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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.

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4 **Assessment of musculoskeletal pain sensitivity and temporal summation by**
5 **cuff pressure algometry: A reliability study**
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33 summation, pain sensitivity
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4 **1. INTRODUCTION**
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6 Musculoskeletal pain is generally accepted to constitute a special diagnostic and therapeutic
7 challenge and a mechanism-based understanding of the factors involved in musculoskeletal pain
8 has gained acceptance in recent years [16]. Chronic musculoskeletal pain is linked with
9 sensitization, initially in the peripheral structures and often later sensitization of central
10 mechanisms [16]. Thus, there is a need for reliable methodologies to assess sensitization
11 mechanisms quantitatively **in chronic pain patients**.
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17 Handheld pressure algometry involving manually applied pressure stimulation to assess
18 pain sensitivity of deep structures has been extensively used and validated [22]; computer-
19 controlled stimulation may reduce variability and allow accurate construction of the stimulus-
20 response function [18]. A large epidemiological study showed that pressure pain thresholds
21 increased with age and were lower in women compared with men [23]. A meta-analysis has
22 further demonstrated the sex difference in pressure pain thresholds [41]. More recent reference
23 data based on 180 healthy subjects demonstrated that young women had lower pressure pain
24 thresholds than young men but in older subjects no sex difference was detected although there
25 was a general age-related increase in pressure pain thresholds [30]. In contrast to pressure
26 algometry [10], a larger tissue volume can be assessed by computer-controlled cuff-algometry
27 [36]. In cuff-algometry, the pain intensity related to inflation of a tourniquet applied around an
28 extremity is used to establish stimulus-response curves allowing assessment of deep-tissue pain
29 sensitivity. Moreover, cuff algometry is less likely to be influenced by local variations in pain
30 sensitivity and is also an examiner-independent technique reducing the potential measurement
31 bias. However, the test-retest reliability of cuff algometry is still to be determined.
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44 The facilitated pain response to sequential stimuli of equal strength has been defined as
45 temporal summation of pain and based on a central integrative mechanism. Temporal summation
46 of pressure-induced pain was facilitated in osteoarthritis pain patients [1] and fibromyalgia
47 patients [46] compared with healthy controls. Recently, also cuff-evoked temporal summation of
48 pain was found to be facilitated in osteoarthritis pain patients compared with asymptomatic
49 controls [45]. In contrast to the facilitatory effects in temporal summation of pain, the
50 conditioned pain modulation (CPM) results in reduced pain sensitivity in healthy subjects. CPM
51 is typically evoked by a painful conditioning stimulus (e.g. cold pressor test) and assessment of
52 the heteronymous pain sensitivity by manual pressure algometry [37;55], although several other
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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.

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4 **2. MATERIALS AND METHODS**
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6 *2.1 Subjects*
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8 In this study 136 healthy subjects between 18 and 65 years of age were included. Minimum 15
9 males and 15 females were included in both age spans from 18 – 44 years (younger), and 45-65
10 years (middle aged). Table 1 includes the number, age and body mass index (BMI) of subjects in
11 each group. Subjects were recruited by advertisement at the local university, the local university
12 hospital (Odense, Denmark), and through a local newspaper. All subjects were naive to pain
13 testing and none of the included subjects suffered from neurological, psychological,
14 cardiovascular diseases, had any pain or used any pain medication during the week prior to
15 participation. All subjects were asked to refrain from physical exercises, coffee and nicotine on
16 the days of participation. The study was conducted in accordance with the Declaration of
17 Helsinki, approved by the local ethical committee (S-20110070; S-20120014) and all subjects
18 provided written informed consent.
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30 *2.2 Procedure*
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32 Each subject was assessed at the same time of day on two different days separated by 1 week;
33 however 19 subjects rescheduled their second appointment. All subjects completed both
34 assessment sessions within 3 weeks. In the first session subjects were thoroughly introduced to
35 the procedures by drawings as well as verbal instructions. All subjects completed one practice
36 trial in the beginning of each of the two sessions. All pain sensitivity assessments were performed
37 with the subject either seated on a plinth without foot support and with both arms resting on the
38 thighs or lying supine on a plinth. In each session manual pressure algometry, cuff algometry and
39 assessment of temporal summation of pain by sequential cuff stimulations were assessed on the
40 upper arm and lower leg. In one of the two sessions the subjects subsequently completed a cold
41 pressor test with the dominant hand with pain sensitivity assessed by cuff algometry. Algometry
42 was performed before, immediately after and 15 min after the cold pressor test. Manual pressure
43 algometry was also recorded before and after the cold pressor test but reported elsewhere [47].
44 Each session lasted approximately 150 minutes and comprised three other conditions performed
45 after the above data collection as part of a larger study on conditioned pain modulation and
46 exercise-induced hypoalgesia [47].
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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 cm². 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

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4 the cPPT and when the subject terminated the pressure inflation was defined as the cPTT. The
5 pain intensity, at the time of termination was defined as the cPTL.
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8 TSP was assessed immediately after assessment of cPPT, and cPTT. Ten repeated cuff
9 pressure stimulations (2 s duration and 1s interval between stimuli) were delivered to the arm and
10 leg by inflation of both cuff chambers with an intensity equivalent to the cPTT recorded during
11 the previous assessment. Pressure with an intensity equivalent to the pain tolerance was chosen to
12 ensure that the first stimulation was perceived as painful by subjects although not extremely
13 painful due to the short stimulation time. To control for an increase in the cPTT after the cold
14 pressor stimulation the pressure intensity used for the repeated cuff inflations were also changed,
15 accordingly. Thus the actual cPTT level during and after the cold pressor test, respectively, were
16 used for repeated cuff stimulations in those particular trials. If such adjustments were not
17 implemented the reduced pain sensitivity of the first stimulus would likely result in less perceived
18 pain in response to the initial stimulation and by itself result in less TSP. Subjects rated their
19 pressure pain intensity continuously during the sequential stimulation on the electronic VAS
20 without returning it to zero in-between the stimulations. In the period between stimuli a constant
21 non-painful pressure of 5 kPa was kept ensuring that the cuff did not move. The VAS score
22 immediately after each stimulus was extracted.
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37 *2.5 Conditioned pain modulation*

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39 The cold pressor test was performed with the subject comfortably seated while immersing the
40 dominant hand into a tank containing circulating ice water at 1-2°C [56]. The subject immersed
41 the hand 5 cm above the wrist for 2 minutes. Cuff algometry cPPT, cPTT and TSP were assessed
42 just before, immediately after ending the 2 minutes cold pressor test, and 15 min after ending the
43 cold pressor test. The subject rated the cold pressor pain intensity on a 0 to 10 numerical rating
44 scale (NRS) where 0 was defined as “no pain” and 10 was “maximal pain”.
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52 *2.6 Statistics*

