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AGE INTERACTIONS ON PAIN SENSITIZATION IN PATIENTS WITH SEVERE KNEE OSTEOARTHRITIS AND CONTROLS

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ABSTRACT

Objectives: Widespread pressure hyperalgesia, facilitated temporal summation of pain (TSP), and impaired conditioned pain modulation (CPM) have been found in knee osteoarthritis (KOA) patients compared with controls and these parameters have further been suggested to be altered in the elderly. This study investigated the influence of age on pressure hyperalgesia, TSP, and CPM in patients with KOA and controls.

Methods: One-hundred-thirty-three severe KOA patients and 50 age and sex-matched asymptomatic controls were assessed by cuff algometry and handheld pressure algometry. Pain sensitivity was assessed around the head of the gastrocnemius muscle to identify mild pain detection (MPDT) and tolerance (PTT) threshold. TSP was assessed by visual analogue scale (VAS) scores of the pain evoked by 10 repetitive cuff stimulations. CPM was assessed as the difference in PTT before and during cuff-induced tonic arm pain. Pressure pain thresholds (PPTs) were assessed by handheld algometry at the tibialis anterior muscle. Two subgroups were analyzed in the age range below and above 65 years. Pearson correlations between age and pain parameters were applied.

Results: Patients demonstrated reduced MPDT, PTT and PPT ($P<0.01$), facilitated TSP ($P<0.02$), and a trend towards impaired CPM ($P=0.06$) compared with controls. A negative correlation was found between MPDT, PTT and PPT and age ($P<0.05$) but no age-related association was found for TSP and CPM.

Discussion: Pressure hyperalgesia was affected by age whereas dynamic pain mechanisms such as TSP and CPM were unaffected suggesting that these parameters are robust for a larger age range and reliable for long-term follow up studies.

Keywords: Osteoarthritis, temporal summation of pain, widespread hyperalgesia, cuff algometry

INTRODUCTION

Severe knee osteoarthritis (KOA) is associated with degeneration of cartilage and pain but only a weak correlation is found between the radiological assessment of KOA and the pain reported by the patients[1,2]. Quantitative sensory testing (QST) have been widely used to assess sensitization in KOA[3]. Increased pain sensitivity to mechanical stimulation has been found in patients with osteoarthritis when assessing pressure pain thresholds (PPTs) by manual single-point pressure algometry compared with controls[4–6]. In addition, patients with KOA have shown pain hypersensitivity to the examiner-independent computer-controlled pressure algometry and cuff algometry[4,5] by measuring cuff mild pain pressure detection thresholds (MPDT) and tolerance (PTT). Today, handheld algometry is considered the golden standard whereas cuff algometry has recently been used in both methodological and clinical settings.

Temporal summation of pain (TSP) represents a pro-nociceptive mechanism[7], facilitated in patients with sensitization such as KOA[5]. In KOA patients, facilitated TSP has been demonstrated when assessed on the lower leg[4,5] and recently preoperative TSP was found to be associated with the development chronic postoperative pain[8,9]. The descending control of nociceptive input along the neuroaxis can be assessed by conditioned pain modulation (CPM) implicating a reduction in the response to a painful test stimulus during administration of a distant conditioning pain stimulus[10,11]. In several chronic musculoskeletal pain conditions including KOA, a less efficient descending control has been found by CPM as compared with gender matched controls[3–5,12].

The majority of KOA patients are above 45 years old[13,14] and the mean age for the first total knee replacement is 65-68 years[15]. Aging is associated with various changes in the nociceptive system where pain threshold have been shown to increase with age when stimuli are brief, localized, and on distal limbs in asymptomatic subjects[16,17]. For instance, cutaneous heat and deep-tissue single-point mechanical pain thresholds were increased for subjects above 55 years compared with younger subjects[18]. In contrast, the more robust cuff stimulus presented with decreased pain thresholds in older

compared with younger asymptomatic subjects[19]. Reduced efficacy of CPM in healthy elderly adults compared with younger adults has been found[20]. However, a potential age effect of the KOA sensitization is still to be investigated.

KOA, as well as other common chronic musculoskeletal syndromes has higher prevalence among women as compared with males[21]. When compared with males, females have higher pain sensitivity and have a greater ability to discriminate among varying levels of pain[22]. Furthermore sex differences in pain threshold and tolerance measures have been most consistently found for pressure pain and cutaneous electrical stimulation, while least consistently found for cutaneous thermal pain stimuli[23].

The aim of this study was to evaluate the effect of age on pain sensitivity in patients with KOA and healthy controls in relations to pressure pain threshold, pain tolerance, TSP and CPM.

