Exaggerated Vasoconstriction in Complex Regional Pain Syndrome-1 Is Associated with Impaired Resistance Artery Endothelial Function and Local Vascular Reflexes

LIOR DAYAN, SERGEI SALMAN, DORON NORMAN, JEAN-JACQUE VATINE, EDWARD CALIF, and GIRIS JACOB

ABSTRACT. ***Objective.*** Local regulatory mechanisms and microvascular function play a major role in the pathogenesis of hemodynamic and trophic changes in patients with complex regional pain syndrome-1 (CRPS). Venoarteriolar and venoarteriolar-myogenic reflexes (VAR, VMR, respectively) as well as endothelial-dependent vasodilatation are important contributors to local vasoregulation. We examined whether VAR and VMR as well as resistance artery endothelial function are damaged in affected limbs of patients with CRPS.

Methods. We measured reactive hyperemic response as an index of resistance artery endothelial function, VAR and VMR in extremity soft-tissue vasculature in patients with CRPS.

Results. Baseline blood flow values were not different between CRPS affected and unaffected upper and lower limbs. Resistance artery endothelial function indices, i.e., values of maximal flow after ischemia and the area under the flow-time curve (AUC), were significantly higher in the unaffected versus CRPS-affected upper limbs (19 ± 3 vs 16 ± 3 ml*min^{-1}*dl^{-1} and 373 ± 71 vs 319 ± 70 units, for maximal flow AUC, respectively) and lower limbs (9 ± 2 vs 6 ± 1.5 ml*min^{-1}*dl^{-1} and 160 ± 51 vs 130 ± 42 units, for maximal flow and AUC, respectively). Flow indices reflecting VAR were lower in the lower, but not upper CRPS-affected limbs compared with unaffected contralaterals (2 ± 0.24 vs 1.55 ± 0.3 ml*min^{-1}*dl^{-1}; p = 0.027). Microvascular myogenic reflex-VMR indices, however, were not different in the upper or in the lower CRPS-affected limbs compared with their unaffected contralaterals.

Conclusion. Impaired balance exists in CRPS-affected limbs between vascular regulation systems responsible for vasoconstriction and vasodilation. (First Release May 1 2008; J Rheumatol 2008; 35:1339–45)

Key Indexing Terms:
COMPLEX REGIONAL PAIN SYNDROME
ENDOTHELIAL FUNCTION
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Complex regional pain syndrome-1 (CRPS) is a condition affecting the limbs, typically occurring after trauma (sometimes minimal) and characterized by severe pain, allodynia, edema, and motor dysfunction associated with autonomic and vascular changes. The formal criteria of the International Association for the Study of Pain (IASP) include the presence of an initiating noxious event, continuing pain disproportionate to the inciting event, evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the affected area, and the absence of any coexisting condition that might otherwise account for the symptoms[1].

Numerous hypotheses have been proposed to explain the features of CRPS[2-4]. Whatever the pathogenesis of the condition, there is no doubt that local vasomotor changes play a pivotal role in the disease pathogenesis and symptomatology[4,5].

Blood flow abnormalities in CRPS are, at least in part, due to vascular adrenergic receptor hypersensitivity following an initial period of reduced sympathetic input[4,5]. Sympathetic overactivation leads to increased vasoconstriction and a reduction in local blood flow, which also contributes to the hyperalgesia[6]. Increased vasoconstriction, due also to other mechanisms, is likely to happen in skin as well as other tissues, particularly in deep somatic domains such

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as bone, muscle, or joints, which contribute to the pain in CRPS[6-8]. Malfunction of local vascular regulatory mechanisms seems to be involved in the pathogenesis of the disturbed hemodynamics, trophic changes, and pain generation in CRPS-affected limbs.

