World J. Surg. 22, 197–202, 1998

WORLD
Journal of
SURGERY

Reflex Sympathetic Dystrophy: Model of a Severe Regional Inflammatory Response Syndrome

R. Jan A. Goris

Department of Surgery, University Hospital Nijmegen, 6500-HB Nijmegen, The Netherlands

Abstract. The systemic inflammatory response syndrome (SIRS) and acute reflex sympathetic dystrophy syndrome (RSD) share clinical signs of severe inflammation, a protracted course, and a similar problem of impaired oxygen utilization. The difference is that SIRS patients have these signs and symptoms systemically and are severely ill in the intensive care unit (ICU), whereas acute RSD patients are in good health and their problems are limited to one extremity. Both conditions seem to be the result of an exaggerated inflammatory response. As RSD patients have a healthy contralateral extremity, they may be their own control in various flux studies. It is hypothesized that this situation is exquisitely suitable for studying the pathophysiology of severe inflammatory responses in humans. Only a few patients are required to perform studies of, for example, oxygen metabolism and cytokine or oxygen radical production. Assessment methods may be utilized, such as nuclear magnetic resonance spectroscopy, which cannot easily be performed in ICU patients.

SIRS, ARDS, MODS, and Sepsis

The systemic inflammatory response syndrome (SIRS), or generalized inflammation syndrome as it was called earlier [1], is the main cause of severe morbidity in surgical patients. The condition SIRS was recently defined by criteria identical to those for sepsis, except for the presence of bacteria and infection [2]. Frequently, the first clinical symptom of SIRS is respiratory dysfunction, referred to as the acute respiratory distress syndrome (ARDS). Mortality is high especially when SIRS leads to the multiple organ dysfunction syndrome (MODS) and sepsis. At present, no therapeutic agent is known to cure ARDS, SIRS, and MODS, all three the clinical expression of an endogenously generated excessive inflammatory response. Appropriate antibiotics may eradicate the causal microorganisms during sepsis but do not prevent the development or progression of MODS in numerous patients.

The difficulty of studying SIRS and MODS patients is enormous, as they are severely ill, mostly on a ventilator in the intensive care unit (ICU), have high mortality, and belong to a heterogeneous population, including their multiplicity of problems (i.e., severe trauma, burns, pancreatitis, severe infection), age, sex, and accompanying diseases. Furthermore, understanding the pathophysiology of sepsis has been hampered by the problem of distinguishing the effects of the activation of endogenous inflammatory and immune mediators from the direct effects of bacteria and their toxins. Such distinction seems of paramount importance, as infection may be a late symptom of SIRS, whereas MODS and sepsis may persist after eradication of the causal infection. Moreover, the impossibility of consistently demonstrating the presence of bacteria or endotoxins in apparantly septic patients has led to the hypothesis of the gut as the undrained abscess and the splanchnic area as the motor of MODS. Finally, although animal models have been developed to demonstrate that SIRS and MODS can be induced by sterile proinflammatory compounds, even in germ-free animals [3], the basic problem of SIRS and MODS has not yet been solved.

For all these reasons it may be of interest to identify a human model wherein a SIRS-like syndrome develops in a restricted area, induced by a purely nonbacterial stimulus. If these signs and symptoms were present in one extremity, the contralateral extremity being normal, the patient may be his or her own control, allowing statistical analysis in a small study population. We propose the acute reflex sympathetic dystrophy syndrome (RSD) as a regional model for severe inflammation.

Acute Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD) may occur after even a minor injury to, fracture of, or operation on an extremity. Almost all publications on RSD refer to the late dystrophic or atrophic stage, whereas we are especially interested in acute RSD. With the acute phase of RSD, regional signs of inflammation are evident in the affected extremity [4], and all functions and structures of the affected area may be altered (Table 1) [4]. RSD is one of the most important causes of (probably preventable) invalidation after an extremity injury or operation. As with SIRS and MODS, no effective, causal treatment is yet known for acute RSD.

Hamburg surgeon Paul Sudeck studied this syndrome extensively. In his first publication in 1900 [5] he noted otherwise unexplained severe bone atrophy on radiographs of affected extremities. In his last publication in 1942 [6], he hypothesized that an untoward regional inflammatory response to injury causes the syndrome. Since then the inflammatory theory has been largely ignored, only to be revitalized some 40 years later by our department [7, 8].

