Nonpainful wide-area compression inhibits experimental pain

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Abstract

Compression therapy, a well-recognized treatment for lymphoedema and venous disorders, pressurizes limbs and generates massive non-noxious afferent sensory barrages. The aim of this study was to study whether such afferent activity has an analgesic effect when applied on the lower limbs, hypothesizing that larger compression areas will induce stronger analgesic effects, and whether this effect correlates with conditioned pain modulation (CPM). Thirty young healthy subjects received painful heat and pressure stimuli (47°C for 30 seconds, forearm; 300 kPa for 15 seconds, wrist) before and during 3 compression protocols of either SMALL (up to ankles), MEDIUM (up to knees), or LARGE (up to hips) compression areas. Conditioned pain modulation (heat pain conditioned by noxious cold water) was tested before and after each compression protocol. The LARGE protocol induced more analgesia for heat than the SMALL protocol ($P < 0.001$). The analgesic effect interacted with gender ($P = 0.015$). The LARGE protocol was more efficient for females, whereas the MEDIUM protocol was more efficient for males. Pressure pain was reduced by all protocols ($P < 0.001$) with no differences between protocols and no gender effect. Conditioned pain modulation was more efficient than the compression-induced analgesia. For the LARGE protocol, precompression CPM efficiency positively correlated with compression-induced analgesia. Large body area compression exerts an area-dependent analgesic effect on experimental pain stimuli. The observed correlation with pain inhibition in response to robust non-noxious sensory stimulation may suggest that compression therapy shares similar mechanisms with inhibitory pain modulation assessed through CPM.

Keywords: Conditioned pain modulation, Mechanical compression, Heat pain, Lymphatic drainage therapy, Compression-induced analgesia

1. Introduction

Endogenous analgesia (EA) is a centrally mediated mechanism that inhibits pain at the spinal level by a "top–down" modulation system, based on a cortico–brain–stem–spinal pathway.[21,55] Endogenous analgesia is based on several mechanisms that can exert pain inhibition. One of the most explored mechanisms of pain modulation is "diffuse noxious inhibitory controls" (DNIC), which represents the phenomenon of "bottom–up" activation of the EA system, mediated by activation of the spino–bulbo–spinal loop.[7,8] The DNIC mechanism is tested psychophysically in humans in the laboratory using the conditioned pain modulation (CPM) paradigm. In this paradigm, an ascending noxious input from a remote (heterotopic or extrasegmental) body area ("conditioning stimulus" [CS]) exerts descending analgesia on the perception of another noxious stimulus ("test stimulus").[72] It is of importance to clarify that beyond CPM, there are several different physiological mechanisms that exert pain inhibition (eg, distraction from painful stimulus,[68] stress-induced analgesia,[10] and vagal activity–related analgesia[27]). These pain inhibitory mechanisms may either stand-alone or be complementary to each other.[35,51]

It has been postulated that 2 factors related to the CS contribute to the efficacy of the DNIC/CPM response: its painfulness and its area. Indeed, the results of many studies point to a moderate positive association between the level of pain induced by the CS and CPM efficiency.[19,57,71] Nevertheless, others showed that painfulness of the conditioning stimuli is not a necessary condition for exerting attenuation of the test stimulus pain; inhibitory effects of non-noxious sensations, such as tonic heat,[38] vibrotactile,[44,64] gastric distention,[11] and deep breathing,[4] have been observed on the perception of various noxious stimuli (electrical stimulation, phasic heat stimuli, and heat pain thresholds).[11,34,37,38] Further-more, it is well established that a larger area for conditioning stimulation exerts stronger pain inhibition, probably because of the effect of spatial summation.[12,36,47] Such a spatial summation effect was also reported for non-noxious sensation,[28,34,46] and therefore may also be relevant for the pain-inhibiting effect of non-noxious "conditioning."

Lymphatic drainage therapy (LDT), also known as compression therapy, is a well-recognized treatment for lymphoedema and venous disorders.[9,29,70] Compression therapy systems include tubular bandages which are inflated to squeeze the limb,

press the liquids up, improve venous return, and reduce edema. In addition to the main effect on the lymphatic system, application of increasing air pressure in the bandages results in massive non-noxious afferent sensory input that may theoretically exert EA. The aim of this study was to explore the effect of LDT-induced mechanical compression on the perception of experimental heat pain stimuli. We hypothesized that the compression will induce pain attenuation and that a larger size of the compression area will exert greater pain attenuation. In addition, we expected that the extent of compression-induced analgesia (CIA) will correlate with CPM efficiency.

2. Methods

2.1. Subjects

The study sample included 30 paid healthy right-handed volunteers (15 men and 15 women), ranging in age from 20 to 40 (mean ± SD: 26.5 ± 3.4 years). Subjects were mainly students recruited by advertisement. The Institutional Review Board of Rambam Health Care Campus approved the study protocol in accordance with the Declaration of Helsinki, and written consent was obtained from each subject before the beginning of the experiment. Participants were enrolled in the study after meeting the following criteria: (1) age above 18 and below 40; (2) absence of acute or chronic pain disorders; (3) no reports of psychiatric, cognitive, and/or neurological disorders; (4) no drugs including, analgesics or antianxiety medications on regular use (except for oral contraceptives); and (5) ability to give informed consent, communicate, and understand the purpose and the instructions of the study.

2.2. Instruments and stimulation parameters

(1) Mechanical compression of the lower limbs was applied by the Lympha Press Optimal® and Lympha Pants® (Mego Afek, Afek AC, Israel) mounted up to the greater trochanter of the femur. The pants contain 24 partially overlapping inflatable cells, which allow compression of different regions of the lower limb. The compression was applied with constant air pressure of 60 mm Hg which is less than the diastolic blood pressure in the area.
(2) The heat test stimulus was 30 second-long tonic heat delivered at fixed temperature of 47°C. As was shown by our studies, this temperature evoked moderate pain sensation.[25,27] This was delivered by a contact-heat Thermal Sensory Analyzer 2001 system (Medoc, Ramat-Yishai, Israel), which delivered the heat stimulations by a 30 × 30 mm Peltier surface stimulator, attached by Velcro straps to the volar surface of the forearm of the subjects' left hand. Baseline temperature was 32.0°C, with an increasing temperature rate of 1°C/s and a return-to-baseline temperature rate of 8°C/s.
(3) The pressure test stimulus was 15 second-long tonic pressure delivered at the fixed intensity of 300 kPa. This stimulation intensity was chosen based on moderate pain scores obtained in our small pilot study. This was delivered by a Computerized Pressure Algometer (AlgoMed; Medoc) with a flat 1-cm² circular probe covered with 1-mm thick rubber. The pressure was applied perpendicular to the dorsal aspect of the distal forearm (between the radius and ulna on the extensor retinaculum). The pressure was measured by kilopascal units. Baseline pressure was 0 kPa, with an increasing rate of 50 kPa/s.
(4) The CS was 65 second-long water immersion. This was delivered by a plastic container, 39 × 28 × 14 cm, with cold water maintained at 8 to 10°C. The temperature was maintained by repeatedly adding ice and constantly monitored

by a thermometer. The right foot of the subjects was immersed up to the level of the ankle.

