Cuff Pressure Algometry in Patients with Chronic Pain as Guidance for Circumferential Tissue Compression for Wearable Soft Exoskeletons: A Systematic Review

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Abstract

In this article, we report on a systematic review of the literature on pressure-pain thresholds induced and assessed by computerized cuff pressure algometry (CPA). The motivation for this review is to provide design guidance on pressure levels for wearable soft exoskeletons and similar wearable robotics devices. In our review, we focus on CPA studies of patients who are candidates for wearable soft exoskeletons, as pain-related physiological mechanisms reportedly differ significantly between healthy subjects and patients with chronic pain. The results indicate that circumferential limb compression in patients most likely becomes painful at approximately 10-18 kPa, and can become unbearable even below 25 kPa. The corresponding ranges for healthy control subjects are 20-42 kPa (painful limits) and 34-84 kPa (unbearable levels). Also, the increase of pain with time tends to be significantly higher, and the adaptation to pain significantly lower, than in healthy subjects. The results of this review provide guidance to designers of wearable robotics for populations with chronic pain regarding rates and magnitudes of tissue compression that may be unacceptable to users.
1. Introduction

A variety of pathologies impair human gait by reducing the ability to control the lower limbs, which gives rise to the opportunity for gait-assistive devices. Recent developments have focused on developing wearable robots to assist with walking, including by way of lower limb exoskeletons. Typically, exoskeletons are composed of rigid materials that impart torque assistance to human joints, but recently, lighter, low-profile soft exoskeletons or exosuits\(^1\) are being developed from materials, such as textiles. The physical interaction between soft exoskeletons and the user will typically involve application of circumferential forces to the user’s limbs via connection cuffs.\(^2\) The growing use of exoskeletons, especially among individuals with various neurological conditions, is increasing the importance of ethics in robotics, and the need to ensure user safety. There is, however, a lack of guidance for the design of safe human-device interfaces regarding mechanical loading of the user’s body, especially for the new generation of soft exoskeletons.

As excessive mechanical loading can lead to soft tissue injury, attempts have been made to establish safe thresholds for the external mechanical loading of tissues. These thresholds have been based on interface pressures at load-bearing sites of the body, but recent studies have shown that the relationship between interface pressure and internal stress is not linear.\(^3\) Internal stress is highly dependent on the nature of the intervening soft tissues, e.g. their thickness,\(^4,5\) tone,\(^5,6\) mechanical stiffness,\(^7\) and integrity,\(^5\) as well as the proximity of bony prominences.\(^4,5,7,8\) Moreover, injury thresholds differ for skin, adipose tissue and muscle, with the lowest threshold for muscle.\(^8\) Thus a safe threshold based solely on interface pressure is not acceptable.\(^3,7,9\) Because measurement of internal pressure is technically and ethically challenging,\(^3\) several other techniques have been used in combination with interface pressure measurements.

The authors propose that pain and discomfort studies using pressure algometry could be a relevant approach to study tissue exposures to mechanical stress for soft robotics applications and wearable robots generally, as pain is the most direct reaction of the human body to excessive external loads.\(^10\) Moreover, pressure-induced muscle pain is mainly related to strain,\(^11\) and is considered a good indicator of potential tissue damage caused by excessive pressure exposures.\(^12\)

In a previous review,\(^13\) we proposed that the findings of studies on computerised pneumatic Cuff Pressure Algometry (CPA) be used to establish indicative guidelines for acceptable levels of mechanical tissue compression in humans using wearable robots. CPA assesses the response of large
volumes of deep somatic tissues to compression,\textsuperscript{11,14-16} as induced by soft exoskeletons, and is a reliable method for quantitative sensory measurements and evaluation of central sensitisation.\textsuperscript{16-23} Typically, two parameters of pain sensation are measured with algometry: the pressure magnitude at which pain occurs (Pain Detection Threshold – PDT), and the pressure magnitude that causes unbearable pain (Pain Tolerance Threshold – PTT).\textsuperscript{13}

Our previous review\textsuperscript{13} focused on healthy subjects’ pain thresholds, induced by CPA at the lower limb. We found that the mean PDTs ranged from 14-34 kPa and the mean PTTs from 37-91 kPa. However, pressure-pain thresholds (PPTs) and pain-related physiological mechanisms differ significantly between healthy subjects and patients with chronic pain. We are unaware of any prior review studies of the corresponding values for patients, especially those with chronic pain.

Chronic pain has been recognized as pain that persists past normal healing time, usually more than 3 to 6 months,\textsuperscript{24} and hence lacks the acute warning function of physiological nociception.\textsuperscript{25} Among the most widely studied subgroup of patients presenting with chronic widespread pain are patients with Fibromyalgia Syndrome (FMS).\textsuperscript{19} Chronic pain is also common in Rheumatoid Arthritis (RA).\textsuperscript{23} In older adults, chronic pain is common,\textsuperscript{26} and is found to be associated with an increased risk and intensity of frailty.\textsuperscript{27-29} Highly prevalent painful conditions at older age, such as Osteoarthritis (OA) are related to disability,\textsuperscript{30,31} especially mobility limitations associated with impairments in balance and gait.\textsuperscript{32-35} Finally, chronic pain is estimated to occur among 40-67 % of patients after Spinal Cord Injury (SCI),\textsuperscript{36-39} who are the target users of many wearable gait-assistive devices.

Clinical studies have demonstrated that patients with chronic pain exhibit hyperalgesia to mechanical stimulation,\textsuperscript{15,23,40,41} even when the stimulus is applied at an unaffected site (generalised hyperalgesia),\textsuperscript{35} and even after the primary cause of pain has disappeared.\textsuperscript{17,23,35,42} Namely, persistent pain can cause changes in the facilitation and/or inhibition of pain by the central nervous system, that can significantly modulate the efficacy of signal transfer at spinal synapses and thus the experience of pain (descending pain modulation; Figure 1).\textsuperscript{43} These changes can lead to central sensitisation, i.e. spinal hyperexcitability,\textsuperscript{44} that may involve an imbalance between the descending pain-modulatory systems, as well as reorganisation of the higher brain centres.\textsuperscript{35}
Central sensitisation results in reduced pain thresholds and pain amplification;\textsuperscript{45} however, pressure-pain thresholds alone do not differentiate between central and peripheral sensitisation.\textsuperscript{23} Therefore, additional tests are used to evaluate changes in central pain modulation that result in generalised hypersensitivity.