Recent studies supporting the inflammatory theory of RSD include the dominant presence of signs and symptoms of inflam-

Table 1. Incidence of clinical signs and symptoms in 156 acute RSD patients within 2 months of onset.

Sign or symptom	Incidence (%)
Unexplained severe pain	92
Difference in skin color	97
Difference in skin temperature	98
Unexplained, obvious edema	86
Limited active range of motion	90
Increase of complaints upon exercising	98
Impossible to exercise	2
Hypesthesia	69
Hyperpathy	75
Incoordination	53
Paresis	98
(Pseudo)paralysis	2

From Veldman et al. [4], with permission.

mation in the affected area at the onset of RSD [2] (Fig. 1A), increased extravasation of indium-labeled immunoglobulin as a sign of increased capillary permeability for macromolecules [9] (Fig. 2), increased deposition of lipofuscin as a sign of oxidative stress [10] (Fig. 3), increased systemic levels of bradykinin and calcitonin gene-related peptide (CGRP) [11], and a therapeutic response to corticosteroids [12] and various oxygen radical scavengers [7, 8].

Acute RSD as a Model of Severe Regional Inflammatory Response Syndrome

Acute RSD patients generally have a diseased extremity and a healthy contralateral extremity; they are in good general health and are ambulatory, allowing studies to be done that are impossible to perform in SIRS and MODS patients. Although no single comparison is perfect, the clinical signs and symptoms, impaired skeletal muscle performance, and changes in oxygen utilization in the affected area of RSD patients have numerous similarities with what may be found on a total body scale in SIRS and MODS patients (Table 2).

Clinical Signs and Symptoms

The first impression upon comparing the aspect of the hand of a patient with acute RSD (Fig. 1A) and that of a patient with SIRS (Fig. 1B) is that there is great similarity. Both are edematous, are pink or cyanotic, and feel warm. Prominent also are skeletal muscle weakness and easy fatigability in both conditions. Whereas in acute RSD patients these signs and symptoms are localized within the affected extremity, however, in SIRS patients they are generalized. This skeletal muscle problem in the sepsis/SIRS/MODS patients may result in severe problems when weaning the patient from the ventilator due to respiratory muscle weakness, critical illness neuropathy, or both. Signs of polyneuropathy are also found in extremities of patients with RSD (Table 1), though in these cases the electromyographic (EMG) examination generally is normal. Thus, by and large, clinical signs and symptoms of acute RSD and SIRS show large areas of overlap, but the disease is localized in one limb with acute RSD but on a whole body scale with SIRS.

Arterial Blood Flow, Oxygen Utilization, Tissue Oxygenation

In well resuscitated patients with ARDS, SIRS, MODS, and sepsis, oxygen metabolism is characterized by high cardiac output and oxygen supply (DO_2), low oxygen consumption (VO_2), high mixed venous oxygen saturation, a low oxygen extraction ratio (OER), and lactic acidemia. This condition has been analyzed in terms of "supply-dependent oxygen consumption" [13], though recent studies have failed to confirm such dependence of VO_2 on DO_2 [14]. Regardless, the OER is low. "Impaired oxygen extraction" therefore may be a better denomination, as it points to the real problem, which is the inability to utilize oxygen despite an increased supply [15].

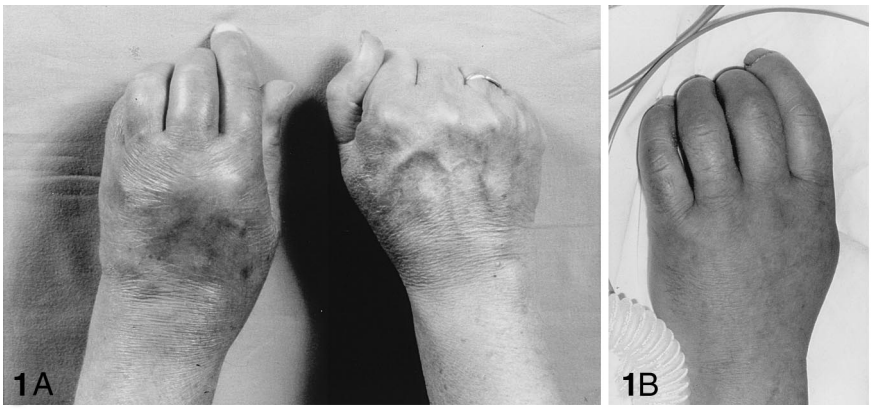
Controversy is present as to the values of tissue PO_2 in the above conditions in ICU patients. Some studies have reported low values, indicating a diffusion problem for oxygen from the erythrocytes to the mitochondria [16, 17], whereas others have reported high values, indicating a cellular defect of oxygen utilization [18]. Either mechanism can explain impaired oxygen extraction. Various experimental studies support both findings [19–22].

