Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry

a reliability study

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ABSTRACT

Chronic musculoskeletal pain is linked with sensitization and standardized methodologies for assessment are needed. This study investigated 1) the test-retest reliability of computer-controlled cuff-pressure algometry (pain thresholds and temporal pain summation) on the arm and leg, and 2) conditioned pain modulation (CPM) assessed by cuff algometry. The influences of age and gender were evaluated. On two different days, cuff pain threshold (cPPT), cuff pain tolerance (cPTT), and temporal summation of pain (TSP) by visual analogue scale scores to 10 repeated cuff stimulations at cPTT intensity, as well as pressure pain threshold (PPT) with handheld pressure algometry were assessed in 136 healthy subjects. In one session cuff pain sensitivity was also assessed before and after the cold-pressor induced CPM. Good to excellent intraclass correlations (ICCs: 0.60 – 0.90) were demonstrated for manual algometry and cuff algometry and no systematic bias between sessions was found for cPPT, cPTT, and TSP on the leg, and cPTT and TSP on the arm. cPPT and cPTT were higher in men compared with women ($P<0.05$). Middle aged subjects had higher PPT, but lower cPPT and cPTT compared with younger subjects ($P<0.05$). TSP were increased in women compared with men ($P<0.05$). Cuff algometry was sensitive to CPM demonstrated as increased cPPT, cPTT and reduced TSP ($P<0.05$). Reliability and sensitivity of computer-controlled cuff algometry for pain assessment is comparable to manual pressure algometry and constitutes a user-independent method for assessment of pain. Difference in age-related pain sensitivity between manual and cuff algometry should be further investigated.

Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: A reliability study

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1. INTRODUCTION

Musculoskeletal pain is generally accepted to constitute a special diagnostic and therapeutic challenge and a mechanism-based understanding of the factors involved in musculoskeletal pain has gained acceptance in recent years [16]. Chronic musculoskeletal pain is linked with sensitization, initially in the peripheral structures and often later sensitization of central mechanisms [16]. Thus, there is a need for reliable methodologies to assess sensitization mechanisms quantitatively in chronic pain patients.

Handheld pressure algometry involving manually applied pressure stimulation to assess pain sensitivity of deep structures has been extensively used and validated [22]; computer-controlled stimulation may reduce variability and allow accurate construction of the stimulus-response function [18]. A large epidemiological study showed that pressure pain thresholds increased with age and were lower in women compared with men [23]. A meta-analysis has further demonstrated the sex difference in pressure pain thresholds [41]. More recent reference data based on 180 healthy subjects demonstrated that young women had lower pressure pain thresholds than young men but in older subjects no sex difference was detected although there was a general age-related increase in pressure pain thresholds [30]. In contrast to pressure algometry [10], a larger tissue volume can be assessed by computer-controlled cuff-algometry [36]. In cuff-algometry, the pain intensity related to inflation of a tourniquet applied around an extremity is used to establish stimulus-response curves allowing assessment of deep-tissue pain sensitivity. Moreover, cuff algometry is less likely to be influenced by local variations in pain sensitivity and is also an examiner-independent technique reducing the potential measurement bias. However, the test-retest reliability of cuff algometry is still to be determined.

The facilitated pain response to sequential stimuli of equal strength has been defined as temporal summation of pain and based on a central integrative mechanism. Temporal summation of pressure-induced pain was facilitated in osteoarthritis pain patients [1] and fibromyalgia patients [46] compared with healthy controls. Recently, also cuff-evoked temporal summation of pain was found to be facilitated in osteoarthritis pain patients compared with asymptomatic controls [45]. In contrast to the facilitatory effects in temporal summation of pain, the conditioned pain modulation (CPM) results in reduced pain sensitivity in healthy subjects. CPM is typically evoked by a painful conditioning stimulus (e.g. cold pressor test) and assessment of the heteronymous pain sensitivity by manual pressure algometry [37;55], although several other

paradigms have been used [37;55]. In chronic pain patients the CPM effect is often impaired [54]. Since the CPM paradigm is frequently used cuff algometry may potentially be used for CPM assessment.

The aims of the present study were to investigate test-retest reliability of computer-controlled cuff algometry and manual pressure algometry in healthy men and women as well as to determine the sensitivity of cuff algometry in response to CPM. It was hypothesized that 1) cuff and pressure algometry would demonstrate good reliability, 2) cuff algometry was sensitive to CPM, 3) women would show higher pain sensitivity compared with men, and 4) older subjects would demonstrate lower pain sensitivity compared with younger subjects.

2. MATERIALS AND METHODS

2.1 Subjects

In this study 136 healthy subjects between 18 and 65 years of age were included. Minimum 15 males and 15 females were included in both age spans from 18 – 44 years (younger), and 45-65 years (middle aged). Table 1 includes the number, age and body mass index (BMI) of subjects in each group. Subjects were recruited by advertisement at the local university, the local university hospital (Odense, Denmark), and through a local newspaper. All subjects were naive to pain testing and none of the included subjects suffered from neurological, psychological, cardiovascular diseases, had any pain or used any pain medication during the week prior to participation. All subjects were asked to refrain from physical exercises, coffee and nicotine on the days of participation. The study was conducted in accordance with the Declaration of Helsinki, approved by the local ethical committee (S-20110070; S-20120014) and all subjects provided written informed consent.

2.2 Procedure

Each subject was assessed at the same time of day on two different days separated by 1 week; however 19 subjects rescheduled their second appointment. All subjects completed both assessment sessions within 3 weeks. In the first session subjects were thoroughly introduced to the procedures by drawings as well as verbal instructions. All subjects completed one practice trial in the beginning of each of the two sessions. All pain sensitivity assessments were performed with the subject either seated on a plinth without foot support and with both arms resting on the thighs or lying supine on a plinth. In each session manual pressure algometry, cuff algometry and assessment of temporal summation of pain by sequential cuff stimulations were assessed on the upper arm and lower leg. In one of the two sessions the subjects subsequently completed a cold pressor test with the dominant hand with pain sensitivity assessed by cuff algometry. Algometry was performed before, immediately after and 15 min after the cold pressor test. Manual pressure algometry was also recorded before and after the cold pressor test but reported elsewhere [47]. Each session lasted approximately 150 minutes and comprised three other conditions performed after the above data collection as part of a larger study on conditioned pain modulation and exercise-induced hypoalgesia [47].

2.3 Manual pressure algometry

Pressure pain thresholds (PPTs) were assessed using a handheld pressure algometer (Somedic Sales AB, Sweden) with a stimulation area of 1 cm^2. The increment rate of pressure was kept at approximately 30 kPa/s and the first time the pressure was perceived as pain, the subject pressed a button, and the actual pressure intensity defined the PPT. Two PPT assessments were completed for each assessment site and the average was used for statistical analysis. Twenty-second intervals between assessments were kept. Two assessment sites were located and marked. Site 1 was located in the middle of the dominant quadriceps muscle, 20 cm proximal to the base of patella. Site 2 was located in the middle of the dominant biceps brachii muscle, 10 cm proximal to the cubital fossa.

2.4 Computer-controlled cuff pressure algometry

Cuff pressure pain thresholds (cPPT), cuff pressure pain tolerance (cPTT), cuff pressure pain tolerance limit (cPTL), and temporal summation of pain (TSP) to repeated cuff stimulations were assessed by a computer-controlled cuff pressure algometer (Nocitech, Denmark and Aalborg University, Denmark, not yet FDA approved) [36]. A 13-cm wide silicone tourniquet cuff (VBM, Germany) with an equal-sized proximal and distal chamber was wrapped around the non-dominant lower leg and non-dominant upper arm. For the arm the tourniquet cuff was mounted with a 3 cm distance between its lower rim and the cubital fossa. For the leg the cuff was mounted with a 5 cm distance between its upper rim and the tibial tuberosity. The two assessment sites were assessed individually in a randomized and counterbalanced order. The cuff pressure was increased with a rate of 1 kPa/s simultaneously in both chambers and the maximal pressure limit was 80 kPa. Air was supplied from a 200 liters external air tank to avoid loud noises from the cuff system during assessment. The participants used an electronic visual analogue scale (VAS) to rate their pressure-induced pain intensity and a button to release the pressure. The electronic VAS was sampled at 10 Hz. Zero and ten cm extremes on the VAS were defined as "no pain" and as "maximal pain", respectively. The participants were instructed to rate the pain intensity continuously on the electronic VAS from when the pressure was defined as first sensation of pain and to press the pressure release button when the pain was intolerable. The pressure value, when the subject rated the sensation of pain as 1 cm on the VAS was defined as

the cPPT and when the subject terminated the pressure inflation was defined as the cPTT. The pain intensity, at the time of termination was defined as the cPTL.