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54 Results are presented as mean and standard deviation (SD), unless otherwise specified. The
55 distribution of BMI and NRS scores during cold pressor test (NRS) deviated from normality
56 (Kolmogorov-Smirnoff test: $P < 0.001$). Thus, BMI, and NRS between men and women and
57 between age groups were analyzed with non-parametric statistics.
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4 To investigate the effect of gender, age groups, assessment site and session on PPT, cPPT,
5 and cPTT mixed-model analysis of covariance's (ANCOVAs) were performed with *assessment*
6 *site* (arm and leg) as within-subject factor, *sessions* (day 1 and day 2) as repeated measures and
7 *gender*, and *age group* (younger and middle age) as group factors. Due to the significant
8 difference in BMI between men and women, BMI was added to the analysis as a covariate.
9 Furthermore, Spearman's Rank Order correlations were run to determine the relationship
10 between manual PPT and cuff cPPT at the arm where the assessment site coincide. For initial
11 analysis of TSP, pain ratings immediately after each of the ten repeated stimulations were
12 analyzed with a 3-way repeated measures ANOVA with *assessment site* (arm and leg) as within-
13 subject factor, *sessions* (day 1 and day 2) and *stimulations* (1-10) as repeated measures. **Due to**
14 **variations in the pain ratings during stimulation 1 and 2 between session 1 and 2**, the mean VAS
15 score was calculated after stimulation 1-4 (VAS-I), stimulations 5-7 (VAS-II), and stimulations
16 8-10 (VAS-III) and the factor *stimulation-epoch* (VAS-I, VAS-II, and VAS-III) was added to the
17 ANOVA. For further analysis of TSP, the ratio between VAS-III and VAS-I was calculated.
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30 For analysis of gender, age group, assessment site, and session on TSP a 4-way ANCOVA
31 was performed with *assessment site* (arm and leg) as within-subject factor, *sessions* (day 1 and
32 day 2) as repeated measures, *gender* and *age group* (younger and middle age) as group factors
33 and *BMI* as covariate. The effect of cold pressor test on cPPT, cPTT, and TSP were analyzed in a
34 mixed-model ANCOVA with *assessment site* (arm and leg) as within-subjects factor, *time*
35 (before, immediately after, 15 min after) as repeated measures, *gender* and *age group* (younger
36 and middle age) as group factors and *BMI* as covariate. In case of significant factors or
37 interactions in the ANCOVAs, the Newman-Keuls (NK) test was used for post-hoc comparisons
38 incorporating correction for the multiple comparisons. Due to unequal sample sizes between age
39 groups, Brown-Forsythe tests were performed on all pain sensitivity variables to examine for
40 unequal variance between groups. *P* values less than 0.05 were considered significant.
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50 The mean, SD, and coefficient of variations (intra and inter CV) of PPT, cPPT, cPTT,
51 cPTL, stimulation epochs (VAS-I, VAS-II, and VAS-III), and the ratio between VAS-III and
52 VAS-I were calculated for each assessment site. Intraclass correlations (ICCs) based on a single
53 rating, consistency, 2-way mixed effect model (ICC_{3,1}) and Bland-Altman methods were used for
54 analysis of reliability. An ICC above 0.75 was taken as excellent reliability, 0.40–0.75 was fair to
55 good reliability, and less than 0.40 defined poor reliability [11]. Mixed model ANCOVAs were
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analyzed in Statistica, version 5.1 (StatSoft Inc., USA). ICCs and Bland Altman methods were calculated in SPSS Statistics, version 21 (IBM, USA)

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4 **3. RESULTS**
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6 *3.1 Demographics*
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8 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; $P < 0.001$).
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15 *3.2 Manual pressure algometry*
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17 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: $P < 0.001$).
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32 *3.3 Cuff algometry*
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34 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.
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41 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 ($r(135) = 0.271$, $P < 0.001$).
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55 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
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4 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

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13 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: $P < 0.007$).

33 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

55 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

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4 within the interval. The intra coefficients of variation at the leg and arm were low with CVs of
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6 14.6 % and 17.7 %, respectively.
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8 Repeatability between days of cPPT, cPTL, cPTT and TSP at the lower leg was good to
9 excellent with ICCs between 0.60-0.87. Results from Bland-Altman demonstrated no systematic
10 bias between sessions at the leg. Repeatability between days of cPPT, cPTL, cPTT and TSP at
11 the upper arm was lower than the leg with ICCs between 0.43-0.90. Results from Bland-Altman
12 demonstrated no systematic bias between sessions for cPTT and TSP at the upper arm; however
13 the results also indicated a systematic mean difference between the two sessions for cPPT and
14 cPTL at the arm, reflected in the 95 % CI of the mean difference, where zero does not lie within
15 the interval. The intra coefficients of variation at the arm were somewhat higher than the leg for
16 all parameters, except cPTT.
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26 *3.6 Cuff-algometry and CPM effects*

27 All 125 subjects completed the cold pressor test. The pain intensity reported during the cold
28 pressor test (NRS: median 8; range 2-10) was not significantly different between men and women
29 (Mann Whitney U; $P < 0.73$) or between age groups (Mann-Whitney U test; $P = 0.75$).
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32 The ANCOVA of cPPTs demonstrated a significant main effect of time (Fig. 5; $F(2,242) =$
33 3.23 , $P < 0.048$). Post-hoc test showed significantly increased cPPT immediately after cold
34 pressor test and 15 min after cold pressor test compared with baseline (NK: $P < 0.003$). There
35 was a significant main effect of time for cPTTs (Fig. 6; $F(2,242) = 10.50$, $P < 0.001$), with post-
36 hoc test showing significantly increased cPTTs immediately after cold pressor test and 15 min
37 after cold pressor test compared with baseline (NK: $P < 0.001$).
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44 The ANCOVA of the ratio between VAS-III and VAS-I demonstrated a significant main
45 effect of time ($F(2,242) = 4.55$, $P < 0.01$) with post-hoc test showing significantly decreased ratio
46 between VAS-III and VAS-I immediately after and 15 min after cold pressor test compared with
47 baseline (NK: $P < 0.004$). However, the ANCOVA also demonstrated significant interactions
48 between time and gender (Fig. 7A; $F(2,242) = 3.49$, $P < 0.04$), and between time and age group
49 (Fig. 7B; $F(2,242) = 5.13$, $P < 0.007$). Post-hoc test showed significantly decreased ratio between
50 VAS-III and VAS-I in women after cold pressor test and 15 min after cold pressor compared with
51 baseline (NK: $P < 0.004$). Post-hoc test also revealed that the ratio between VAS-III and VAS-I
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was significantly decreased in middle aged subjects after cold pressor test and 15 min after cold pressor compared with baseline (NK: $P < 0.004$).

