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Comparison of muscle and joint pressure-pain thresholds in patients with complex regional pain syndrome and upper limb pain of other origin

Tina Mainka [a,*,1], Florian S. Bischoff [a,1], Ralf Baron [b], Elena K. Krumova [c], Volkmar Nicolas [d], Werner Pennekamp [d], Rolf-Detlef Treede [e], Jan Vollert [a], Andrea Westermann [a], Christoph Maier [a]

[a] Department of Pain Medicine, Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Ruhr-University Bochum, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany
[b] Sektion Neurologische Schmerzforschung und Therapie, Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, 24105 Kiel, Germany
[c] Department of Neurology, Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Ruhr-University Bochum, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany
[d] Institute of Diagnostic Radiology, Interventional Radiology and Nuclear Medicine, Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Ruhr-University Bochum, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany
[e] Center for Biomedicine and Medical Technology Mannheim, Heidelberg University, 68167 Mannheim, Germany

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ABSTRACT

Pain localized in the deep tissues occurs frequently in complex regional pain syndrome (CRPS). In addition, hyperalgesia to blunt pressure over muscles is common in CRPS, but it often appears in limb pain of other origin as well. Considering that 3-phase bone scintigraphy (TPBS) reveals periarticular enhanced bone metabolism in CRPS, joint-associated hyperalgesia to blunt pressure might be a more specific finding than hyperalgesia over muscles. In 34 patients with upper limb pain (18 CRPS, 16 non-CRPS; diagnosed in accordance to the Budapest criteria) and in 18 healthy controls, pressure-pain thresholds (PPT) were assessed bilaterally over the thenar (PPT_{Thenar}), the metacarpophalangeal (PPT_{MCP}), and the proximal interphalangeal (PPT_{PIP}) joints using a pressure algometer (Somedic, Sweden). Beforehand, all patients had received TPBS for diagnostic purposes independently of the study. Region-of-interest (ROI) ratios (mineralization phase) for the MCP and PIP, excluding fracture sites, were correlated with the PPT. In CRPS, all ROI ratios were significantly increased and all PPT of the affected hand were decreased compared to non-CRPS (PPT_{Thenar}: 243 ± 150 kPa vs 358 ± 197 kPa, PPT_{MCP}: 80 ± 67 kPa vs 159 ± 93 kPa, PPT_{PIP}: 80 ± 56 kPa vs 184 ± 110 kPa; $P < .01$) and controls (PPT_{Thenar}: 478 ± 106 kPa, PPT_{MCP}: 254 ± 50 kPa, PPT_{PIP}: 275 ± 76 kPa; $P < .01$). A PPT_{Thenar} below 293 kPa revealed 77% sensitivity but only 63% specificity, whereas a PPT_{PIP} below 102 kPa had 82% sensitivity and 94% specificity to identify CRPS. Only in CRPS were PPT_{MCP} and PPT_{PIP} correlated significantly inversely with the ROI ratio (MCP: $r = -0.439$, PIP: $r = -0.447$). PPT_{PIP} shows higher specificity for CRPS type I than PPT_{Thenar} without loss of sensitivity. Therefore, measurement of joint PPT could be a noninvasive diagnostic tool reflecting increased bone metabolism assessed by TPBS as a sign of bone pathophysiology.

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1. Introduction

Many patients with complex regional pain syndrome (CRPS) report pain in the depth of the limb rather than superficially in the skin [3,26,32,37], pointing to the importance of deep somatic structures such as bones, joints, tendons, and muscles in the pathophysiology of CRPS. Also, sympathetically maintained pain, driven by sympathetic–afferent coupling, is predominantly located in the deep somatic tissues in CRPS [36]. These tissues have already been mentioned in the historical description of CRPS type I: in 1900, a spotty decalcification in x-rays was described appearing in the disease later known as Morbus Sudeck [38]. Nevertheless, the deep somatic structures have only rarely been studied systematically in the recent past, probably because they are difficult to assess.

Within the standardized Quantitative Sensory Testing protocol by the German Research Network on Neuropathic Pain, the

* Corresponding author. Tel.: +49 234 302 6366.
E-mail address: tina.mainka@rub.de (T. Mainka).
[1] The first 2 authors contributed equally to this article, and both should be considered first author.

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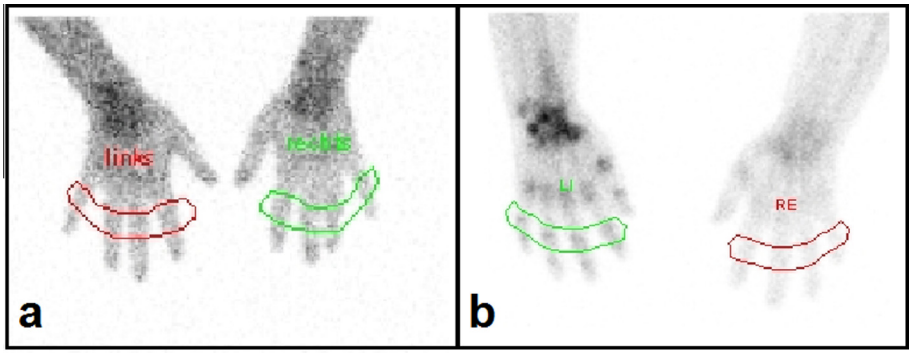

