

## REFLEX SYMPATHETIC DYSTROPHY

### An Exaggerated Regional Inflammatory Response?

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Reflex sympathetic dystrophy (RSD) is a potentially incapacitating syndrome, occurring in an extremity, usually after minor trauma or surgery. Contusions, distortions, and fractures are injuries that may induce RSD. The reported incidence of RSD after fractures is 7% to 37% after a Colles's fracture<sup>5, 14</sup> and 30% after tibial shaft fracture.<sup>54</sup> Minor operations such as carpal tunnel release and arthroscopy may be complicated by RSD.<sup>15, 43</sup> In 10% of patients, RSD develops spontaneously.<sup>68</sup> Early recognition and treatment of RSD are necessary because RSD patients are at risk of severe disability of the affected extremity, eventually resulting in unemployment.<sup>51</sup> We review the history, pathophysiology, and treatment of RSD, with special attention to the role that an exaggerated inflammatory process may play in acute RSD.

#### HISTORY

In 1864, the signs and symptoms of RSD were first described in detail in soldiers suffering from gunshot wounds inflicted during the Civil War.<sup>47</sup> Mitchell<sup>46</sup> named the syndrome *causalgia* because of the burning pain

in the affected limb. A role for the sympathetic system in the pathophysiology of RSD was first suggested by Leriche in 1916.<sup>41</sup>

Livingston<sup>44</sup> described a "vicious cycle" as an explanation for the pathogenesis of RSD. He theorized that activation of the nociceptors leads to excitation of internuncial pool of neurons of the spinal cord, with induction of increased activity of the efferent sympathetic system. The subsequent vasoconstriction, with ischemia of the tissue, may stimulate the nociceptors, with re-excitation of the spinal cord. Another hypothesis addresses the development of crosstalk between peripheral nerves in an "artificial synapse."<sup>18</sup>

A totally different view on the pathogenesis of RSD was introduced by Sudeck,<sup>61</sup> who described the similarity in symptoms between an inflammatory reaction and RSD. In his last publication,<sup>61</sup> as a professor emeritus at the University of Hamburg, he stated "the hypothetical inflammatory agent is an endogenous pro-inflammatory substance, specifically inducing hyperemia, and is probably related to histamin."

Recently, the "sympathetic" theory was replaced<sup>36, 48, 55, 59</sup> by the hypothesis that an upregulated sensitivity of  $\alpha$ -adrenoreceptors

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for catecholamines may induce RSD.<sup>3, 4, 20, 38, 52</sup> Other hypotheses on the pathogenesis of RSD refer to an involvement of the central nervous system and to an exaggerated peripheral (neuro)inflammatory response to tissue injury.<sup>50, 56, 69</sup> The numerous synonyms for RSD indicate that a consensus concerning the pathophysiology of RSD is still lacking (Table 1). In 1986, RSD was defined by the International Association for the Study of Pain (IASP) as "continuous pain in a portion of an extremity after trauma, which may include fracture but does not involve a major nerve, associated with sympathetic hyperactivity."<sup>32</sup> In 1991, the Ad Hoc Committee of the American Association for Hand Surgery defined RSD as "a pain syndrome in which the pain is accompanied by loss of function and evidence of autonomic dysfunction."<sup>2</sup> Recently, the IASP renamed RSD *complex regional pain syndrome* (CRPS) to avoid any mechanistic term in its appellation.<sup>59</sup> A disadvantage of that denomination is that patients who meet all criteria of CRPS but without pain are excluded. For that reason, we proposed to alter the name to *complex regional dysfunction system*.<sup>64</sup>

## PATHOPHYSIOLOGY

### Psychosocial Factors

Various predisposing psychosocial factors, such as emotional instability, nervousness, depression, anxiety, and certain life events have been linked to the development of RSD.<sup>22, 23, 65</sup> A critical review of the relevant literature, however, reveals no evidence for predisposing psychosocial factors.<sup>11, 45</sup> In the only prospective study, performed for this report, 160 patients received a battery of psychological and personality tests 1 day after sustaining a Colles's fracture.<sup>66</sup> No difference was found in the results of the tests between

**Table 1.** SYNONYMS OF REFLEX SYMPATHETIC DYSTROPHY

Causalgia
Algodystrophy
Post-traumatic dystrophy
Sudeck's atrophy
Pourfour du Petit syndrome
Shoulder-hand syndrome
Postinfarctional sclerodactylia
Complex regional pain syndrome

patients who eventually did or did not develop RSD.

DeGood et al<sup>16</sup> compared pain intensity and emotional distress of patients with chronic RSD, low back pain, or headache. They found that RSD patients had the highest level of pain intensity but relatively less emotional distress than the other chronic pain patients.

### Sympathetic Nervous System

The hypothesis that a hyperactive sympathetic nervous system induces RSD is mainly supported by the presence of hyperhidrosis and vasomotor instability in extremities with RSD and by the reduction of complaints after sympathectomy<sup>10, 12</sup>—especially the reduction of pain.<sup>1, 31, 49, 70</sup> Most studies, however, were retrospective. In double-blind randomized studies, no difference was found between sympathetic blockade and placebo treatment.<sup>9, 33, 53</sup> Recent studies<sup>20, 21, 29</sup> demonstrated diminished concentrations of norepinephrine and neuropeptide Y in RSD extremities compared with the unaffected side, thereby refuting the theory of a hyperactive sympathetic system in RSD. Those findings have introduced a new view on the pathogenesis of RSD—namely, upregulation in sensitivity of the  $\alpha$ -adrenoreceptors for circulating catecholamines.<sup>4, 20, 38</sup>

### Inflammatory Response

Paul Sudeck<sup>61</sup> proposed that RSD could be caused by an exaggerated inflammatory response after injury or operation of an extremity. In a prospective study by Veldman et al,<sup>69</sup> 829 RSD patients were examined for the signs and symptoms of RSD to be diagnosed as RSD, the following criteria were used:

1. At least four of the following five:
  - Unexplained diffuse pain
  - Difference in skin color compared with the other extremity
  - Diffuse edema
  - Difference in skin temperature compared with the other extremity
  - Limited active range of motion
2. Occurrence or increase in the aforementioned signs and symptoms after using the extremity
3. Aforementioned signs and symptoms present in an area larger than the area

of primary injury or operation and including the area distal to the primary injury

In acute RSD patients examined within 2 months after the onset of the disease, the signs and symptoms of inflammation were observed (Table 2). From the onset of the disease, neurologic symptoms also were found in the affected limb, such as hypesthesia, hyperpathy, incoordination, tremor, involuntary movements, muscle spasms, and paresis. Sympathetic signs were found in only 57% of the acute RSD patients.