Spatial and temporal summation of pain are normal phenomena, and their magnitude depends on descending pain-facilitating systems,\textsuperscript{46,47} therefore they are used for examinations of central pain facilitation.\textsuperscript{21,35,45-50} Spatial Summation of Pain (SSP) is defined as an increased perception of pain at the same magnitude of mechanical stimulation when larger, compared with smaller areas of body tissue are stimulated (Figure 2a).\textsuperscript{51,52} This explains why pain is induced at lower pressures when compression is performed at the lower limb compared to the upper limb, and with wide compared to narrow pressure cuffs.

Temporal Summation of Pain (TSP) is defined as gradually increasing perception of pain that occurs when a series of identical painful stimuli is applied with a frequency above 0.3 Hz (Figure 2b).\textsuperscript{16,45,53-56} A typical protocol of mechanically painful stimulation for evaluation of TSP is 10 repeated stimuli with 1-second inter-stimulus interval.\textsuperscript{42} The stimulation intensity and the initial stimulus being painful are important for evoking TSP.\textsuperscript{57}
In the case of central sensitisation, SSP and TSP are facilitated, i.e., the perceived pain increases more prominently (SSP) or rapidly (TSP) with the applied stimuli (Figure 3). Facilitated SSP is found in patients with knee OA, and facilitated TSP in patients with chronic painful OA, FMS, and whiplash-associated disorder.

A particular form of descending pain-inhibitory systems is the Conditioned Pain Modulation (CPM). In contrast to the pain-increasing effects of SSP and TSP, CPM results in reduced pain sensitivity in healthy subjects when two painful stimuli are applied simultaneously (the ‘pain inhibits pain’ paradigm). The testing of CPM is used to address the complex balance between the descending
inhibition and facilitation of nociceptive processing\textsuperscript{64} and the transition from acute to chronic pain.\textsuperscript{65} The general recommendation for testing is to use extra-segmental or contralateral sites, such as the upper arm and lower leg.\textsuperscript{66,67} Previous studies have concluded that CPM is impaired in OA of the hip\textsuperscript{68} and knee,\textsuperscript{41} in temporomandibular disorders,\textsuperscript{69} in fibromyalgia,\textsuperscript{70} and with increasing age.\textsuperscript{62,71}

This study is a systematic review of the literature on pressure-induced pain, as established by CPA, specifically in patients with chronic pain. We believe that CPA-parameters can help identify the acceptable mechanical stress applied by gait-assistive robotic devices, in order to avoid user discomfort and soft-tissue damage. We also believe that patients with chronic pain are an important group of potential users of such devices, due to the mobility impairments often associated with their medical conditions. The purpose of this review is to gain insight into the acceptable levels of external pressure for soft robotic devices, as design guidance for potential patient end users.
2. Method

2.1. Literature Search and Study Selection
A systematic literature search was performed in May 2017, using the following databases: Academic Search Complete, AMED, Biomedical Reference Collection: Expanded, CINAHL®Complete, CINAHL Plus® with Full Text, General Science Full Text™, MEDLINE, PsycARTICLES®, PsycINFO®, Scopus, and SPORTDiscus with Full Text. The keywords used to identify articles of interest were "cuff", "algometry" and "patient". Results not reporting on quantitative sensory testing performed by cuff algometry, or not including patients with chronic pain were excluded. Figure 4 illustrates the search and screening process. A second reviewer repeated the search and screening process to ensure that the process was accurate and repeatable.

2.2. Data Extraction and Synthesis
Data extracted from the selected studies included: 1) the patients' characteristics (age, sex, anthropometric characteristics and medical condition), 2) the assessment methods (tourniquet cuff characteristics and positioning, compression rates and durations, pain-intensity rating, etc.), 3) the variables studied, and 4) the findings of the study.

The relevant independent variable was pneumatic cuff inflation pressure, and the relevant dependent variables were PDT and PTT. Other variables, especially TSP and CPM were also studied, but were not a filter criterion for inclusion in the review.
Figure 4: Literature search and study selection
3. Results

3.1. Participants
The search identified 18 relevant studies, 7 of which also included healthy controls. Four studies were of patients with chronic widespread pain or fibromyalgia, and then individual studies were of patients with osteoarthritis, chronic musculoskeletal pain, chronic back pain, chronic pain of different etiologies, lateral epicondylalgia, and patellofemoral pain. Six studies included only females, and the remaining 12 studies involved both male and female participants. The mean age of participants was 60+ years in 8 studies, and under 40 years of age in 4 studies. Fourteen studies reported the mean BMI or the weight and height of the participants, and two studies reported the mean circumference of the limb studied.

3.2. Assessment methods
All studies were performed on the lower leg, and 2 also on the upper limb. CPA was performed using a 13 cm wide double-chamber tourniquet cuff in 15 studies, 6 studies additionally used only one chamber to assess SSP, and one also used a single-chamber tourniquet. Three studies did not describe the tourniquet cuff used.

Participants in all studies rated their pressure-induced pain intensity on an electronic Visual Analogue Scale (VAS), with 0 indicating “no pain” and 10 cm “maximal pain”. All ratings were recorded at 10 Hz. PDT was defined as the inflation-pressure magnitude when the rating on VAS either exceeded 0 cm, was equal to 1 cm, or exceeded 2 cm. Five studies did not explicitly define the rating on the VAS when PDT occurs.

In 8 studies, single-point pressure algometry was performed in addition to CPA. Other tests were performed in some studies, such as assessment of maximal isokinetic muscle strength, manual tender point examination and tender point count, myalgic score, questionnaires to assess depression, anxiety, and pain catastrophizing, self-reporting of somatosensory symptoms of neuropathic pain, thermal pain sensitivity, exercise-induced hypoalgesia, cold-pressor test, and provocation tests with hypertonic saline solution, but these are beyond the scope of this systematic review.
3.3. Variables studied

The current review was primarily of PDT and PTT considering the context of soft-robotics/soft exoskeleton applications. 4 studies reported only PDTs,22,49,77,79 and the remainder both PDTs and PTTs. 4 studies also assessed Spatial Summation of Pain (SSP),21,49,59,79 13 studies Temporal Summation of Pain (TSP),21,22,50,59,72,73,76-82 and 8 studies Conditioned Pain Modulation (CPM).40,72,73,76,78,81,82

9 studies reported the results in the form of Mean ± SD and 9 studies as Mean ± SEM. 5 studies49,72,73,76,78 only presented the results graphically, and in those instances the data were scaled and rounded to the closest whole number.

3.4. Findings

The studies reviewed are summarized and ordered chronologically in Table 1. The key mean values are rounded to the closest whole number and compared in Table 2.