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6 **4. DISCUSSION**
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8 This study demonstrated that reliability and sensitivity of computer-controlled cuff algometry for
9 pain assessment is comparable to manual pressure algometry. Cuff assessments at the lower leg
10 were more reliable than assessment on the arm. The pain sensitivity in women was generally
11 higher compared with men for both pressure and cuff algometry. The pain sensitivity increased
12 with age when assessed by cuff algometry whereas manual pressure algometry demonstrated
13 decreased pain sensitivity with age. Cuff algometry was sensitive to CPM and temporal
14 summation of pain could be reliably assessed and modulated by CPM.
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22 *4.1 Reliability of pain assessment*
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24 Test-retest data on manual pressure algometry demonstrated excellent ICC values (>0.8)
25 confirming previous studies reporting ICCs above 0.7 [4;8;12;26;33;39;50]. The Bland-Altman
26 analysis showed however a systematic mean difference between the two sessions for the PPT
27 values assessed on the leg and arm.
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31 The cuff pressure pain thresholds demonstrated comparable ICC values as manual pressure
32 algometry but also a systematic mean difference between the two sessions was detected on the
33 arm. The cuff pain tolerance was reliably detected in both the arm and leg with excellent ICCs
34 (0.87 and 0.90). The VAS score at cuff pain tolerance was also recorded with high ICC but a
35 Bland-Altman systematic mean difference for the two sessions was found for the arm. Finally,
36 the VAS scores provided immediately after each of the repeated cuff stimulations and the ratio
37 between VAS-III and VAS-I reflecting temporal summation of pain were recorded with good to
38 excellent ICCs in the leg. The blocks of VAS scores (VAS-I, II, III) demonstrated a better
39 reliability than the VAS-ratio probably reflecting the higher variability between sessions in the
40 VAS-I affecting the VAS-ratio. In general, the test-retest analysis in the 125 healthy subjects
41 showed good to excellent ICCs and no systematic mean difference between the two sessions for
42 the cuff algometry used on the leg.
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53 Consistently for both cuff and manual pressure algometry a systematic mean difference in
54 pain thresholds assessed on the arm was found between the two sessions and also for the pain
55 intensity detected at the tolerance level when assessed on the arm. The specific reason for this
56 effect on the arm is not clear. Nonetheless, the mean difference between the two sessions in the
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4 cPPT and cPTL assessed on the arm is only approximately 10 %. Many studies have based the
5 pressure algometry pain thresholds on the average of at least two trials [33;34] and the present
6 study showed high ICC and good reliability based on the average of two repetitions.
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10 11 *4.2 Pain sensitivity difference between arm and leg*

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13 The pain sensitivity assessed by manual pressure algometry was significantly lower in the leg
14 compared with the arm as shown previously with assessments on hand and foot [3;43] or knee
15 and forearm [53]. Similar findings have been reported for thermal pain sensitivity [43]. The
16 specific mechanism for the regional difference is not known but is likely to include the degree of
17 overlapping receptive fields and differences in innervation density of nociceptors. In contrast,
18 assessment with cuff algometry demonstrated significantly increased pain sensitivity in the leg
19 compared with the arm. Not only was the pressure intensity at pain tolerance lower in the leg
20 compared with the arm but the VAS scores obtained during repeated cuff stimulations for
21 assessment of temporal summation was also higher. The better effect of cuff stimulation at the
22 leg may illustrate the effect of spatial summation and excitation of more nociceptors from a larger
23 volume below the cuff mounted on the leg [24] compared with the arm. Similar spatial
24 summation effect has been demonstrated following cuff assessments with two different widths of
25 cuffs applied on the leg [36].
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39 *4.3 Gender and age effects on the pain sensitivity*

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41 Previously, robust gender effects with increased pressure pain sensitivity in women compared
42 with men have been reported for pressure algometry [6;23;32;41;43] in line with the present
43 findings and now also shown with cuff algometry when assessing the pain tolerance parameter.
44 The pressure pain threshold assessed by cuff algometry was not different between women and
45 men which may suggest that this parameter is less sensitive to gender differences.
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50 The pressure pain sensitivity assessed by manual pressure algometry was decreased with
51 age contrasting the increased pain sensitivity detected by cuff algometry in middle aged subjects
52 compared with younger subjects. Previous data on aging effects on pressure pain thresholds are
53 mixed depending among other factors on assessment modality, stimulus duration, and area [13].
54 In a large study including 740 subjects, Jensen et al. [23] found an increase with age in pressure
55 pain thresholds assessed on pericranial muscles. In contrast, pressure pain thresholds assessed on
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4 fingers were reported to be decreased in older compared with young subjects [7;28]. The contrast
5 in findings with pressure and cuff algometry may suggest that the spatial integration is a major
6 determinant for the age-related effects. Nonetheless, spatial summation was not found to be age-
7 dependent when testing with different probe sizes for pressure algometry [28]. **Alternatively,**
8 **pressure and cuff algometry assess different mechanisms, which is supported by the weak**
9 **correlation between thresholds between those two measures. Similar findings have been reported**
10 **for pain thresholds assessed by electrical, thermal and mechanical modalities [31]. A fundamental**
11 **difference between pressure and cuff algometry is the ischemia accompanying cuff algometry.**
12 **Based on the current data an ischemic pain component cannot be excluded. However, Issberner et**
13 **al. [21] demonstrated that 7 to 10 min tourniquet-induced ischemia at rest did not induce pain or**
14 **significant changes in the tissue pH level whereas simultaneous contractions (i.e. the submaximal**
15 **effort tourniquet technique) progressively induced pain and reduced the tissue pH-level.**
16 **Moreover, when inducing pain by ischemic muscle contractions for 2 min, the pressure pain**
17 **thresholds assessed by pressure algometry increased compared with baseline measures [17]. Thus,**
18 **it is not likely that the ischemia during cuff assessment paradigms (done at rest, for maximum**
19 **100 s) induced any pain or sensitization of the deep-tissue nociceptors.**

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

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

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

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4 Immediately after the cold pressor test the cuff pain threshold and cuff pain tolerance
5 increased significantly in both the arm and leg. Previous studies reported similar findings with
6 decreased cuff pain sensitivity [19] and increased pressure tolerance levels to computer-
7 controlled pressure algometry [35] assessed on the leg when conditioning stimulus was applied
8 on the arm. The CPM magnitude did not differ between the leg and arm in agreement with a
9 previous studies [35]. Age or gender effects were not found on the cold pressor stimulation pain
10 intensity or the immediate CPM effect on cuff pressure pain threshold or tolerance in the present
11 study in contrast with previous studies using manual pressure or heat as test stimuli
12 demonstrating reduced pain inhibition associated with ageing [9;27;29;40;52] and in women
13 compared with men [2;14;15;20]. These contrasting findings suggest that the age and gender
14 effects may be highly dependent on the modality used as test stimulus. Nonetheless, comparable
15 CPM effects between men and women assessed with pressure pain as test stimulus have been
16 reported [38;44;51;57]. The combined temporal summation of deep-tissue pain and CPM has
17 been reported for manually applied repeated pressure stimulations [5] and now also shown with
18 cuff algometry. In contrast with Cathcart et al. [5] the stimulation intensity used for the temporal
19 pain summation was adjusted and increased after the cold pressor test, as an attempt to account
20 for the pain sensitivity changes, and still the temporal summation effect was significantly reduced
21 in women and middle aged participants although to a minor degree and the implications of such a
22 small effect is up for discussion. The fact that temporal summation of pain was more expressed in
23 women at baseline compared with men may suggest that robust temporal summation of pain is
24 needed before a clear CPM effect can be detected.
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44 *4.5 Limitations*