In this large population of RSD patients, we could identify a subgroup with the "classical" three-phasic RSD—primarily "warm," a second phase of vasolability, and a late "cold" phase.<sup>60</sup> But a substantial number of RSD patients retained a warm skin temperature for years. In 13% of the acute RSD patients, the skin temperature of the affected extremity was colder than in the healthy contralateral extremity from the onset, considered "primarily cold RSD." Those findings are in disagreement with the classical subdivision of RSD patients in three stages based on skin temperature. In our view, therefore, the classical subdivision has to be revised to a subdivision of "primarily warm" and "primarily cold" skin temperature at the onset, especially because the last-mentioned group has a worse outcome as to function,<sup>27</sup> a higher incidence of recurrence of RSD,<sup>68</sup> and more frequently requiring amputation.<sup>17</sup>

Because, in 1982, our department of anesthesiology decided not to perform any more

sympathetic blockades in acute warm RSD patients,<sup>19</sup> we were left without any meaningful therapeutic option. We therefore started various studies in acute and chronic RSD patients. From our scientific work in acute respiratory distress syndrome, sepsis, and multiple organ dysfunction syndrome, we hypothesized that a regional, exaggerated inflammatory response to injury may induce the early inflammatory and late dystrophic changes in RSD. Various investigations support that view.

## NEW INVESTIGATIONS

### Arterial Blood Flow, Oxygen Utilization, Tissue Oxygenation, and Lactate Flux

We assessed arterial blood flow and venous oxygen saturation in eight patients with acute warm RSD of one hand. Arterial blood flow was assessed scintigraphically by the left-to-right distribution of <sup>99m</sup>technetium-dimethylphosphonate tracer. Venous oxygen saturation ( $S_vO_2$ ) was measured via blood samples obtained from the antecubital vein. Arterial flow to the RSD extremity was significantly increased and the  $S_vO_2$  was extremely high (Table 3).

In one patient, we could perform a flux study of both upper extremities. Arterial flow was assessed by echo Doppler and venous samples were obtained by retrograde cannulation of the antecubital vein. Arterial blood

Table 2. CLINICAL SIGNS AND SYMPTOMS OF ACUTE REFLEX SYMPATHETIC DYSTROPHY IN 156 PATIENTS

Inflammatory Signs and Symptoms	Percentage	Neurologic	Percentage
Pain	92	Hypesthesia	69
Edema	86	Hyperpathy	75
Difference in skin temperature	98	Incoordination	53
Difference in skin color	97	Tremor	54
Limited range of motion	90	Involuntary movements	19
Increase in complaints after exercise	98*	Muscle spasms	11
		Paresis	98
Atrophy	Percentage	Sympathetic	Percentage
Skin	38	Hyperhidrosis	57
Nails	15		
Muscle	40		

Patients examined within 2 months after its onset.<sup>68</sup>

\*Note: the remaining 2% of patients were unable to exercise the affected limb at all.

Data from Veldman PH, Reynen HM, Arntz IE, et al: Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. *Lancet* 342:1012-1016, 1993.

**Table 3.** VENOUS OXYGEN SATURATION AND ARTERIAL BLOOD FLOW DISTRIBUTION IN ACUTE WARM REFLEX SYMPATHETIC DYSTROPHY AND IN HEALTHY UPPER EXTREMITIES ( $n = 8$ )

	RSD (%)	Healthy (%)	Difference (%)	Significance
Venous oxygen saturation	86.5	68.7	17.8 ± 4.6	$P < 0.001$
Arterial flow	69.4 ± 7.4	30.6 ± 3.1		$P < 0.001$

gas and lactate samples were obtained from the femoral artery. Again,  $S_vO_2$  and arterial flow were high whereas oxygen consumption and oxygen extraction were low. Despite a high oxygen supply, the lactate in the RSD extremity was increased by a factor of five (Table 4). This increased lactate flux despite elevated arterial blood flow in RSD limbs indicates tissue hypoxia and is caused either by cellular intoxication with impaired oxygen utilization or by an oxygen diffusion problem between the arterioles and mitochondria. In any case, the data obtained in this study indicated tissue hypoxia despite supranormal arterial oxygen supply in extremities with acute RSD. This odd combination of high oxygen supply and tissue hypoxia seems to be found consistently in areas affected by severe inflammation, burn injury, varicose ulcers, malignant tumors, ischemia/reperfusion, and in feet affected by diabetes mellitus.<sup>25</sup>

### Phosphorus 31 Nuclear Magnetic Resonance Spectroscopy

Phosphorus 31 nuclear magnetic resonance spectroscopy (<sup>31</sup>P-NMR) is a noninvasive technique to measure the high-energy phosphate compounds of skeletal muscle. It is applied in investigations of various human metabolic skeletal muscle disorders. By analyzing the spectra obtained, it is possible to assess the concentrations of substrates necessary for skeletal muscle activity, such as adenosine

triphosphate (ATP), phosphocreatine (PCr), and the degradation product inorganic phosphate (Pi). During skeletal muscle exercise, PCr is consumed for the resynthesis of ATP, whereas resynthesis of PCr (from anorganic phosphate and creatine) is oxygen dependent. Under ischemic or hypoxic conditions, therefore, cellular ATP cannot be resynthesized by oxidative phosphorylation.