Patients with chronic pain show significantly decreased pressure-induced pain thresholds on the lower leg compared to healthy participants.15,21,49,50,59,73,78 When using both chambers of a double-chambered cuff at the lower leg, mean PDT ranged from 8.8 kPa19 to 34 kPa21 in patients (and 16 kPa73 to 37 kPa72 in healthy controls), but 19 of the 28 mean PDT levels that were assessed across the studies in patients were under 20 kPa (median across the studies was 17.9 kPa). Mean PTT levels ranged from 23 kPa76 to 75 kPa72 in patients (and 34.2 kPa73 to 84 kPa72 in healthy controls), with 14 of the 24 assessed mean PTT levels for patients under 40 kPa (median across the studies was 38 kPa). For the upper limb, the mean PDT levels ranged from 18.8 kPa59 to 25.3 kPa21 in patients (and 24.9 kPa59 to 36.8 kPa21 in healthy controls), and mean PTT levels from 47.9 kPa59 to 76.1 kPa21 in patients (and 65.7 kPa59 to 90.5 kPa21 in healthy controls). PDTs and PTTs were significantly higher for the upper limb than the lower limb when compared within the same individuals in one study.59 Despite the different pressure levels at PTT, no significant difference in pain rating on the VAS at PTT was found between patients and healthy controls, suggesting similar experience of pain intensity at the point where pain becomes unbearable.15,59

TSP in patients ranged from normal72 to facilitated,50,59,73 and CPM ranged from preserved59,78 to impaired.72,78 A higher degree of TSP was found in patients with longer lasting pain.21 Significantly higher PDT and PTT were found during single-chamber compression compared to double-chamber compression, indicating SSP.59,78 One study only found significant SSP in healthy controls, but not in
Age was found to correlate significantly negatively with pressure-pain thresholds but not TSP or CPM, indicating that increasing age may mainly affect the peripheral nociceptive system and to a lesser extent the central nociceptive mechanisms.\textsuperscript{73}

Single-point algometry results showed significant differences in PPTs in relation to testing site: PPTs on the affected side were significantly lower than contralaterally.\textsuperscript{21,49}
### Reference: Jespersen et al. (2007)\(^1\)

**Participants**
- Patients with fibromyalgia: 48 female
  - Age: median 49 years, range 22-60 years
  - Circ.: 37.4 ± 0.5 cm
- Healthy controls: 16 female
  - Age: median 45 years, range 25-60 years
  - Circ.: 35.7 ± 1.0 cm
  - n = 64

**Experimental Procedure**
A) CPA:
- double-chamber tourniquet cuff (width 13 cm)
- dominant lower leg
- infiltration rate: 0.5 kPa/s; maximum pressure limit: 100 kPa
- electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz
  - supine position
B) Maximal isokinetic knee muscle strength
C) Tenderpoints and myalgic score
D) Depression, symptoms and functions

**Variables**
- Independent: Pneumatic cuff inflation pressure
- Dependent: Pain Threshold (PDT)
  - Pressure-Pain Tolerance (PTT)
  - Pressure-Pain Limit (VAS at PTT)

**Findings**
- Pain thresholds (Mean ± SEM):
  - Patients: 15.4 ± 1.1
  - Controls: 19.9 ± 2.2

- PDT and PTT were significantly lower in patients compared to healthy controls. No significant difference in VAS at PTT between patients and healthy controls was found. No significant correlation was found between leg circumference and pressure-pain thresholds. CPA-parameters were significantly correlated to isokinetic muscle strength.

### Reference: Amris et al. (2010)\(^2\)

**Participants**
- Patients with chronic widespread pain (fibromyalgia): 75 female, 6 male
  - Age: 45.7 ± 10.9 years
  - BMI: 28.3 ± 5.9 kg/m²
  - n = 81

**Experimental Procedure**
A) CPA:
- double-chamber tourniquet cuff (width 13 cm)
- dominant lower leg
- infiltration rate: 1 kPa/s; maximum pressure limit: 100 kPa
- electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz
  - supine position
B) Self-reporting of somatosensory symptoms of neuropathic pain
C) Self-reporting of depression, anxiety, and pain catastrophizing
D) Manual tender point examination and tender point count

**Variables**
- Independent: Pneumatic cuff inflation pressure
- Dependent: PDT
  - PTT

**Findings**
- Pain thresholds (Mean ± SD):
  - PDT (kPa): 8.8 ± 6.0
  - PTT (kPa): 30.9 ± 17.5

### Reference: Lemming et al. (2012)\(^3\)

**Participants**
- Patients with chronic widespread pain: 25 female
  - Age: 36 years (SEM 1.3)
  - Weight: 68.3 kg (SEM 2.9)
  - Height: 166 cm (SEM 1.0)
  - Circ.: 38 cm (SEM 0.7)
  - n = 81

**Healthy controls:**
- 20 female
  - Age: 41 years (SEM 2.0)
  - Weight: 66.9 kg (SEM 2.2)
  - Height: 168 cm (SEM 2.0)
  - Circ.: 38 cm (SEM 0.6)
  - n = 35

**Experimental Procedure**
A) CPA:
- double-chamber tourniquet cuff (width 13 cm)
- lower leg around the midportion of m. triceps surae and arm at the level of the heads of mm. biceps and triceps brachii
- infiltration rate: 1 kPa/s; maximum pressure limit: 100 kPa
- electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz
  - supine position
  - 3 repetitions
    - Assessment:
      - SSP: random inflations of:
        - A1) single chamber
        - A2) both chambers
      - TSP: tonic 10-minute stimulation:
        - 1) at 25 kPa
        - 2) at [PDT+PTT]/2 intensity
      - 2 repetitions, separated by 7 minutes
      - calculation of maximal VAS, time to maximal VAS, area under the time-VAS curve and TS-index
B) Saline-induced muscle and referred pain

**Variables**
- Independent: Pneumatic cuff inflation pressure
- Dependent: PDT
  - PTT
  - PTI
  - SSP
  - TSP

**Findings**
- Pain thresholds (Mean ± SEM):
  - Patients:
    - PDT (kPa): 18.8 ± 2.3
    - PTT (kPa): 47.9 ± 4.5
    - PTI (kPa): 9.7 ± 0.1
  - Controls:
    - PDT (kPa): 24.9 ± 5.6
    - PTT (kPa): 65.7 ± 6.2
    - PTI (cm): 9.8 ± 0.2

- PTT with double cuff was significantly higher in controls than in patients both in the leg and arm. PDT and PTI did not differ significantly between the two groups in arm (double cuff) or leg (both cuffs).
- SSP: At the leg, PDT and PTT were significantly higher during single cuff stimulation compared with double cuff stimulation. No significant differences in pressure-pain thresholds between single and double cuff were found between controls and patients.
- TSP: TSI and VASpeak were significantly higher and the time to VASpeak significantly shorter in patients than in controls. One-third of the patients and 4 controls exhibited habituation to pain.
### Reference