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46 The change in cuff pain sensitivity after the cold pressor test could be due to habituation after
47 repeated cuff testing since a control group without the cold pressor test was not included.
48 However, recent studies demonstrated that the cuff pain sensitivity was not significantly different
49 after 15 min quiet rest compared with before in healthy subjects and in patients with chronic pain
50 [48;49]. The statistical analysis did not account for the unequal sample sizes in the two age
51 groups, which could affect the robustness of the ANCOVA. Finally, computer-controlled cuff
52 algometry as used in this study is not widely available and results on test-retest reliability may
53 not replicate with different cuff devices that are not as automated. More often used is computer-
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4 controlled pressure algometry minimizing the variability caused by the manual pressure
5 stimulation and future studies should compare this modality with the cuff algometry.
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10 *4.6 Conclusion*

11 Computer-controlled cuff algometry for pain assessment is a reliable methodology likewise
12 manual pressure algometry but constitutes a more standardized and examiner-independent
13 method for assessment of pain sensitivity. Difference in age-related pain sensitivity between
14 manual and cuff algometry should be further investigated. The usability of cuff algometry was
15 also demonstrated for assessment of CPM.
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4 **FIGURE LEGENDS**
5

6 **Fig. 1:** Mean (+ SEM, N = 136) pressure pain thresholds (PPT) assessed by manual algometry
7 recorded at the dominant leg and arm in younger and middle aged men and women. Significantly
8 different between age groups (*, NK: $P < 0.05$), gender (†, NK: $P < 0.05$), and assessment sites (#,
9 NK: $P < 0.05$).
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15 **Fig. 2:** Mean (+ SEM, N = 125) pressure pain thresholds (cPPT) and pressure pain tolerance
16 (cPTT) assessed by computerized cuff algometry recorded at two assessment sites (non-dominant
17 lower leg and non-dominant upper arm) in younger and middle aged men and women.
18 Significantly different between age groups (*, NK: $P < 0.05$), gender (†, NK: $P < 0.05$) and
19 assessment sites (#, NK: $P < 0.05$).
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25 **Fig. 3:** Mean (+ SEM, N = 125) VAS scores immediately after each of the ten repeated
26 stimulations assessed by computerized cuff algometry recorded at two assessment sites (non-
27 dominant lower leg and non-dominant upper arm). Significantly different compared with
28 stimulation 1-7 (†, NK: $P < 0.05$) and compared with stimulation 1-4 (*, NK: $P < 0.05$).
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35 **Fig. 4:** Mean (+ SEM, N = 125) ratio between VAS-III and VAS-I reflecting temporal
36 summation of pain assessed by computerized cuff algometry recorded at two assessment sites
37 (non-dominant lower leg and non-dominant upper arm) in younger and middle aged men and
38 women. Significantly different between gender (†, NK: $P < 0.05$).
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44 **Fig. 5:** Mean (+ SEM, N = 125) pressure pain threshold (cPPT) assessed by computerized cuff
45 algometry recorded at the non-dominant lower leg (A) and the non-dominant upper arm (B)
46 before, immediately after cold pressor test, and 15 min after cold pressor test in younger and
47 middle aged men and women. The cold pressor test was applied to the dominant hand.
48 Significantly different compared with baseline values (*, NK: $P < 0.05$).
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55 **Fig. 6:** Mean (+ SEM, N = 125) pressure pain tolerance (cPTT) assessed by computerized cuff
56 algometry recorded at the non-dominant lower leg (A) and the non-dominant upper arm (B)
57 before, immediately after cold pressor test, and 15 min after cold pressor test in younger and
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4 middle aged men and women. The cold pressor test was applied to the dominant hand.
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6 Significantly different compared with baseline values (*, NK: $P < 0.05$).
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10 **Fig. 7:** Mean (+ SEM, N = 125) ratio between VAS-III and VAS-I reflecting temporal
11 summation of pain assessed by computerized cuff algometry recorded at two assessment sites
12 (non-dominant lower leg and non-dominant upper arm) in younger and middle aged (A) men and
13 women (B) before, immediately after cold pressor test, and 15 min after cold pressor test. The
14 cold pressor test was applied to the dominant hand. Significantly different compared with
15 baseline values (*, NK: $P < 0.05$).
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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
[Click here to download Figure: Figure 1.tif](#)