Several mechanisms have been suggested to explain the venoarteriolar reflexes (VAR) and venoarteriolar-myogenic reflexes (VMR). While venous congestion elicits adjacent arteriolar constriction in the VAR, intrinsic myogenic stretch reflex causes vasoconstriction in the VMR. Since both reflexes depend on local sympathetic activation, among other things, we hypothesized that they might be altered in affected limbs of patients with CRPS compared with the unaffected contralaterals. To investigate the hypothesis, we measured reactive hyperemic response as an index of resistance artery endothelial function, VAR, and VMR in the extremities of patients with CRPS.

MATERIALS AND METHODS

Subjects. A group of 17 patients with a history of trauma to only one of their limbs (8 in the upper, 9 in the lower) that developed CRPS-1 (diagnosis according to IASP criteria) were recruited from the local pain clinic and Reuth Medical Center, which specializes in multidisciplinary treatment of CRPS, where they were diagnosed and followed by a pain medicine specialist.

Inclusion and exclusion criteria. Inclusion criteria included: (1) patients with no known serious medical conditions, taking no medications affecting the autonomic nervous system; (2) patients must be able to discontinue medications that might interfere with measurements in a way that will not harm their health. Exclusion criteria included: (1) Unresolved musculoskeletal injury (non-union, malunion). (2) Clinical evidence for peripheral vascular disease. (3) Debilitating diseases such as endstage renal failure, congestive heart failure (New York Heart Association Class > I), and ischemic heart disease (Canadian Cardiovascular Society Class > I). (4) Use of essential drugs that might affect resistance artery endothelial function (i.e., angiotensin-converting enzyme inhibitors, beta-blockers). (5) Inability to withstand pain caused by the examination (i.e., cuff occlusion, prolonged supine lying, limb hanging, etc.).

Time since trauma that preceded the CRPS ranged from 13 to 23 months. All patients recalled periods of severe exacerbation in hyperalgesia and vasomotor changes in the recent past, yet reported some remission at the time the experiments were undertaken.

In addition, a group of 10 age-matched healthy subjects was recruited. Baseline blood flow of both upper limbs served as a control measure.

All studies were performed in a quiet darkened room with ambient temperature ~24°C following an overnight fast, at the Recanati Autonomic Dysfunction Center, Rambam Medical Center. No smoking or alcoholic and monoamine containing beverages were allowed during the last 12 hours prior to the study. Drugs were discontinued for at least 5 $t_{1/2}$. All subjects signed an informed consent form approved by the local Institutional Review Board for Helsinki.

Reactive hyperemia

Forearm and leg vasculature study. A sphygmomanometer cuff was applied to the right arm and inflated to 45 mm Hg for 7 s to prevent venous egress. During this period forearm volume changes per time (correlates with blood flow changes) were measured by strain-gauge plethysmography (ECR5; D.E. Hokanson Inc., Bellevue, WA, USA). A 7-s deflation was allowed before the following measurement. The cutaneous flow of the hand or ankle was excluded by inflating a wrist cuff to a level greater than systolic blood pressure. Baseline forearm blood flow was the average of at least 4 stable repeated flow measurements (Figure 1A).

Reactive hyperemia was induced by a pneumatic cuff (S300 Aneroid sphygmomanometer; D.E. Hokanson Inc.) placed above the sphygmomanometer cuff, which was inflated to greater than systolic pressure for 5 min. A rapid deflation was then allowed and a series of post-ischemic forearm blood flow measurements was performed as described. These sequences of flow measurements were shown to be correlated with resistance artery endothelial function (Figure 1B)[9,10].

VAR and VMR response. Two types of VAR can be assessed, as described[11]. (1) Pure VAR — A cuff is inflated to a steady pressure of 40 mm Hg for 4 min to produce venous congestion and causes a reflexive regional arteriolar vasoconstriction. The reduced blood flow is then measured by intermittently inflating a second surrounding cuff to 70 mm Hg. This additional inflation was shown to be sufficient to provide additional transient venous occlusion to measure blood flow. (2) Venoarteriolar and myogenic response (VMR) — With the subject in supine position (to avoid systemic baroreflex changes), blood flow was measured during 40-cm dependency of the leg or forearm below cardiac level for 4 min. It activates in parallel the myogenic responses by increasing arterial wall pressure, and venoarteriolar response by gravitationally increasing venous pressure. Blood flow is then measured by strain-gauge plethysmography. VMR activation results in local vasoconstriction and reduced blood flow.