**Graven-Nielsen et al. (2012)**

<table>
<thead>
<tr>
<th>Patients with knee OA:</th>
<th>Experimental Procedure</th>
<th>Variables</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 female, 12 male</td>
<td>A) Single-point pressure algometry (hand-held):</td>
<td>Independent: Probe pressure Pneumatic cuff inflation pressure</td>
<td>Pain thresholds (Mean ± SEM):</td>
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<tr>
<td>n = 69</td>
<td>- 1 cm² probe</td>
<td>Dependent: PPT Cuff PPT SSP CPM</td>
<td>A) Single-point algometry - pain thresholds, as established from the provided charts:</td>
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<td>- test sites:</td>
<td>A)</td>
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<td>A1) peripatellar region (7 sites)</td>
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<td>Patients</td>
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<td></td>
<td>A2) m. tibialis anterior</td>
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<td>affected</td>
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<td>A3) m. extensor carpi radialis longus</td>
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<td>- 2-3 repetitions</td>
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<td>351 ± 22</td>
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### Reference

**Jespersen et al. (2013)**

<table>
<thead>
<tr>
<th>Patients with lateral epicondylalgia:</th>
<th>Experimental Procedure</th>
<th>Variables</th>
<th>Findings</th>
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<tbody>
<tr>
<td>22 female</td>
<td>CPA: double-chamber tourniquet cuff (width 13 cm):</td>
<td>Independent: Probe pressure Pneumatic cuff inflation pressure</td>
<td>Pain thresholds (Mean ± SEM):</td>
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<tr>
<td>n = 60</td>
<td>length 61 cm: lower leg around the widest part of m. gastrocnemius length 13 cm: lower arm over the extensor region</td>
<td>Dependent: PDT PTTVAS at PTT SSP TSP</td>
<td>Lower arm</td>
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<td>- inflation rate: 1 kPa/s</td>
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<td>Double cuff</td>
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<td></td>
<td>- electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz (PDT: VAS &gt; 0)</td>
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<td>Patients</td>
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<td></td>
<td>- 3 repetitions</td>
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<td>PDT (kPa)</td>
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<td>Assessment: SSP:</td>
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<td>PTT (kPa)</td>
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<td>- lower leg</td>
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<td>VAS at PTT (cm)</td>
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<td>- random inflations of:</td>
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<td>1) single chamber</td>
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<td>PDT (kPa)</td>
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<td>2) both chambers</td>
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<td>TSP:</td>
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<td>VAS at PTT (cm)</td>
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<td>- tonic 10-minute stimulation at (PDT+PTT)/2 intensity</td>
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<td>- TS-index was calculated</td>
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PPTs in patients were significantly lower than in controls. PPTs on the affected side in patients were significantly lower than contralaterally. PPTs at different test sites differed significantly.
### Reference

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<th>Patients with knee OA:</th>
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<th>Variables</th>
<th>Findings</th>
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<tr>
<td>79 Patients with knee OA:</td>
<td>A) Single-point pressure algometry (hand-held):</td>
<td>Independent:</td>
<td>Pain thresholds (Mean ± SD):</td>
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<tr>
<td>4 female, 13 male</td>
<td>- 1 cm² probe</td>
<td>Probe pressure</td>
<td>PPT (kPa)</td>
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<tr>
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<td>- test sites:</td>
<td>Pneumatic cuff inflation pressure</td>
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<tr>
<td>- BMI: 29.7 ± 5.6 kg/m²</td>
<td>A1) peripatellar region (8 sites)</td>
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<td>Cuff PPT (kPa)</td>
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<td>A2) m. tibialis anterior</td>
<td>Dependent:</td>
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<td><strong>n = 17</strong></td>
<td>B) CPA:</td>
<td>PPT</td>
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<td>- double-chamber tourniquet cuff (width 13 cm)</td>
<td>Cuff PPT</td>
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<td>- lower leg at the level of the heads of m. gastrocnemius</td>
<td>Cuff PTT</td>
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<td>- inflation rate: 0.5 kPa/s; maximum pressure limit: 100 kPa</td>
<td>SSP</td>
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<td>- electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz</td>
<td>TSP</td>
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<td>- 2 repetitions</td>
<td>CPM</td>
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<td>Assessment:</td>
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<td>B1) proximal chamber only</td>
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<td>B2) distal chamber only</td>
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<td>B3) both chambers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TSP:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 10 repeated stimulations: 1 s of (Cuff PPT + Cuff PTT)/2 intensity, 1 s of 5 kPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assessment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- conditioning stimulus: inflation of 7.5 cm wide cuff to constant pressure (4 cm VAS) at the left arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- test stimulus: single-point algometry</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Reference

<table>
<thead>
<tr>
<th>Patients with end-stage knee OA after revision-TKA:</th>
<th>Experimental Procedure</th>
<th>Variables</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>79 Patients with end-stage knee OA after revision-TKA:</td>
<td>A) CPA:</td>
<td>Independent:</td>
<td>Baseline pain thresholds, as established from the provided charts (Mean ± SEM):</td>
</tr>
<tr>
<td>20 with pain (P):</td>
<td>- double-chamber tourniquet cuff (width 13 cm)</td>
<td>Pneumatic cuff inflation pressure</td>
<td>A1) Proximal chamber only</td>
</tr>
<tr>
<td>14 female, 6 male</td>
<td>- lower leg at the level of the heads of m. gastrocnemius</td>
<td>Dependent:</td>
<td></td>
</tr>
<tr>
<td>- Age: 61.5 ± 1.8 years</td>
<td>- inflation rate: 1 kPa/s; maximum pressure limit: 100 kPa</td>
<td>PPT</td>
<td></td>
</tr>
<tr>
<td>- BMI: 30.7 ± 1.2 kg/m²</td>
<td>- electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz</td>
<td>Cuff PPT</td>
<td></td>
</tr>
<tr>
<td>20 pain-free (NP):</td>
<td>- 2 random inflations of:</td>
<td>Cuff PTT</td>
<td></td>
</tr>
<tr>
<td>8 female, 12 male</td>
<td>A1) proximal chamber only</td>
<td>SSP</td>
<td></td>
</tr>
<tr>
<td>- Age: 65.7 ± 1.3 years</td>
<td>A2) distal chamber only</td>
<td>TSP</td>
<td></td>
</tr>
<tr>
<td>- BMI: 31.5 ± 0.9 kg/m²</td>
<td>A3) both chambers</td>
<td>CPM</td>
<td></td>
</tr>
<tr>
<td><strong>n = 40</strong></td>
<td>TSP:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 10 repeated stimulations: 1 s of (PPT+PTT)/2 intensity, 1 s of 5 kPa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assessment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- conditioning stimulus: inflation of 7.5 cm wide cuff to constant pressure (4 cm VAS) at the left arm</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>- test stimulus: single-point algometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>before, during and 5 minutes after conditioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B) Single-point pressure algometry (hand-held)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Amris et al. (2014)³⁴