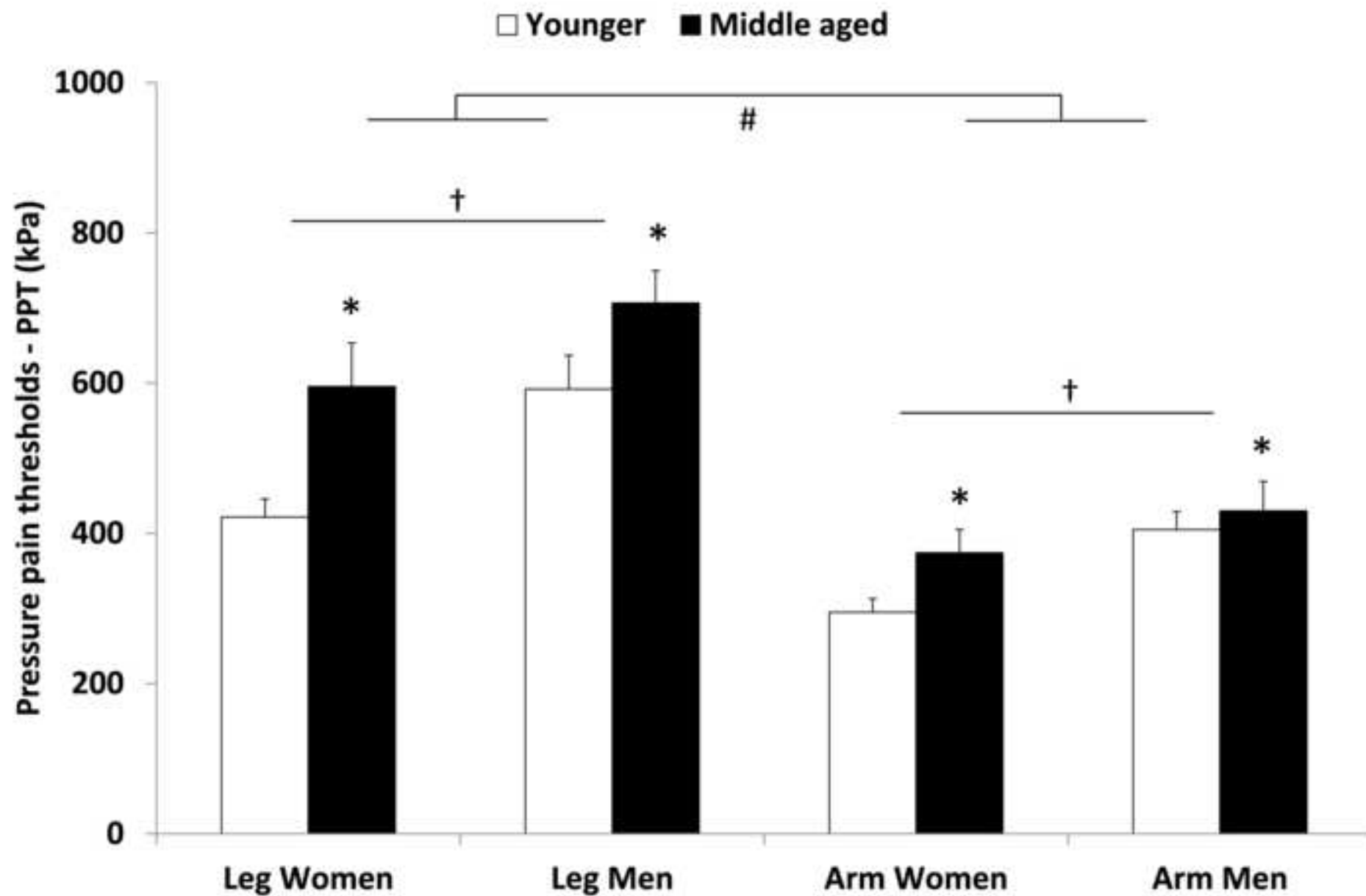


Figure2

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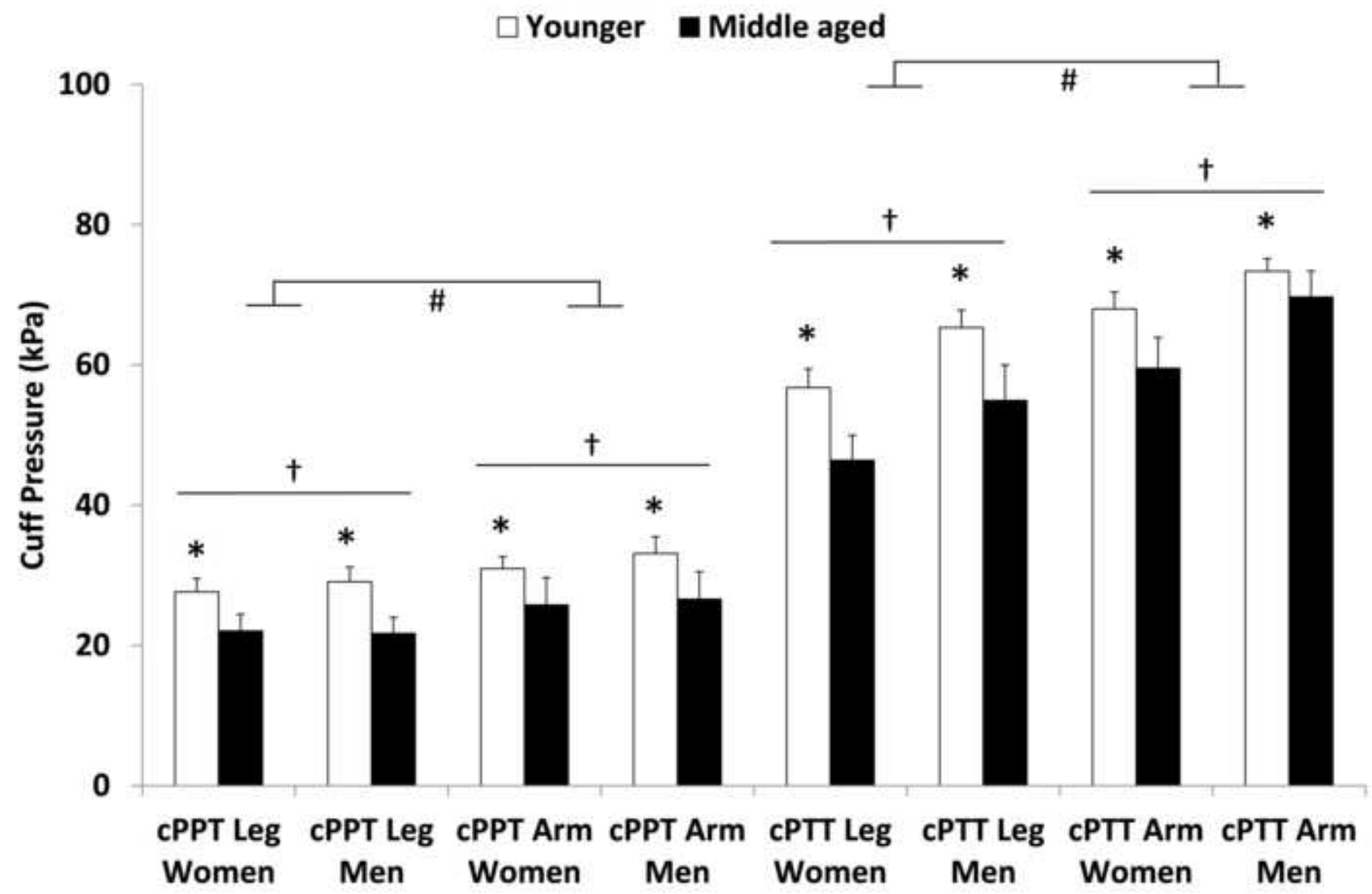