Pain ratings of heat and pressure stimuli were assessed continuously by the computerized visual analog scale (COVAS), whereas pain intensity ratings from the CS were assessed verbally using numerical pain scale (NPS). Both scales are ranging from 0, denoting "no pain," to 100, denoting "the worst imaginable pain." Pain ratings to CS were obtained 10 and 20 seconds after the initiation and at the end of the CS (65 seconds).

2.3. Training session

At the beginning of the experimental session, all subjects underwent short training to familiarize them with the devices and with the sensations evoked by the various painful stimulation modalities. They were trained to report their perceived pain intensity using the NPS and the COVAS. The training included the following:
(1) Exposure to 3 short contact-heat stimuli (43, 45, and 47°C), each lasting for 7 seconds from the time that the stimulation intensity reached the destination temperature. The thermode was moved following each stimulus to a completely distinct adjacent area of skin.
(2) Exposure to 2 short pressure stimuli (150 and 400 kPa), each lasting for 7 seconds from the time that the stimulation intensity reached the destination pressure. Subjects were asked to rate the level of pain intensity induced by each stimulation using the COVAS.
(3) Exposure to cold water by immersing their foot in the container for 10 seconds. They were asked to rate the level of pain intensity by NPS at the end of the immersion.

2.4. Experiment protocol

All experiments were conducted in the same setting by 2 investigators. One investigator (O.B.-B.) managed the area of compression, and the other (L.H.) blinded to the area of compression and managed the sensory assessments. The test area was hidden from view by means of a stand with curtain that covered the subject from the chest downwards. The experiment was performed in a quiet room with an ambient temperature of 23°C. The pre- and post-compression assessments were performed in seated position. The full protocol is presented in **Figure 1**. After the familiarization stage, the experiment begun with delivery of heat and pressure baseline (precompression) "test stimuli" performed in a pseudo-random order. After a 10-minute break, as part of the standard CPM paradigm, subjects immersed their right foot into the cold water bath (the CS) for 65 seconds; at the 30th second, a repeat heat test stimulus was delivered. Note that the CPM response was assessed for the heat test stimulus only. Ten minutes after the baseline precompression CPM assessment, subjects were tested under 3 compression protocols while lying down, delivered by Lympha pants, each lasting 12 minutes after achieving the destination pressure. The compression protocols were performed in a random sequential order, in one session. In each protocol, the sustained compression was delivered to different areas of the limbs: (1) up to the ankles (SMALL), (2) up to the knees (MEDIUM), and (3) up to the hip joints (LARGE). During each compression protocol, the investigators confirmed with the subjects that the compression did not cause any pain or discomfort. In case of discomfort, the body position was changed until no longer uncomfortable. All participants received an explanation regarding the approximate duration of the compression protocol; no indications or suggestions were made regarding expected CIA.

Heat and pressure test stimuli were delivered sequentially during each compression protocol in the same order and manner
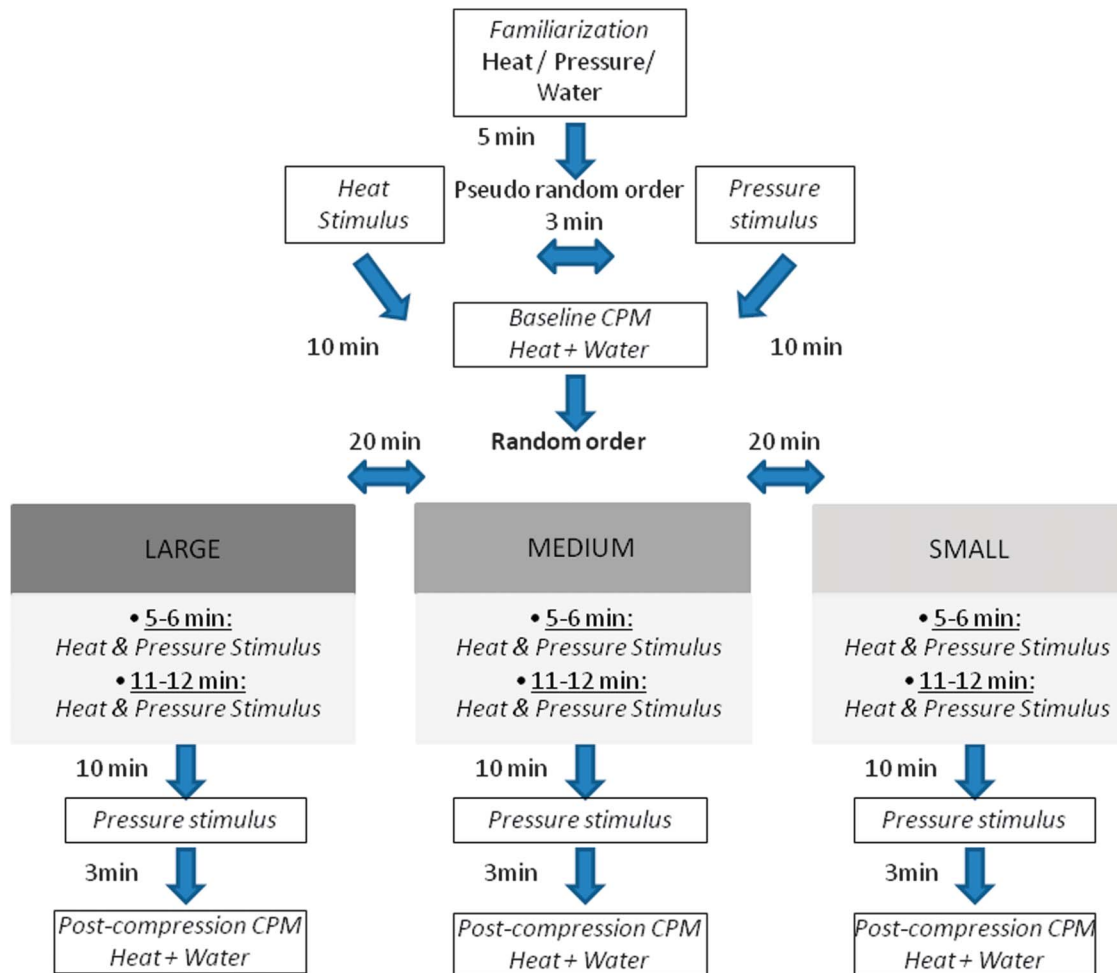
Figure 1. Schematic representation of the experimental design. CPM, conditioned pain modulation; SMALL, compression area up to the ankle; MEDIUM, compression area up to the knees; LARGE, compression area up to the hip joint.

as the baseline test stimulations, twice: at 5 to 6 and 11 to 12 minutes of the compression. Analgesic effect of each compression protocol was assessed as a difference between the heat or pressure pain scores obtained during the compression vs baseline (the CIA responses).