We assumed that minute-to-minute blood pressure changes were equal for both limbs under examination during the entire measurement. Accordingly, changes in blood flow accurately reflect the changes in arterial resistance since the arterial resistance is correlated with blood flow and blood pressure.

Calculations and statistical analysis. Data are presented as mean ± SEM. The Wilcoxon matched-paired test was used to compare affected and unaffected limbs. Statistical significance was set at $p < 0.05$. Data were analyzed using Excel (Microsoft, Redmond, WA, USA) and GraphPad Prism (version 4.03; GraphPad Software, San Diego, CA, USA). The acceptable approach for evaluating changes in flow after ischemic cessation is to consider the parameters of area under the flow-time curve (AUC) and maximal flow increments compared with basal flow. The post-ischemic highest blood flow (maximal flow) and the AUC of the reactive hyperemia response were calculated and considered indexes of forearm endothelial function.

RESULTS

General characteristics and management modalities (i.e., primary intervention at the time of the injury that elicited the CRPS) and current medications for pain control are shown in Table 1. Representative results for blood flow measurements are shown in Figure 1.

Although not statistically significantly different, blood flow in the CRPS-affected upper limbs tended to be slightly higher than in the nonaffected contralaterals (Figure 2, top). To examine this finding, we took a group of 10 healthy, age-matched subjects and compared blood flows of both upper limbs with those of our subjects. The results (unaffected upper limb 3.813 ± 0.55; CRPS-affected upper limb 4.249 ± 0.50 $ml*min^{-1}*dl^{-1}$; healthy subjects' right upper limb 5.174 ± 0.49, healthy subjects' left upper limb 4.414 ± 0.57 $ml*min^{-1}*dl^{-1}$) showed no statistical difference between the groups (one-way ANOVA and post-hoc Tukey test to compare all pairs of columns).

Endothelial function indices, i.e., maximal flow after ischemia and the area under the flow-time curve (AUC), were significantly higher in the unaffected compared to CRPS-affected upper limbs (19 ± 3 vs 16 ± 3 $ml*min^{-1}*dl^{-1}$ for maximal flow and 373 ± 71 vs 319 ± 70 units for AUC)