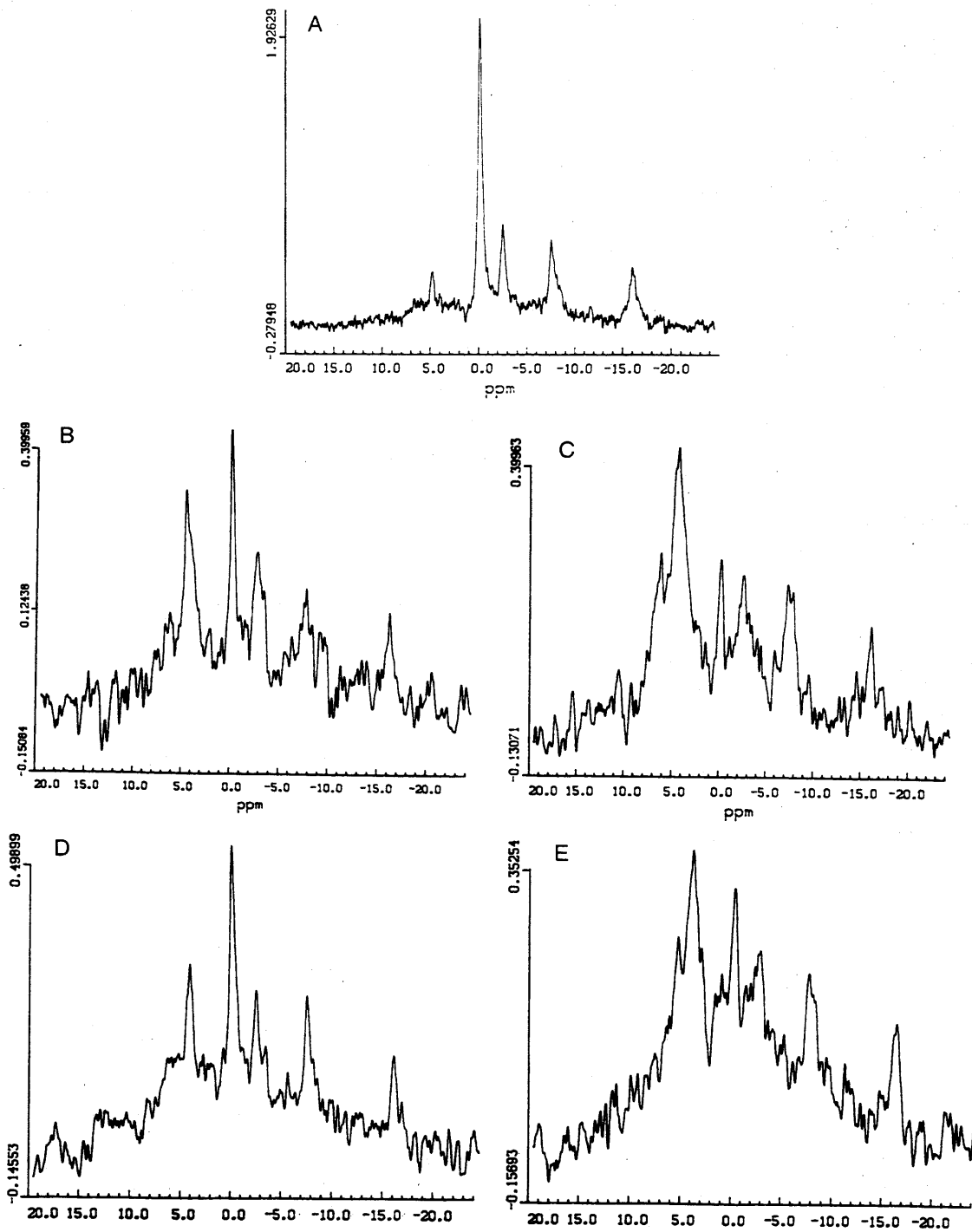
We applied the technique in 11 chronic RSD patients whose legs were affected.<sup>30</sup> <sup>31</sup>P-NMR spectra were obtained at the level of the calf muscle in a 1.5-Tesla NMR apparatus and were compared with the spectra of the healthy limbs. The Pi:PCr ratio in the RSD limbs was  $0.24 \pm 0.02$ , whereas that in the healthy control limb was  $0.13 \pm 0.02$  ( $P < 0.01$ ). That finding indicates diminished oxygen availability to the tissue in these late, severe cases of RSD.

One young (21 years) male patient, who had no signs of RSD when using free-radical-scavenger treatment (explained in the section on another approach to treatment) and who had returned to work, complained of paresis and relapse of RSD symptoms in his hand whenever he stopped taking his medication. We could obtain <sup>31</sup>P-NMR spectra of the thenar muscles of both hands 2 weeks after stopping his medication. Spectra were obtained before, directly after, and 2 minutes after exercises consisting of pumping a sphygmomanometer to a predetermined level (Fig. 1). Measurements were performed with a 6.3-Tesla magnet at the Philips Physics Labora-

**Table 4.** FLUX STUDY IN FEMALE PATIENT (52 YEARS OLD) WITH ACUTE WARM REFLEX SYMPATHETIC DYSTROPHY OF THE RIGHT HAND\*

	RSD Hand	Healthy Hand
Venous lactate concentration	1172 mmol/L	783 mmol/L
Arterial lactate concentration	630 mmol/L	630 mmol/L
Arterial flow (via echo Doppler)	160 mL/minute	125 mL/minute
Lactate flux	86.7 mmol/minute	19.1 mmol/minute
Oxygen extraction factor	0.19	0.31
Oxygen consumption	30.4 mL O <sub>2</sub> /minute	39 ml O <sub>2</sub> /minute

\*Performed by bilateral retrograde cannulation of the antecubital vein.