TSP was assessed immediately after assessment of cPPT, and cPTT. Ten repeated cuff pressure stimulations (2 s duration and 1s interval between stimuli) were delivered to the arm and leg by inflation of both cuff chambers with an intensity equivalent to the cPTT recorded during the previous assessment. Pressure with an intensity equivalent to the pain tolerance was chosen to ensure that the first stimulation was perceived as painful by subjects although not extremely painful due to the short stimulation time. To control for an increase in the cPTT after the cold pressor stimulation the pressure intensity used for the repeated cuff inflations were also changed, accordingly. Thus the actual cPTT level during and after the cold pressor test, respectively, were used for repeated cuff stimulations in those particular trials. If such adjustments were not implemented the reduced pain sensitivity of the first stimulus would likely result in less perceived pain in response to the initial stimulation and by itself result in less TSP. Subjects rated their pressure pain intensity continuously during the sequential stimulation on the electronic VAS without returning it to zero in-between the stimulations. In the period between stimuli a constant non-painful pressure of 5 kPa was kept ensuring that the cuff did not move. The VAS score immediately after each stimulus was extracted.

2.5 Conditioned pain modulation

The cold pressor test was performed with the subject comfortably seated while immersing the dominant hand into a tank containing circulating ice water at 1-2ºC [56]. The subject immersed the hand 5 cm above the wrist for 2 minutes. Cuff algometry cPPT, cPTT and TSP were assessed just before, immediately after ending the 2 minutes cold pressor test, and 15 min after ending the cold pressor test. The subject rated the cold pressor pain intensity on a 0 to 10 numerical rating scale (NRS) where 0 was defined as “no pain” and 10 was “maximal pain”.

2.6 Statistics

Results are presented as mean and standard deviation (SD), unless otherwise specified. The distribution of BMI and NRS scores during cold pressor test (NRS) deviated from normality (Kolmogorov-Smirnoff test: $P < 0.001$). Thus, BMI, and NRS between men and women and between age groups were analyzed with non-parametric statistics.

To investigate the effect of gender, age groups, assessment site and session on PPT, cPPT, and cPTT mixed-model analysis of covariance's (ANCOVAs) were performed with *assessment site* (arm and leg) as within-subject factor, *sessions* (day 1 and day 2) as repeated measures and *gender*, and *age group* (younger and middle age) as group factors. Due to the significant difference in BMI between men and women, BMI was added to the analysis as a covariate. Furthermore, Spearman's Rank Order correlations were run to determine the relationship between manual PPT and cuff cPPT at the arm where the assessment site coincide. For initial analysis of TSP, pain ratings immediately after each of the ten repeated stimulations were analyzed with a 3-way repeated measures ANOVA with *assessment site* (arm and leg) as within-subject factor, *sessions* (day 1 and day 2) and *stimulations* (1-10) as repeated measures. Due to variations in the pain ratings during stimulation 1 and 2 between session 1 and 2, the mean VAS score was calculated after stimulation 1-4 (VAS-I), stimulations 5-7 (VAS-II), and stimulations 8-10 (VAS-III) and the factor *stimulation-epoch* (VAS-I, VAS-II, and VAS-III) was added to the ANOVA. For further analysis of TSP, the ratio between VAS-III and VAS-I was calculated.

For analysis of gender, age group, assessment site, and session on TSP a 4-way ANCOVA was performed with *assessment site* (arm and leg) as within-subject factor, *sessions* (day 1 and day 2) as repeated measures, *gender* and *age group* (younger and middle age) as group factors and *BMI* as covariate. The effect of cold pressor test on cPPT, cPTT, and TSP were analyzed in a mixed-model ANCOVA with *assessment site* (arm and leg) as within-subjects factor, *time* (before, immediately after, 15 min after) as repeated measures, *gender* and *age group* (younger and middle age) as group factors and *BMI* as covariate. In case of significant factors or interactions in the ANCOVAs, the Newman-Keuls (NK) test was used for post-hoc comparisons incorporating correction for the multiple comparisons. Due to unequal sample sizes between age groups, Brown-Forsythe tests were performed on all pain sensitivity variables to examine for unequal variance between groups. *P* values less than 0.05 were considered significant.

The mean, SD, and coefficient of variations (intra and inter CV) of PPT, cPPT, cPTT, cPTL, stimulation epochs (VAS-I, VAS-II, and VAS-III), and the ratio between VAS-III and VAS-I were calculated for each assessment site. Intraclass correlations (ICCs) based on a single rating, consistency, 2-way mixed effect model ($ICC_{3,1}$) and Bland-Altman methods were used for analysis of reliability. An ICC above 0.75 was taken as excellent reliability, 0.40–0.75 was fair to good reliability, and less than 0.40 defined poor reliability [11]. Mixed model ANCOVAs were

analyzed in Statistica, version 5.1 (StatSoft Inc., USA). ICCs and Bland Altman methods were calculated in SPSS Statistics, version 21 (IBM, USA)

3. RESULTS

3.1 Demographics

The BMI was significantly higher in men as compared with women (Mann-Whitney U test; $P < 0.002$; Table 1) and higher in middle aged subjects compared with younger subjects (Mann-Whitney U test; $P < 0.001$).

3.2 Manual pressure algometry

The ANCOVA of the PPTs showed significant main effects of gender (Fig. 1, $F(1,131) = 13.39$, $P < 0.001$), age group ($F(1,131) = 6.60$, $P < 0.009$), assessment site ($F(1,132) = 194.80$, $P < 0.001$), and sessions ($F(1,132) = 8.72$, $P < 0.004$). Post-hoc test showed significantly increased PPTs at the arm and leg in men compared with women and in middle aged subjects compared with younger subjects (NK: $P < 0.006$). In men and women PPT at the leg was significantly higher compared with PPT at the arm (NK: $P < 0.001$). PPTs were significantly lower in the second session compared with the first session (NK: $P < 0.001$).

3.3 Cuff algometry

Due to technical problems, 1 subject was not tested with the cuff algometer on the upper arm and 11 subjects were not tested on the lower leg in one of the two sessions and therefore cuff data from 125 subjects were analyzed. These subjects were not significantly different on age and BMI compared with the total sample.

The ANCOVA of the cPPTs demonstrated a significant main effect of age group (Fig. 2, $F(1,120) = 6.27$, $P < 0.017$) and a significant interaction between sessions and assessment site ($F(1,121) = 4.80$, $P < 0.026$). Post-hoc test showed significantly higher cPPTs in younger subjects compared with middle aged subjects (NK: $P < 0.009$). cPPT at the upper arm was significantly higher compared with the lower leg (NK: $P < 0.001$). cPPT at the upper arm was significantly higher in the second session compared with the first session (NK: $P < 0.001$). There was a significant correlation between the manual PPT and the cuff cPPT on the arm ($r(135) = 0.271$, $P < 0.001$).

The ANCOVA of the cPTTs demonstrated significant main effects of gender (Fig 2; $F(1,120) = 11.80$, $P < 0.001$), age group $F(1,120) = 8.64$, $P < 0.004$), and assessment site ($F(1,121) = 81.77$, $P < 0.001$). Post-hoc test showed significantly increased cPTTs in men

compared with women and in younger subjects compared with middle aged subjects (NK: $P < 0.001$). cPTT at the upper arm was significantly higher compared with the lower leg (NK: $P < 0.001$).

3.4 Temporal summation by cuff pain

The ANCOVA of the pain ratings immediately after the repeated stimulations demonstrated significant interactions between assessment sites and stimulations (Fig 3; $F(9,1116) = 7.32$, $P < 0.001$), and between sessions and stimulations ($F(9,1116) = 2.26$, $P < 0.017$). Post-hoc test showed significantly increased pain ratings after stimulation 10 compared with pain ratings after stimulation 1-7, and significantly increased pain ratings after stimulation 5 compared with pain ratings after stimulation 1-4 (NK: $P < 0.036$) indicating that the repeated sequence of cuff pressure stimuli at the same intensity delivered to the leg and to the arm produced a progressive increase in pain ratings. Post-hoc test also revealed that pain ratings after all 10 stimulations at the lower leg was significantly increased compared with pain ratings at the upper arm (NK: $P < 0.001$). Pain ratings after stimulation 1 and 2 were significantly higher in the second session compared with the first session (NK: $P < 0.007$).

For the stimulation-epochs (VAS-I, II and III, Table 2), the ANCOVA demonstrated a significant interaction between stimulation-epochs and session ($F(2,248) = 3.19$, $P < 0.04$), and a significant main effect of assessment sites ($F(1,124) = 22.22$, $P < 0.001$). Post-hoc test showed that for both assessment sites stimulation-epoch VAS-III was significantly higher compared with VAS-II and VAS-I, and VAS-II was significantly higher compared with VAS-I (NK: $P < 0.001$). VAS-I, VAS-II, and VAS-III at the lower leg was significantly higher compared with the upper arm (NK: $P < 0.001$). VAS-I was significantly higher in session 2 compared with session 1 (NK: $P < 0.001$). The ANCOVA of the ratio between VAS-III and VAS-I demonstrated a significant main effect of gender (Fig. 4; $F(1,120) = 4.59$, $P = 0.039$). Post-hoc test showed significantly higher VAS ratio in women compared with men (NK: $P < 0.009$).

3.5 Pressure and cuff algometry between-days repeatability

Repeatability between days of PPTs at the leg and arm were high with ICCs of 0.89 and 0.87, respectively (Table 2). However, results from Bland-Altman did not demonstrate reasonable agreement for PPTs reflected in the 95 % CI of the mean difference, where zero does not lie

within the interval. The intra coefficients of variation at the leg and arm were low with CVs of 14.6 % and 17.7 %, respectively.

