>Neck</td>
<td>Cervical</td>
<td>Upper arm</td>
<td>Thoracic outlet</td>
</tr>
<tr>
<td>Elbow</td>
<td>Operation</td>
<td>Neurovascular compression</td>
<td>Wrist</td>
<td>Thoracic outlet</td>
<td>Thoracic outlet</td>
<td></td>
</tr>
<tr>
<td>Soft tissue trauma</td>
<td></td>
<td>Neurovascular compression</td>
<td>Operation</td>
<td>Wrist</td>
<td>Wrist</td>
<td>Untraceable</td>
</tr>
<tr>
<td>Finger</td>
<td>Soft tissue trauma</td>
<td>Neurovascular compression</td>
<td>Operation</td>
<td>Wrist</td>
<td>Wrist</td>
<td>Untraceable</td>
</tr>
<tr>
<td>Hand</td>
<td>Operation</td>
<td>Neurovascular compression</td>
<td>Operation</td>
<td>Wrist</td>
<td>Wrist</td>
<td>Untraceable</td>
</tr>
<tr>
<td>Wrist</td>
<td>Neurovascular compression</td>
<td>Operation</td>
<td>Operation</td>
<td>Wrist</td>
<td>Wrist</td>
<td>Untraceable</td>
</tr>
<tr>
<td>Lower arm</td>
<td>Operation</td>
<td>Neurovascular compression</td>
<td>Operation</td>
<td>Wrist</td>
<td>Wrist</td>
<td>Untraceable</td>
</tr>
<tr>
<td>Elbow</td>
<td>Neurovascular compression</td>
<td>Operation</td>
<td>Operation</td>
<td>Wrist</td>
<td>Wrist</td>
<td>Untraceable</td>
</tr>
<tr>
<td>Operation</td>
<td>Neurovascular compression</td>
<td>Operation</td>
<td>Operation</td>
<td>Wrist</td>
<td>Wrist</td>
<td>Untraceable</td>
</tr>
</tbody>
</table>

**Table 3. Patient characteristics. Smoking habits, age, and duration of disease per group.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Smokers (%)</th>
<th>Age mean (range)</th>
<th>Duration of disease in months mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>16</td>
<td>31</td>
<td>47 (21-69)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15</td>
<td>60</td>
<td>50 (24-74)</td>
<td>2 (1-7)</td>
</tr>
<tr>
<td>II</td>
<td>47</td>
<td>40</td>
<td>50 (21-91)</td>
<td>8 (1-59)</td>
</tr>
<tr>
<td>III</td>
<td>14</td>
<td>57</td>
<td>43 (16-65)</td>
<td>40 (2-120)</td>
</tr>
</tbody>
</table>

The experiment was performed in a controlled room with a temperature between 24°C and 25°C. The subject was seated in a chair with the hand placed at heart level on the stage of the microscope. Capillary microscopy was performed in the nailfold of the most symptomatic finger. Relative motion between the skin and the microscope was prevented by embedding the finger in a mass of clay. Images of capillaries were recorded during 1 min. Subsequently, arterial occlusion was induced for 1 min by means of inflating a cuff around the upperarm to 230 mmHg. After acute deflation of the cuff capillary images were recorded during reactive hyperaemia, again during a 1 min period. Capillary red blood cell velocity and capillary diameter were assessed off-line in at least three capillaries. The measurements at heart level were followed by a 5 min period during which the stage of the microscope was lowered 35 cm and the patient was allowed to adapt to the dependent position before the measurements were repeated.

Subsequently, the affected extremity of the patient was placed on a pillow, again at heart level. The laser Doppler probe holder was attached to the pulp of the same finger with double sided adhesive tape. To avoid rotation of the probe, it was fastened to the holder with adhesive tape. LDF measurements were performed at unheated skin to assess skin blood flow under physiological conditions. Simultaneously, skin temperature was measured at the dorsum of the same digit. The metal thermocouple was attached to the skin by means of adhesive tape. After attachment of the probes, the signals were allowed to equilibrate until stable signals were obtained for at least 3 min. LDF was assessed under resting conditions (3 min recording), as well as during reactive hyperaemia (3 min recording), following release of 3 min arterial occlusion (cuff pressure of 230 mmHg). Reactive hyperaemia was used to obtain an impression of the possible effect of large vessels, between the upperarm and hand, on microvascular reactivity [7]. The arm was then lowered until the fingers were 35 cm below heart level. After stabilization of blood flow during at least 3 min, the foregoing measurements were repeated.