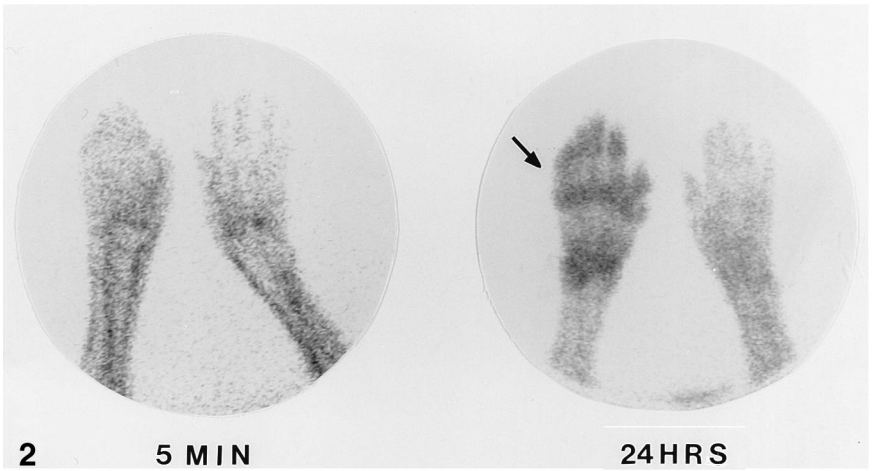
In acute RSD patients we identified a similar syndrome of impaired oxygen extraction. In eight patients with acute RSD of one upper extremity after a Colles fracture, arterial flow was assessed by the left-to-right distribution of a ^{99m}Tc-MDP tracer during the arterial flow phase. Venous blood samples were obtained from both antecubital veins for analysis of venous oxygen saturation. Arterial flow and venous oxygen saturation were significantly elevated despite severe pain and the near-impossibility of performing any muscular work with the affected extremity (Table 3).

In another series of eight patients after a Colles fracture (five with acute RSD and three patients without RSD) the antecubutal veins of both arms were retrogradely cannulated to obtain blood samples to measure gases and lactate from the deep muscular compartment. Arterial samples were obtained from the femoral artery, and flow was assessed by Doppler echocardiography. The OER in the acute RSD extremities was consistently below 0.20, $>$0.20 in the Colles control extremities, and around 0.30 in normal control extremities (Table 4). The results of the oxygen and lactate flux studies of one patient are shown in Table 5. Lactate flux was increased fourfold in the acute RSD extremity, indicating tissue hypoxia despite increased arterial flow.

It should be mentioned that this method of assessing oxygen (and metabolite) flux is subject to a number of possible methodologic errors. Indeed, arterial flow is optimally expressed in milliliters per minute, the accuracy of which is not good using a noninvasive method. Furthermore, venous blood samples are obtained for blood gas analysis via the antecubital vein, which mostly drains blood from the skin and subcutaneous tissues. Retrograde sampling from this vein provides samples from the muscular deep compartment, but it is not known what proportion of blood is drained by the deep or the superficial venous system. Interpretation of such flux studies should therefore be viewed with caution. The data obtained indicated tissue hypoxia despite supranormal arterial oxygen supply.