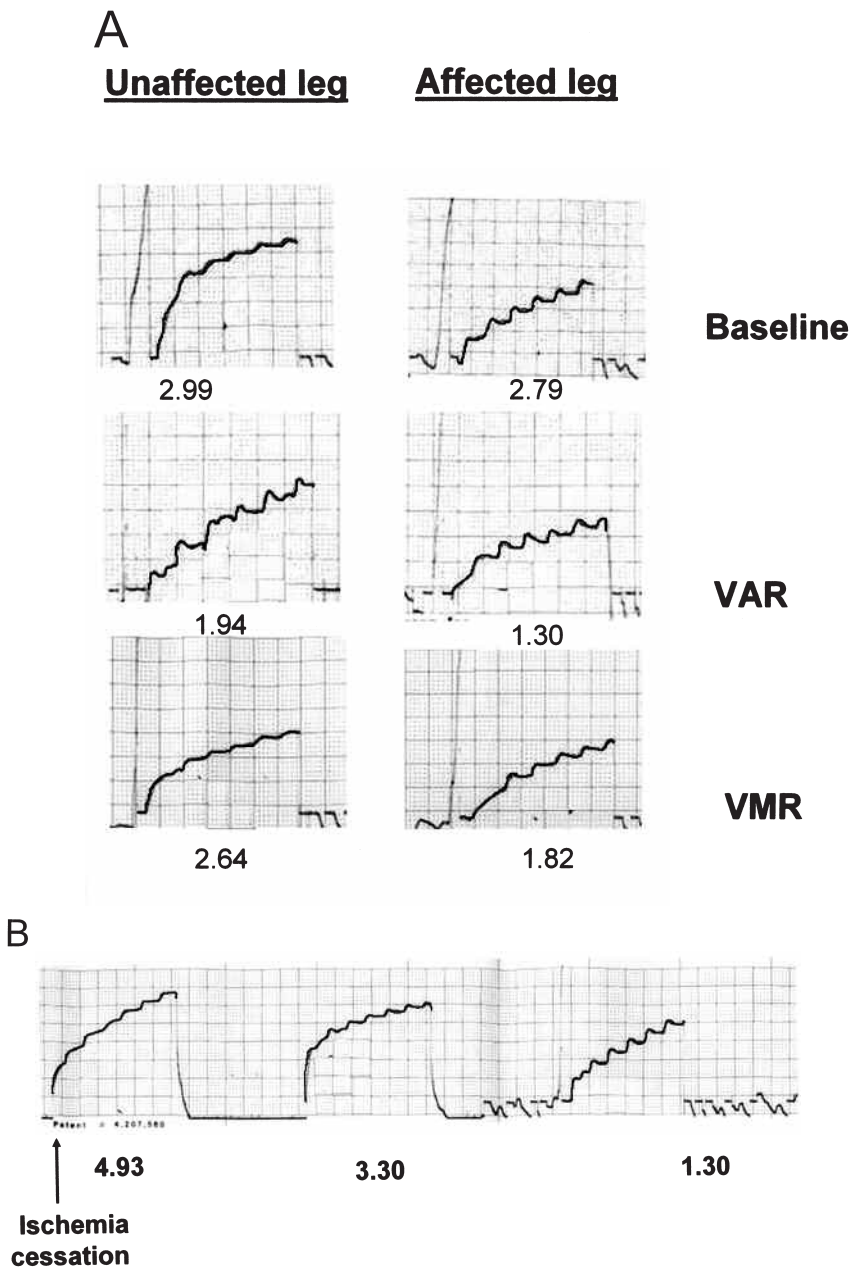

Figure 1. Measurement of changes in leg circumference by venous occlusion plethysmography. Leg blood flow is calculated as the ratio of the rate of increase in leg circumference (slope of the curve) to the calibration (i.e., reading sensitivity) and is expressed as ml/min/100 ml leg volume. The reading sensitivity is adjusted ad-hoc per each reading. A. Results of baseline, VAR, and VMR measurements. B. Results of postischemic hyperemia: 3 consecutive readings from the leg of the same subject; note the decrease in blood flow. In this case, the maximal flow was taken as the first reading after cessation of ischemia.

and lower limbs (9 ± 2 vs 6 ± 1.5 ml*min^{-1}*dl^{-1} for maximal flow and 160 ± 51 vs 130 ± 42 units for AUC) (Figure 2, middle and lower panels).

Flow responses to VAR were lower in the lower limbs, but not the upper CRPS limbs compared with their unaffected contralaterals (Figure 2). Activation of VAR caused significantly exaggerated vasoconstriction (expressed as decrease in blood flow following venous congestion) in the CRPS-affected lower, but not upper, limbs, compared with their unaffected contralaterals (2 ± 0.24 vs 1.55 ± 0.3 ml*min^{-1}*dl^{-1}; p = 0.027; Figure 3, upper panels). Blood flows in response to VMR, however, were not different in the upper or in the lower CRPS-affected limbs compared with their unaffected contralaterals (Figure 3, lower panels).

Table 1. Patients' general characteristics.