**Patients with chronic widespread pain:**
- 271 female
  - Age: 45.5 ± 9.7 years
  - BMI: 26.9 ± 5.5 kg/m²

n = 271

**CPA:**
- double-chamber tourniquet cuff (width 13 cm)
  - lower leg
  - electronic VAS

**Independent:**
- Pneumatic cuff inflation pressure

**Dependent:**
- PDT
- PTT

#### Pain thresholds (Mean ± SD):

<table>
<thead>
<tr>
<th></th>
<th>TPC: 0-8</th>
<th>TPC: 9-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT (kPa)</td>
<td>15.0 ± 8.4</td>
<td>11.7 ± 7.2</td>
</tr>
<tr>
<td>PTT (kPa)</td>
<td>37.1 ± 14.2</td>
<td>30.7 ± 14.6</td>
</tr>
</tbody>
</table>

### Henriksen et al. (2014)³⁷

**Patients with tibiofemoral OA:**
- Exercise therapy group (EG)
  - 22 female, 3 male
  - Age: 65.0 ± 8.9 years
  - BMI: 28.9 ± 4.1 kg/m²

- Control group (CG)
  - 17 female, 6 male
  - Age: 62.3 ± 7.1 years
  - BMI: 28.2 ± 4.6 kg/m²

n = 48

**CPA:**
- double-chamber tourniquet cuff
  - affected lower leg, at the bulky part of m. gastrocnemius
  - inflation rate: 1 kPa/s
  - electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz
  - 3 repetitions
  - Assessment of TSP:
    - tonic 6-minute stimulation at 125 % PPT
    - the area under the time-VAS curve was calculated

**Independent:**
- Pneumatic cuff inflation pressure

**Dependent:**
- PDT
- TSP

#### Pain thresholds (Mean ± SD):

<table>
<thead>
<tr>
<th></th>
<th>EG</th>
<th>CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT (kPa)</td>
<td>18.2 ± 6.1</td>
<td>19.1 ± 6.8</td>
</tr>
<tr>
<td>TSP (mm x s)</td>
<td>8,887 ± 4,340</td>
<td>6,768 ± 4,388</td>
</tr>
</tbody>
</table>

12-week therapeutic program reduced patients’ sensitivity to painful stimuli and TSP upon sustained noxious pressure stimulation.

### Vladimirova et al. (2015)³⁰

**Patients with RA:**
- 38 female
  - Age: median 56 years, range 46-69 years

**Healthy controls:**
- 38 female
  - Age: median 39 years, range 32-44 years

n = 76

**CPA:**
- tourniquet cuff (length 61 cm)
  - dominant lower leg, widest part
  - electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz
    - (PDT: VAS > 0 cm)
  - 3 repetitions
  - Assessment of TSP:
    - tonic 10-minute of stimulation with (PDT+PTT)/2 intensity
    - TS-index was calculated

**Independent:**
- Pneumatic cuff inflation pressure

**Dependent:**
- PDT
- PTT
- TS-index

#### Pain thresholds (Mean ± SEM):

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT (kPa)</td>
<td>16.4 ± 1.2</td>
<td>24.9 ± 2.0</td>
</tr>
<tr>
<td>PTT (kPa)</td>
<td>40.5 ± 2.5</td>
<td>55.9 ± 3.1</td>
</tr>
</tbody>
</table>

PDT and PTT in patients were significantly lower compared with the healthy controls.

**TSP:** TS-index in patients was significantly higher compared with the healthy controls.

RA patients suffer from nonarticular pain hypersensitivity and facilitated temporal summation, indicating central pain sensitisation.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Participants</th>
<th>Experimental Procedure</th>
<th>Variables</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Vaegter et al. (2016)⁵⁴  | Patients with chronic musculoskeletal pain (lower back, neck, shoulder or elbow): Low pain sensitivity (LPS): 21 female, 9 male  - Age: 47.3 ± 12.3 years  - BMI: 25.5 (18.2-42.7) kg/m²  
High pain sensitivity (HPS): 21 female, 10 male  - Age: 43.5 ± 9.9 years  - BMI: 25.9 (17.7-47.6) kg/m²  
n = 61 | A) Single-point pressure algometry (hand-held):  - 1 cm² probe  - 4 test sites:  A1) dominant m. quadriceps femoris (20 cm proximal to the base of patella)  A2) nondominant m. quadriceps femoris (20 cm proximal to the base of patella)  A3) dominant m. biceps brachii (10 cm proximal to the cubital fossa)  A4) nondominant upper m. trapezius - 2 repetitions - used for subgrouping of patients | Independent:  - Probe pressure  
Pneumatic cuff inflation pressure  Dependent:  - PPT  - cPPT  - cPTT  - VAScPTT  - TSP | Baseline pain thresholds (Mean ± SD):  
A) Single-point pressure algometry:  
<table>
<thead>
<tr>
<th>LPS</th>
<th>HPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1) PPT (kPa)</td>
<td>538 ± 390</td>
</tr>
<tr>
<td>A2) PPT (kPa)</td>
<td>574 ± 390</td>
</tr>
<tr>
<td>A3) PPT (kPa)</td>
<td>321 ± 247</td>
</tr>
<tr>
<td>Widespread PPT (kPa)</td>
<td>612.9 ± 343.9</td>
</tr>
</tbody>
</table>
| B) CPA:  
<table>
<thead>
<tr>
<th>LPS</th>
<th>HPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cPPT (kPa)</td>
<td>28.9 ± 14.0</td>
</tr>
<tr>
<td>cPTT (kPa)</td>
<td>57.6 ± 17.0</td>
</tr>
<tr>
<td>VAScPTT (cm)</td>
<td>7.7 (1.16-9.99)</td>
</tr>
<tr>
<td>VAS I (cm)</td>
<td>2.2 ± 1.5</td>
</tr>
<tr>
<td>VAS II (cm)</td>
<td>3.1 ± 1.7</td>
</tr>
<tr>
<td>VAS III (cm)</td>
<td>3.6 ± 2.1</td>
</tr>
</tbody>
</table>
| cPPT and cPTT were significantly lower in HPS compared to LPS.  
TSP: VAS III was significantly higher than VAS II, and VAS II was significantly higher than VAS I.  
VAS-I-III were significantly higher in HPS compared to LPS.  
TSP was more pronounced in HSP and it was further facilitated after aerobic exercise, but not after isometric exercises.  
cPPT and Widespread PPT were increased in response to the cold pressor test and exercises in both groups. | |
| | | |
| Soriano-Maldonado et al. (2016)⁵⁵ | Patients with tibiofemoral OA: 61 female, 39 male  - Age: 63.4 ± 9.3 years  - BMI: 28.9 ± 3.6 kg/m²  
n = 100 | CPA:  - double-chamber tourniquet cuff  - affected lower leg at the bulky part of the gastrocnemius muscle  - inflation rate: 1 kPa/s  - electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz  - 3 repetitions  
Assessment of TSP:  - tonic stimulation at 125 % PPT, 6 minutes - calculation of the area under the time-VAS curve | Independent:  - Pneumatic cuff inflation pressure  
Dependent:  - PPT  - TSP | Baseline pain thresholds (Mean ± SD):  
PPT (kPa) | 18.5 ± 6.4  
TSP (mm × s) | 14,423 ± 8,024 |
### Experimental Procedure