As mentioned before, this high arterial oxygen supply, with high mixed venous oxygen saturation and high lactate levels, are characteristic of the septic, ARDS, SIRS, and MODS patient. This odd combination of high oxygen supply and tissue hypoxia is also consistently found in areas of severe inflammation, such as in





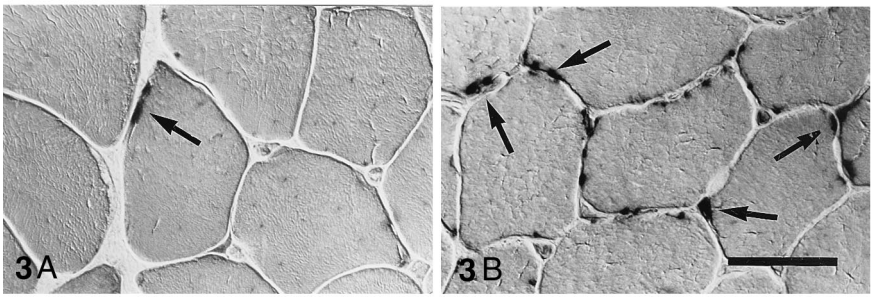


Fig. 1. A. Hand of patient with acute reflex sympathetic dystrophy. **B.** Hand of patient with SIRS.

Fig. 2. Indium-111 immunoglobulin G (^{111}In-IgG) scintigraphy of an acute RSD hand, obtained 24 hours after injection of the tracer. The affected hand shows accumulation of ^{111}In-IgG, indicating increased permeability of capillaries for large protein molecules. (From Oyen et al. [9], with permission.)

Fig. 3. Gastrocnemius biopsy obtained from a 39-year-old healthy person (**A**) and from a leg affected with RSD for 1 year from a 39-year-old patient (**B**). The dark spots show areas with increased acid phosphatase activity, representing deposits of lipofuscin. (Bar: 50 μm; acid phosphatase stain.)

joints affected by rheumatoid arthritis, in burned extremities, in varicose ulcers, around malignant tumors, in areas with an ischemia–reperfusion injury, and in diabetic feet [15]. When assessed, the Pasteur effect was found in these areas, consisting of increased glucose utilization. In the literature on varicose ulcers the above condition has been called "hyperemic hypoxia" [23].

To further assess tissue oxygenation, we performed phosphorus nuclear magnetic resonance (P-NMR) analysis of the calf-muscles in patients with severe RSD in one lower extremity. P-NMR spectroscopy allows noninvasive assessment of inorganic phosphate (P_i) and high-energy phosphorus compounds such as adenosine triphosphate (ATP) and phosphocreatine (PCr). At rest, P_i/PCr ratios in RSD extremities were abnormally high (0.24 ± 0.02 vs. 0.13 ± 0.02 in the healthy limb) [24]. As phosphocreatine is synthesized from creatine and inorganic phosphate in an oxygen-dependent step, this finding indicates a lack of oxygen at the mitochondrial level. In a patient with moderate RSD of one hand, assessment in a 6.3-tesla NMR device demonstrated early, profound depletion of PCr and a dramatic increase in inorganic phosphate upon modest muscular work compared to the healthy hand (Fig. 4). Performing P-NMR spectroscopy in septic ICU patients is fraught with technical problems, and few experimental data are available [25].

Therapeutic Efforts to Improve Oxygen Utilization

In ARDS, SIRS, MODS, and sepsis patients, current ICU treatment includes optimizing the DO_2 to increase VO_2. Even supranormal levels of DO_2 have been propagated [26], though these levels have not been demonstrated to improve survival.

With RSD, sympathetic blockade is still widely utilized, though no therapeutic effect could be demonstrated in double-blind placebo-controlled studies [27–29]. Although sympathetic blockade increases limb arterial flow and venous oxygen saturation,

Table 2. SIRS versus acute RSD: clinical signs and symptoms, condition of patient, and oxygen transport.

SIRS	Acute RSD
Clinical signs and symptoms	
Generalized vasodilatation	Regional vasodilatation
Generalized permeability edema	Regional permeability edema
Impairment of eventually all organ functions	Impairment of eventually all extremity functions
Skeletal and respiratory muscle weakness	Skeletal muscle weakness
Easy skeletal muscle fatigability	Easy skeletal muscle fatigability
Eventually self-perpetuating	Eventually self-perpetuating
Condition of patient	
On ventilator in ICU	Ambulatory
30% Mortality	No mortality
Control population?	Healthy control extremity
Oxygen metabolism	
High cardiac output	High arterial flow to area
Low oxygen consumption	Low oxygen consumption in area
High systemic lactate	High lactate flux in area
Tissue hypoxia?	Tissue hypoxia

Table 3. Venous oxygen saturation and arterial blood flow distribution in healthy versus acute RSD upper extremities ($n = 8$).