In all subjects, we initially performed capillary microscopy and subsequently laser Doppler flowmetry. We opted for this sequence instead of random allocation because the duration of arterial occlusion was shorter for capillary microscopy than for laser Doppler flowmetry. The chance that the induction of reactive hyperaemia during capillary microscopy has an effect on the results of laser Doppler flowmetry was thus kept to a minimum.

In nearly all capillary microscopy experiments, reactive hyperaemic responses had subsided within 1-2 min, as has also been demonstrated by others [17]. Since capillary microscopy and laser Doppler flowmetry were performed with an interval of at least 15 min, it is unlikely that the induction of reactive hyperaemia during capillary microscopy has an effect on the results of laser Doppler flowmetry.

Since reflex sympathetic dystrophy patients frequently suffer from allodynia and hyperalgesia, usually they cannot tolerate the inflated cuff for longer than 1 min without moving their hand under the microscope. We, therefore, opted for the induction of 1 min arterial occlusion in the case of assessment of the hyperaemic response during capillary microscopy. Since movement of the hand does not interfere with laser Doppler flowmetry, we opted for the induction of 3 min arterial occlusion in the case of assessment of total (mainly thermoregulatory) skin blood flow. We feel that this difference is allowed, because arterial occlusions of 1 min [18] and 3 min [19] have been shown to induce a clearcut hyperaemic response.

**Equipment**

**Intravital video capillary microscopy.** The experimental set-up has been described in detail before...
[20]. Briefly, a Leitz microscope is equipped with a Ploem-opak and a Pol cube for incident illumination. A television camera (Philips Newvicon XQ 1275, 2/3 inch tube) is positioned in the intermediate plane of the microscope. Images are displayed onto a monitor screen (Philips LDH 2122; 12 inch) and stored on video-tape by a video cassette recorder (Sony Betamax SL-C9 ES) for offline analysis, using the temporal correlation method incorporated in the automated Capiflow software [21].

**Laser Doppler flowmetry (LDF)/skin temperature (ST).** The LDF instrument and technique have been described in detail before [22]. Briefly, LDF is a non-invasive technique based on the principle of the Doppler shift of laser light, back-scattered by moving blood cells. Measurements were executed with the Perimed PF3 (Perimed, Linköping, Sweden). An output of 1 V was calibrated against 100 Perfusion Units (PU). Skin temperature was assessed using an electronic thermometer (78214C, Hewlett Packard) and a circular metal thermocouple (0.8 cm²). The synchronously assessed analog output from the LDF and ST were digitized by an Analog to Digital converter and consequently stored on hard disk. Offline analysis was performed, employing a software programme developed in our institute.

**Off-line analysis**

**Capillary microscopy.** From the capillary microscopy recordings we obtained the red blood cell velocity under resting conditions (RBCVr, µm/s) and at peak of reactive hyperaemia (RBCVp, µm/s), both at heart level and in the dependent position. The individual heart level-to-dependent ratios for red blood cell velocity under resting conditions (R-RBCVr) and for peak red blood cell velocity (R-RBCVp) were calculated to evaluate the effectiveness of the sympathetically independent postural vasoconstrictive mechanism at the nutritive level of the skin microcirculation. These ratios were defined as the flow values obtained at heart level divided by those obtained in the dependent position. A ratio lower than the one found in controls indicates an impaired constrictive mechanism. The lower this ratio is, the more this mechanism will be impaired.

**Skin temperature.** Skin temperature (ST) was obtained under resting conditions, both at heart level and in the dependent position.