Characteristic	Upper Limb, n = 8	Lower Limb, n = 9
Age, yrs	50 ± 3	43 ± 4
Female, n	3	4
Symptom duration, mo	40 ± 12	46 ± 110
Height, cm	171 ± 3	173 ± 2
Weight, kg	73 ± 5	83 ± 5
Systolic BP, mmHg	115 ± 5	135 ± 5
Diastolic BP, mmHg	75 ± 3.8	83 ± 3
Heart rate, beats/min	71 ± 4	72 ± 4
Primary injury	Fracture of distal radius (4) Fracture of head of radius (1) Fracture of scaphoid (3)	Ankle sprain (2) Ankle fracture (2) Fracture of calcaneus (2) Fracture of Tibia (2)
Management of primary injury	ORIF (2) Cast (6)	ORIF (4) Cast (2) RICE (2)
Medications	NSAID (8) BDZ (1) Opiates (1) TCA (1)	NSAID (8) BDZ (2) Opiates (1) TCA (2)

BP: blood pressure; ORIF: open reduction and internal fixation; NSAID: nonsteroidal antiinflammatory drug; RICE: rest, ice, compression, and elevation, BDZ: benzodiazepines; TCA: tricyclic antidepressants.

DISCUSSION

Our study revealed that affected limbs of patients with CRPS-1 have impaired resistance artery endothelial-dependent dilation function, along with exaggerated arteriolar vasoconstriction following activation of the venoarteriolar reflex (VAR). This in the setting of preserved microvascular myogenic reflex (VMR).

The arterial endothelium plays a crucial role in vascular tone regulation by the release of vasoactive substances, including nitric oxide (NO)[13]. Endothelial dysfunction results in impaired vasodilation. The method we used to assess endothelial function was postischemic reactive hyperemia; this method was shown to be suitable for measurement of resistance artery endothelial function (which, in contrast with conduit arteries, is not exclusively NO-dependent) when only the second and third rather than the first readings after the cessation of ischemia are taken into account[10,14]. Higashi and Yoshizumi, however, demonstrated that the peak forearm blood flow in response to reactive hyperemia is almost identical to the forearm blood flow in response to acetylcholine, which is an endothelial-dependent vasodilator[9,14]. We took both peak flow after cessation of ischemia and the area under the flow-time curve as measures of reactive hyperemia to cover both aspects of the debate. Studying the reactive hyperemic response allowed us to assess endothelial function in resistance arteries, which are known to be affected in CRPS. In agreement with Schattschneider, *et al*[15], we suggest the possibility that the local impairment in endothelial function in CRPS-affected limbs might be related to free radical production. Free radicals are known to damage the endothelium; thus endothelial dysfunction may result from decreased production or inactivation of NO by oxygen-derived free radicals[16,17]. It has been demonstrated that free radical infusion produces CRPS-like symptoms in a rat model[18]. Accordingly, treatment with free radical scavengers reduced the risk of developing CRPS[19] and helped to relieve symptoms[20]. This assumption is limited by the fact that we did not measure free radicals in our patients at the period between the traumatic event and development of CRPS.

We also showed that VAR, but not VMR, is overwhelmed in the affected lower, but not upper, limbs compared with their unaffected contralaterals. We explain these findings with the notion that while VAR is a response that depends mostly upon intact local autonomic nervous system functions[21], VMR is an inherent arteriolar-muscle constriction reflex in response to dilatation that depends on intrinsic cellular mechanisms (e.g., the epithelial Na+ channel, EnaC, mechanosensitive ion channels[22]), and thus seems to be independent of neural transmission. Thus, impaired VAR and intact VMR might reflect the adrenergic hypersensitivity that exists in lower limbs in those with CRPS. Few theories exist that explain the adrenergic hypersensitivity in CRPS; one is that following an injury there is a sprouting of postganglionic sympathetic nerve fibers, as well as variable up- or down-regulation of adrenoceptor subtypes[23,24].