Parameter	RSD	Healthy	Difference	p
SvO_2 (%)	86.5	68.7	17.8 ± 4.6	<0.001
Arterial flow (%)	69.4 ± 7.4	30.6 ± 3.1		<0.001

SvO_2: venous oxygen saturation.

limb VO_2 and transcutaneous PO_2 is not increased [30]. Thus in both the systemic and the regional inflammatory response syndromes it seems that increasing VO_2 does not solve the problem.

Another approach is to improve oxygen extraction. In a series of eight patients with acute severe RSD after a Colles fracture, we demonstrated that arterial flow and venous oxygen saturation significantly decreased after 1 week of low-dose (100 g/day IV) mannitol, and the clinical signs and symptoms of inflammation were significantly alleviated (Table 4). Apparently the oxygen radical scavenger mannitol was able to influence the inflammatory signs and the impaired oxygen extraction.

The corollary to this finding is found in the work of S Powers' group, who demonstrated that in ARDS patients arterial oxygenation is improved by intravenous mannitol, because it improves pulmonary oxygen diffusion [31]. Bernard reported that in ARDS patients oxygen extraction and consumption is improved by intravenous administration of the radical scavenger *N*-acetylcysteine [32]. In patients with fulminant hepatic failure caused by acetaminophen intoxication, intravenous *N*-acetylcysteine increased the DO_2 (from 856 to 975 ml/min/m^2) and VO_2 (from 127 to 184 ml/min/m^2); the OER increased from 0.16 to 0.21 [33]. Acetaminophen intoxication is caused by failure of the oxygen detoxification mechanisms, especially depletion of glutathione. Administration of *N*-acetylcysteine replenishes thiol groups, required for the synthesis of glutathione, thereby apparently contributing to the repair of oxygen extraction processes.

Thus SIRS, sepsis, MODS, and acute RSD patients have in common clinical signs of severe inflammation and an odd syndrome of impaired oxygen utilization. This combination of high arterial blood supply and low tissue oxygen availability has also been found in areas with severe inflammation (for review see [15]). Increasing the oxygen supply has not been demonstrated to improve the outcome of patients with SIRS or acute RSD. Efforts resulting in improved oxygen extraction have been more successful.

Table 4. Lactate flux study in a 52-year-old woman with acute RSD of the right hand.

Parameter	Right hand (RSD)	Left hand (normal)
Arterial flow (ml/min)	160	125
Oxygen extraction fraction	0.19	0.31
Oxygen consumption (ml/min)	30.4	39.0
Venous lactate (ml/L)	1172	783
Arterial lactate (ml/L)	630	630
Lactate flux (ml/min)	86.7	19.1

Table 5. Venous oxygen saturation and arterial blood flow distribution in acute RSD of upper extremities before and after 1 week of low-dose intravenous mannitol ($n = 8$).

Parameter	Before	After	Difference	p
SvO_2 (%)	86.5	80.1	6.4 ± 2.8	<0.01
Arterial flow (%)	69.4 ± 7.4	62.9 ± 5.6	6.5 ± 4.9	0.012

SvO_2: venous oxygen saturation.

Hypothesis

It is hypothesized that the special situation of acute RSD patients, with a healthy extremity and a contralateral diseased extremity may provide opportunities to study more in detail the causes and effects of severe inflammatory responses to injury and infection. Such studies may contribute to an improved outcome for both conditions.

Résumé

Le syndrome de réponse inflammatoire systémique (SIRS) et le syndrome de dystrophie sympathique réflexe aigu (ARSD) ont en commun des signes cliniques d'inflammation sévère, une évolution prolongée et un problème d'utilisation défectueuse d'oxygène. Alors que chez les premiers (SIRS) ces signes sont systémiques dans un contexte grave généralisé, chez les seconds (ARSD), les problèmes sont limités à une extrémité chez un sujet en bonne santé. Dans les deux cas, cependant, la pathologie résulte d'une réponse inflammatoire exagérée. Comme les patients ARSD ont une deuxième extrémité saine, ils peuvent servir comme leur propres contrôles dans les études de débit. On émet l'hypothèse que cette situation pourrait étre propice à l'etude de la pathophysiologie de la réponse inflammatorie sévère chez l'homme. Même si peu de patients sont nécessaires pour effectuer les études sur le métabolisme de l'oxygène, sur les cytokines ou sur la production de radicaux libres, on a besoin également de méthodes telles la spectroscopie par RMN, mais qui ne peut pas étre réalisée facilement chez les patients en soins intensifs.