Figure3
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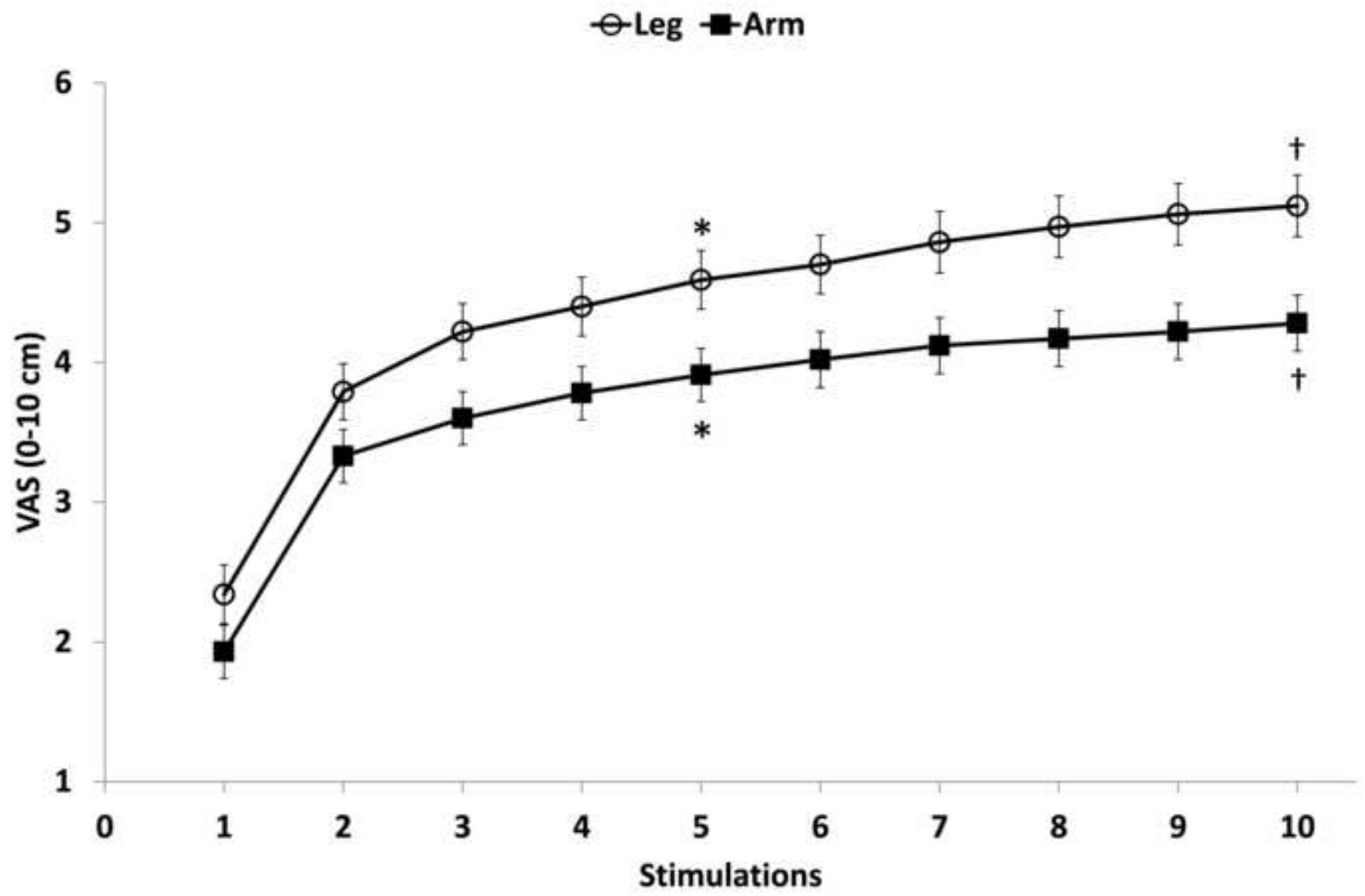


Figure4

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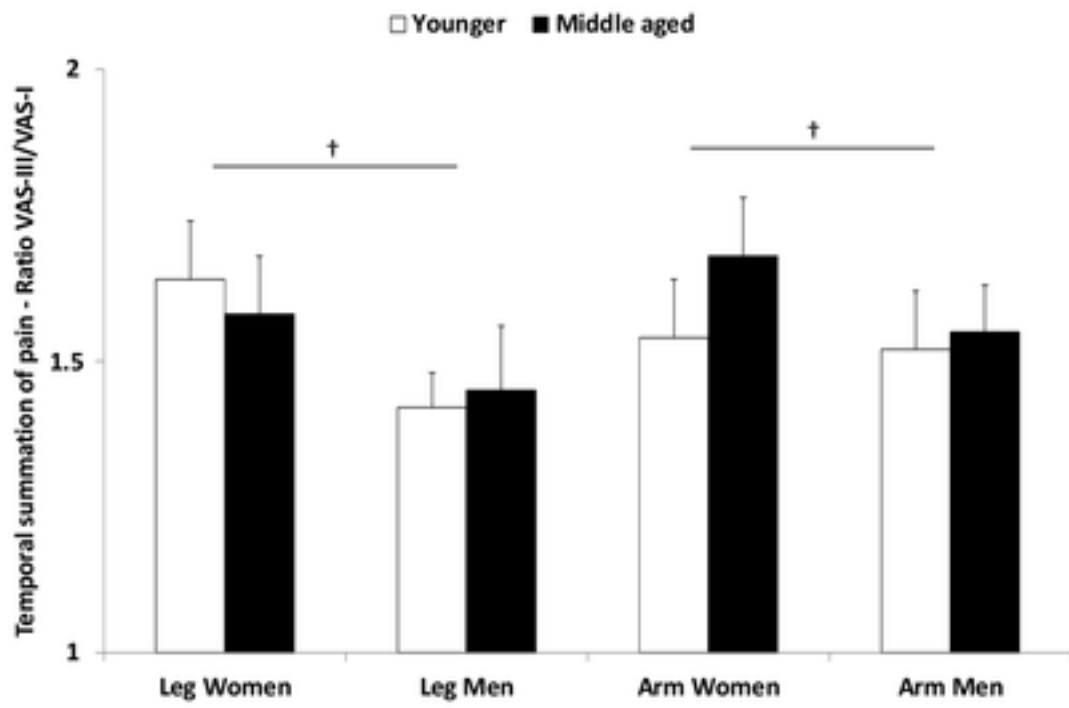