Whether it is a component of the injury (i.e., crush or shear) or a consequence of the injury that causes the adrenergic hypersensitivity (e.g., impaired central regulation) is unclear. Sympathetic innervation is one of the regulatory

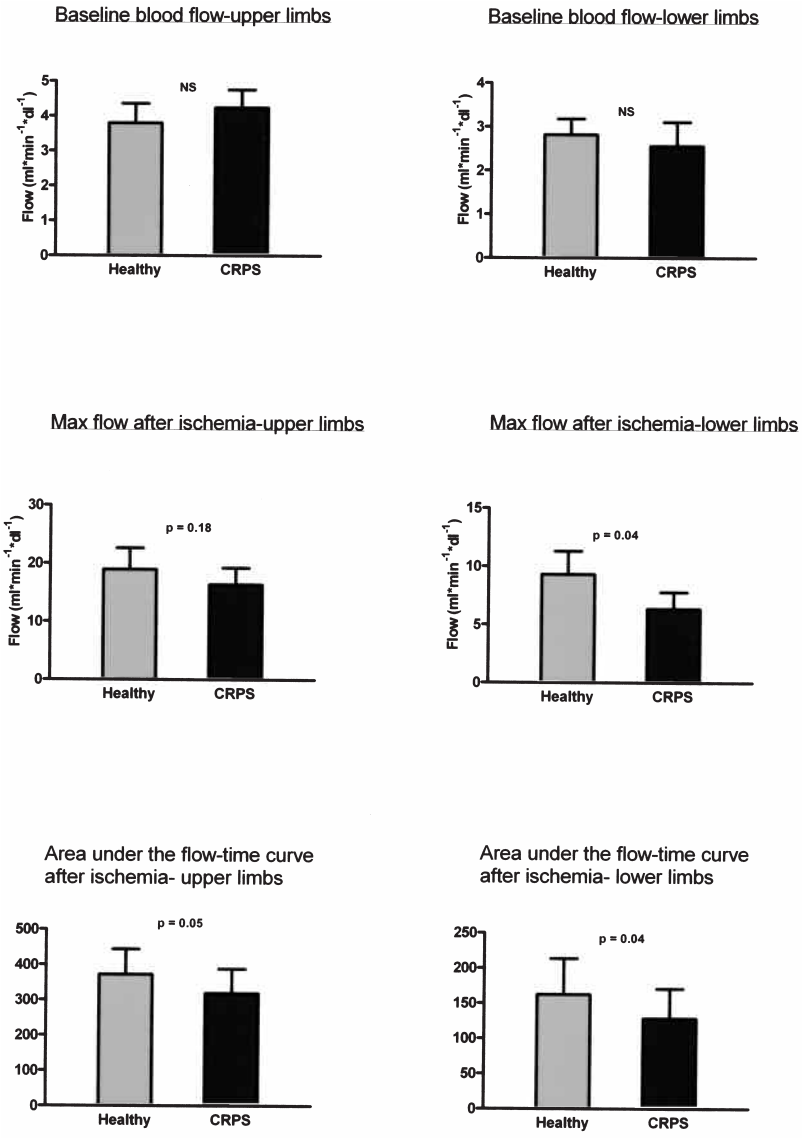

Figure 2. Blood flow characteristics in the upper and lower limbs (left and right columns, respectively): baseline flow (upper 2 panels), maximal flow after ischemia (middle 2 panels), and the area under the flow-time curve after ischemia (lower 2 panels). NS: nonsignificant.

systems responsible for constriction and dilatation in any vascular bed. The endothelium acts to oppose vasoconstriction. Our findings point out that disruption in this cross-talking exists in CRPS-affected limbs, and impaired VAR and vasodilatory endothelial function results in exaggerated vasoconstriction, unopposed by adequate vasodilatory compensation.

Impaired VAR thus might be the result of the local changes that occur in soft tissue of CRPS-affected limbs. Blood flow following induction of the VAR was found to be different between affected and unaffected lower, but not upper, limbs. The reason for this might be that while vasoregulatory reflexes, among them VAR, are well developed in the lower extremities (in order to allow prolonged standing capability by preventing blood pooling and blood pressure drop), their role in the upper extremities might be of marginal physiologic importance[25].