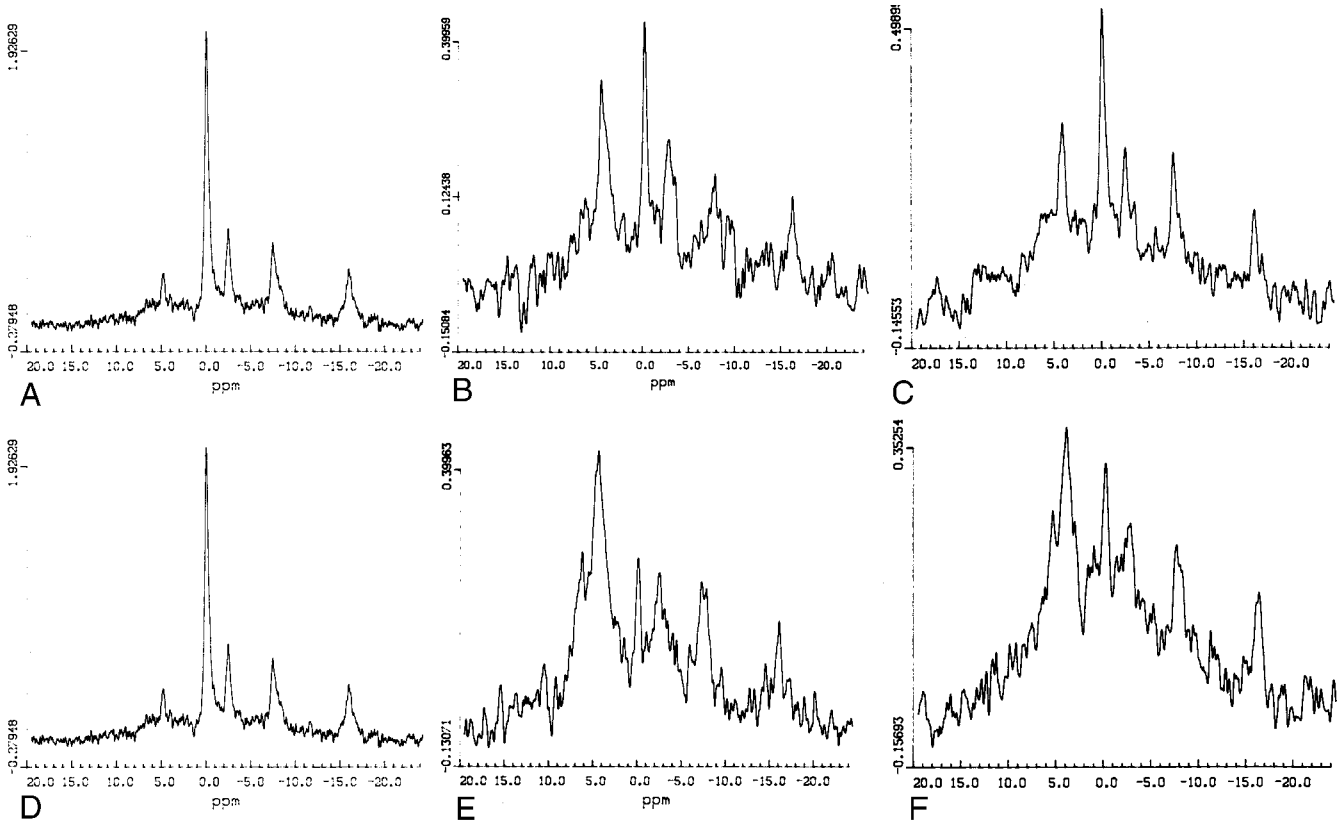


Fig. 4. P-NMR spectroscopy of a healthy hand (**A, B, C**) and an RSD-affected hand (**D, E, F**) from a 21-year-old patient before exercise (**A**), directly after exercise (**B, E**), and after a 2-minute resting period (**C, F**). The first peak is inorganic phosphate, the second is phosphocreatine (PCr), and the three following peaks are ATP. The patient apparantly stopped exercising the affected hand upon depletion of PCr (**E**) but before the ATP levels changed. The return to normal was slower in the RSD-affected hand (**F**).