To evaluate possible residual analgesic effect, the pressure pain sensitivity was tested at 10 minutes after the completion of each compression protocol (**Fig. 1**). Following the postcompression pressure pain assessment, heat pain test stimulus combined with CS was delivered, and pain scores were obtained. The baseline CPM effect was calculated as the difference in mean pain ratings of the heat test stimulus delivered under CS vs the heat test stimulus delivered stand-alone. For the postcompression conditions, the CPM was calculated as the difference between the pain scores to heat test stimulus delivered under CS from precompression heat pain "test stimulus."

Negative values indicate efficient CPM or efficient CIA.

Twenty-minute rest intervals were provided in between each of the 3 compression protocols. The total duration of the experimental session was approximately 2 hours and 15 minutes.

2.5. Data analysis

Data were processed and analyzed using Excel (Microsoft Corp, Redmond, WA) and JMP (SAS Institute, Cary, NC) software. The results are expressed as mean ± SE, unless mentioned otherwise.

Two separate repeated-measures analyses of variance (rmANOVAs, using mixed models) were performed on the data. The first was a one-way model comparing the pain scores with the baseline precompression test stimulus pain scores with the pain scores of the test stimuli delivered under each compression protocol (termed SMALL, MEDIUM, and LARGE, based on the area of applied compression) at 2 time points of assessment (T1: 5-6 minutes; T2: 11-12 minutes), for males and females. This was to determine, by post hoc Tukey tests, whether there was any pain reduction at each individual time and protocol relative to baseline. The second model evaluated the effect of the compression protocols, the time points of test stimulus pain assessment, and the effect of gender and their interaction on the changes in pain perception relatively to the baseline pain scores (difference scores). Although this might have been accomplished with appropriate contrasts to the previous analysis, this analysis uses a simpler design to determine whether there are differences in pain reduction, with specific regard to time, compression protocol, and their interaction.

In addition, we also analyzed the postcompression CPM and pressure pain score data using 2 methods. Repeated-measures ANOVA (mixed model) used the compression protocol (baseline, SMALL, MEDIUM, and LARGE), gender, and their interaction. A second analysis model used difference scores of CPM and pressure pain relative to baseline. Repeated-measures ANOVA (mixed model) used the compression protocol (SMALL, MEDIUM, and LARGE), gender, and their interaction.

Pearson correlations were used to explore possible relations between the analgesic effect of each one of the compression protocols and (1) the pain ratings to the test stimulus under CS at baseline and (2) baseline CPM effect. In addition, the correlation analysis was applied for the CPM responses tested pre- and post-compression. Statistical significance was defined as $P \leq 0.05$.

3. Results

3.1. Subject subgroups based on test stimuli pain reports

The main aim of the study was to explore the analgesic effect of mild compression on painful experimental stimuli. During the data analysis, we noticed that some subjects experienced only mild pain from the "test stimuli." We therefore decided to report two sub-sets of analyses: for the whole group, and; for the sub-group of subjects whose mean COVAS score to the baseline test-stimuli was >20. Based on previous experience of our lab and other labs, pain scores <20 are considered as too mild a pain experience for inclusion in analyses.[3,26,73] Using this cutoff, we aimed to eliminate the possible floor effect on the precompression pain scores.

No subjects reported pain due to any compression protocol.

3.2. Compression-induced analgesia effect on experimental heat pain

For the whole group, a significant effect of the compression protocol ($P = 0.017$), with no effect of gender ($P = 0.776$), or significant compression protocol X gender interaction ($P = 0.062$). Overall, the heat pain scores decreased significantly following the LARGE protocol from 38.6 ± 2.9 (baseline) to 31.8 ± 2.9 at T1 ($P = 0.013$) and to 32.2 ± 2.9 at T2 ($P = 0.023$). Nonsignificant decrease from the baseline was observed for SMALL (35.4 ± 2.9, $P = 0.689$, T1 and 35.0 ± 2.9, $P = 0.543$, T2) and MEDIUM protocols (33.6 ± 2.9, $P = 0.153$, T1 and 34.3 ± 2.9, $P = 0.307$, T2). The males and females were no different in their baseline heat pain perception (43.8 ± 4.5 and 44.3 ± 4.1, respectively, $P = 0.1$). Males and females were also of same age: 26.5 ± 2.8 (mean $\pm$ SD) and 26.4 ± 4.0 years, respectively.

For the group of subjects with the mean heat pain scores >20, N = 24 (26.2 ± 3.0 years, 13 females), significant effect of the compression protocol ($P < 0.001$) was in interaction with gender ($P = 0.015$), rmANOVA. More specifically, the heat pain scores assessed at both time points during the LARGE compression protocol were lower than the baseline pain scores ($P = 0.001$ for T1 and $P = 0.002$ for T2). In addition, pain assessed at T1 during the MEDIUM compression protocol was also significantly lower than the pain at baseline ($P = 0.005$), **Figure 2A**. The interaction with gender was based on the lower pain scores during the MEDIUM protocol in males ($P = 0.030$, T1) and during the LARGE protocol in females ($P = 0.050$, T2), **Figure 2B**.

Second rmANOVA model indicated that greater extent of pain reduction relative to baseline ($P = 0.025$) was due to the LARGE as compared with the SMALL protocols ($P = 0.019$), with no effect of the assessment time points ($P = 0.434$). Significant interaction between the stimulation protocol and gender pointed to greater analgesic effect of the MEDIUM as compared with the SMALL protocol in males ($P = 0.013$), and of the LARGE as compared with the MEDIUM protocol in females ($P = 0.047$), **Figure 2C**.

3.3. Compression-induced analgesia effect on experimental pressure pain

For the whole group, there was neither a significant effect of the compression protocol at either time ($P = 0.332$) nor effect of

gender ($P = 0.106$), or compression protocol at either time X gender interaction ($P = 0.855$). Across all conditions, the pressure pain scores were in the range between 17.9 ± 3.1 and 24.9 ± 3.1. The males and females were no different in their baseline pressure pain perception (21.1 ± 4.4 vs 28.6 ± 4.4, respectively, $P = 0.277$).