Baseline blood flow, on the other hand, was not found to be significantly different between CRPS-affected and unaffected limbs and healthy subjects' upper limbs. The reason might be that all measurements were taken in a resting supine position, where regulation mechanisms are quiescent. This might support our theory that it is the regulatory mechanisms that are affected in CRPS, since these mechanisms act in changes of posture. Indeed, from clinical observations, many patients pay attention to vasogenic changes during posture changes.

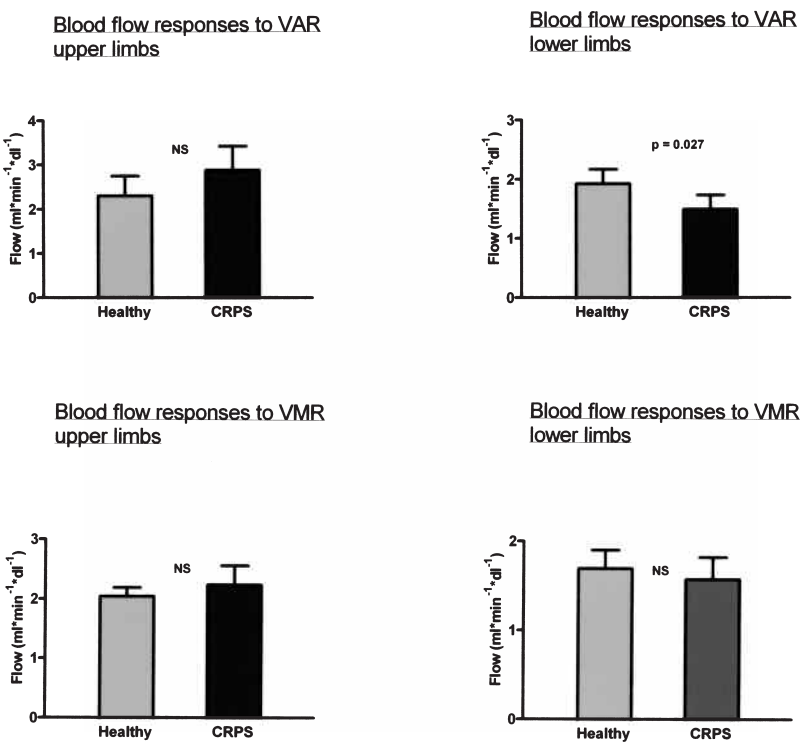

Figure 3. Blood flow responses to reflexes (VAR, upper 2 panels; VMR, lower 2 panels) in the upper limbs (left) and lower limbs (right).

In line with our observations, we believe that CRPS is a result of local injury and its consequences. Yet we are unable to conclude whether there is predisposition of a limb to develop CRPS. We believe that the initializing injury and its treatment patterns might determine whether CRPS will develop in a given limb. Patients with apparently similar injury on radiographs might sustain totally different soft-tissue damage, comply differently with the treatment regimen according to their pain perception (e.g., early mobilization), and undergo different although apparently similar treatment (e.g., tight or loose casting technique). These factors, we believe, eventually determine the path for development of CRPS.

The limitations of our study are as follows. (1) We compared one limb with its counterpart rather than with a normal subject's limb. Although one cannot assume normalcy of the contralateral limb, the fact that CRPS tends to affect only one limb might indicate that local rather than systemic effectors dominate its pathogenesis. Another reason we used same-subject limbs was to get a complete matching between the limbs, since our techniques are highly sensitive to changes in blood pressure, limb position, etc. (2) The group of subjects selected for study were chosen for their homogenic pain pattern, i.e., all experienced some remission in pain at the time the studies were undertaken; thus we were unable to determine correlations between vascular status (regulation, endothelial function) and pain severity from our results.

In conclusion, we showed that 2 important vascular effectors are impaired in CRPS-affected limbs, leading to impaired vasodilatation with exaggerated vasoconstriction. The uniqueness of these findings is that soft tissue vasculature was assessed between 2 limbs of a single individual. We also showed that the vascular smooth muscle adequately responds to physiologic stimuli. This suggests future strategies for treatment of CRPS-1 in various stages of its development.

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