Resumen

El Síndrome de Respuesta Inflamatoria Sistémica (SRIS) y el Síndrome de Distrofia Simpática Refleja Aguda (DSRA) comparten signos clínicos de inflamación severa, una evolución tórpida y problemas similares de alteración de la oxigenación. La diferencia reside en que los pacientes con SRIS exhiben tales signos y síntomas en forma sistémica y se encuentran gravemente enfermos en una unidad de cuidado intensivo, en tanto que aquellos con DSRA se mantienen en buen estado de salud y sus problemas se limitan a una extremidad. Ambas entidades parecen ser el resultado de una respuesta inflamatoria exagerada. Por cuanto el paciente con DSRA tiene la extremidad contralateral normal, él mismo puede servir como control en estudios de flujo. Formulamos la hipótesis de que esta situación es particularmente adecuada para la realización de estudios, por ejemplo, de metabolismo del oxígeno o de producción de citocinas o de radicales de oxígeno. Asímismo, también pueden utilizarse métodos de evaluación tales como espectroscopia de RNM, los cuales no son fácilmente aplicables a los pacientes en las unidades de cuidado intensivo.

Acknowledgments

The data presented were obtained thanks to the dedicated contributions of Y. Arntz, M.D., L. van Dongen, M.D., Ph.D., A. Heerschap, M.Ph., L. van der Laan, M.D., L. Leenen, M.D., Ph.D., W. Oyen, M.D., Ph.D., H. Reijnen, M.D., Ph.D., H. ter Laak, M.D., Ph.D., and P. Veldman, M.D., Ph.D.

References

1. Goris, R.J.A., te Boekhorst, T.P.A., Nuytinck, J.K.S., Gimbrère, J.S.F.: Multiple organ failure: generalized autodestructive inflammation? Arch. Surg. *120*:1099, 1985
2. ACCP/SCCM Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit. Care Med. *20*:864, 1992
3. Goris, R.J.A., Boekholtz, W.K.F., van Bebber, I.P.T., Schillings, P.H.M., Schuurmans-Stekhoven, J.H.: Multiple organ failure without bacteria: an experimental model. Arch. Surg. *121*:987, 1986
4. Veldman, P.H.J.M., Reynen, H.M., Arntz, I.E., Goris, R.J.A.: Signs and symptoms of reflex sympathetic dystrophy: a prospective study of 829 patients. Lancet *342*:1012, 1993
5. Sudeck, P.: Über die acute entzündliche Knochenatrophie. Arch. Klin. Chir. *62*:147, 1900
6. Sudeck, P.: Die sogen: acute Knochenatrophie als Entzündungsvorgang. Chirurg *15*:449, 1942
7. Goris, R.J.A.: Treatment of reflex sympathetic dystrophy with hydroxyl radical scavengers. Unfallchirurg *88*:330, 1985
8. Goris, R.J.A., Dongen, L.M., Winters, H.A.H.: Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy? Free Radic. Res. Commun. *3*:13, 1987
9. Oyen, W.J.G., Arntz, I.E., Claessens, A.M.J., van der Meer, J.W.M., Corstens, F.H.M., Goris, R.J.A.: Reflex sympathetic dystrophy of the hand: an excessive inflammatory response? Pain *55*:151, 1993
10. Tilman, P.B.J., Stadhouders, A.M., Jap, P.H.K., Goris, R.J.A.: His-