#### A) Single-point pressure algometry (hand-held):
- 1 cm² probe
- test sites:
  - A1) knee: center of the patella
  - A2) m. tibialis anterior, 5 cm distal to the tibial tuberosity
  - A3) elbow: lateral epicondyle of the humerus
- 2 repetitions
- reclining position

#### B) CPA:
- double-chamber tourniquet cuff (width 13 cm)
- affected lower leg, 5 cm distal to the tibial tuberosity
- inflation rate: 1 kPa/s; maximum pressure limit: 100 kPa
- electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz
  - PDT: VAS = 1 cm

**Assessment:**
- 10 repeated stimulations: 1 s of PTT intensity, 1 s of 5 kPa
  - test stimulus: PDT and PTT on contralateral lower leg

**CPM:**
- conditioning stimulus: inflation of 7 cm wide cuff to constant pressure 60 kPa at left arm
- test stimulus: PDC and PTT on contralateral lower leg

#### CPM:
- 2 repetitions

**Assessment:**
- 10 repeated stimulations: 1 s of PTT intensity, 2 s of 5 kPa
- test stimulus: PDC and PTT on contralateral lower leg

### Variables

#### Independent:
- Probe pressure
- Pneumatic cuff inflation pressure

#### Dependent:
- PPT
- PDT
- PTT
- TSP
- CPM

### Findings

#### Pain thresholds, as established from the provided charts (Mean ± SEM):

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT (kPa)</td>
<td>G1: 17.6 ± 7.8</td>
<td>G2: 17.0 ± 7.9</td>
</tr>
<tr>
<td>PTT (kPa)</td>
<td>G1: 34.1 ± 14.5</td>
<td>G2: 35.5 ± 14.5</td>
</tr>
<tr>
<td>cPPT (kPa)</td>
<td>G1: 8.7 ± 2.0</td>
<td>G2: 8.7 ± 1.9</td>
</tr>
<tr>
<td>cPTT (cm)</td>
<td>G1: 2.0</td>
<td>G2: 1.9</td>
</tr>
</tbody>
</table>

**CPM:**
- Before conditioning
- After conditioning

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before conditioning</th>
<th>After conditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT (kPa)</td>
<td>G1: 20.0 ± 9.4</td>
<td>G2: 23.0 ± 14.3</td>
</tr>
<tr>
<td>PPT (kPa)</td>
<td>G1: 44.1 ± 19.4</td>
<td>G2: 44.1 ± 21.8</td>
</tr>
</tbody>
</table>

#### Findings

A significant difference between PPTs in patients and controls was found. There were no significant differences in PDT or PTT between patients and controls.

**TSP:** No significant differences were found between patients and controls in the increase in VAS.

**CPM:** Patients had a 78 % lower CPM response in PDT and 20 % lower CPM response in PTT compared to controls.

---

**Reference**

**Graven and Vaegter and Rathleff (2016)**

- **Patients with patellofemoral pain:**
  - 20 female
  - Age: median 20.0 years, range 19.0-21.0 years
  - Weight: median 63.8 kg, range 8.3 kg
  - Height: median 170 cm, range 5 cm

- **Pain-free controls:**
  - 20 female
  - Age: median 20.5 years, range 20.0-21.0 years
  - Weight: median 61.7 kg, range 7.4 kg
  - Height: median 169 cm, range 5 cm

- **Patients with chronic pain:**
  - Facilitated TSP, impaired CPM
  - Group 1: 30 female, 15 male
  - Age: 48.0 ± 12.5 years

- **Group 2:**
  - Normal TSP, impaired CPM
  - 101 female, 47 male

- **Group 3:**
  - Facilitated TSP, normal CPM
  - 30 female, 15 male

- **Group 4:**
  - Normal TSP, normal CPM
  - 69 female, 53 male

- **n = 400**
A) Single-point pressure algometry (hand-held):
- 1 cm² probe
- lower limb: m. tibialis anterior

B) CPA:
- double-chamber tourniquet cuff (width 13 cm)
- lower leg at the level of the head of m. gastrocnemius
- conditioning stimulus: inflation of 7.5 cm wide cuff to constant pressure 60 kPa
- test stimulus: PPT on ipsilateral lower leg

MPDT (kPa)

<table>
<thead>
<tr>
<th>Group</th>
<th>&lt; 65 years</th>
<th>&gt; 65 years</th>
<th>&lt; 65 years</th>
<th>&gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>143 ± 52</td>
<td>178 ± 76</td>
<td>135 ± 78</td>
<td>135 ± 78</td>
</tr>
<tr>
<td>B</td>
<td>227 ± 63</td>
<td>199 ± 59</td>
<td>123 ± 45</td>
<td>123 ± 45</td>
</tr>
<tr>
<td>C</td>
<td>214 ± 39</td>
<td>234 ± 47</td>
<td>152 ± 36</td>
<td>152 ± 36</td>
</tr>
<tr>
<td>D</td>
<td>258 ± 42</td>
<td>268 ± 49</td>
<td>124 ± 54</td>
<td>124 ± 54</td>
</tr>
</tbody>
</table>

No significant difference in PPTs was found between the groups. Group D showed significantly higher PDT values compared with groups A and B and higher PTT values compared with group A.

TSP: Significantly less TSP: B, C, D compared with A; C, D comp. with B.

CPM: Groups A and C showed significantly impaired CPM compared with groups B and D. No significant difference was found between the groups with facilitated and normal TSP.

Patients showed lower PPTs compared with controls.

TSP in patients was significantly facilitated compared with controls.

CPM: Unsignificant impairment in patients compared with controls.

