

**Wasner G, Schattschneider J, et al Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. Brain 2001;124:587-599.**

Design: Basic science (physiologic) study

Brief summary of findings:

- 25 unilateral CRPS patients (18 women, 7 men, mean age 47), 15 non-CRPS chronic pain patients (7 men, 8 women, mean age 42), and 20 healthy control subjects (9 men, 11 women, mean age 27) were studied at a university neurology clinic in Kiel, Germany
- CRPS patients all had spontaneous pain and evoked pains not restricted to the distribution of a peripheral nerve; pain was increased by movement, with at least one symptom of motor impairment (strength, tremor, dystonia) with evidence of current or past edema, skin temperature asymmetries or sweating abnormalities
- Non-CRPS pain patients had not had edema or trophic disturbances, and had been stable for several months
- All participants had measurements of temperature with infrared thermometers bilaterally at the tips of the digits (second finger or first toe); measurements of digital blood flow were simultaneously done with laser Doppler flowmetry
- Participants wore cotton suits containing tubes in which water circulated at 12° C to cool the whole body and at 50° C to warm the whole body
- Cooling was done first, until the skin temperature on the unaffected side (right side of healthy controls) was close to 25° C
- Warming was done until the skin temperature on the unaffected side was close to 35° C (right side of healthy controls)
- Sympathetic vasoconstrictor activity was considered high when the skin temperature in the healthy side was  $\leq 25^{\circ}$  C, intermediate when it was about 30° C, and absent when it was  $\geq 35^{\circ}$  C
- Skin temperature differences ( $\Delta T$ ) was calculated as the temperature on the affected side minus the temperature on the healthy side
- In addition to the skin temperature, sympathetic activity was evaluated with plasma noradrenalin in the venous effluent from veins in the dorsum of both hands in 5 CRPS patients
- In healthy controls and in non-CRPS patients, whole-body cooling led to bilateral decrease in skin temperature, accompanied by symmetrical temperature and skin blood flow increase with whole-body warming, with only small  $\Delta T$  between hands
- In CRPS patients, whole-body cooling led to decreases in skin blood flow and temperature in the unaffected extremity, but there were three patterns of response on the affected side
  - o “Warm” regulation, seen in 11 CRPS patients, was characterized by the lack of sympathetic vasoconstrictor response, seen as higher skin temperatures and blood flow on the affected side throughout the cooling-warming cycle

- With “intermediate” regulation, seen in 7 patients, the affected side was either warmer and vasodilated during high levels of sympathetic activity and vasoconstricted during low levels of sympathetic activity, or vice versa
- With “cold” regulation, seen in 7 CRPS patients, vasoconstriction was greater in the affected limb throughout the cooling-warming cycle, and the affected limb remained colder than the healthy limb until well after the end of prolonged whole-body warming, when the temperature differences disappeared
- In CRPS patients, the average maximum  $\Delta T$  was  $4.5^{\circ}\text{C}$ ; in non-CRPS patients, it was  $1.0^{\circ}\text{C}$ , and in healthy controls, it was  $1.3^{\circ}\text{C}$
- If maximum  $\Delta T$  of  $2.2^{\circ}\text{C}$  was used as a cutoff for normal/abnormal values, 6 of 25 CRPS patients were false negative, 1 non-CRPS patient was false-positive, and no healthy subject was false-positive
- There was an association between duration of CRPS and the pattern of sympathetic response: the “warm” CRPS had an average duration of 4 months; the “intermediate” had an average duration of 15 months, and the “cold” CRPS had an average duration of 28 months
- In the 5 CRPS patients who had noradrenalin levels measured, 2 were cold, 2 were warm, and 1 was intermediate
  - For the 2 warm and the 2 cold CRPS patients, noradrenalin levels were lower on the affected side than on the unaffected side; the intermediate CRPS patients had higher noradrenalin levels on the affected than on the unaffected side

Authors’ conclusions:

- Three distinct vascular regulation patterns were seen: cold, intermediate, and warm
  - Warm CRPS had higher skin temperature and blood flow throughout the whole body warming-cooling cycle; the pattern was vice versa for cold CRPS, and the intermediate CRPS was sometimes warmer and sometimes colder on the affected than on the unaffected side
- The vascular regulation pattern was associated with duration of CRPS: acute CRPS was warm, chronic CRPS was cold, and intermediate CRPS was of intermediate duration
- Acute CRPS, with warm regulation, appears to be due to unilateral functional inhibition of sympathetic vasoconstrictor outflow
- Chronic CRPS, with cold regulation, may involve adaptive supersensitivity to circulating catecholamines, since low noradrenalin levels are associated with enhanced vasoconstriction
- Skin temperature differences greater than  $2.2^{\circ}\text{C}$  might be useful in distinguishing CRPS from other painful extremity syndromes with high sensitivity and specificity, but the difficulty in performing the evaluation could limit its clinical application

Comments:

- Sensitivity and specificity should be calculated in the spectrum of patients likely to receive it in clinical practice (the perfect specificity in healthy patients should be ignored)
- The sensitivity in CRPS is 76% (19 of 25 were positive), and the specificity is 93% (14 of 15 non-CRPS patients were negative), using  $\Delta T$  of 2.2° C as the cutoff value
- Other cutoff values are not explored, which precludes constructing a receiver operating characteristic curve (ROC curve); the area under this curve can be helpful in estimating the ability of a test to distinguish cases of a disease from non-cases
- As the authors acknowledge, the practical difficulties of performing the test are a barrier to its clinical application, but it is useful in researching the pathophysiology of CRPS
- There is inadequate information about the treatment histories of the CRPS group; specifically, whether they had had sympathetic blocks or other treatment that influences the autonomic nervous system
- Resting skin temperature differences were not reported; only the temperature differences during the thermoregulatory challenges were reported; thus, the skin temperature differences for warm and cold CRPS under ordinary circumstances is not known

Assessment: for evidence that skin temperature differences during whole-body cooling and warming and warming can be used as a clinical test for CRPS: inadequate

For evidence that CRPS is characterized by inhibition of sympathetic cutaneous responses on the affected side to systemic sympathetic nervous system activity: adequate