Figure5

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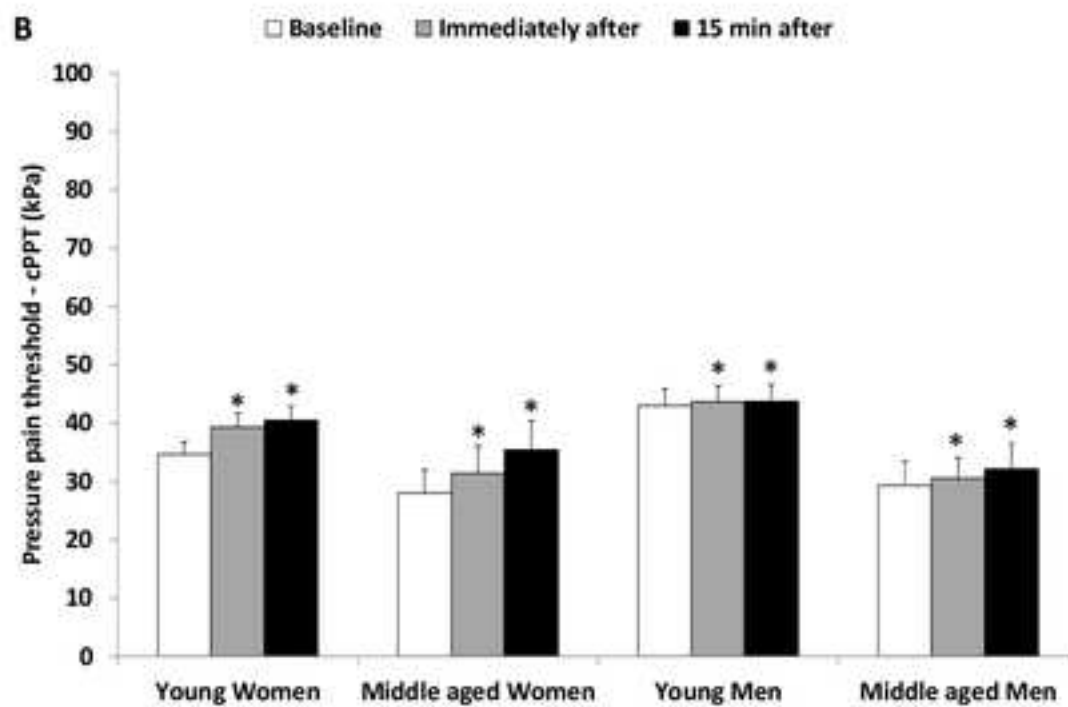
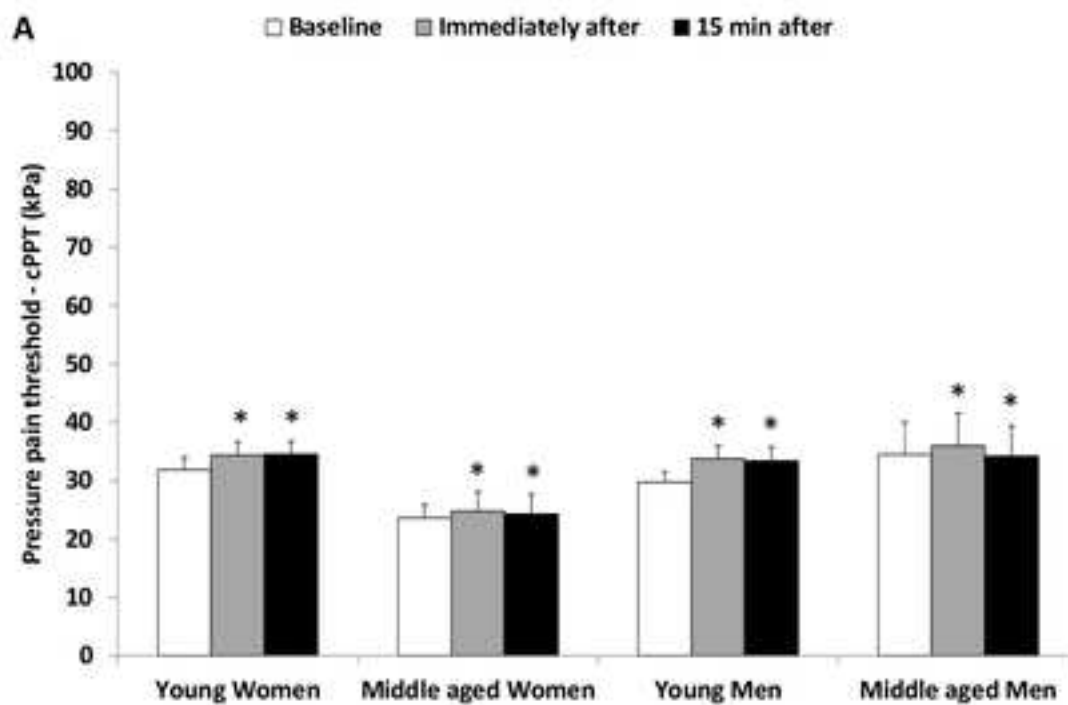


Figure6

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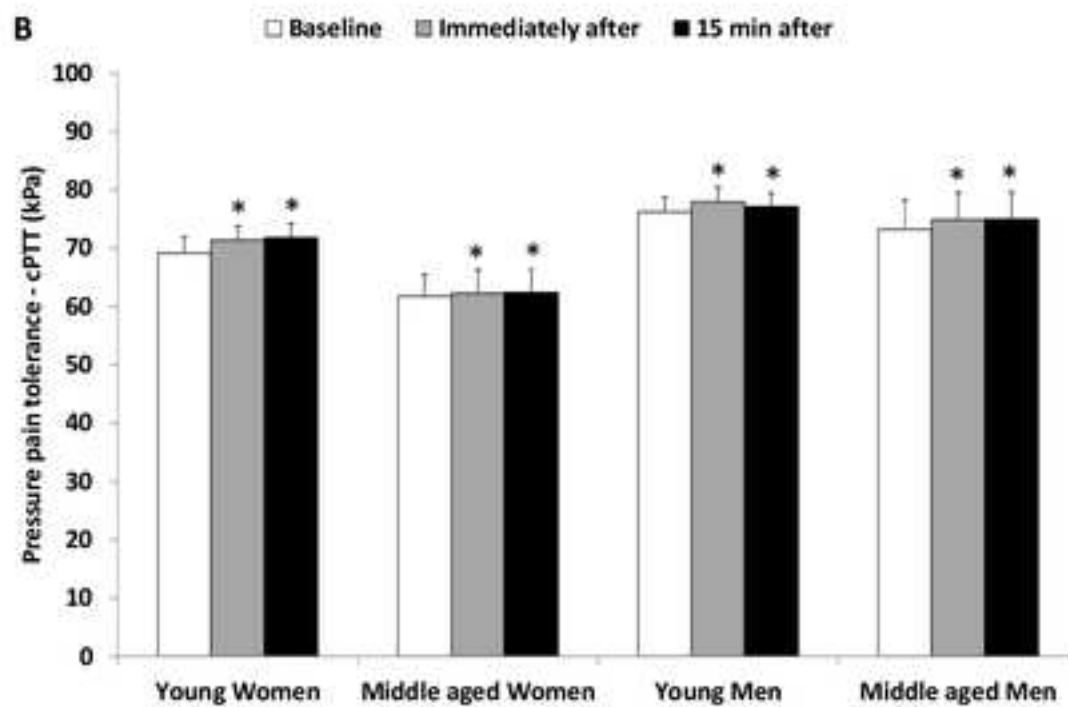
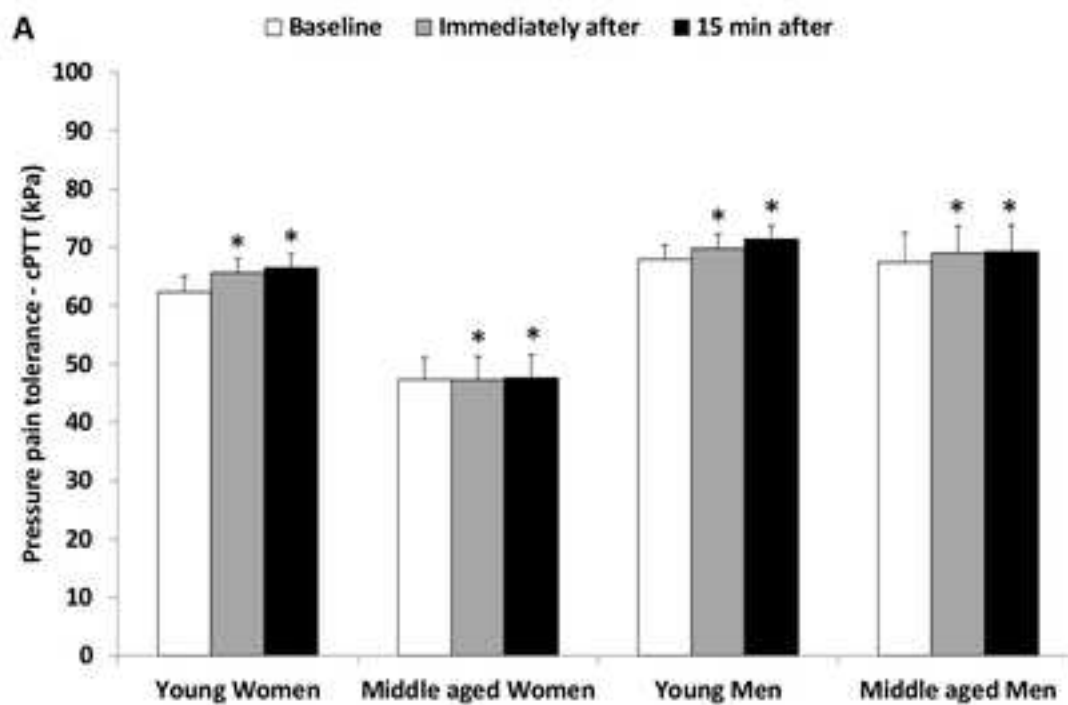