For the group of subjects with the mean pressure pain scores >20, N = 17 (26.9 ± 3.9 years, mean $\pm$ SD, 10 females), there was a significant effect of the stimulation protocol at either time ($P = 0.010$) with no effect of gender ($P = 0.592$), or compression protocol at either time X gender interaction ($P = 0.833$). The post hoc analysis revealed that except the T2 time point of LARGE protocol stimulation, the pressure pain scores under all compression protocols were lower than those assessed at baseline (**Fig. 3A**), with no difference between males and females (**Fig. 3B**).

As shown by the ANOVA on pain reduction, no difference in the extent of pressure pain reduction across the compression protocols, relative to baseline, was observed ($P = 0.857$), with no effect of gender ($P = 0.835$), or assessment time points ($P = 0.724$), **Figure 3C**.

In addition, we tested the postcompression effect on the pressure pain scores in the group of 17 subjects. The results were similar to those obtained during the compression: lower pain scores obtained 10 minutes after completing each compression protocol ($P < 0.001$), with no effect of gender ($P = 0.704$), or compression protocol X gender interaction ($P = 0.228$). The second rmANOVA model confirmed that there was no difference in extent of pressure pain reduction between the compression protocols ($P = 0.545$), with no interaction with gender ($P = 0.112$).

3.4. Effect of the compression area on conditioned pain modulation efficiency

The CPM response was calculated for subjects whose pain scores to the test stimulus was >20.

There was a significant effect of the stimulation protocol ($P = 0.032$) that was in interaction with gender ($P = 0.025$). The post hoc analysis indicated that CPM assessed after MEDIUM protocol was more efficient that after the SMALL protocol ($P = 0.019$) (**Fig. 4A**), with no difference between males and females. The interaction with gender was based on the lower CPM response after the SMALL protocol in males as compared with the baseline ($P = 0.041$) (**Fig. 4B**).

The second rmANOVA model indicated that the changes in the CPM response after exposure to the compression protocols ($P = 0.015$) were due to the increased CPM efficiency after the MEDIUM protocol and reduced CPM efficiency after SMALL protocol ($P = 0.011$), relative to baseline. This effect was mainly attributed to males but not females ($P = 0.038$; compression protocol X gender interaction $P = 0.032$), **Figure 4C**.

The pain scores of the CS were no different across the baseline and postcompression CPM assessments (45.8 ± 3.7 at baseline, 49.0 ± 3.7 after the SMALL protocol, 47.7 ± 3.7 after the MEDIUM protocol, and 48.5 ± 3.7 after the LARGE protocol; $P = 0.203$). A trend for overall higher pain scores was observed for females (54.1 ± 5 vs 41.5 ± 5, $P = 0.088$); however, this borderline effect of gender was not in interaction with the stimulation protocol ($P = 0.855$).

All subjects rated the baseline water pain >20 on NPS.