Age correlated significantly with pain thresholds but not TSP or CPM.
Table 1: Summary of studies reviewed. Abbreviations: Circ. – Lower leg circumference; CPM - Conditioned Pain Modulation; cPPT - Cuff Pressure Pain Threshold; cPTT - Cuff Pressure Pain Tolerance; CPP - Cuff Pressure Pain Tolerance; Cuff PTT - Cuff Pressure Pain Tolerance; MPDT - Mild Pain Detection Threshold, OA - Osteoarthritis; PDT - Pain Detection Threshold; PPT - Pressure Pain Threshold; PTT - Pain Tolerance Intensity; TTK - Pain Tolerance Threshold; RA - Rheumatoid Arthritis; SSP - Spatial Summation of Pain; TS-index - Temporal Summation Index; TSP - Temporal Summation of Pain; VAScPTT - Score on the Visual Analogue Scale at cPTT; VAS at PTT - Score on the Visual Analogue Scale at PTT.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Experimental Procedure</th>
<th>Variables</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaeger et al. (2017a)</strong></td>
<td></td>
<td></td>
<td>Pain Thresholds (Mean ± SD):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPT (kPa)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A2</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>A3</td>
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<td></td>
<td></td>
<td></td>
<td>A4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cPPT (kPa)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cPTT (kPa)</td>
</tr>
<tr>
<td><strong>Vaeger et al. (2017b)</strong></td>
<td>Patients with chronic back pain: Cervical pain (CP): 12 female, 5 male</td>
<td>CPA: - double-chamber tourniquet cuff (width 13 cm) - left lower leg, 5 cm distal to the tibial tuberosity - inflation rate: 1 kPa/s; maximum pressure limit: 100 kPa - electronic VAS (0 - no pain, 10 - maximal pain), sampling at 10 Hz (cPPT: VAS &gt; 2 cm) - 2 repetitions - seated position</td>
<td>cPPT</td>
</tr>
<tr>
<td></td>
<td>Cervical radiating pain (CRP): 10 female, 7 male</td>
<td>TSP: - 10 repeated stimulations: 1 s of cPTT intensity, 1 s of 5 kPa - 3 mean values calculated: VAS I (stimulation 1-4), VAS II (stimulation 5-7) and VAS III (stimulation 8-10)</td>
<td>cPTT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assessment: CPA on left lower leg</td>
<td>VAScPTT</td>
</tr>
<tr>
<td></td>
<td>Low back pain (BP): 9 female, 9 male</td>
<td>cPPT: conditioning stimulus: infiltration of 7.5 cm wide cuff to constant pressure 30 kPa right lower leg, 8 cm distal to the tibial tuberosity</td>
<td>TSP</td>
</tr>
<tr>
<td></td>
<td>Cervical pain (CP): 12 female, 6 male</td>
<td>cPPT: - test stimulus: - conditioned pain modulator chamber tourniquet cuff (width 13 cm)</td>
<td>CPM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Pain thresholds (Mean ± SD):</td>
</tr>
<tr>
<td></td>
<td>Low back pain (BP): 9 female, 9 male</td>
<td>Patients with localized pain. CPM: Patients with CRP had a reduced CPM response compared with patients with CP.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low back radiating pain (BRP): 12 female, 6 male</td>
<td></td>
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</tr>
</tbody>
</table>
Table 2: Summary of PDT, PTT and PPT data across the studies. *The minimal and maximal values for patients are indicated in bold. PDT - Pain Detection Threshold, PPT - Pressure-Pain Threshold, PTT - Pain Tolerance Threshold.*

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>PDT (kPa)</th>
<th>CPA</th>
<th>PTT (kPa)</th>
<th>Single-point algometry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td>Controls</td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Jespersen et al. (2007)</td>
<td>64</td>
<td>15</td>
<td>20</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>Amris et al. (2010)</td>
<td>81</td>
<td>9</td>
<td>-</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>Lemming et al. (2012)</td>
<td>35</td>
<td>18 - 23</td>
<td>23 - 29</td>
<td>39 - 52</td>
<td>50 - 62</td>
</tr>
<tr>
<td>Graven-Nielsen et al. (2012)</td>
<td>69</td>
<td>25 - 34</td>
<td>35 - 42</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jespersen et al. (2013)</td>
<td>60</td>
<td>21 - 23</td>
<td>25 - 36</td>
<td>51 - 62</td>
<td>56 - 80</td>
</tr>
<tr>
<td>Skou et al. (2013)</td>
<td>17</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skou et al. (2013)</td>
<td>40</td>
<td>10 - 19</td>
<td>-</td>
<td>25 - 53</td>
<td>-</td>
</tr>
<tr>
<td>Amris et al. (2014)</td>
<td>271</td>
<td>12 - 15</td>
<td>-</td>
<td>31 - 37</td>
<td>-</td>
</tr>
<tr>
<td>Henrikse et al. (2014)</td>
<td>48</td>
<td>18</td>
<td>19</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vladimirova et al. (2015)</td>
<td>76</td>
<td>16</td>
<td>25</td>
<td>41</td>
<td>56</td>
</tr>
<tr>
<td>Vaegter et al. (2016)</td>
<td>61</td>
<td>18 - 29</td>
<td>-</td>
<td>46 - 58</td>
<td>-</td>
</tr>
<tr>
<td>Soriano-Maldonado et al. (2016)</td>
<td>100</td>
<td>19</td>
<td>-</td>
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<td>Vaegter and Graven-Nielsen (2016)</td>
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4. Discussion

4.1. Participants

The literature search for this review specifically targeted studies of CPA on patients with chronic pain. The results of our search indicate that most of the research focused on middle- or older-age adults with chronic musculoskeletal pain or osteoarthritis. As these conditions also hamper mobility, we believe these groups are a reasonable reflection of potential candidates for assistive soft exoskeletons for mobility.

4.2. Pressure-induced pain thresholds in patients with chronic pain

The studies reviewed reveal a common pattern in pressure-pain sensitivity in patients with chronic pain, indicating hypersensitivity to mechanical stimulation.15

When CPA was performed using both chambers of a double-chambered cuff at the lower leg, the mean PDT levels were under 20 kPa (median 17.9 kPa) for patients in 19 of 28 cases, and the mean PTT levels under 40 kPa (median 38 kPa) in 14 of 24 cases. Compared to the PPTs of healthy participants, that we found in our previous review (PDTs typically 20-27 kPa, PTTs typically over 40
kPa), these levels are notably lower, which needs to be considered by exoskeleton developers. On the other hand, higher pain sensitivity was found in the lower limb compared to the upper limb both in patients and healthy controls, and the rating of unbearable pain intensity on the VAS was similar between patients and healthy controls.

Generalized hyperalgesia was found in patients with widespread pain as well as patients with localized primary pain, indicating changes in central pain modulating mechanisms. Although these changes show heterogeneity across different diagnoses, in general facilitation of pronociceptive mechanisms (TSP) and impairment of antinociceptive mechanisms (CPM) was found, indicating central sensitisation. Because of central sensitisation, pain thresholds at all sites of the body are lower than normal, which needs to be considered when components of the exoskeleton interface with segments other than the lower limbs. However, no significant differences in SSP were found between healthy controls and patients, and the central pain-modulating mechanisms were not significantly influenced by increasing age in the studies reviewed.