**Reproducibility**

The reproducibility of capillary microscopy has been documented earlier [17]: the coefficient of variation (CV) for the RBCV at rest was 59%, whereas the coefficient for the peak RBCV was 25%. A coefficient of variation for the peak RBCV of about 30% is comparable to the coefficients for rest and peak parameters as measured by means of laser Doppler flowmetry [23-25].

**Statistics**

Data are presented per stage and as function of duration of the syndrome. To characterize group values medians are presented together with their interquartile ranges, because the data obtained were not equally distributed. The non-parametric Mann Whitney-U test was used to test for significant differences between the three patient-groups and the healthy volunteers. For the analysis of the differences between the two positions the paired Wilcoxon signed-ranks test was used. Differences were regarded to be statistically significant when \( P<0.05 \). Regression analysis was used to describe the vasoconstrictive indices as a function of the duration of the syndrome in order to study the influence of time on potential vasoconstrictive disturbances. Regression equations are presented with 95% confidence intervals of the slope.

**RESULTS**

**Capillary microscopy at heart level**

As compared to healthy volunteers (Table 4), red blood cell velocity at rest (RBCVr) was significantly decreased at stage II \( (P<0.01) \) and stage III \( (P<0.05) \), whereas maximum red blood cell velocity during reactive hyperaemia (RBCVp) was significantly reduced only at stage III \( (P<0.001) \).

**Laser Doppler flowmetry at heart level**

As compared to controls (Table 4), thermoregulatory skin blood flow at rest (LDFr, see Fig. 1) evolved from an increase at stage I of the syndrome \( (P<0.01) \) to a decrease at stage II \( (P<0.05) \) and III \( (P<0.05) \). A similar pattern was found for maximum skin blood flow during reactive hyperaemia (LDFp); as compared to healthy volunteers, it was significantly higher in stage I patients \( (P<0.01) \) and tended to be lower in stage III patients \( (P=0.08) \).
Table 4. The capillary microscopy, laser Doppler flow and skin temperature data in the three patient groups and in the control group. The median values and interquartile ranges are presented. Data were obtained by capillary microscopy, laser Doppler flowmetry and skin temperature measurement, obtained at heart level and in the dependent position, for both individual patient groups and controls. Abbreviations: HL, heart level; DEP, dependent; RBCVr, red blood cell velocity under resting conditions (µm/s); R-RBCVr, dependent to heart level ratio for RBCVr; LDFr, mean flow under resting conditions (perfusion units); R-LDFr, dependent to heart level ratio for LDFr; Skin temp, skin temperature (°C).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Controls</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCVr</td>
<td>HL</td>
<td>DEP</td>
<td>HL</td>
<td>DEP</td>
</tr>
<tr>
<td>318</td>
<td>(21-492)</td>
<td>(108-270)</td>
<td>322</td>
<td>(159-419)</td>
</tr>
<tr>
<td>(231-492)</td>
<td>(108-270)</td>
<td>322</td>
<td>(159-419)</td>
<td>(87-224)</td>
</tr>
<tr>
<td>R-RBCVr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.06 (1.18-2.85)</td>
<td>1.97 (1.35-2.80)</td>
<td>1.15 (0.86-2.20)</td>
<td>1.04 (0.93-1.60)</td>
<td></td>
</tr>
<tr>
<td>(231-492)</td>
<td>(108-270)</td>
<td>322</td>
<td>(159-419)</td>
<td>(87-224)</td>
</tr>
<tr>
<td>LDFr</td>
<td>HL</td>
<td>DEP</td>
<td>HL</td>
<td>DEP</td>
</tr>
<tr>
<td>81</td>
<td>(51-109)</td>
<td>(9-49)</td>
<td>152</td>
<td>(80-195)</td>
</tr>
<tr>
<td>(231-492)</td>
<td>(108-270)</td>
<td>322</td>
<td>(159-419)</td>
<td>(87-224)</td>
</tr>
<tr>
<td>R-LDFr</td>
<td>HL</td>
<td>DEP</td>
<td>HL</td>
<td>DEP</td>
</tr>
<tr>
<td>1.82 (1.41-7.69)</td>
<td>1.41 (1.20-2.44)</td>
<td>1.09 (0.82-1.39)</td>
<td>1.14 (0.90-1.82)</td>
<td></td>
</tr>
<tr>
<td>(231-492)</td>
<td>(108-270)</td>
<td>322</td>
<td>(159-419)</td>
<td>(87-224)</td>
</tr>
<tr>
<td>Skin temp.</td>
<td>HL</td>
<td>DEP</td>
<td>HL</td>
<td>DEP</td>
</tr>
<tr>
<td>31.7</td>
<td>(31.0-33.1)</td>
<td>32.2</td>
<td>(31.4-32.6)</td>
<td>32.2</td>
</tr>
</tbody>
</table>

