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Disordered conditioned pain modulation system in patients with posttraumatic cold intolerance[☆]

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KEYWORDS

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Summary *Background:* Conditioned pain modulation (CPM) is a phenomenon of 'pain inhibiting pain' that is important for understanding idiopathic pain syndromes. Because the pathophysiology of posttraumatic cold intolerance is still unknown but it could involve similar mechanisms as idiopathic pain syndromes, we evaluated the functioning of the CPM system in patients with posttraumatic cold intolerance compared to healthy controls.

Methods: Fourteen healthy controls and 24 patients diagnosed with cold intolerance using the Cold Intolerance Symptom Severity questionnaire were included in the study. Of the 24 patients with cold intolerance, 11 had a nerve lesion and 13 an amputation of one or more digits. To quantify the CPM, pain threshold for mechanical pressure was measured at the affected region as a baseline measure. Then, the contralateral hand received a cold stimulus of ice water to evoke the noxious conditioning. After the cold stimulus, the pain threshold for mechanical pressure was determined again.

Results: The absolute and relative changes in algometer pressure (CPM effect) between pre- and post-conditioning were significantly smaller in the cold intolerance group compared to the control group (absolute $p = 0.019$, relative $p = 0.004$). The CPM effect was significantly different between the control group and the subgroups of nerve lesion ($p = 0.003$) and

[☆] **Presentations:** Results, preliminary results and part of the results have been presented at: 1. The 11th Triennial Congress of the International Federation of Societies for Surgery of the Hand, Seoul, South Korea, 2010 and 2. Federation of European Societies for Surgery of the Hand (FESSH), Antwerp, Belgium, 2012.

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amputation patients ($p = 0.011$).

Conclusions: In this study, we found a CPM effect after a cold stimulus in both controls and patients. A significant weaker CPM effect compared to the controls was found, as in other chronic pain conditions. The CPM system within patients with cold intolerance is altered.

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Cold intolerance is a disabling chronic pain disorder that occurs in the first months after a trauma to the upper extremity, and generally does not diminish over time.^{1–7}

It is defined as abnormal pain, with or without discoloration, numbness, weakness or stiffness of the hand and fingers after exposure to mild-to-severe cold.^{8–11} Although this condition is a frequent consequence of upper-extremity trauma, the incidence is particularly high following upper-extremity nerve injury and amputation to one or more digits (56–100%) and is also predominant in patients with a fracture of the hand (38%).^{1,2,5,6,12–16} Posttraumatic cold intolerance is a bothersome and disabling symptom, affecting both work and leisure activities.^{4–6,17}

Unfortunately, the exact pathophysiology of cold intolerance is still unknown. Recent studies have shown that the presence and severity of posttraumatic cold intolerance cannot be explained solely by disordered thermoregulation^{6,18–21} as demonstrated by Duraku et al.,²⁰ who found no direct correlation between cold intolerance and re-warming patterns in different peripheral nerve injury models. Based on this, Duraku et al. suggested that treatments focussing on vasoregulation may therefore not diminish symptoms of cold-intolerant patients. It is thought that more neurological mechanisms play an important role in the development of cold intolerance.^{6,7} Until now, however, it is not well understood why only a select number of the patients develop cold intolerance while others do not.^{6,7,12,22}

An explanation why some patients develop more cold intolerance than others could relate to the interpersonal variability in pain modulation.²³ Especially, variability in how 'pain inhibits pain' in individual patients could play a role. This 'pain inhibiting pain' can be evaluated by quantifying the conditioned pain modulation (CPM) effect.²⁴ The CPM effect can be examined by measuring the pain intensity during a stimulus before and after the application of a noxious 'conditioning' stimulus at another body location. A reduction in the magnitude of the 'test-pain' in response to the 'conditioning stimuli' is considered the CPM effect.

With the CPM effect, the function of the central descending inhibitory system can be assessed.^{24,25} This central descending inhibitory system is of interest because it can inhibit or facilitate transmission of noxious information; a number of recent studies have shown that this system is involved in the pathophysiology of chronic pain^{25–27} and that pain modulation patterns are reduced in various patient groups with idiopathic acute and chronic pain syndromes.^{28–34} To our knowledge, the CPM effect has never been investigated in patients with cold intolerance.

The primary objective of this study was to evaluate the functioning of the CPM system in patients with post-traumatic cold intolerance and to compare it with a group of healthy controls. Throughout this article, the authors will use the terminology of CPM as advised by Yarnitsky et al.^{23,35}

Methods

Participants

Patients with a nerve lesion to the median and/or ulnar nerve or an amputation of one or more digits were included when suffering cold intolerance. Cold intolerance was diagnosed with the Cold Intolerance Symptom Severity (CISS) questionnaire that has a minimum score of 0 and a maximum score of 100 points.^{3,36} Based on the range of Dutch normative values, a patient with a score of 30 or higher is defined as having abnormal cold tolerance.^{3,36} Patients and controls were included when they were 18 years or older and had sufficient knowledge of the Dutch language to follow the instructions of the researcher and be able to complete the CISS questionnaire. The trauma was at least 10 months or older. Medication, smoking and patient characteristics were registered. The study was approved by the Medical Ethical Committee of our hospital (MEC 2009-363) and all patients provided written informed consent.

Measurements

Patients were evaluated using a standardised CPM protocol. The assessments were always performed in the same order, by the same researcher, in the same room with monitored surrounding temperatures of 23 °C (± 1.0). The patients first acclimatised to the room temperature for 30 min. The results were reported, stored and statistical calculations were performed using SPSS for Windows version 17.0.

The pain threshold for mechanical pressure was measured at the affected region using an algometer. A pressure stimulus was applied on the location where the patient experienced the most complaints of cold intolerance and it was repeated three times with a 1-min time interval. Pain intensities were logged using a numbered rating pain score, Numeric Rating Scale (NRS), from zero (no pain at all) to 10 (worst pain imaginable). To achieve a sufficient noxious stimulus, the NRS pain score must be at least six points.

The most commonly known noxious conditioning paradigm to evoke a CPM-like effect was used,²⁴ which is a cold stimulus. In this test, the contralateral hand was immersed

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