Repeatability between days of cPPT, cPTL, cPTT and TSP at the lower leg was good to excellent with ICCs between 0.60-0.87. Results from Bland-Altman demonstrated no systematic bias between sessions at the leg. Repeatability between days of cPPT, cPTL, cPTT and TSP at the upper arm was lower than the leg with ICCs between 0.43-0.90. Results from Bland-Altman demonstrated no systematic bias between sessions for cPTT and TSP at the upper arm; however the results also indicated a systematic mean difference between the two sessions for cPPT and cPTL at the arm, reflected in the 95 % CI of the mean difference, where zero does not lie within the interval. The intra coefficients of variation at the arm were somewhat higher than the leg for all parameters, except cPTT.

3.6 Cuff-algometry and CPM effects

All 125 subjects completed the cold pressor test. The pain intensity reported during the cold pressor test (NRS: median 8; range 2-10) was not significantly different between men and women (Mann Whitney U; $P < 0.73$) or between age groups (Mann-Whitney U test; $P = 0.75$).

The ANCOVA of cPPTs demonstrated a significant main effect of time (Fig. 5; $F(2,242) = 3.23$, $P < 0.048$). Post-hoc test showed significantly increased cPPT immediately after cold pressor test and 15 min after cold pressor test compared with baseline (NK: $P < 0.003$). There was a significant main effect of time for cPTTs (Fig. 6; $F(2,242) = 10.50$, $P < 0.001$), with post-hoc test showing significantly increased cPTTs immediately after cold pressor test and 15 min after cold pressor test compared with baseline (NK: $P < 0.001$).

The ANCOVA of the ratio between VAS-III and VAS-I demonstrated a significant main effect of time ($F(2,242) = 4.55$, $P < 0.01$) with post-hoc test showing significantly decreased ratio between VAS-III and VAS-I immediately after and 15 min after cold pressor test compared with baseline (NK: $P < 0.004$). However, the ANCOVA also demonstrated significant interactions between time and gender (Fig. 7A; $F(2,242) = 3.49$, $P < 0.04$), and between time and age group (Fig. 7B; $F(2,242) = 5.13$, $P < 0.007$). Post-hoc test showed significantly decreased ratio between VAS-III and VAS-I in women after cold pressor test and 15 min after cold pressor compared with baseline (NK: $P < 0.004$). Post-hoc test also revealed that the ratio between VAS-III and VAS-I

was significantly decreased in middle aged subjects after cold pressor test and 15 min after cold pressor compared with baseline (NK: $P < 0.004$).

4. DISCUSSION

This study demonstrated that reliability and sensitivity of computer-controlled cuff algometry for pain assessment is comparable to manual pressure algometry. Cuff assessments at the lower leg were more reliable than assessment on the arm. The pain sensitivity in women was generally higher compared with men for both pressure and cuff algometry. The pain sensitivity increased with age when assessed by cuff algometry whereas manual pressure algometry demonstrated decreased pain sensitivity with age. Cuff algometry was sensitive to CPM and temporal summation of pain could be reliably assessed and modulated by CPM.

4.1 Reliability of pain assessment

Test-retest data on manual pressure algometry demonstrated excellent ICC values (>0.8) confirming previous studies reporting ICCs above 0.7 [4;8;12;26;33;39;50]. The Bland-Altman analysis showed however a systematic mean difference between the two sessions for the PPT values assessed on the leg and arm.

The cuff pressure pain thresholds demonstrated comparable ICC values as manual pressure algometry but also a systematic mean difference between the two sessions was detected on the arm. The cuff pain tolerance was reliably detected in both the arm and leg with excellent ICCs (0.87 and 0.90). The VAS score at cuff pain tolerance was also recorded with high ICC but a Bland-Altman systematic mean difference for the two sessions was found for the arm. Finally, the VAS scores provided immediately after each of the repeated cuff stimulations and the ratio between VAS-III and VAS-I reflecting temporal summation of pain were recorded with good to excellent ICCs in the leg. The blocks of VAS scores (VAS-I, II, III) demonstrated a better reliability than the VAS-ratio probably reflecting the higher variability between sessions in the VAS-I affecting the VAS-ratio. In general, the test-retest analysis in the 125 healthy subjects showed good to excellent ICCs and no systematic mean difference between the two sessions for the cuff algometry used on the leg.

Consistently for both cuff and manual pressure algometry a systematic mean difference in pain thresholds assessed on the arm was found between the two sessions and also for the pain intensity detected at the tolerance level when assessed on the arm. The specific reason for this effect on the arm is not clear. Nonetheless, the mean difference between the two sessions in the

cPPT and cPTL assessed on the arm is only approximately 10 %. Many studies have based the pressure algometry pain thresholds on the average of at least two trials [33;34] and the present study showed high ICC and good reliability based on the average of two repetitions.

4.2 Pain sensitivity difference between arm and leg

The pain sensitivity assessed by manual pressure algometry was significantly lower in the leg compared with the arm as shown previously with assessments on hand and foot [3;43] or knee and forearm [53]. Similar findings have been reported for thermal pain sensitivity [43]. The specific mechanism for the regional difference is not known but is likely to include the degree of overlapping receptive fields and differences in innervation density of nociceptors. In contrast, assessment with cuff algometry demonstrated significantly increased pain sensitivity in the leg compared with the arm. Not only was the pressure intensity at pain tolerance lower in the leg compared with the arm but the VAS scores obtained during repeated cuff stimulations for assessment of temporal summation was also higher. The better effect of cuff stimulation at the leg may illustrate the effect of spatial summation and excitation of more nociceptors from a larger volume below the cuff mounted on the leg [24] compared with the arm. Similar spatial summation effect has been demonstrated following cuff assessments with two different widths of cuffs applied on the leg [36].

4.3 Gender and age effects on the pain sensitivity

Previously, robust gender effects with increased pressure pain sensitivity in women compared with men have been reported for pressure algometry [6;23;32;41;43] in line with the present findings and now also shown with cuff algometry when assessing the pain tolerance parameter. The pressure pain threshold assessed by cuff algometry was not different between women and men which may suggest that this parameter is less sensitive to gender differences.

The pressure pain sensitivity assessed by manual pressure algometry was decreased with age contrasting the increased pain sensitivity detected by cuff algometry in middle aged subjects compared with younger subjects. Previous data on aging effects on pressure pain thresholds are mixed depending among other factors on assessment modality, stimulus duration, and area [13]. In a large study including 740 subjects, Jensen et al. [23] found an increase with age in pressure pain thresholds assessed on pericranial muscles. In contrast, pressure pain thresholds assessed on

fingers were reported to be decreased in older compared with young subjects [7;28]. The contrast in findings with pressure and cuff algometry may suggest that the spatial integration is a major determinant for the age-related effects. Nonetheless, spatial summation was not found to be age-dependent when testing with different probe sizes for pressure algometry [28]. Alternatively, pressure and cuff algometry assess different mechanisms, which is supported by the weak correlation between thresholds between those two measures. Similar findings have been reported for pain thresholds assessed by electrical, thermal and mechanical modalities [31]. A fundamental difference between pressure and cuff algometry is the ischemia accompanying cuff algometry. Based on the current data an ischemic pain component cannot be excluded. However, Issberner et al. [21] demonstrated that 7 to 10 min tourniquet-induced ischemia at rest did not induce pain or significant changes in the tissue pH level whereas simultaneous contractions (i.e. the submaximal effort tourniquet technique) progressively induced pain and reduced the tissue pH-level. Moreover, when inducing pain by ischemic muscle contractions for 2 min, the pressure pain thresholds assessed by pressure algometry increased compared with baseline measures [17]. Thus, it is not likely that the ischemia during cuff assessment paradigms (done at rest, for maximum 100 s) induced any pain or sensitization of the deep-tissue nociceptors.

Finally, the age-related differences in pressure and cuff algometry may also illustrate that cuff algometry provides a better assessment of the deep-tissue pain sensitivity than pressure algometry. Actually, Gibson and Farrell [13] concluded that decreased pain sensitivity was likely to be assessed in elderly when stimuli applied on extremities are phasic, of lesser spatial extent and cutaneous. The increased pressure pain sensitivity in women compared with men have been reported to be age-dependent with less or no difference for older subjects [30;32] but this was not found in the present study. Nonetheless, data was not collected on the use of contraceptives or status of menopause or menstrual cycle, which may affect the pain perception in the female participants [42] and limit the interpretation.

4.4 Temporal summation and conditioned pain modulation assessed by cuff pain algometry

This study demonstrated robust temporal summation of cuff induced pain in line with a recent study [45]. Interestingly, women demonstrated a higher degree of temporal summation of pain when comparing the first and last stimulations. Similar findings have been reported for temporal summation of heat pain [25].