4.3. Differences across the reviewed studies

4.3.1 Pressure-induced pain thresholds

The reviewed studies report over threefold differences in patients’ PDTs and PTTs, and over twofold differences in healthy controls’ PDTs and PTTs. As the prominent outliers occur together in certain studies, and the thresholds differ largely among the healthy control groups as well, we expect that the differences might be mostly due to the assessment methods and use of subjective rating scales.

4.3.2 Assessment methods

The assessment of TSP differed among the studies according to the number and duration of the mechanical stimuli and the magnitude of compression. The tonic stimuli lasted 6-10 minutes and their magnitude was set to either 25 kPa, 125 % of PDT or the mean between the assessed PDT and PTT. The 6-minute tonic stimulation was therefore performed at 22.8-23.9 kPa of compression, and the 10-minute tonic stimulation was performed at 28.5-63.7 kPa of compression. The intermittent stimulation consisted of 10 consequent compressions of different magnitudes and durations. Stimulations that lasted 1 second were performed at either the mean value of PDT and PTT (16.5-58.8 kPa), or at PTT (40.2-75 kPa); the 2-second stimulation was performed at PTT (46.3-57.6 kPa). The inter-stimulus intervals ranged from 1 to 2 seconds. As sustained constant pressure was previously shown to result in adaptation to pain in healthy adults, whereas oscillating pressure caused an increase in pain intensity with time, the comparison of these results may not be adequate.
4.3.3. Terminology and definition of pressure-induced pain thresholds

As discussed in our previous systematic review, the terminology and definitions of measured parameters in CPA need to be standardized. In the articles reviewed, the pressure magnitude at which pain occurs was termed Cuff Pressure-Pain Threshold (cPPT, Cuff PPT), Mild Pain Detection Threshold (MPDT), or Pain Detection Threshold (PDT); and the pressure magnitude that causes unbearable pain was termed Cuff Pressure-Pain Tolerance (cPTT, Cuff PTT), or Pain Tolerance Threshold (PTT).

Moreover, PDT was defined as the pressure magnitude when the rating on VAS either exceeded 0 cm, was equal to 1 cm, or exceeded 2 cm, and 5 studies did not explicitly define the rating on VAS at PDT. To enable comparison of the results across studies, we propose that experimental procedures and scientific reports follow a well-defined standard.

4.4 CPA-derived guidance for the development of soft exoskeleton circumferential pressure

We note that there have been several different approaches employed so far in the study of external loading of the human body during the use of devices that assist with locomotion, ranging from animal studies, computer simulations, artificial tissue testing, human cadaveric tissue testing, and usability testing on humans.

Computer simulations of exoskeleton interactions and physical experiments performed on artificial or cadaveric tissues lack the realism of functional anatomical structures, such as nerves, blood and lymph vessels, and homeostatic mechanisms, as in human beings. While efficiently simulating the gross biomechanics of human-robot interactions does provide highly valuable design insights, such testing approaches have many limitations by way of the complete effect on living tissues.

There are limited published studies on testing of exoskeletons performed on humans in vivo. Many focus on the measurement of interface pressures alone while offering little insight into the effects of the external loading/assistance on perception of comfort, and soft tissue viability and physiology. We were only able to find one previous study of perceived pressure, and one where algometry was performed in the context of tissue loading by wearable devices. In the latter study, pressure sensitivity was assessed at 9 anatomical points on the lower limb using single-point algometry where large differences were identified, with PDTs ranging from 282-628 kPa. As discussed in our previous paper, that study emphasized that the limits were not valid for sustained non-punctual external loading.

As pain is a good indicator of potential tissue damage caused by overpressure, CPA is possibly the most relevant method to use to inform soft exoskeleton design. However, it does not provide insight into the pre-pain discomfort perception or the influence of cyclical compression during walking. Therefore, we propose a modification of this method to better simulate the loading of soft tissues during the use of wearable robots that apply intermittent pressure (e.g. to promote movement of joints) or tonic pressure (e.g. to inhibit movement of joints) to the lower limbs for longer durations.
Moreover, wearable devices should not cause pain nor discomfort, therefore we suggest adapting algometry to measuring discomfort. Further research is needed to understand whether the described physiological mechanisms of pain perception apply to the perception of discomfort as well. Finally, we acknowledge that the reported PDTs and PTTs represent cuff-inflation pressures and not the interface pressure. Although both have been found to be directly related and to not differ significantly when using a 6 cm wide cuff, the exact relationship between cuff-inflation and interface pressure still needs to be established.

4.5 Limitations
The present review summarizes pain-inducing pressure thresholds achieved by CPA in patients with chronic pain. We propose that these results can help inform safe thresholds for circumferential compression of the lower limbs in potential wearable robotics users. However, the pressures reported are cuff-inflation pressures and not interface pressures, and the exact relationship between the two still needs to be further studied. Moreover, CPA studies focus on painful mechanical loading of tissues and do not provide insight into the pre-pain discomfort perception which is the point of interest in wearable robotics design. Finally, CPA testing is performed in static conditions with the participant in a supine position, and with compression of short durations, thus more research is needed to understand the development of discomfort during longer durations of cyclical compression in the upright position, as applied during the use of soft lower-limb exoskeletons.

5. Conclusions
For this review, we identified 18 studies where computerized cuff pressure algometry was performed on patients with chronic pain. Most of the patients identified were middle- or older-age adults with chronic musculoskeletal pain or osteoarthritis.

The patients’ mean levels for PDT at the lower leg were typically under 20 kPa (median 17.9 kPa), and the mean PTT levels under 40 kPa (median 38 kPa), which is notably lower than the pressure-induced pain thresholds of healthy participants (PDTs typically 20-27 kPa, PTTs typically over 40 kPa).13 Significantly higher pain sensitivity was found in the lower limb compared to the upper limb, and with wider tourniquet cuffs. Furthermore, in patients both sustained constant pressure and oscillating pressure caused an increase in pain intensity with time. As patients with chronic pain are potential candidates for gait-assistive soft exoskeletons, hypersensitivity to pressure-induced pain needs to be considered when designing the physical human-device interface.

The results acquired by cuff pressure algometry give important insight into the relationship between external loading and pain in patients with chronic pain. We believe that a modification of this method
could be used to gain insight into the development of discomfort during longer durations of cyclical compression, which may occur when soft robotics are used for wearable assistive device applications.

6. Acknowledgements

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7. References