3.5. Comparison between conditioned pain modulation and compression-induced analgesia (N = 24)

Baseline CPM was more efficient than each of the CIA protocols (averaging across CIA at T1 and T2, $P < 0.001$). More specifically,
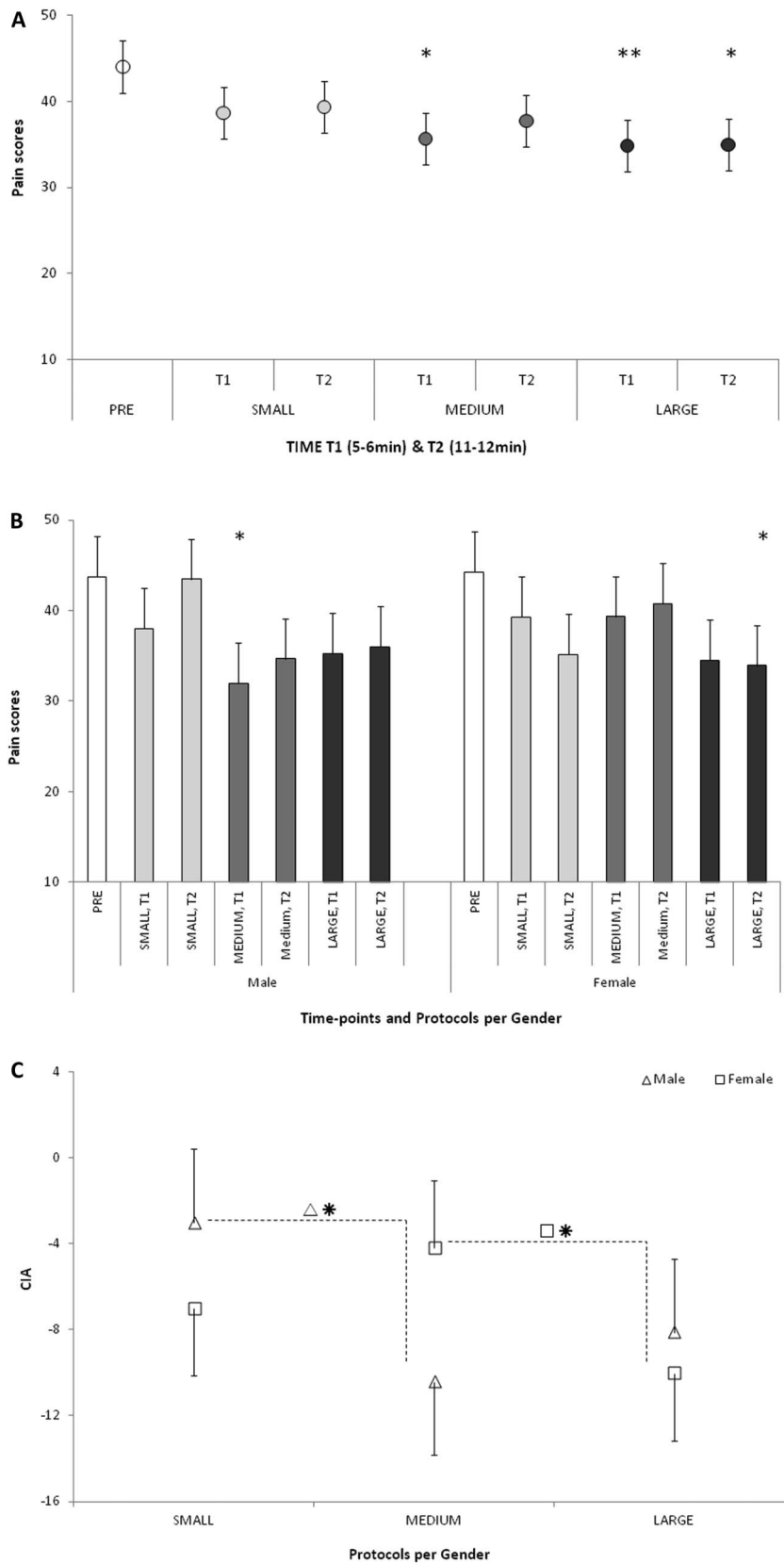
Figure 2. The CIA effect on heat pain scores in 3 compression protocols. (A) Overall, significant pain reduction from the precompression baseline was observed during MEDIUM protocol at T1, and during LARGE protocol at T1 and T2. (B) For males, the maximal pain reduction from the baseline was observed at T1 during MEDIUM protocol; for females, the maximal pain reduction was observed at T2 during LARGE protocol. (C) In males, the MEDIUM protocol induced more efficient CIA than the SMALL protocol; in females, the LARGE protocol induced more efficient CIA than the SMALL protocol. $*P \leq 0.05$; $**P \leq 0.01$. CIA, compression-induced analgesia; SMALL, compression area up to the ankle; MEDIUM, compression area up to the knees; LARGE, compression area up to the hip joint.
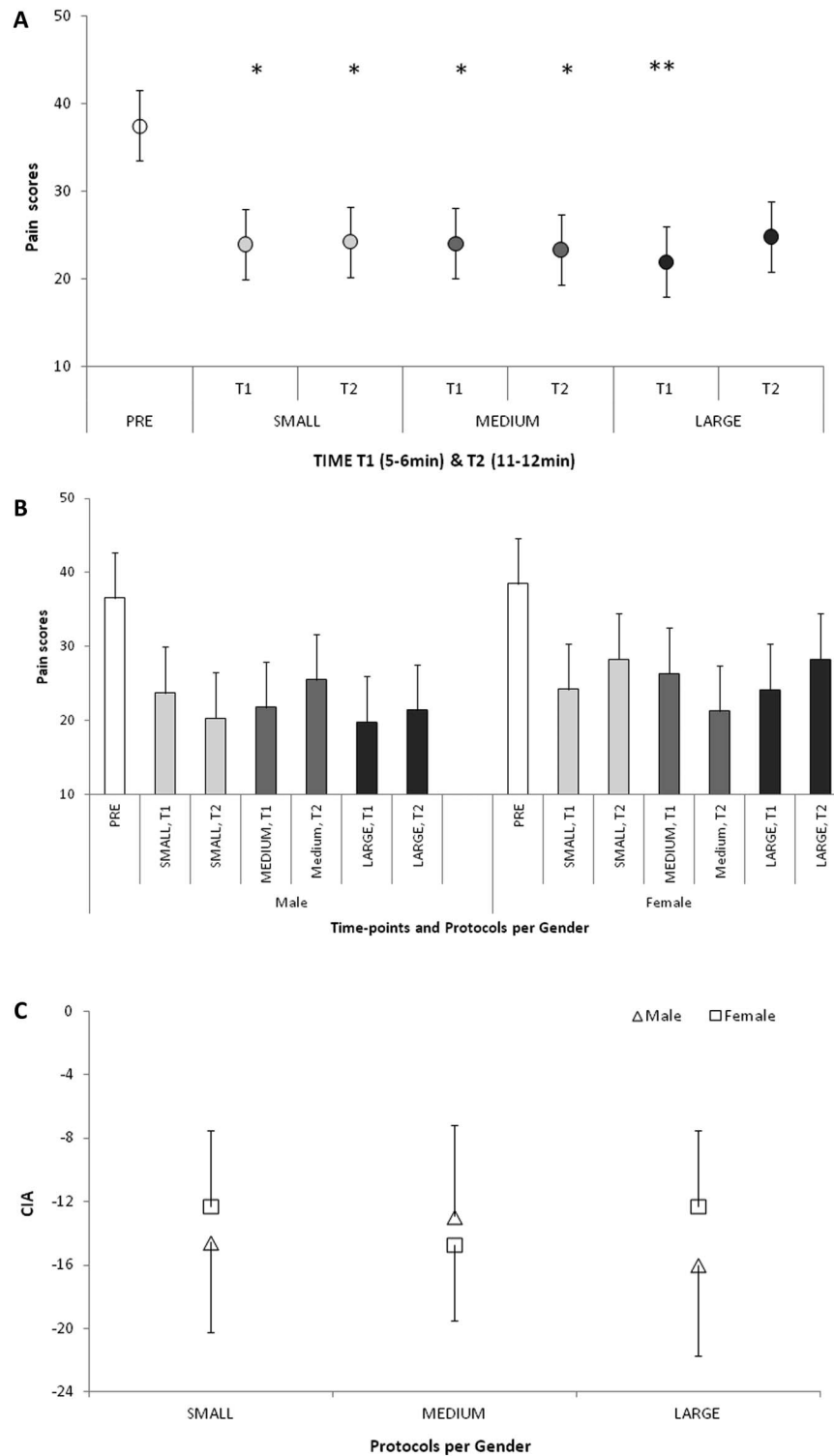
Figure 3. The CIA effect on the pressure pain scores in 3 compression protocol. (A) Overall, significant pain reduction from the precompression baseline was observed during all compression protocols at both T1 and T2 time points, except the pain scores at T2 during the LARGE protocol. (B) No gender differences were observed for the maximal pain reduction. (C) No differences in the efficiency of 3 compression protocols between males and females. *$P \leq 0.05$; **$P \leq 0.01$. CIA, compression-induced analgesia; SMALL, compression area up to the ankle; MEDIUM, compression area up to the knees; LARGE, compression area up to the hip joint.

baseline CPM (-14.3 ± 2.3) was more efficient than the CIA for SMALL (-5.0 ± 2.3, $P < 0.001$) and for MEDIUM compression protocols (-7.3 ± 2.3, $P = 0.004$). A borderline difference was found between the CPM and the CIA for LARGE protocol (-9.1 ± 2.3, $P = 0.055$). No effect of gender or gender interaction was observed.