Immediately after the cold pressor test the cuff pain threshold and cuff pain tolerance increased significantly in both the arm and leg. Previous studies reported similar findings with decreased cuff pain sensitivity [19] and increased pressure tolerance levels to computer-controlled pressure algometry [35] assessed on the leg when conditioning stimulus was applied on the arm. The CPM magnitude did not differ between the leg and arm in agreement with a previous studies [35]. Age or gender effects were not found on the cold pressor stimulation pain intensity or the immediate CPM effect on cuff pressure pain threshold or tolerance in the present study in contrast with previous studies using manual pressure or heat as test stimuli demonstrating reduced pain inhibition associated with ageing [9;27;29;40;52] and in women compared with men [2;14;15;20]. These contrasting findings suggest that the age and gender effects may be highly dependent on the modality used as test stimulus. Nonetheless, comparable CPM effects between men and women assessed with pressure pain as test stimulus have been reported [38;44;51;57]. The combined temporal summation of deep-tissue pain and CPM has been reported for manually applied repeated pressure stimulations [5] and now also shown with cuff algometry. In contrast with Cathcart et al. [5] the stimulation intensity used for the temporal pain summation was adjusted and increased after the cold pressor test, as an attempt to account for the pain sensitivity changes, and still the temporal summation effect was significantly reduced in women and middle aged participants although to a minor degree and the implications of such a small effect is up for discussion. The fact that temporal summation of pain was more expressed in women at baseline compared with men may suggest that robust temporal summation of pain is needed before a clear CPM effect can be detected.

4.5 Limitations

The change in cuff pain sensitivity after the cold pressor test could be due to habituation after repeated cuff testing since a control group without the cold pressor test was not included. However, recent studies demonstrated that the cuff pain sensitivity was not significantly different after 15 min quiet rest compared with before in healthy subjects and in patients with chronic pain [48;49]. The statistical analysis did not account for the unequal sample sizes in the two age groups, which could affect the robustness of the ANCOVA. Finally, computer-controlled cuff algometry as used in this study is not widely available and results on test-retest reliability may not replicate with different cuff devices that are not as automated. More often used is computer-

controlled pressure algometry minimizing the variability caused by the manual pressure stimulation and future studies should compare this modality with the cuff algometry.

4.6 Conclusion

Computer-controlled cuff algometry for pain assessment is a reliable methodology likewise manual pressure algometry but constitutes a more standardized and examiner-independent method for assessment of pain sensitivity. Difference in age-related pain sensitivity between manual and cuff algometry should be further investigated. The usability of cuff algometry was also demonstrated for assessment of CPM.

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REFERENCES

[1] Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. Pain 2010;149:573-581.

[2] Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. Pain 2008;140:465-471.

[3] Blankenburg M, Boekens H, Hechler T, Maier C, Krumova E, Scherens A, Magerl W, Aksu F, Zernikow B. Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. Pain 2010;149:76-88.

[4] Brennum J, Kjeldsen M, Jensen K, Jensen TS. Measurements of human pressure-pain thresholds on fingers and toes. Pain 1989;38:211-217.

[5] Cathcart S, Winefield AH, Rolan P, Lushington K. Reliability of temporal summation and diffuse noxious inhibitory control. Pain Res Manag 2009;14:433-438.

[6] Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. Pain 2003;101:259-266.

[7] Cole LJ, Farrell MJ, Gibson SJ, Egan GF. Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. Neurobiol Aging 2010;31:494-503.

[8] Delaney GA, McKee AC. Inter- and intra-rater reliability of the pressure threshold meter in measurement of myofascial trigger point sensitivity. Am J Phys Med Rehabil 1993;72:136-139.

[9] Edwards RR, Fillingim RB, Ness TJ. Age-related differences in endogenous pain modulation: a comparison of diffuse noxious inhibitory controls in healthy older and younger adults. Pain 2003;101:155-165.

[10] Finocchietti S, Nielsen M, Morch CD, Arendt-Nielsen L, Graven-Nielsen T. Pressure-induced muscle pain and tissue biomechanics: a computational and experimental study. Eur J Pain 2011;15:36-44.

[11] Fleiss JL. The design and analysis of clinical experiments. New York: Wiley, 1986.

[12] Geber C, Klein T, Azad S, Birklein F, Gierthmuhlen J, Huge V, Lauchart M, Nitzsche D, Stengel M, Valet M, Baron R, Maier C, Tolle T, Treede RD. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): a multi-centre study. Pain 2011;152:548-556.

[13] Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. Clin J Pain 2004;20:227-239.

[14] Goodin BR, McGuire L, Allshouse M, Stapleton L, Haythornthwaite JA, Burns N, Mayes LA, Edwards RR. Associations between catastrophizing and endogenous pain-inhibitory processes: sex differences. J Pain 2009;10:180-190.

[15] Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, Yarnitsky D. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter? Pain 2008;136:142-149.

[16] Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010;6:599-606.

[17] Graven-Nielsen T, Jansson Y, Segerdahl M, Kristensen JD, Mense S, Arendt-Nielsen L. Experimental pain by ischaemic contractions compared with pain by intramuscular infusions of adenosine and hypertonic saline. Eur J Pain 2003;7:93-102.

[18] Graven-Nielsen T, Mense S, Arendt-Nielsen L. Painful and non-painful pressure sensations from human skeletal muscle. Exp Brain Res 2004;159:273-283.

[19] Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis Rheum 2012;64:2907-2916.

[20] Honigman L, Yarnitsky D, Sprecher E, Weissman-Fogel I. Psychophysical testing of spatial and temporal dimensions of endogenous analgesia: conditioned pain modulation and offset analgesia. Exp Brain Res 2013;228:493-501.

[21] Issberner U, Reeh PW, Steen KH. Pain due to tissue acidosis: a mechanism for inflammatory and ischemic myalgia? Neurosci Lett 1996;208:191-194.

[22] Jensen K, Andersen HØ, Olesen J, Lindblom U. Pressure-pain threshold in human temporal region. Evaluation of a new pressure algometer. Pain 1986;25:313-323.

[23] Jensen R, Rasmussen BK, Pedersen B, Lous I, Olesen J. Cephalic muscle tenderness and pressure pain threshold in a general population. Pain 1992;48:197-203.

[24] Khanian BM, Arendt-Nielsen L, Frøkjær JB, Graven-Nielsen T. Deformation and pressure propagation in deep somatic tissue during painful cuff algometry. Eur J Pain 2015.

[25] Koltyn KF, Knauf MT, Brellenthin AG. Temporal summation of heat pain modulated by isometric exercise. Eur J Pain 2013;17:1005-1011.

[26] Koo TK, Guo JY, Brown CM. Test-retest reliability, repeatability, and sensitivity of an automated deformation-controlled indentation on pressure pain threshold measurement. J Manipulative Physiol Ther 2013;36:84-90.

[27] Lariviere M, Goffaux P, Marchand S, Julien N. Changes in pain perception and descending inhibitory controls start at middle age in healthy adults. Clin J Pain 2007;23:506-510.

[28] Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain 2005;115:410-418.

[29] Lemley KJ, Drewek B, Hunter SK, Hoeger Bement MK. Pain relief after isometric exercise is not task-dependent in older men and women. Med Sci Sports Exerc 2014;46:185-191.

[30] Magerl W, Krumova EK, Baron R, Tolle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. Pain 2010;151:598-605.

[31] Neziri AY, Curatolo M, Nuesch E, Scaramozzino P, Andersen OK, Arendt-Nielsen L, Juni P. Factor analysis of responses to thermal, electrical, and mechanical painful stimuli supports the importance of multi-modal pain assessment. Pain 2011;152:1146-1155.

[32] Neziri AY, Scaramozzino P, Andersen OK, Dickenson AH, Arendt-Nielsen L, Curatolo M. Reference values of mechanical and thermal pain tests in a pain-free population. Eur J Pain 2011;15:376-383.

[33] Nussbaum EL, Downes L. Reliability of clinical pressure-pain algometric measurements obtained on consecutive days. Phys Ther 1998;78:160-169.

[34] Ohrbach R, Gale EN. Pressure pain thresholds in normal muscles: reliability, measurement effects, and topographic differences. Pain 1989;37:257-263.

[35] Oono Y, Nie HL, Matosa RL, Wang K, Arendt-Nielsen L. The inter- and intra-individual variance in descending pain modulation evoked by different conditioning stimuli in healthy men. Scand J Pain 2011;2:162-169.

[36] Polianskis R, Graven-Nielsen T, Arendt-Nielsen L. Spatial and temporal aspects of deep tissue pain assessed by cuff algometry. Pain 2002;100:19-26.

[37] Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain 2009;144:16-19.

[38] Pud D, Sprecher E, Yarnitsky D. Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. Neurosci Lett 2005;380:209-213.

[39] Reeves JL, Jaeger B, Graff-Radford SB. Reliability of the pressure algometer as a measure of myofascial trigger point sensitivity. Pain 1986;24:313-321.

[40] Riley JL, III, King CD, Wong F, Fillingim RB, Mauderli AP. Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults. Pain 2010;150:153-160.

[41] Riley JL, III, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998;74:181-187.

[42] Riley JL, III, Robinson ME, Wise EA, Price DD. A meta-analytic review of pain perception across the menstrual cycle. Pain 1999;81:225-235.

[43] Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123:231-243.

[44] Rosen A, Feldreich A, Dabirian N, Ernberg M. Effect of heterotopic noxious conditioning stimulation on electrical and pressure pain thresholds in two different anatomical regions. Acta Odontol Scand 2008;66:181-188.