**Figure 1.** A  $^{31}\text{P}$  NMR spectra of healthy (A, B, D) and RSD (C, E) hand in a 21-year-old patient (see text) before, during, and after exercise of the hand. The first peak is anorganic phosphate (Pi), the second peak phosphocreatine (PCr), the three following peaks three phosphor groups of adenosine triphosphate (ATP). A, The  $^{31}\text{P}$  NMR spectrum of the healthy hand at rest. B,  $^{31}\text{P}$  NMR spectrum of the healthy hand during exercise. C, Directly following exercise, PCr has almost disappeared in the affected hand while Pi is strongly increased. D,  $^{31}\text{P}$  NMR spectrum after 2 minutes of exercise of the healthy hand. E, Two minutes after exercise PCr increases and Pi decreases but not as far as in the healthy control hand.

tory in Eindhoven. Upon exercising, we could demonstrate a quick and profound drop in skeletal muscle PCr, followed by slow recovery at rest (see Fig. 1).

These observations with  $^{31}\text{P}$ -NMR, in particular, convinced us that RSD patients are unable, rather than unwilling, to exercise.

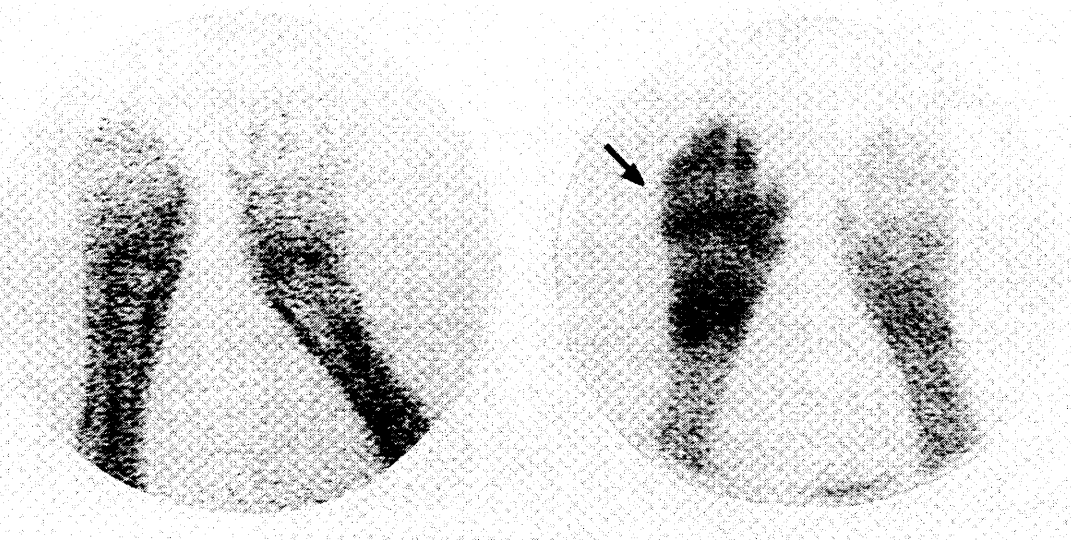
### Indium-111-Immunoglobulin G Scintigraphy

Indium-111-immunoglobulin (In-111-IgG) scintigraphy is an established technique for recognizing infectious and inflammatory lesions by accumulation of the labeled high-molecular-weight immunoglobulin in the affected area. The extravasation of In-111-IgG is caused by increased vascular permeability for macromolecules as a result of inflammatory damage to the vascular endothelium. In-111-IgG scintigraphy was performed in 23 patients with RSD of one hand.<sup>50</sup> In 17 patients, RSD was present for less than 5 months; in six patients, for longer than 5 months. Images were obtained by a gamma camera, immediately, 5 minutes after, and 4, 24, and 48 hours after intravenous injection of In-111-IgG. The uptake of In-111-IgG was expressed as the uptake ratio between the affected and unaffected hands. In the acute phase of RSD, 14 of 17 RSD patients had a progressive accumulation of the labeled immunoglobulin in the

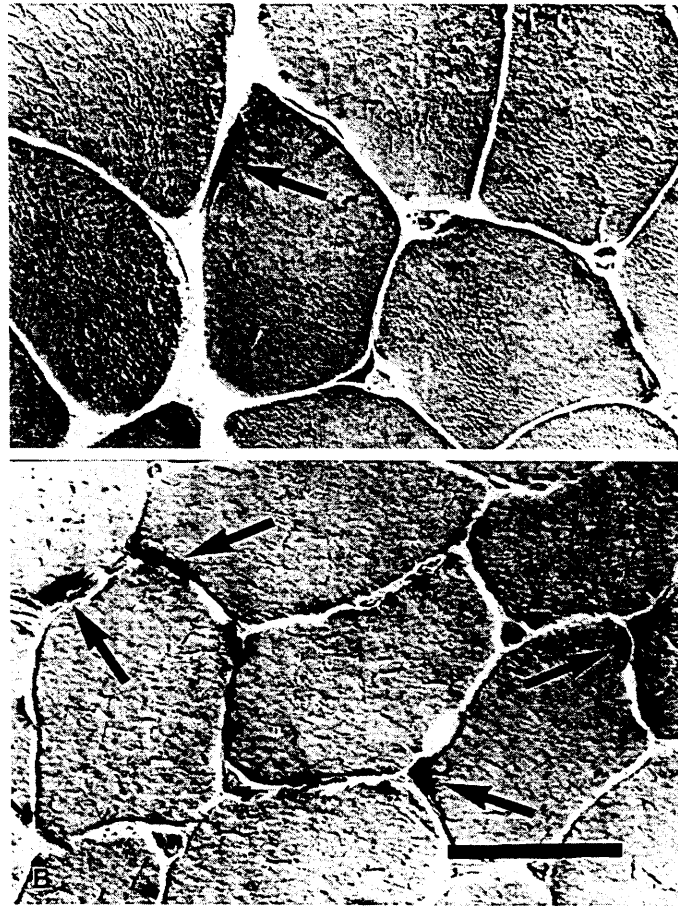
affected hand (Fig. 2) independent of the arterial flow. In chronic RSD patients, the scintigrams were normal in five of the six patients. From that study, it was concluded that, in acute RSD, extravasation of macromolecules is present in the affected area, indicating a regional inflammatory process.