Positive correlation was found between the heat pain scores obtained during foot water immersion (the conditioned test stimulus) and the heat pain scores obtained during compression. This was demonstrated for each protocol at each time point (T1 and T2); LARGE ($r = 0.64$, $P < 0.001$; $r = 0.38$, $P = 0.001$, respectively), MEDIUM ($r = 0.37$, $P = 0.001$; $r = 0.38$, $P = 0.001$,
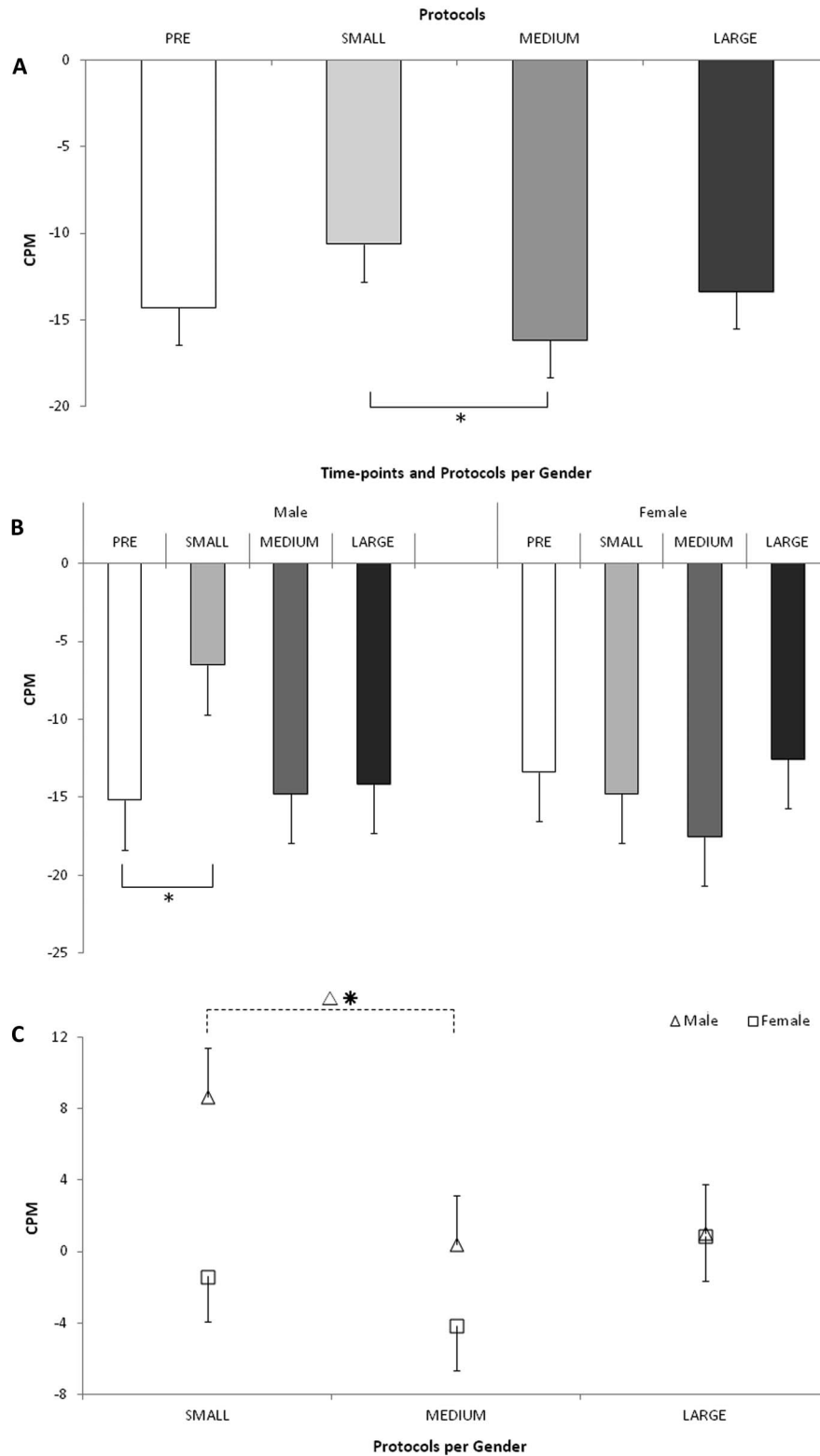
Figure 4. The CPM response at the precompression baseline and after 3 compression protocols. (A) Overall, no significant difference was found between the pre- and post-compression CPM assessment. However, the CPM was more efficient after the MEDIUM protocol as compared with the SMALL protocol. (B) For males, lower CPM efficiency was observed following the SMALL as compared with the MEDIUM compression protocols; for females, similar CPM responses were denoted across all conditions. (C) For males, the CPM efficiency was reduced from the baseline following the SMALL as compared with the changes in CPM efficiency following the MEDIUM protocol. *$P \leq 0.05$. CPM, conditioned pain modulation; SMALL, compression area up to the ankle; MEDIUM, compression area up to the knees; LARGE, compression area up to the hip joint.

respectively), and SMALL ($r = 0.46$, $P < 0.001$; $r = 0.46$, $P < 0.001$, respectively) (**Fig. 5**). Furthermore, a positive correlation was observed between the precompression CPM efficiency and the CIA at both time points in the LARGE stimulation protocol ($r = 0.42$, $P \leq 0.001$ at T1; $r = 0.24$, $P = 0.014$ at T2) (**Fig. 6**).

3.6. Spread of pain scores to the heat test stimuli under different conditions

In addition to the presented statistical analyses, we performed a descriptive analysis of the number of subjects that showed facilitation during different conditioning stimuli (water immersion or compression). Among 24 subjects, 1 subject had heat pain facilitation during the water immersion, meaning nonefficient CPM response; 9 subjects demonstrated the pain facilitation (nonefficient CIA) during the SMALL protocol, 7 subjects demonstrated nonefficient CIA during the MEDIUM protocol, and 6 subjects demonstrated nonefficient CIA during the LARGE protocol. Same subject who had nonefficient CPM demonstrated also nonefficient CIA during 3 compression protocols (see Fig. 1 in the Supplementary Materials, available online at http://links.lww.com/PAIN/A274). Despite the efficient CPM, 5 subjects had nonefficient CIA during 3 compression protocols.

4. Discussion

To the best of our knowledge, this is the first study to investigate the analgesic effect of LTD-evoked mechanical compression. The main finding of our study is that mild mechanical compression applied to the lower body reduces perception of remote experimental pain stimuli. Furthermore, this analgesic effect was larger for larger stimulation area (the compression up to the thigh vs ankle), thus confirming the contribution of spatial summation of non painful conditioning stimulation to pain attenuation. Furthermore, the CIA was positively correlated with the CPM effect, which may suggest that conditioned pain modulation and compression-induced inhibitory pain modulation share similar physiological mechanisms.