[45] Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen OH, Laursen MB, Arendt-Nielsen L. Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. Pain 2013;154:1588-1594.

[46] Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck Jr CJ. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain 2003;102:87-95.

[47] Vaegter HB, Handberg G, Graven-Nielsen T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. Pain 2014;155:158-167.

[48] Vaegter HB, Handberg G, Graven-Nielsen T. Hypoalgesia After Exericse and Cold Pressor Test are Reduced in Chronic Musculuskeletal Pain Patients with High Pain Sensitivity. Clin.J.Pain. 2015.

[49] Vaegter HB, Handberg G, Graven-Nielsen T. Isometric exercises reduce temporal summation of pressure pain in humans. Eur.J.Pain. 2015.

[50] Walton DM, Macdermid JC, Nielson W, Teasell RW, Chiasson M, Brown L. Reliability, standard error, and minimum detectable change of clinical pressure pain threshold testing in people with and without acute neck pain. J Orthop Sports Phys Ther 2011;41:644-650.

[51] Wang K, Svensson P, Sessle BJ, Cairns BE, Arendt-Nielsen L. Painful conditioning stimuli of the craniofacial region evokes diffuse noxious inhibitory controls in men and women. J Orofac Pain 2010;24:255-261.

[52] Washington LL, Gibson SJ, Helme RD. Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. Pain 2000;89:89-96.

[53] Wylde V, Palmer S, Learmonth ID, Dieppe P. Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. Osteoarthritis Cartilage 2011;19:655-658.

[54] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 2010;23:611-615.

[55] Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. Eur J Pain 2010;14:339.

[56] Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur.J.Pain., Vol. %20. doi: 10.1002/ejp.605. 2014. p. 10.

[57] Zheng Z, Wang K, Yao D, Xue CC, Arendt-Nielsen L. Adaptability to pain is associated with potency of local pain inhibition, but not conditioned pain modulation: a healthy human study. Pain 2014;155:968-976.

FIGURE LEGENDS

Fig. 1: Mean (+ SEM, N = 136) pressure pain thresholds (PPT) assessed by manual algometry recorded at the dominant leg and arm in younger and middle aged men and women. Significantly different between age groups (*, NK: $P < 0.05$), gender (†, NK: $P < 0.05$), and assessment sites (#, NK: $P < 0.05$).

Fig. 2: Mean (+ SEM, N = 125) pressure pain thresholds (cPPT) and pressure pain tolerance (cPTT) assessed by computerized cuff algometry recorded at two assessment sites (non-dominant lower leg and non-dominant upper arm) in younger and middle aged men and women. Significantly different between age groups (*, NK: $P < 0.05$), gender (†, NK: $P < 0.05$) and assessment sites (#, NK: $P < 0.05$).

Fig. 3: Mean (+ SEM, N = 125) VAS scores immediately after each of the ten repeated stimulations assessed by computerized cuff algometry recorded at two assessment sites (non-dominant lower leg and non-dominant upper arm). Significantly different compared with stimulation 1-7 (†, NK: $P < 0.05$) and compared with stimulation 1-4 (*, NK: $P < 0.05$).

Fig. 4: Mean (+ SEM, N = 125) ratio between VAS-III and VAS-I reflecting temporal summation of pain assessed by computerized cuff algometry recorded at two assessment sites (non-dominant lower leg and non-dominant upper arm) in younger and middle aged men and women. Significantly different between gender (†, NK: $P < 0.05$).

Fig. 5: Mean (+ SEM, N = 125) pressure pain threshold (cPPT) assessed by computerized cuff algometry recorded at the non-dominant lower leg (**A)** and the non-dominant upper arm (**B)** before, immediately after cold pressor test, and 15 min after cold pressor test in younger and middle aged men and women. The cold pressor test was applied to the dominant hand. Significantly different compared with baseline values (*, NK: $P < 0.05$).

Fig. 6: Mean (+ SEM, N = 125) pressure pain tolerance (cPTT) assessed by computerized cuff algometry recorded at the non-dominant lower leg (**A)** and the non-dominant upper arm (**B)** before, immediately after cold pressor test, and 15 min after cold pressor test in younger and

middle aged men and women. The cold pressor test was applied to the dominant hand. Significantly different compared with baseline values (*, NK: $P < 0.05$).

Fig. 7: Mean (+ SEM, N = 125) ratio between VAS-III and VAS-I reflecting temporal summation of pain assessed by computerized cuff algometry recorded at two assessment sites (non-dominant lower leg and non-dominant upper arm) in younger and middle aged (**A)** men and women (**B)** before, immediately after cold pressor test, and 15 min after cold pressor test. The cold pressor test was applied to the dominant hand. Significantly different compared with baseline values (*, NK: $P < 0.05$).

Summary

Reliability and sensitivity of computer-controlled cuff algometry for pain assessment is comparable to manual pressure algometry and constitutes a user-independent method for assessment of pain.

Figure1
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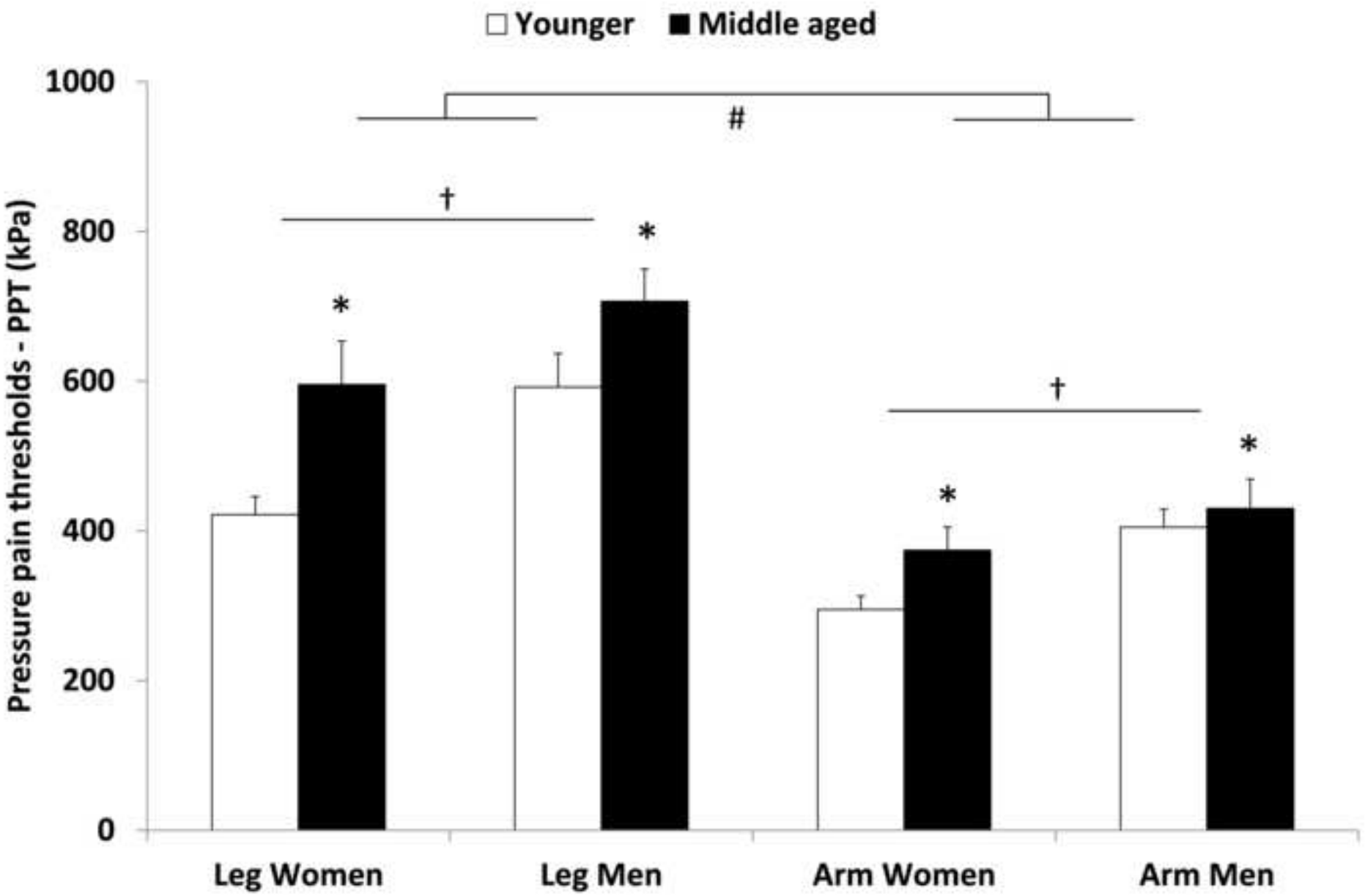