### Histology

Obtaining tissue from an RSD patient for histologic analysis is difficult because any additional injury may trigger an increase of severity or recurrence of RSD. For that reason, we performed biopsies only in chronic, severe RSD cases.<sup>62</sup> Biopsies were taken from the gastrocnemius muscle of RSD-affected legs. Duration of RSD varied from 12 to 46 months. Analysis by light microscope showed extreme accumulation of lipofuscin in the skeletal muscle of RSD patients. Lipofuscin is a degeneration product, produced during lipid peroxidation of the cellular membrane. With age, the amount of lipofuscin in tissue increases slowly. In the gastrocnemius muscle of RSD patients, the amount of lipofuscin observed was clearly increased compared with the gastrocnemius muscle of persons of the same age but without RSD (Fig. 3). On electron microscope, sarcolemma blebbing, swelling, and vesiculation of the mitochondria; disintegration of myofibrils, and Z-band irregularities were observed in the skeletal



**Figure 2.** Indium-111-IgG scintigraphy of a RSD patient. RSD developed after contusion of the left hand, 3 months prior to the scintigraphy. The left scintigram shows both hands 5 min after In-111-IgG injection, the right scintigram 24 h after injection. The right scintigram shows accumulation (arrow) of In-111-IgG in the affected hand by RSD.



**Figure 3.** Biopsy of the gastrocnemius muscle (acid phosphatase staining) *A*, Obtained from of a 39-year-old healthy person. *B*, from a 39-year-old patient's leg affected by RSD for more than 1 year. The dark spots (*arrows*) show areas with increased acid phosphatase activity, representing the deposits of lipofuscin. bar = 50  $\mu$ m.

muscle of chronic RSD patients.<sup>62</sup> Those cellular abnormalities could be provoked by oxidative stress.

### Anti-Inflammatory Therapy

In a prospective, placebo-controlled study, Christensen et al<sup>13</sup> demonstrated that corticosteroids significantly decrease the complaints of RSD. Unfortunately, the corticosteroid dosages have to be 20 to 100 mg daily for long periods, which may induce deleterious side effects.<sup>13, 37</sup>

Based on the hypothesis that RSD is an exaggerated inflammatory response, we evaluated free-radical scavengers as treatment of acute RSD.<sup>26</sup> The approach was suggested by recent knowledge that free radicals are generated during inflammatory processes and in-

duce tissue damage. Treatment consisted of low-dose continuous intravenous infusion of mannitol or local application of dimethyl sulfoxide (DMSO).<sup>24</sup> In a crossover study, DMSO had a significantly better result than placebo (Fig. 4).<sup>26</sup> The therapeutic effects of local DMSO application in acute RSD were confirmed by two other studies, an open study by Langendijk et al<sup>39</sup> and a study by Geertzen et al<sup>23</sup> comparing DMSO to intravenous ismelin blocks.

We also assessed the effects of 1 week of intravenous mannitol treatment on arterial flow and oxygen extraction in patients with severe acute warm RSD of one upper extremity (Table 5). Besides important improvement in clinical signs and symptoms of acute inflammation, the mannitol significantly decreased arterial flow and  $S_{a}O_2$  saturation, indicating improved tissue extraction.



**Figure 4.** A and C, Acute warm RSD of the left hand before treatment. B, Result of 1 week treatment with DMSO cream: a decrease of redness and edema. D, Increase of active range of motion. At this time, the pain level also was reduced.

*Illustration continued on opposite page*

### Neuroinflammatory Mediators

It is known from various animal studies that bradykinin, substance P (SP), and calcitonin gene-related peptide (CGRP) provoke an inflammatory reaction with hyperalgesia in a hindlimb.<sup>40, 42</sup> Schwartzman and Kerrigan<sup>57</sup> suggested that SP may have an important role in the pathogenesis of the neurologic-complication dystonia in RSD patients,<sup>57</sup> and Schott<sup>55, 56</sup> hypothesized that SP and CGRP are involved in the inflammatory reaction and the accompanying motor and sensor disturbances of RSD. Analysis of blood samples obtained from 61 RSD patients showed significantly increased systemic levels of bradykinin and CGRP compared with 21 controls.<sup>8</sup>

### Experimental Model

We developed an animal model that allows for continuous intra-arterial infusion of the free radical donor *tert*-butylhydroperoxide (*tert*-BuOOH) or a placebo in one hindlimb of nonanesthetized rats.<sup>63</sup> In placebo-infused rats, no measurable signs of inflammation were found in the infused paw. In the *tert*-BuOOH-infused hindlimbs, we found increased skin temperature, edema, redness of the skin, impaired function, spontaneous pain behavior, and increased sensitivity to mechanical and thermal pain stimuli (Fig. 5). Those signs and symptoms are similar to those found in acute RSD patients. In addition, the observed pain sensations in the free



Figure 4 (Continued).



Figure 5. Feet of a rat after 24 h infusion with a free radical donor. The infused foot (*right*) is clearly swollen and has a red color, but the control foot is unaffected.

**Table 5.** VENOUS OXYGEN SATURATION AND ARTERIAL BLOOD FLOW DISTRIBUTION IN ACUTE WARM REFLEX SYMPATHETIC DYSTROPHY UPPER EXTREMITIES ( $n = 8$ ), BEFORE AND AFTER 1 WEEK OF LOW-DOSE INTRAVENOUS MANNITOL

	Before (%)	After (%)	Difference (%)	Significance
Venous oxygen saturation	86.5	80.1	$6.4 \pm 2.8$	$P < 0.01$
Arterial flow	$69.4 \pm 7.4$	$62.9 \pm 5.6$	$6.5 \pm 4.9$	$P = 0.012$

radical-infused animals were similar to the pain sensations present in an animal model of neuropathic pain<sup>6,7</sup> currently used as a model of RSD.<sup>34</sup> In contrast to the neuropathic animal model, in which the pain sensations appear 5 days postoperatively, in our animal model, the pain sensations are present within 24 hours of infusion.