Figure 7

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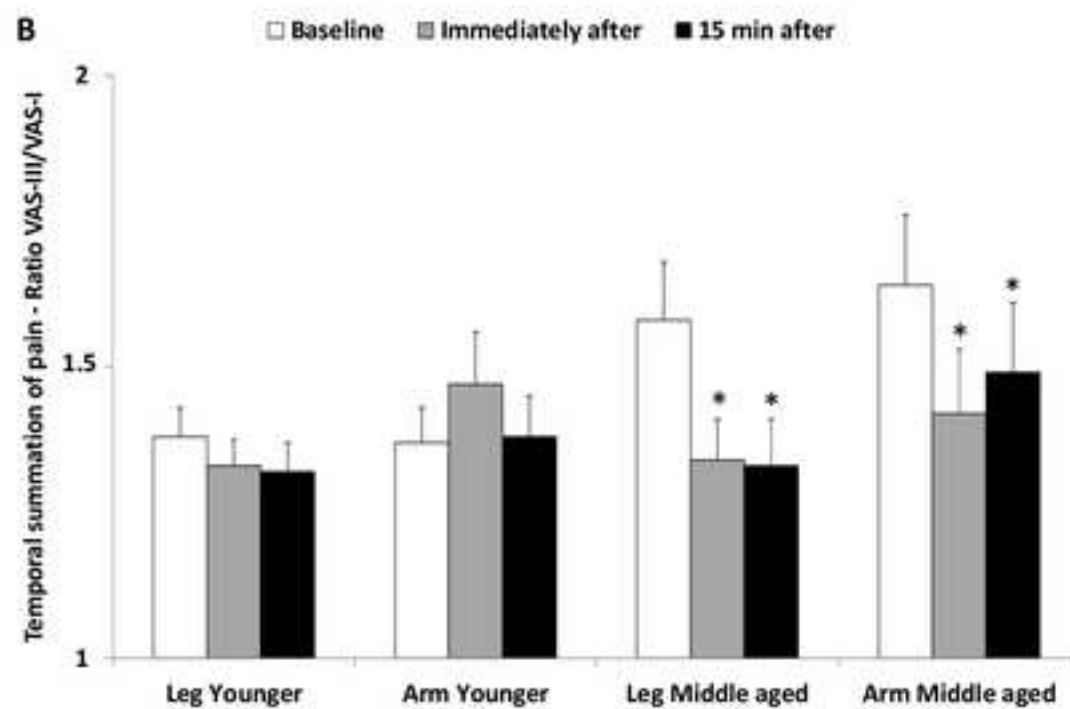
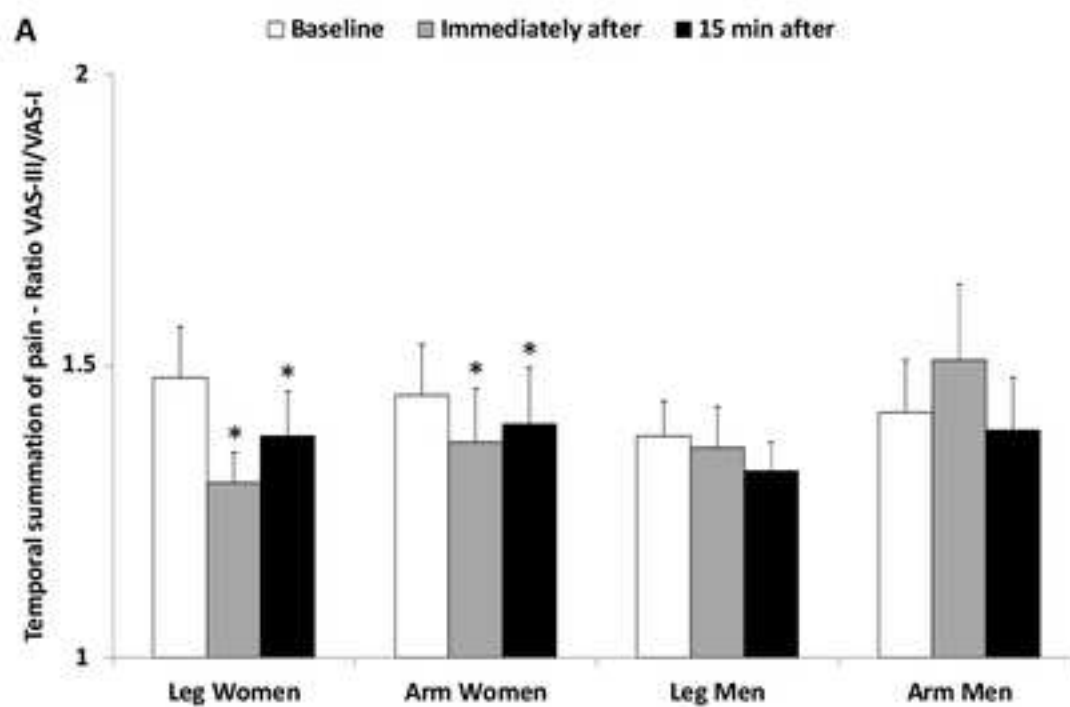


Table 1: Number of subjects included (N), age, and body mass index (BMI) for the two age groups (Younger and Middle aged) of women and men

	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).			

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			
		1 st session Mean ± SD	2 nd 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