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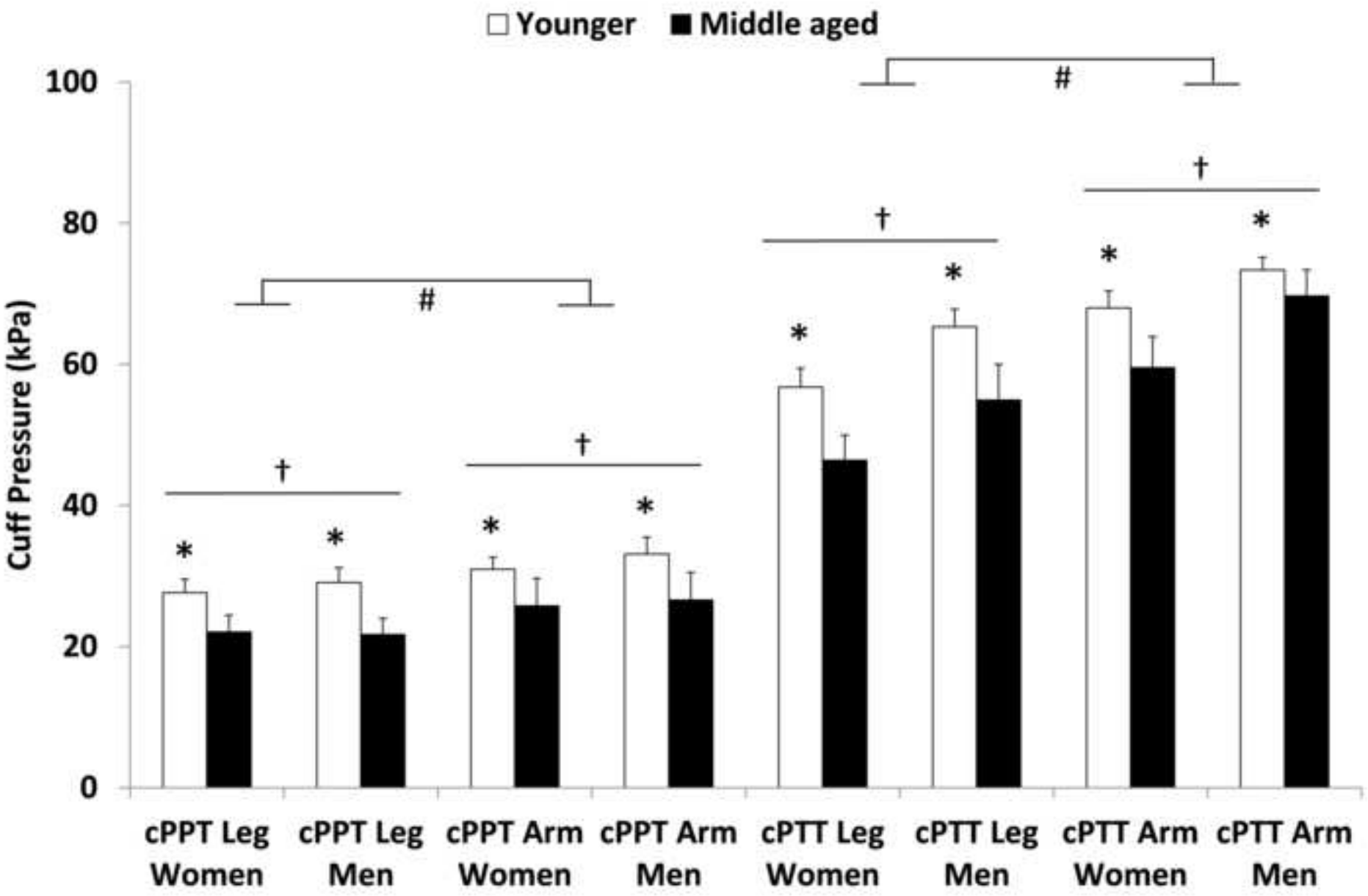

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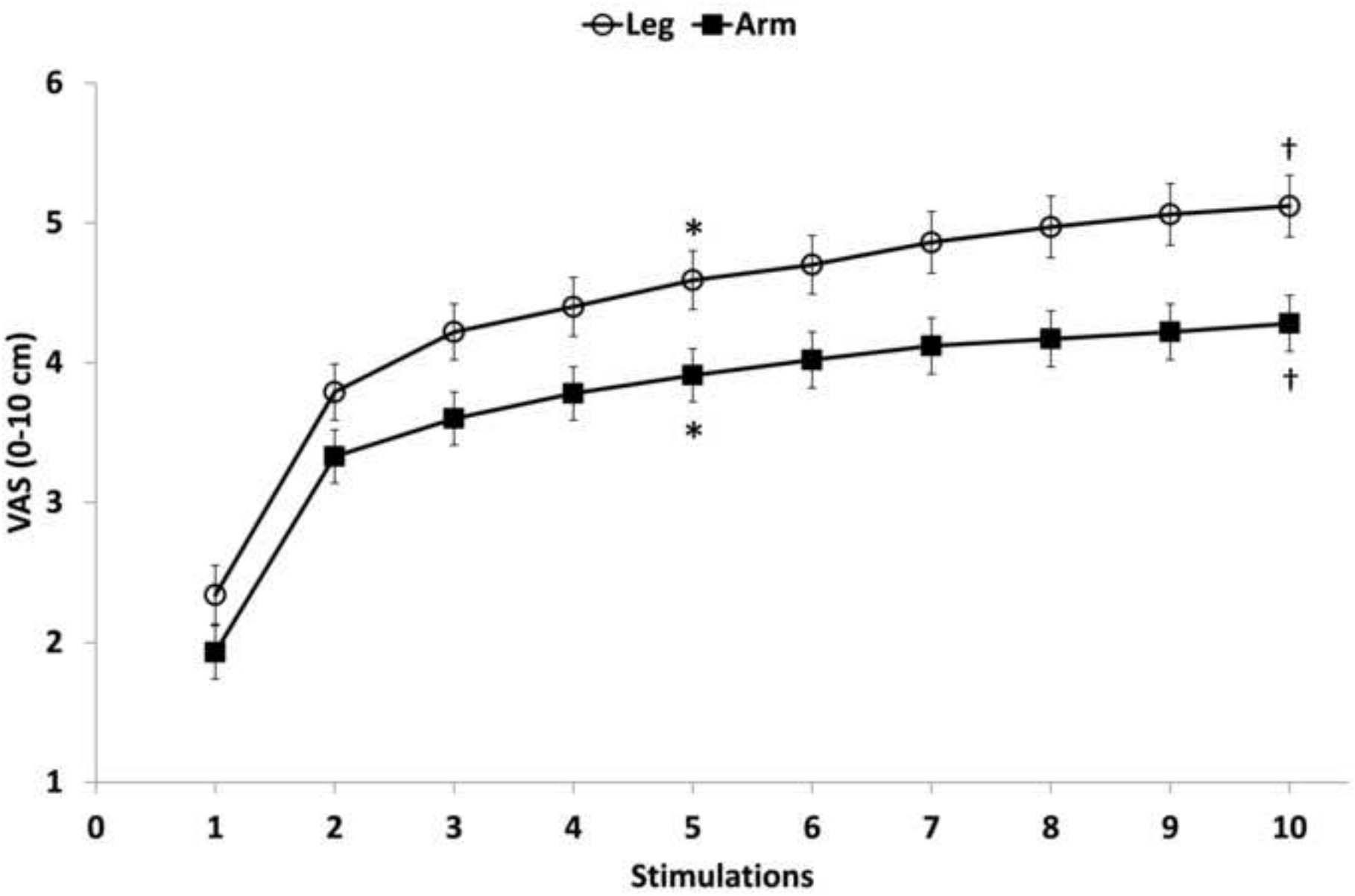

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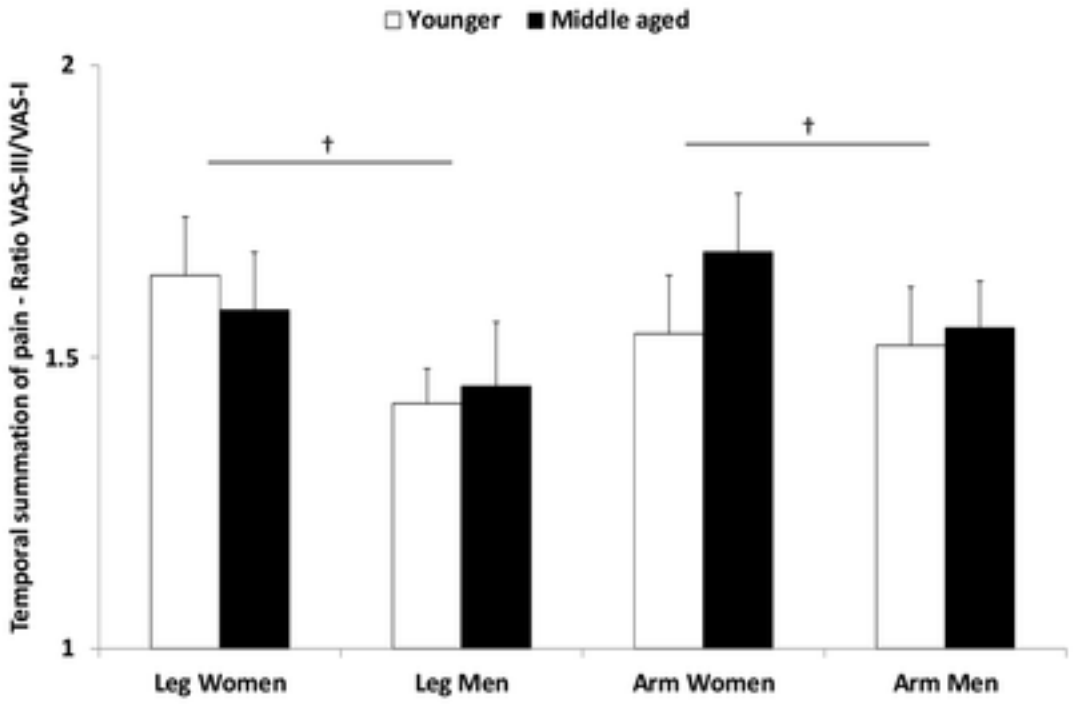