### ANOTHER APPROACH TO TREATMENT

During the last 15 years, we progressively adapted our treatment schedule for RSD to new knowledge and increasing experience. During that period, we examined more than 1500 RSD patients, 90% of them referred from other clinics. Our present approach is summarized here.

#### Free-Radical-Scavenger Treatment

In 1982, we started treating acute RSD patients with free-radical scavengers. Patients with severe, acute RSD are treated with intravenous mannitol (10%, 1 L/24 hours) for 1 week. Care should be taken in patients with renal failure because hyperosmolality may occur. When renal function is normal, osmolality is not increased significantly.

Subsequently, the patients are treated with application of DMSO cream (50%) on the skin of the affected area five times daily for approximately 2 to 3 months.

Less severe cases of RSD are treated initially with DMSO cream.

#### Vasodilation Treatment

The decreased arterial flow found in "primarily cold" RSD probably contributes to the worse outcome found in that subgroup. "Primarily cold" RSD patients therefore, are treated early and rigorously with vasodilators

such as verapamil (one or two times, orally, 240-mg sustained release/24 hours), ketanserin (two times orally, 20 or 40 mg/24 hours),<sup>28</sup> or pentoxifyline (one or two times, orally, 400 mg/24 hours) to optimize perfusion of the affected extremity. When the skin temperature remains cold despite the vasodilators, sympathetic blockade is performed at an early stage.

#### Attention to Painful Trigger Points

In about 50% of RSD patients, a "trigger point" is present. A trigger point is defined as a specific painful area within the affected RSD extremity in which the pain is not directly caused by RSD. Examples are tendinitis of the tendons of one or both biceps muscles, epicondylitis lateralis or medialis, carpal tunnel syndrome, neuroma, trigger finger, anterior metatarsalgia, "jumper knee," or tendinitis of the patella tendon. Our hypothesis is that these trigger points may induce, sustain, or worsen RSD, possibly by a local process of neurogenic inflammation. During the treatment of RSD, the trigger points are identified and given specific treatment, which may include the operative removal of a neuroma, local injection of bupivacaine followed by methylprednisolone for tendinitis,<sup>67</sup> or use of an orthosis for immobilization of a painful joint.

#### Physical Therapy?

Muscular work is accompanied by an increase in oxygen consumption, and may induce free-radical production.<sup>35,58</sup> In addition, it is almost pathognomonic of RSD patients that muscular work of the affected extremity induces or increases the inflammatory signs and symptoms, especially pain, within the affected extremity.<sup>69</sup> For that reason, we advise RSD patients to actively exercise their affected extremity, but within their pain

threshold. In our department, physical therapy is started when the acute RSD signs and symptoms have largely disappeared, and consists of mobilizing the affected joints within the pain threshold. Aggressive physical therapy induces an increase in RSD complaints and may be a torture for the patient.

### Reflex Sympathetic Dystrophy with Severe Disability

Some cases of RSD are resistant to any of the presently known modes of treatment. In such patients, a completely different approach is necessary, addressing their severe disability. Such an approach should include providing an orthosis, a wheelchair, and adaptation of their home situation, as appropriate.

### CONCLUSION

How do these findings fit with the hypothesis that an exaggerated inflammatory response is involved in the pathogenesis of RSD? The scintigraphic study demonstrated vascular leakage for macromolecules in the acute phase of RSD, such as is found in inflammatory processes. Impaired oxygen extraction, also found in acute RSD-affected extremities, is another phenomenon detectable in areas of inflammation. In chronic RSD patients, the increased Pi/PCr ratios at rest indicate an alteration in the energy balance of the affected tissue. Infusion of free radicals in a hindlimb of a nonanaesthetized rat mimics the acute signs and symptoms of RSD. During inflammatory- and hypoxia-related processes, free radicals are generated. In biopsies of chronic RSD cases, increased lipofuscin is found, indicating oxidative stress. Treatment of RSD patients with free-radical scavengers reduces the signs and symptoms of this syndrome, while increasing oxygen extraction.

All these findings support the hypothesis that RSD is the result of an exaggerated inflammatory response to injury or operation.