The analgesic effect of mild body compression is expected. There are many reports showing that non-noxious somatosensory stimuli exert inhibitory pain modulation; this was demonstrated for various sensations, including tonic heat and vibrotactile.[38,44,64] In line, some clinical procedures that involve nonpainful sensory stimulation, such as acupuncture,[39,40,65] TENS,[5,15,17,41,56] and hydrotherapy,[2,16,22,48] are applicable for pain treatment. Pain reduction evoked by non-noxious somatosensory stimulation was observed not only in the psychophysical level but also in the neurophysiological level. For example, light touch reduced amplitudes of cortical pain-evoked potentials reflecting decreased activity in the anterior cingulate cortices and primary somatosensory cortex.[44] Furthermore, brain-imaging studies showed that analgesic effect of electroacupuncture was associated with suppressive effect on the brain structures associated with the medial pain system (secondary somatosensory, cingulate and inferior frontal cortices, and amygdala) and involved in pain perception and processing. This suppression counteracts or minimizes the subsequent C-fiber–induced neuronal excitation mediated
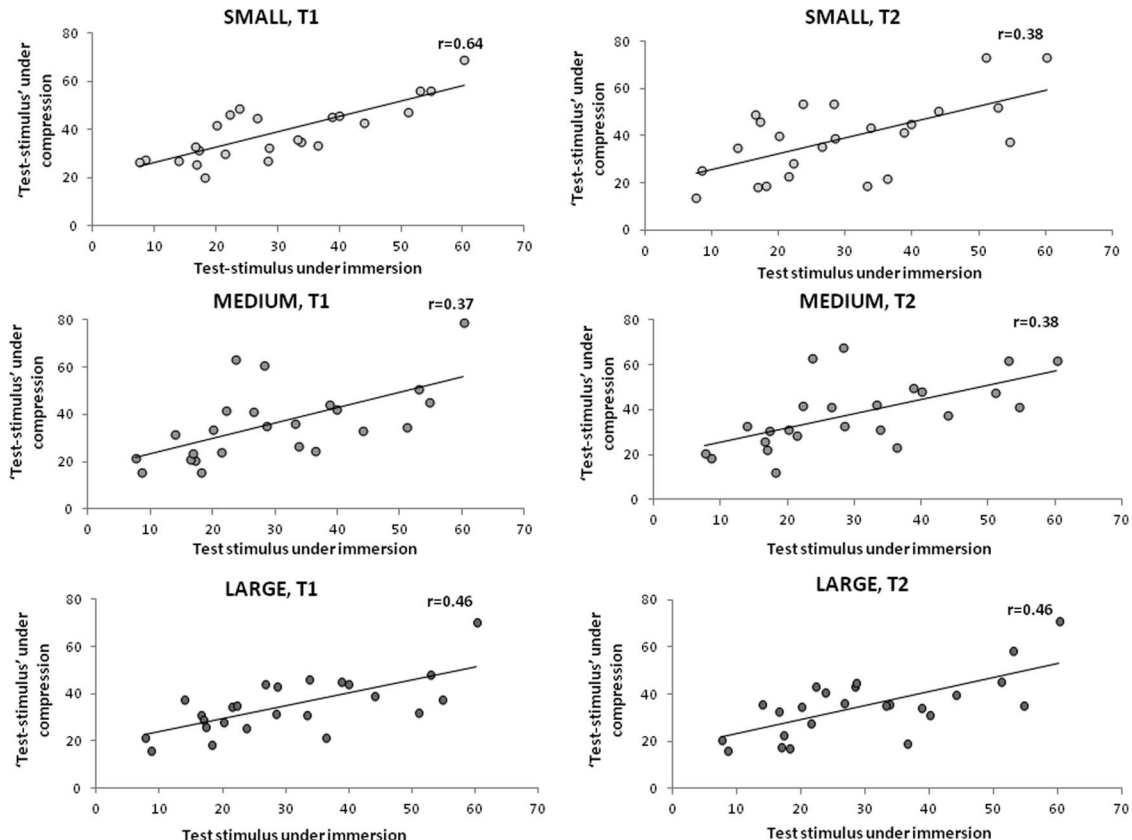

Figure 5. Relationship between the heat pain scores assessed under immersion at baseline and during each compression protocol. Significant correlations were found between the pain scores to test stimulus conditioned to water immersion, and heat pain scores to the test stimulus assessed during each of the compression protocols, at both testing time points. All $P \leq 0.001$. SMALL, compression area up to the ankle; MEDIUM, compression area up to the knees; LARGE, compression area up to the hip joint.
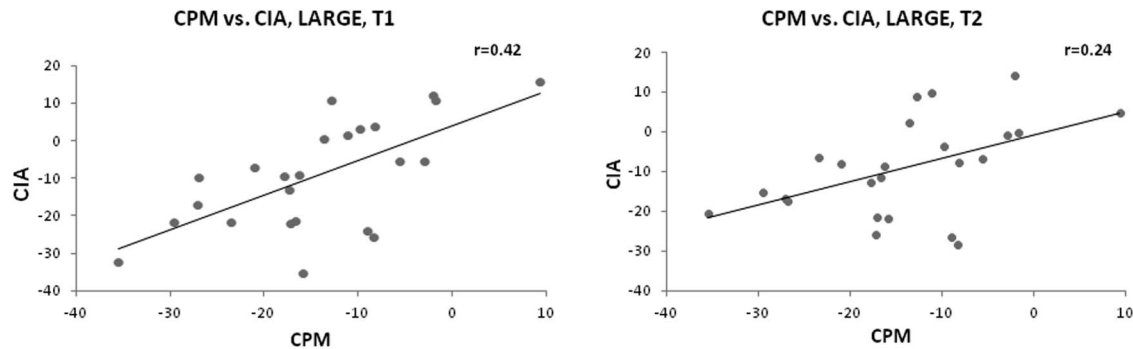
Figure 6. Relationships between CPM and CIA. Significant correlations were found between the baseline precompression CPM response and the CIA obtained during the LARGE protocol at both testing time points. All $P \leq 0.01$. CIA, compression-induced analgesia; CPM, conditioned pain modulation; LARGE, compression area up to the hip joint.

activation through the spinothalamic and spinopontoamygdaloid pain pathways.[63,65]

4.1. Mechanism underlying the analgesic effect of large-body compression

Compression-induced analgesia could arise from various underlying mechanisms, alone or complementary to each other, which may comprise different elements in the pain modulatory pathways:

(1) The large body area compression stimulus applied by air pressure may have an analgesic effect due to massive afferent sensory input, as was suggested by Wall and Melzack in their "Gate Control Theory of Pain"[49,69]; in which activity of large fibers (Aβ) exerts an inhibitory effect by supraspinal circuits on the small fibers (C), by specific circuitry in the dorsal horn, thus reducing pain. This theory may also explain the neurophysiologic and psychophysical effect of touch-induced analgesia in humans by inhibiting the activity of Aδ and C fibers.[40,44] It was suggested that the latter is mediated by a spinal/subcortical gating of the ascending nociceptive input, which sequentially results in the modulation of supraspinal cortical responses.[30,44,53] Importantly, wide dynamic range neurons within the spinal dorsal horn, which may be affected by DNIC, receive convergent input from both mechano receptive Aβ fibers and nociceptive Aδ and C fibers.[13] As such, the dorsal horn integrates ascending, descending, and intraspinal signals and may act as a modulator in the inhibition process.[66]

(2) The autonomic nervous system (ANS) may be another key player. Pain regulation is an integral component of the sympathetic and the parasympathetic systems. Parasympathetic activation induces pain inhibition, as demonstrated, for example, in the study of Sedan[62] in which parasympathetic activation by nonpainful gastric distension attenuated experimental pain response in healthy subjects, probably by gastric vagal afferents. In turn, reduced parasympathetic activity due to reduced vagal function in chemotherapy-induced neuropathy patients correlated with enhanced experimental pain.[52] Lymphatic drainage has significant effects on the ANS, expressed by dampening sympathetic activity while increasing parasympathetic activity and manifested by increase in heart rate variance and cardiac parasympathetic activity in normal subjects.[33] Venous velocity increases by 2- to 4-fold by the electronic LD device[18,32,74] along with an increase in intrathoracic pressure, blood pressure, and venous return.[67] These changes activate arterial and cardiopulmonary

baroreceptors, sensitive to increased blood pressure and volume, which in turn activates the endorphins-rich brainstem area at the vagal nerve nucleus, nucleus tractus solitarious, which allow interactions between cardiovascular and pain regulatory systems during respiration.[14] Indeed, activation of the nucleus tractus solitarious by baroreceptors decreases the vagal output to the heart and activates pain inhibitory mechanisms.[14,59]

(3) It is well established that excitability in the primary motor cortex (M1) is important for pain inhibition; enhancement of M1 excitability, for example by repeated transcranial magnetic stimulation, influences the nociceptive processing exerted directly at thalamic and spinal levels, and indirectly by activation of limbic, cortical, and subcortical structures associated with inhibitory pain modulation.[20,43,54] Increase in M1 excitability was also reported in response to large-area non-noxious somatosensory stimuli. This was demonstrated by reduced motor activity threshold, increased amplitude of motor-evoked potentials, and increased intracortical facilitation in response to whole-hand or whole-body water flow stimulation[60,61] and in response to whole-hand mesh-flow electrical stimulation.[23,24] Thus, the theoretical increase in M1 excitability in large-body compression can be attributed to CIA in our study.

(4) Attentional distraction affects the perception of painful stimuli.[42,51] We assume that distraction may be part of the CIA in our study because every compression protocol exercised pain reduction to some extent. However, because of significant effect of the compression area (LARGE vs SMALL) on pain reduction, we suggest that cognitive attention recruitment in response to a CS has a small role in our results.

(5) The conditioned pain modulation is one of the relevant physiological mechanisms that may explain our findings. Because DNIC influence wide dynamic range neurons, which are activated by nonpainful mechanical stimulation, it is reasonable to assume that the analgesic effect may occur because of the DNIC phenomena, given that the compression stimulus was not painful. The pre-eminent factor that influences both DNIC and CPM efficiency is the size of the CS. Several studies on both animals and humans have revealed that nociceptive activity increases concomitantly with the size of the surface area stimulated up to a certain point, after which its activity gradually decreases regardless of the continued augmentation in the size of the surface area stimulated.[12,45] These experiments demonstrate that spatial summation triggers inhibitory feedback mechanisms onto multireceptive neurons when the stimulated surface is 2-3

times larger than the initially stimulated area.[6,12] These results can be applicable to our findings on pain modulation by non-noxious mechanical compression when larger compression area exerted stronger heat pain reduction compared with the small compression area. Interestingly, the CIA effect on perceived pain was also detected 10 minutes after the end of compression. The poststimulation analgesic effect is not entirely surprising; as it is well known that the effect of DNIC can last for tens of minutes, depending on the stimulation paradigm.[58] In our case, the conditioning stimulation is more robust than in most studies reported, encompassing very large body areas, so this might contribute to its persistence. Additional evidence for similarity between CIA and CPM is that the pain perception of the test stimulus under cold-water immersion positively correlated with the test stimulus under compression, for all 3 compression protocols. Importantly, only for the LARGE compression protocol, the CPM was significantly correlated with CIA, additionally highlighting the role of stimulated area in producing pain inhibition.

Despite that, in general, the CPM was more efficient than the CIA, different compression protocols induced different CIA in males and females for heat pain. The greater analgesic effect in males was obtained in the MEDIUM protocol, whereas females had greater analgesic effect in the LARGE protocol. These findings can be attributed to greater muscle mass in males.[1,31,50] It is reasonable therefore to assume that the relatively low pressure used in the compression (60 mm Hg) was not enough to press the quadriceps muscle against the deep vein circumflex associated with the femur in males; whereas the same pressure was sufficient for females, thus reducing pain through the ANS for the MEDIUM compression protocol.

Furthermore, among the 3 compression-induced protocols, the more efficient CPM response was obtained after the MEDIUM compression protocol, and less efficient after the SMALL protocol. Because CPM was tested not during but minutes after completing compression, we suggest that stronger analgesic effect induced by the LARGE protocol reached a ceiling effect, such that no further pain reduction was obtained in the subsequent CPM assessment. In line with this explanation, the MEDIUM protocol that was less efficient in term of CIA, therefore, might have induced some additive effect on the consequently tested CPM response, explaining greater CPM efficiency after the MEDIUM compression protocol. Reduction of the CPM efficiency after the SMALL protocol was gender related and found in males. This finding is hard to explain. We may suggest that lower pain scores in males to foot immersion in cold noxious water (a CS) may have negative additive effect to SMALL compression protocol directed to the feet.

Our main study limitation is a small sample size for subjects who experienced pressure pain in baseline. This may be the reason for the dissimilarity between CIA on heat as compared to pressure pain; in contrast to its effect on heat pain, the CIA effect on pressure pain was similar for all applied compression protocols. Future study on larger samples is needed to conclude whether the CIA effect is modality dependent.

5. Conclusions

This study is the first to demonstrate that large-body area mild LDT compression exerts an analgesic effect on experimental pain stimuli. We suggest that CIA shares similar mechanisms with various facets of inhibitory pain modulation, when the mechanism of CPM seems to us a main contributing factor. We suggest, therefore, that compression therapy may be potentially used for pain treatment.

Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A274.

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