topathologic findings in skeletal muscle tissue of patients suffering from reflex sympathetic dystrophy. Micron Microsc. Acta *21*:271, 1990
11. Blair, S.J.: Role of neuropeptides in the pathogenesis of reflex sympathetic dystrophy. In Program and Abstracts of Symposium on Reflex Sympathetic Dystrophy. Brussels, 1996, p. 8
12. Christensen, K., Jensen, E.M.K., Noer, I.: The reflex sympathetic dystrophy syndrome: response to treatment with systemic corticosteroids. Acta Chir. Scand. *148*:653, 1982
13. Shumacker, P.T., Cain, S.M.: The concept of a critical oxygen delivery. Intensive Care Med. *13*:223, 1987
14. Ronco, J.J., Fenwick, J.C., Tweeddale, M.G., Wiggs, B.R., Phang, P.T., Cooper, D.J., Cunningham, K.F., Russell, J.A., Walley, K.R.: Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. J.A.M.A. *270*:1724, 1993
15. Goris, R.J.A.: Conditions associated with impaired oxygen extraction. In Tissue Oxygen Utilisation, G. Gutierrez, J.L. Vincent, editors. Berlin, Springer, 1991, pp. 350–369
16. Beerthuijzen, G.I.J.M., Goris, R.J.A., Kreuzer, F.J.A.: Early detection of shock in critically ill patients by skeletal muscle pO_2 assessment. Arch. Surg. *124*:853, 1989
17. Beerthuijzen, G.I.J.M., Goris, R.J.A.: Is skeletal muscle pO_2 related to the severiry of multiple organ failure? Prog. Clin. Biol. Res. *308*:137, 1998
18. Boekstegers, P., Weidenhöfer, S., Pilz, G., Werdan, K.: Peripheral oxygen availability within skeletal muscle in sepsis and septic shock: comparison to limited infection and cardiogenic shock. Infection *19*:317, 1991
19. Beerthuijzen, G.I.J.M., Goris, R.J.A., Kreuzer, F.J.A.: Skeletal muscle pO_2 during imminent shock. Arch. Emerg. Med. *6*:172, 1989
20. Fry, D.E., Silver, B.B., Rink, R.D., Van Arsdall, L.R., Flint, L.M.: Hepatic cellular hypoxia in murine peritonitis. Surgery *85*:652, 1979
21. Mela, L., Bacalco, L.V., Miller, L.D.: Defective oxidative metabolism of rat liver mitochondria in hemorrhaghic and endotoxin shock. Am. J. Physiol. *220*:571, 1971
22. Clemens, M., Chaudry, I.H., Baue, A.E.: Oxidative capability of hepatic tissue in late sepsis. Adv. Shock Res. *6*:55, 1981
23. Partsch, H.: Hyperaemic hypoxia in venous ulceration. Br. J. Dermatol. *110*:249, 1984
24. Jacobs, D.O., Maris, J., Fried, R., Settle, R.G., Rolandelli, R.R., Koruda, M.J., Chance, B., Rombeau, J.L.: In vivo phosphorus 31 magnetic resonance spectroscopy of rat hind limb skeletal muscle during sepsis. Arch. Surg. *123*:1425, 1988
25. Heerschap, A., den Hollander, J.A., Reynen, H.M., Goris, R.J.A.: Metabolic changes in reflex sympathetic dystrophy: a ^{31}P NMR spectroscopy study. Muscle Nerve *16*:363, 1993
26. Shoemaker, W.C., Appel, P.L., Kram, H.B., Waxman, K., Lee, T.: Prospective trial of supranormal values of survivors as a therapeutic goal in high risk surgical patients. Chest *94*:1176, 1988
27. Jadad, A.R., Caroll, D., Glynn, C.J., McQuay, H.J.: Intravenous regional sympathetic block for pain relief in reflex sympathetic dystrophy: a systemic review and a randomized double blind crossover study. J. Pain Manage. *10*:13, 1995
28. Blanchard, J., Ramamurthy, S., Walsh, N., Hoffman, J., Schoenfeld, L.: Intravenous regional sympatholysis: a double-blind comparison of guanethidine, reserpine, and normal saline. J. Pain Symptom Manage. *5*:357, 1990
29. Ramamurthy, S., Hoffman, J.: Intravenous regional guanethidine in the treatment of reflex sympathetic dystrophy/causalgia: a double-blind study. Guanethidine Study Group. Anesth. Analg. *81*:718, 1995
30. Brothers, T.E., Wakefield, T.W., Jacobs, L.A., Lindenauer, S.M.: Effects of lumbar sympathectomy on canine transcutaneous oxygen tension. Surgery *113*:433, 1993
31. Rhodes, G.R., Newell, J.C., Shah, D., Scovill, W.A., Tauber, J., Dutton, R.E., Powers, S.R.: Increased oxygen consumption accompanying increased oxygen delivery with hypertonic mannitol infusion in adult respiratory distress syndrome. Surgery *84*:490, 1978
32. Bernard, J.R.: N-Acetylcysteine in experimental and clinical acute lung injury. Am. J. Med. *91*(Suppl.3c):54, 1991
33. Harrison, P.M., Wendon, J.A., Gimson, A.E.S., Alexander, G.J.M., Williams, R.: Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N. Engl. J. Med. *324*:1852, 1991