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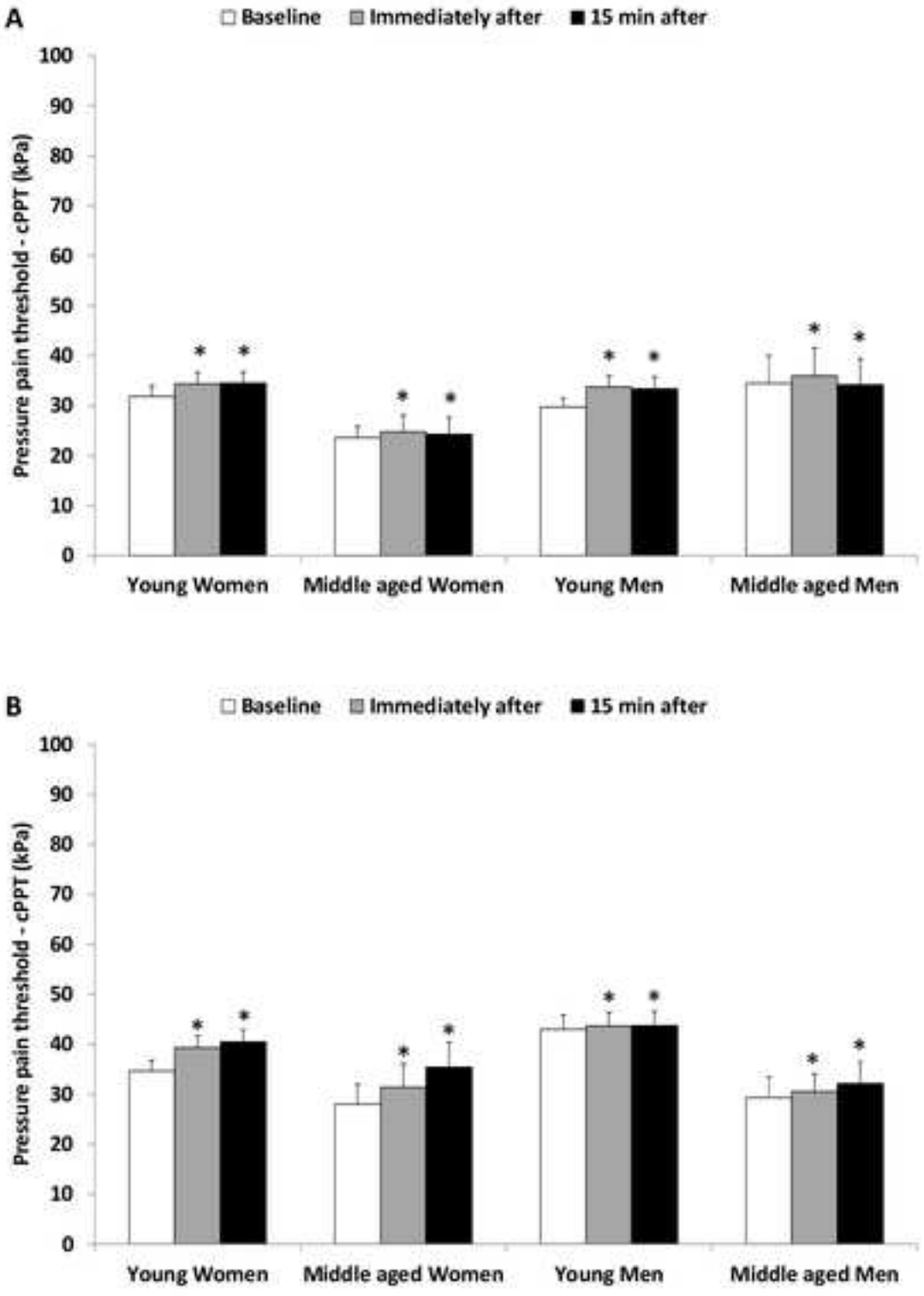

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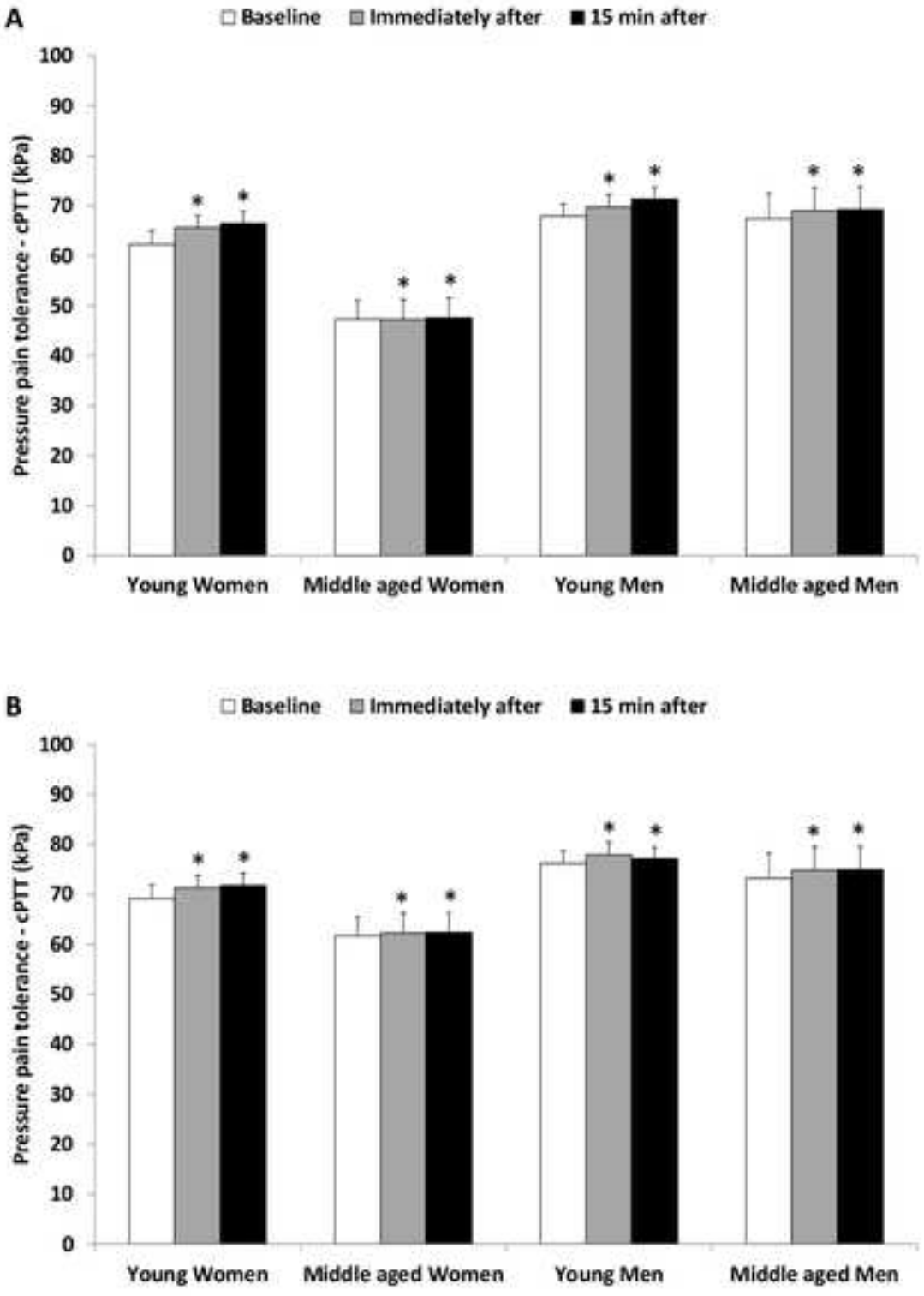

