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Cold-induced vasodilatation in cold-intolerant rats after nerve injury

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Summary *Purpose:* Cold-induced vasodilatation (CIVD) is a cyclic regulation of blood flow during prolonged cooling of protruding body parts. It is generally considered to be a protective mechanism against local cold injuries and cold intolerance after peripheral nerve injury. The aim of this study was to determine the role of the sympathetic system in initiating a CIVD response.
Methods: Eight rats were operated according to the spared nerve injury (SNI) model, eight underwent a complete sciatic lesion (CSL) and six underwent a sham operation. Prior to operation, 3, 6 and 9 weeks postoperatively, both hind limbs were cooled and the skin temperature was recorded to evaluate the presence of CIVD reactions. Cold intolerance was determined using the cold plate test and mechanical hypersensitivity measured using the Von Frey test.
Results: No significant difference in CIVD was found comparing the lateral operated hind limb for time (preoperatively and 3, 6 and 9 weeks postoperatively; $p = 0.397$) and for group (SNI, CSL and Sham; $p = 0.695$). SNI and CSL rats developed cold intolerance and mechanical hypersensitivity.
Conclusion: Our data show that the underlying mechanisms that initiate a CIVD reaction are not affected by damage to a peripheral nerve that includes the sympathetic fibres. We

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conclude that the sympathetic system does not play a major role in the initiation of CIVD in the hind limb of a rat.
Clinical relevance: No substantial changes in the CIVD reaction after peripheral nerve injury imply that the origin of cold intolerance after a traumatic nerve injury is initiated by local factors and has a more neurological cause. This is an important finding for future developing treatments for this common problem, as treatment focussing on vaso-regulation may not help diminish symptoms of cold-intolerant patients.
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Abnormal pain after exposure to cold is one of the most common long-term complaints of patients after a nerve injury. The incidence of cold intolerance in humans with a nerve injury is estimated to range from 56% to 83%.[1–4] Unfortunately, the only remedy prescribed for cold intolerance is to instruct this patient group to avoid cold stimulations.[5] An important reason why treatment is unavailable may be that the pathophysiology of cold intolerance is still unclear, in particular the mechanism of cold-induced vasodilatation (CIVD).

CIVD is a cyclic regulation of blood flow during prolonged cooling of protruding body parts, such as the hands, feet, chin and nose.[6,7] Lewis first described CIVD in 1930,[8] and it is generally seen as a protective mechanism for local cold injuries.[9,10] In healthy humans, CIVD generally occurs after a minimum cooling time of 5 min in an environment of maximally 15 °C.[11] However, changes in CIVD response in individuals who live in cold environments appear to be neither guaranteed nor predictable.[12] The presence and nature of a CIVD reaction depend on a large number of variables. For example, a higher body core temperature as well as the intake of food leads to a stronger and faster CIVD reaction.[6,13–15] Changes in the CIVD reaction have been described in patients with cold intolerance after a traumatic peripheral nerve injury.[16–19] It has been suggested that there is a relation between CIVD and the treatment of posttraumatic cold intolerance.[19]

It is undisputed that the sympathetic nervous system plays a role in the magnitude of CIVD, as the magnitude of CIVD is strongly dependent on central body temperature.[14,20] However, it is still debated whether the sympathetic system initiates the CIVD response or if peripheral triggers are responsible. Flouris et al. (2008) exposed 10 appropriately dressed adults to −20 °C and observed oscillatory changes in finger blood flow that were related to body core temperature.[21] They concluded that these changes, which they called CIVD, appeared to be the "eventuality of the thermoregulatory function based on the suppression and activation of the sympathetic vasoconstrictor system." Daanen (2009), however, argued that these changes should not be named CIVD, as the finger skin temperatures ranged from 7.2 to 33.5 °C and the observed fluctuations during the experiment did not resemble the typical cyclic CIVD reaction.[22] Later, Flouris and Cheung (2009) concluded from investigating changes in heat balance during exposure of hands to cold air that "CIVD is a centrally originating phenomenon caused by sympathetic vasoconstrictor withdrawal."[23] It was challenged that these observations showed that finger blood flow and body heat content were unrelated.[24] As eliminating the sympathetic drive is hard to accomplish in humans without side effects, we decided to investigate the role of the sympathetic system in rat paws in a systematic way.

Although the locations where CIVD is observed differ between rats (mainly tail and paws) and humans (mainly fingers and toes), the mechanism and control seem to be comparable. The arterio-venous anastomoses (AVAs) that are under sympathetic control are the anatomical structures where CIVD is observed.[24–27] In this study, we evaluated the CIVD reaction in rats with different types of nerve injury because this allows us to standardise the nerve lesion and to exclude additional factors caused by the trauma such as vascular damage. To do so, a spared nerve injury model (SNI) and complete sciatic lesion (CSL) model[28,29] were used. The SNI and CSL models are well-documented nerve injury models that are known to be cold intolerant.[29,30] As in cold stress testing, evaluation of the CIVD reaction may be a tool to assess the quality of the thermoregulatory system in rats after peripheral nerve injuries. It is presently unknown if the timing and amplitude of the CIVD reaction during cold stress are modified in rats with peripheral nerve injuries and whether the presence or absence of a CIVD reaction is related to cold intolerance.

The aim of this study was to determine the role of the sympathetic system in initiating a CIVD response. To do so, prior to operation as well as 3, 6 and 9 weeks post-operatively, both hind limbs were cooled and the skin temperature was recorded to evaluate the presence and absence of CIVD reactions. The rats were assessed to observe whether they experienced cold intolerance and mechanical hypersensitivity.

Material and methods

A recently developed and validated set-up[31] was used to measure the CIVD response bilaterally. All animal experimental procedures were approved by the Animal Experiment Commission of the Erasmus MC and were performed in accordance with the National Institutes of Health guidelines on animal care.

Twenty-two male Wistar rats, (weights 350–500 g) were randomly divided into three groups. In the first group ($n = 8$) the left hind limb was operated according to the SNI model of Decosterd and Woolf[29]; in the second group ($n = 8$) the left hind limb of the rats underwent a CSL[30]; and in the third group ($n = 6$) the left hind limb was operated according to the Sham

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