Fig. 1. Mineralization phase of 3-phase bone scintigraphy. (a) Patient with chronic synovitis (ROI score of PIP joint = 0.88). (b) Patient with complex regional pain syndrome after distal radial fracture (ROI score PIP joint = 2.11). ROI, region of interest; PIP, proximal interphalangeal.

pressure-pain threshold (PPT) measured by an algometer is the only parameter addressing deep somatic tissues [21,35]. In the upper limb, it is usually assessed over the thenar. In CRPS, hyperalgesia to pressure stimuli is the most frequent abnormal positive sign, but a decreased PPT also occurs frequently in upper limb pain of other origin, eg, in peripheral nerve injuries [12,25] or in other neurological diseases like postherpetic neuralgia or even restless legs syndrome [1,25]. PPT measured over muscle does not exclusively assess pain sensation of the muscle because it also might be influenced by painful sensations due to affection of other under- or overlying structures including skin, tendons, and bones. Because the periosteum and mineralized bone as well as the joint structures are supplied by afferent C fibers, the distal hand joints would also feature as a valid target to induce pain on blunt pressure [9,23]. In an older uncontrolled study, the PPT of interphalangeal joints were investigated in patients with reflex sympathetic dystrophy. Interestingly, lower PPT were found in the affected limb, confirming the distal hand joints to be involved in the pathogenesis of CRPS [7]. This can also be depicted by the mineralization phase of 3-phase bone scintigraphy (TPBS). In the early stage of the disease, a periarticular enhancement of ^{99}technetium uptake of the distal hand joints of the whole affected limb independently of any preceding trauma can be displayed (Fig. 1) [8,20,29,33,41]. This finding indicates an increased periarticular bone metabolism, revealing a raised activity of osteoblastic cells, which might be triggered by inflammatory processes [5].

The aim of the present study was to assess and compare the PPT of the thenar and distal hand joints in patients with CRPS, patients with upper limb pain of other origin, and healthy controls. Additionally, this study investigated whether the periarticular enhancement of the distal hand joints in the mineralization phase of the TPBS correlates with the deep hyperalgesia to blunt pressure of muscles, joints, or both. Furthermore, this study aimed to determine the specificity and sensitivity of the investigated PPT to identify patients with CRPS compared to chronic upper limb pain of other origins.

2. Methods

2.1. Patients and healthy controls

The study was conducted from October 2010 to September 2011 after approval of the ethics committee of Ruhr-University Bochum (October 2010, registration no. 3648-10, NCT01623141). In our clinic, TPBS has for many years now been established as an additional diagnostic tool for investigation of patients with the clinical suspicion of CRPS. Thus, 35 consecutive patients who were sent from the Department of Pain Medicine and from the Department of Surgery to the Institute of Diagnostic Radiology, Interventional Radiology, and Nuclear Medicine of the University Hospital Bergmannsheil GmbH in Bochum for TPBS independently from this study were included. Written informed consent was obtained from all patients and healthy volunteers after thorough explanation of the study goal and the necessary examinations according to the Declaration of Helsinki. All patients had unilateral upper limb pain. Exclusion criteria were disease duration of over 12 months, type II CRPS, bilateral upper limb pain, other diseases of the upper extremity (eg, polyarthrosis, rheumatoid arthritis), and insufficient German-language skills.

All patients were assessed by at least 2 physicians with special qualifications in pain medicine. In unclear cases, the diagnosis was made by the most experienced investigator. Patients with CRPS type I, diagnosed in accordance to the revised Budapest criteria [14], were allocated to the CRPS group ($n = 18$); patients with confirmed other diagnoses were assigned to the non-CRPS group ($n = 17$). One patient had to be excluded from the control group after initial analyses as a result of an unclear diagnosis.

For measurement of PPT, an additional group of healthy subjects ($n = 18$; age [years, mean ± SD]: 41.2 ± 11.3, male: $n = 9$, right-handed: $n = 16$) was recruited from family, friends, and colleagues, using a previously established screening tool for healthy subjects of the IMI–Europain consortium (http://www.imi.europa.eu) including the following exclusion criteria: age under 18 years, missing informed consent, insufficient German-language skills, current or recent pain, recent intake of analgesic or any other drugs besides contraceptives, recent intake of alcohol or energy drinks, history of chronic internal, dermatological, neurological, or psychiatric diseases, abnormal neurological examination, recent sleep restriction, or unusual physical exercise.

2.2. Investigations

2.2.1. Three-phase bone scintigraphy

TPBS was not performed in healthy controls. In all patients, the same standardized routine protocol for TPBS was used utilizing a Siemens E.CAM 180 dual-head gamma camera and ^{99m}technetium-labeled methylene diphosphonate (^{99m}Tc-MDP, approximately 10 MBq/kg body weight) as a tracer. In the perfusion phase, 30 dynamic frames were recorded (2 s/frame, 128 × 128 matrix). The following blood-pool phase was captured by a sequence of 9 frames (10 s/frame, 256 × 256 matrix). Two to 3 h after injection of the tracer, the mineralization phase was obtained as a static frame (5 min, 256 × 256 matrix) and quantitatively examined using region-of-interest (ROI)-based evaluation, which allows a specific analysis of tracer uptake in predefined areas, measured as counts per pixel. This evaluation was carried out by an

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