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### References

1. AbuRahma AF, Robinson PA, Powell M, et al: Sympathectomy for reflex sympathetic dystrophy: Factors affecting outcome. *Ann Vasc Surg* 8:372-379, 1994
2. Amadio PC, Mackinnon SE, Merritt WH, et al: Reflex sympathetic dystrophy syndrome: Consensus report of an ad hoc committee of the American Association for Hand Surgery on the definition of reflex sympathetic dystrophy syndrome. *Plast Reconstr Surg* 87:371-375, 1991
3. Arner S: Intravenous phentolamine test: Diagnostic and prognostic use in reflex sympathetic dystrophy. *Pain* 46:17-22, 1991
4. Arnold JM, Teasell RW, MacLeod AP, et al: Increased venous alpha-adrenoceptor responsiveness in patients with reflex sympathetic dystrophy. *Ann Intern Med* 118:619-621, 1993
5. Atkins RM, Duckworth T, Kanis JA: Features of algodystrophy after Colles' fracture. *J Bone Joint Surg Br* 72:105-110, 1990
6. Attal N, Jazat F, Kayser V, et al: Further evidence for 'pain-related' behaviours in a model of unilateral peripheral mononeuropathy. *Pain* 41:235-251, 1990
7. Bennet GJI, Xie YKA: A peripheral mononeuropathy in the rat that produces disorders of pain sensation like those seen in man. *Pain* 33:87-107, 1988
8. Blair SJ: Role of the neuropeptides in the pathogenesis of reflex sympathetic dystrophy. *In Programs and Abstracts of Reflex Sympathetic Dystrophy*. Brussels, 1996, p 18
9. Blanchard J, Ramamurthy S, Walsh N, et al: Intravenous regional sympathectomy: A double-blind comparison of guanethidine, reserpine, and normal saline. *Journal of Pain and Symptom Management* 5:357-361, 1990
10. Bonica JJ: Causalgia and other reflex sympathetic dystrophies. *In Bonica JJ, Liebeskind JC, Albe-Fessard DG (eds): Advances in Pain Research and Therapy*. New York, Raven Press, 1979, pp 141-166
11. Bruehl S, Carlson CR: Predisposing psychological factors in the development of reflex sympathetic dystrophy. A review of the empirical evidence. *Clin J Pain* 8:287-299, 1992
12. Chelimsky TC, Low PA, Naessens JM, et al: Value of autonomic testing in reflex sympathetic dystrophy. *Mayo Clin Proc* 70:1029-1040, 1995
13. Christensen K, Jensen EM, Noer I: The reflex dystrophy syndrome. Response to treatment with systemic corticosteroids. *Acta Chir Scand* 148:653-655, 1982
14. de Bruijn HP: Functional treatment of Colles fractures: A prospective clinical study [thesis]. Maastricht University, 1987
15. de Lee JC: Complications of arthroscopy and arthroscopic surgery: Results of a national survey. *Arthroscopy* 1:200-214, 1985
16. DeGood DE, Cundiff GW, Adams LE, et al: A psychosocial and behavioral comparison of reflex sympathetic dystrophy, low back pain, and headache patients. *Pain* 54:317-322, 1993
17. Dielissen PW, Claassen AT, Veldman PH, et al: Amputation for reflex sympathetic dystrophy. *J Bone Joint Surg Br* 77:270-273, 1995
18. Doupe J, Cullen CH, Chance GQ: Post-traumatic pain

- and the causalgic syndrome. *J Neurol Neurosurg Psychiatry* 7:33-48, 1944
19. Driessens JJ, van der Werken C, Nicolai JPA, et al: Clinical effects of regional intravenous guanethidine (Ismeline) in reflex sympathetic dystrophy. *Acta Anaesthesiol Scand* 27:505-509, 1983
  20. Drummond PD, Finch PM, Edvinsson L, et al: Plasma neuropeptide Y in the symptomatic limb of patients with causalgic pain. *Clin Auton Res* 4:113-116, 1994
  21. Drummond PD, Finch PM, Smythe GA: Reflex sympathetic dystrophy: The significance of differing plasma catecholamine concentrations in affected and unaffected limbs. *Brain* 114:2025-2036, 1991
  22. Egle UT, Hoffmann SO: Psychosomatic correlations of sympathetic reflex dystrophy (Sudeck's disease). Review of the literature and initial clinical results. *Psychother Psychosom Med Psychol* 40:123-135, 1990
  23. Geertzen JH, de Bruijn HP, de Bruijn Kofman AT, et al: Reflex sympathetic dystrophy: Early treatment and psychological aspects. *Arch Phys Med Rehabil* 75:442-446, 1994
  24. Goris RJA: Treatment of reflex sympathetic dystrophy with hydroxyl radical scavengers. *Unfallchirurg* 88:330-332, 1985
  25. Goris RJA: Conditions associated with impaired oxygen extraction. In Gutierrez G, Vincent JL (eds): *Tissue oxygen utilization*. Berlin, Springer Verlag, 1991, pp 350-369
  26. Goris RJA, Dongen LM, Winters HA: Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy? *Free Radic Res Commun* 3:13-18, 1987
  27. Goris RJA, Reynen JAM, Veldman PHJM: Chapter 32: De posttraumatische dystrofie. In: van Mourik JB, Patka P (eds): *Letsels van Enkel en Voet*. 1990, pp 435-446
  28. Hanna MH, Peat SJ: Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled crossover trial. *Pain* 38:145-150, 1989
  29. Harden RN, Duc TA, Williams TR, et al: Norepinephrine and epinephrine levels in affected versus unaffected limbs in sympathetically maintained pain. *Clin J Pain* 10:324-330, 1994
  30. Heerschap A, den Hollander JA, Reynen H, et al: Metabolic changes in reflex sympathetic dystrophy: A <sup>31</sup>P NMR spectroscopy study. *Muscle Nerve* 16:367-373, 1993
  31. Herz DA, Looman JE, Ford RD, et al: Second thoracic sympathetic ganglionectomy in sympathetically maintained pain. *J Pain Symptom Manag* 8:483-491, 1993
  32. International Association for the Study of Pain: Description of chronic pain syndromes and definitions of pain terms. *Pain (suppl 3):S28-S30*, 1986
  33. Jadad AR, Carroll D, Glynn CJ, et al: Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: A systematic review and a randomized, double-blind crossover study. *J Pain Symptom Manag* 10:13-20, 1995
  34. Jänig W: Experimental approach to reflex sympathetic dystrophy and related syndromes [editorial]. *Pain* 46:241-245, 1991
  35. Ji LL, Fu R: Responses of glutathione system and antioxidant enzymes to exhaustive exercise and hydroperoxide. *J Appl Physiol* 72:549-554, 1992
  36. Kozin F: Reflex sympathetic dystrophy syndrome. *Curr Opin Rheumatol* 6:210-216, 1994
  37. Kozin F, McCarty DJ, Sims J, et al: The reflex sympathetic dystrophy syndrome. Clinical and histologic studies: Evidence for bilaterality, response to corticosteroids and articular involvement. *Am J Med* 60:321-331, 1976
  38. Kurvers HA, Jacobs MJ, Beuk RJ, et al: Reflex sympathetic dystrophy: Evolution of microcirculatory disturbances in time. *Pain* 60:333-340, 1995
  39. Langendijk PNJ, Zuurmond WWA, van Apeldoorn HAC, et al: Goede resultaten van behandeling van acute reflectoïr-sympathische dystrofie met een 50% dimethylsulfoxide-creme. *Ned Tijdschr Geneesk* 137:500-503, 1993
  40. Legat FJ, Griesbacher T, Lembeck F: Medication by bradykinin of rat paw oedema induced by collagenase from *Clostridium histolyticum*. *Br J Pharmacol* 112:453-460, 1994
  41. Leriche R: De la causalgie, envisagée comme une nevrite du sympathique et de son traitement par la dénudation et l'excision des plexus nerveux périphériques. *Presse Med* 24:178-180, 1916
  42. Levine JD, Clark R, Devor M, et al: Intraneuronal substance P contributes to the severity of experimental arthritis. *Science* 226:547-549, 1984
  43. Lichtman DM, Florio RL, Mack GE: Carpal tunnel release under local anaesthesia: Evaluation of the outpatient procedure. *J Hand Surg* 4:544-546, 1979
  44. Livingston WK: Pain mechanisms: A physiological interpretation of causalgia and its related states. In London, MacMillan, 1944
  45. Lynch ME: Psychological aspects of reflex sympathetic dystrophy: A review of the adult and paediatric literature. *Pain* 49:337-347, 1992
  46. Mitchell SW: On the diseases of nerves, resulting from injuries. In: Flint A (ed): *Contributions relating to causation and prevention of diseases*. New York, US Sanitary Commission Memoirs, 1867
  47. Mitchell SW, Morehouse GR, Keen WW: Gunshot wounds and other injuries of nerves. In Philadelphia, JB Lippincott & Co, 1864
  48. Ochoa JL, Verdugo RJ: Reflex sympathetic dystrophy: A common clinical avenue for somatoform expression. *Neurol Clin* 13:351-363, 1995
  49. Olcott C4, Eltherington LG, Wilcosky BR, et al: Reflex sympathetic dystrophy: The surgeon's role in management. *J Vasc Surg* 14:488-492, 1991
  50. Oyen WJ, Arntz IE, Claessens RM, et al: Reflex sympathetic dystrophy of the hand: An excessive inflammatory response? *Pain* 55:151-157, 1993
  51. Poplawski ZJ, Wiley AM, Murray JF: Post-traumatic dystrophy of the extremities. *J Bone Joint Surg Am* 65:642-655, 1983
  52. Raja SN, Turnquist JL, Meleka S, et al: Monitoring adequacy of alpha-adrenoceptor blockade following systemic phentolamine administration. *Pain* 64:197-204, 1996
  53. Ramamurthy S, Hoffman J: Intravenous regional guanethidine in the treatment of reflex sympathetic dystrophy/causalgia: A randomized, double-blind study. *Guanethidine Study Group. Anesth Analg* 81:718-723, 1995
  54. Sarangi PP, Ward AJ, Smith EJ, et al: Algodystrophy and osteoporosis after tibial fractures. *J Bone Joint Surg Br* 75:450-452, 1993
  55. Schott GD: Visceral afferents: Their contribution to 'sympathetic dependent' pain. *Brain* 117:397-413, 1994
  56. Schott GD: An unsympathetic view of pain. *Lancet* 345:634-636, 1995
  57. Schwartzman RJ, Kerrigan J: The movement disorder of reflex sympathetic dystrophy. *Neurology* 40:57-61, 1990