Fig. 1. Laser Doppler flow values as measured in skin at rest. Data are presented as medians (bars) and interquartile ranges (error bars). On left y-axis rest flow and on right y-axis the ratio of rest flow values at heart level and dependent position. On x-axis the four groups. □, heart level; □, dependent; □, heart level-to-dependent ratio. *; P < 0.05, **; P < 0.01, ***; P < 0.001 (as compared to controls).

Skin temperature at heart level

As compared to controls (Table 4), skin temperature was significantly higher at stage I (P < 0.01) and tended to be lower at stage III (P = 0.08).

Postural changes

Capillary microscopy. Changing from heart level to the dependent position resulted in a reduction of red blood cell velocity at rest (RBCVr) in controls (Table 4), the ratio of flow velocity at heart level and in the dependent position being about 2.06. This ratio was unchanged in stage I patients, but decreased with progression of the syndrome (P = 0.07 at stage II, P < 0.05 at stage III). Nutritive peak flow (RBCVp) slightly decreased with dependency in controls, resulting in a heart level-to-dependent ratio of about 1.18. This ratio was still unaffected at stage I and stage II, but was significantly lower in stage III patients (P < 0.05 compared to controls, P = 0.06 compared to stage I). Linear regression analysis showed that both R-RBCVr and R-RBCVp did not change as a function of duration of the syndrome.

A consequence of the changes in the postural vasoconstrictive mechanisms is that the various parameters at dependency differ from those assessed at heart level. No significant differences were observed any more, between RSD patients and controls, in red blood cell velocity under resting conditions or at peak of reactive hyperaemia.

Laser Doppler flowmetry. In the control subjects LDF at rest (LDFr, see Fig. 1) decreased when the position of the hand was changed from heart level to the dependent position, resulting in a flow ratio of 1.82. As compared to controls, the reduction of flow was far less at all stages of the syndrome (stage I, P < 0.05; stage II, P < 0.0001; stage III P < 0.01). As compared to heart level, peak flow during reactive hyperaemia (LDFp) was also reduced in dependency resulting in a ratio of 1.3. Similar to rest flow this ratio was reduced with progression of the syndrome. As compared to healthy volunteers, the heart level-to-dependent peak LDF ratios (R-LDFp) were significantly lower in stage II (P < 0.05) and stage III (P < 0.05) RSD patients. Moreover, R-LDFp was significantly lower in stage II patients as compared to stage I patients (P < 0.05) and in stage III patients as compared to stage II patients (P < 0.05). Linear regression analysis revealed a marginal, but nevertheless statistically significant decrease in R-LDFr [y = 1.1 – (0.005 × duration of the syndrome); 95% confidence interval −0.009 to −0.001] as a function of duration of the syndrome (see Fig. 2). R-LDFp did not change as a function of duration of the syndrome.