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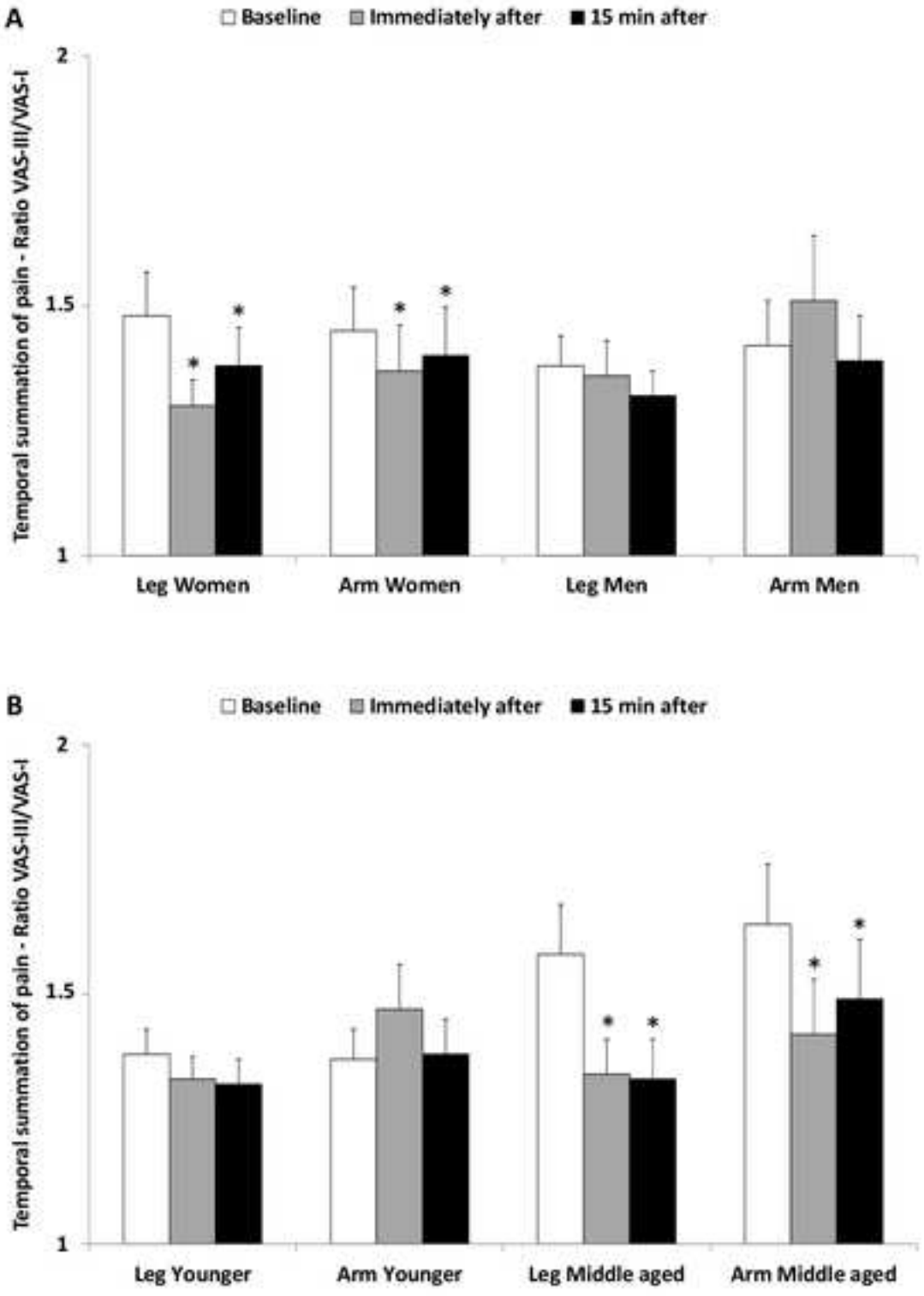

Table1

Table 1: Number of subjects included (N), age, and body mass index (BMI) for the two age groups (Younger and Middle aged) of women and men

	N	Age (years)	BMI (%)
Women	68	31.7 ± 14.0	22.9 ± 3.5
Younger	51	24.2 ± 5.5	22.6 ± 3.4
Middle aged	17	53.9 ± 5.2	23.6 ± 3.5*
Men	68	31.7 ± 13.7	24.2 ± 3.1#
Younger	51	24.6 ± 5.0	23.3 ± 2.4
Middle aged	17	53.0 ± 8.1	26.9 ± 3.5*
Significantly increased compared with women (#, P = 0.002) and the younger age group (*, P < 0.001).			

Table2

Table 2: Intraclass correlations (ICCs) and Bland/Altman analyses for pain assessment parameters. 'PPT': Pressure Pain Threshold with manual algometry. 'cPPT': Pain Threshold with cuff algometry. 'cPTT': Pain Tolerance with cuff algometry. 'cPTL': Pain Tolerance Limit with cuff algometry. 'VAS': Visual Analogue Scale. 'CV': Coefficient of Variation. 'SD': Standard deviation.

Site	Pain sensitivity parameter	ICC					Bland and Altman			
		1st session Mean ± SD	2nd session Mean ± SD	Intra CV (%)	Inter CV (%) session 1 and 2	ICC3,1 (95 % CI)	Mean difference (95 %CI)	Percent bias (95 % CI)	SD diff (kPa)	95 % limits of agreement (kPa)
Leg	Manual PPT (kPa)	543 ± 264	509 ± 243	14.6	48.6 47.7	0.89 (0.84-0.92)	34 (6 – 62)	6.3% (1.1% – 11.4%)	163	-292 – 360
	Cuff cPPT (kPa)	26.7 ± 12.9	27.4 ± 11.8	17.7	48.3 43.0	0.79 (0.70-0.85)	-0.7 (-2.5 – 1.1)	-2.6% (-9.4% – 4.2%)	10.3	-21.3 – 19.9
	Cuff cPTT (kPa)	58.4 ± 18.4	60.6 ± 19.5	12.4	31.5 32.2	0.87 (0.81-0.91)	-2.2 (-4.6 – 0.1)	-3.8% (-7.8% – 0.1%)	13.1	-28.4 – 23.9
	Cuff cPTL (cm)	6.5 ± 2.5	6.7 ± 2.9	17.9	38.5 43.3	0.74 (0.63-0.82)	-0.2 (-0.6 – 0.2)	-2.9% (-9.7% – 3.7%)	2.5	-5.1 – 4.7
	VAS-I (cm)	3.7 ± 2.1	3.9 ± 2.9	37.1	56.8 59.0	0.73 (0.62-0.81)	-0.2 (-0.6 – 0.1)	-6.5% (-16.3% – 2.9%)	2.0	-4.3 – 3.8
	VAS-II (cm)	4.7 ± 2.4	4.9 ± 2.4	33.0	51.1 49.0	0.70 (0.58-0.79)	-0.2 (-0.6 – 0.2)	-3.8% (-12.5% – 4.7%)	2.3	-4.8 – 4.4
	VAS-III (cm)	5.1 ± 2.5	5.1 ± 2.5	32.1	49.0 49.0	0.71 (0.59-0.80)	-0.1 (-0.5 – 0.4)	-1.2% (-9.3% – 6.9%)	2.3	-4.7 – 4.6
	Ratio between VAS-III and VAS-I	1.53 ± 0.62	1.43 ± 0.50	17.5	32.0	0.60 (0.43-0.72)	0.09 (-0.01 – 0.20)	5.88% (-0.7% – 13.1%)	0.60	-0.6 – 1.2
Arm	Manual PPT (kPa)	367 ± 160	334 ± 162	17.7	43.6 48.5	0.87 (0.82-0.91)	32 (14 – 51)	8.7% (3.8% – 13.9%)	110	-188 – 252
	Cuff cPPT (kPa)	30.4 ± 15.1	34.5 ± 15.8	21.4	49.7 45.8	0.85 (0.79-0.90)	-4.1 (-6.0 – -2.2)	-13.5% (-19.7% – -7.3%)	11.1	-26.2 – 18.0
	Cuff cPTT (kPa)	69.1 ± 16.1	70.6 ± 15.4	6.7	23.3 21.8	0.90 (0.87-0.93)	-1.5 (-3.1 – 0.1)	-2.2% (-4.5% – 0.1%)	9.3	-20.1 – 17.1
	Cuff cPTL (cm)	6.1 ± 2.6	5.6 ± 2.9	25.3	42.6 51.8	0.82 (0.75-0.87)	0.5 (0.1 – 0.8)	7.6% (1.5% – 13.5%)	2.1	-3.8 – 4.7
	VAS-I (cm)	3.2 ± 2.1	3.2 ± 2.3	51.7	65.6 71.9	0.65 (0.51-0.75)	0.0 (-0.4 – 0.4)	0.2% (-12.0% – 12.3%)	2.3	-4.5 – 4.5
	VAS-II (cm)	4.0 ± 2.3	3.9 ± 2.5	44.9	57.5 64.1	0.66 (0.52-0.76)	0.2 (-0.3 – 0.6)	4.0% (-6.5% – 14.2%)	2.4	-4.7 – 5.0
	VAS-III (cm)	4.2 ± 2.3	4.1 ± 2.6	43.6	54.8 65.0	0.65 (0.51-0.75)	0.2 (-0.3 – 0.6)	4.0% (-6.2% – 14.2%)	2.5	-4.9 – 5.2
	Ratio between VAS-III and VAS-I	1.55 ± 0.69	1.53 ± 0.93	22.6	42.46	0.43 (0.19-0.59)	0.02 (-0.15 – 0.19)	1.29% (-9.7% - 12.3%)	0.99	-1.9 – 2.0