58. Sjodin B, Hellsten Westing Y, Apple FS: Biochemical mechanisms for oxygen free radical formation during exercise. *Sports Med* 10:236-254, 1990
59. Stanton-Hicks M, Jänig W, Hassenbusch S, et al: Reflex sympathetic dystrophy: Changing concepts and taxonomy. *Pain* 63:127-133, 1995
60. Steinbrocker O: The shoulder-hand syndrome. Associated painful homolateral disability of the shoulder and swelling and atrophy of the hand. *Am J Med* 3:402-407, 1947
61. Sudeck P: Die sogenannte akute Knochenatrophie als Entzündungsvorgang. *Chirurg* 15:449-458, 1942
62. Tilman PBJ, Stadhouders AM, Jap PHK, et al: Histopathologic findings in skeletal muscle tissue of patients suffering from reflex sympathetic dystrophy. *Micron and Microscopica Acta* 21:271-272, 1990
63. van der Laan L, Kapitein PJC, Oyen WJG, et al: A novel animal model to evaluate oxygen derived free radical damage in soft tissue. *Free Radic Res* 26:363-372, 1997
64. van der Laan L, Veldman PHJM, Goris RJA: Letter to the editor. *Pain* 69:in press 1997
65. Van Houdenhove B, Vasquez G, Onghena P, et al: Etiopathogenesis of reflex sympathetic dystrophy: A review and biopsychosocial hypothesis. *Clin J Pain* 8:300-306, 1992
66. van Spaendock KPM, van Heusden HA, The R, et al: Posttraumatische dystrofie en persoonlijkheidstype. In: Goris RJA (ed): *Posttraumatische Dystrofie*. Nijmegen, Post Academisch Onderwijs Geneeskunde Katholieke Universiteit Nijmegen, 1992, pp 39-43
67. Veldman PH, Goris RJA: Shoulder complaints in patients with reflex sympathetic dystrophy of the upper extremity. *Arch Phys Med Rehabil* 76:239-242, 1995
68. Veldman PHJM, Goris RJA: Multiple reflex sympathetic dystrophy: Which patients are at risk for developing a recurrence of reflex sympathetic dystrophy in the same or another limb. *Pain* 64:463-466, 1996
69. Veldman PH, Reynen HM, Arntz IE, et al: Signs and symptoms of reflex sympathetic dystrophy: Prospective study of 829 patients. *Lancet* 342:1012-1016, 1993
70. Wang JK, Johnson KA, Ilstrup DM: Sympathetic blocks for reflex sympathetic dystrophy. *Pain* 23:13-17, 1985

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