A consequence of the changes in the postural vasoconstrictive mechanisms is that the various parameters at dependency differ from those assessed at heart level. In the dependent position, thermoregulatory skin blood flow under resting conditions (LDFr, see Fig. 1), as compared to controls, remained significantly higher in stage I patients.
denervation may account for the increase in thermoregulatory skin blood flow at heart level as observed at stage I. Since sympathetic denervation has been reported to cause increased sensitivity of vascular structures to catecholamines [29, 30], the observed decrease in thermoregulatory blood flow as measured at heart level at stages II and III may be explained by hypersensitivity to catecholamines of skin microvessels. The hypothesis of sympathetic denervation is supported by a study of Drummond and colleagues [31] who observed a decrease in venous plasma levels of noradrenaline, collected in the affected limb of RSD patients. Moreover, Arnold and colleagues [32] presented direct in vivo evidence for hypersensitivity of venous \( \alpha \)-adrenoceptors to noradrenaline in limbs affected by RSD.

As alluded to before, constriction of thermoregulatory skin microvessels consequent to dependency of an extremity is predominantly controlled by a sympathetically mediated venoarteriolar response of local origin [26, 27] and to a minor extent by a local myogenic response [7, 26]. Hence, it can not be excluded that myogenic dysfunction is involved in the impairment for this vasoconstrictive response as observed at all stages of the RSD syndrome. However, the finding in our study that the vasoconstrictive response to dependency was undisturbed at the non-sympathetically controlled [8] nutritive level of skin microcirculation at stages I and II of the RSD syndrome is in favour of the hypothesis of sympathetic dysfunction.

At the nutritive level of skin microcirculation, the vasoconstrictive response to dependency is considered to be controlled by local factors, such as vasoactive metabolic substances accumulating during ischaemia and tissue oxygenation [7, 8]. The observed impairment of the vasoconstrictive response at the nutritive level of skin microcirculation at stage III of the RSD syndrome therefore may be caused by locally acting vasoactive metabolites resulting from longstanding impairment of the nutritive skin blood flow.

A limitation of the methodological approach used in our study is that it provides an indirect measure of sympathetic tone. The most direct way to study efferent sympathetic nerve activity would be micro-electrode recordings. These are however difficult to calibrate [31] because the signal is changed by slight adjustments to the position of the electrode tip. In addition, positioning the electrode correctly is technically difficult and may be painful, possibly influencing efferent sympathetic nerve activity through a somatosympathetic reflex.

The venoarteriolar response to dependency acts as an important oedema prevention mechanism. It limits the expected rise in capillary hydrostatic pressure [26] and allows a build-up of capillary oncotic pressure [33]. Failure of this response, as observed at all stages of RSD, will expose the skin microvascular bed to raised capillary pressures. This increase in capillary pressure in combination with
an increase in thermoregulatory skin blood flow, as observed at heart level at stage I and in the dependent position at both stages I and II, may contribute to oedema formation. The latter is observed at all stages of the RSD syndrome, but most frequently at stages I and II (see Table 1), which is in line with our microcirculatory findings. Moreover, raised capillary pressures may promote thickening of capillary basement membranes [34], which has been reported to occur in RSD patients [35]. Ultimately, these structural changes of capillary basement membranes may contribute to impairment of nutrition of the skin, resulting in trophic changes, which develop frequently in patients with longstanding RSD (see Table 1). Tissue hypersensitivity to catecholamines may also explain the deterioration of complaints, and the occurrence of vasocostriction in response to stimuli known to provoke an increase in circulating catecholamines, such as emotion and cold.

So far, most hypotheses in the literature concerning involvement of the sympathetic nervous system postulate that an increase in efferent sympathetic nerve activity, through a somato-sympathetic reflex, plays a pivotal role within the pathophysiological mechanisms underlying RSD [2-5]. Hence, treatment of RSD has mainly focused on blocking of the alleged increase in efferent sympathetic nerve activity by means of sympathectomy, the results of which have not been invariably satisfactory [6]. If, however, sympathetic dysfunction mainly results from increased sensitivity to catecholamines consequent to sympathetic denervation, blocking of adrenoceptors might yield interesting therapeutic perspectives with respect to the sympathetically maintained complaints. The latter is supported by reported beneficial effects of intravenous phenolamine [36] and oral phenoxybenzamine [37] in patients with RSD.

REFERENCES