METHODS

Participants

One hundred thirty-five patients (age range: 44-89 years; 84 females) were recruited from the Outpatient Clinic, Ortopaedic Department Frederikshavn, Aalborg University Hospital. Fifty age-matched asymptomatic and pain-free controls (age range 53-79 years; 25 females) were recruited among siblings/spouse or announcements. Patients diagnosed with severe KOA who were scheduled for total knee replacement were invited to participate in the study. Clinical KOA was defined following the American College of Rheumatology criteria[24], and patients previously diagnosed with rheumatoid arthritis, fibromyalgia, and fractured knee were excluded from the study. The present study focused on two subgroups of KOA patients and controls in the age range up to 65 years (≤ 65 years) and above 65 years and older (> 65 years). Demographics, radiological Kellgren-Lawrence evaluations (KL scores), visual analogue scale (VAS, 0-10 cm) score of the maximum pain the last 24 h, and body mass index (BMI) were collected (table 1). The study was approved by the local ethical committee (N-20120015)

and conducted in accordance with the Helsinki Declaration. All participants received oral and written information about the study, and signed the informed consent form.

Protocol

Participants were requested not to take any analgesic medication 24 hours before QST examination and KOA patients indicated their most painful knee. Examinations took place in a quiet, temperature-controlled room with the participant in a relaxed supine position. Assessment methods were carefully explained to participants prior to examination. The mechanism-based QST with cuff algometry included assessments of 1) hyperalgesia measured at the lower leg, 2) TSP, and 3) CPM. Moreover, conventional handheld pressure algometry (single-point algometry) were used for assessment of the pain sensitivity at the lower leg and as a golden standard for pressure pain sensitivity. All parameters were recorded 3 times at the most affected KOA side for patients and at the dominant side for controls and the mean of the individual trials was applied for further analysis.

Cuff algometer

The deep-tissue pain sensitivity was evaluated by cuff pressure stimulations using a computer-controlled cuff-algometer (Nocitech, Denmark & Aalborg University, Denmark)[19]. The setup consists of two cuffs (a single and a double chamber, VBM, Germany), an electronic visual analogue scale (VAS) and a pressure release button, which the participants used to rate their pain intensity and release the pressure, respectively. The single chamber cuff was 7-cm wide, while the double chamber cuff was 13-cm wide with an equal-sized proximal and distal chamber. 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.

Cuff algometry for assessment of hyperalgesia at the lower leg

Mild pain detection threshold (MPDT) and pressure tolerance threshold (PTT) were recorded by the computer-controlled cuff algometer at the lower leg as a measure of hyperalgesia. A single chamber

and a double chamber configuration of the cuff were used for single and double cuff assessment. The cuff was wrapped around the middle of the lower leg at the level of the heads of the gastrocnemius muscle. The pressure was increased by 1 kPa/s; the maximal pressure limit was 100 kPa. The participants were instructed to rate the pain intensity continuously on the electronic VAS from when the pressure was defined as pain and to press the pressure release button when the pain was intolerable (PTT). The MPDT was defined as the first pressure value where the VAS was exceeding 2 cm. Lower MPDT and PTT indicates increased pain sensitivity.

Temporal summation of pain (TSP)

TSP was assessed by the computer-controlled cuff algometer using the double chamber tourniquet cuff. Ten cuff pressure stimuli (1-s duration, 1-s break) were delivered to the lower leg by simultaneous inflation of both cuff chambers to an intensity equivalent with the mean of the MPDT and PTT recorded during the assessment of the pain sensitivity[25]. In the period between stimuli, a constant non-painful pressure of 1 kPa was kept to ensure that the cuff did not move. The participants rated their pain intensity continuously during the sequential stimulation on the electronic VAS without returning it to zero in between stimulations. The mean VAS score during the 1-s non-stimulation interval after each of the 10 stimuli was extracted. For analysis of TSP, the mean VAS score was calculated from the first to the 4th stimulus (VAS-I) and from the 8th to the 10th stimulus (VAS-II)[26]. The TSP-effect was defined as the difference between VAS-I and VAS-II (i.e. VAS-II minus VAS-I). A higher value of TSP-effect indicates facilitated TSP.

Conditioned pain modulation (CPM)

Experimental tonic pain was provoked at the arm contralateral to the most pain affected knee by applying constant cuff stimulation at the level of 60 kPa (conditioning stimulus). This value was found equivalent to a general pain perception of 5 cm on the VAS in a preliminary assessment. If not

tolerated, the conditioned stimulus was reduced to 30 kPa. Assessment of PTT was performed using the single chamber cuff on the ipsilateral lower leg (test stimulus) simultaneously with the conditioning stimulus. The conditioning stimulus was terminated when the PTT assessment was completed. The CPM-effect was defined as the difference between the PTT during tonic arm pain minus the PTT without the tonic arm pain. A smaller increase in PTT during conditioning indicates less CPM.

Pain sensitivity to handheld algometry

A handheld algometer (Somedic AB, Sweden) was used for measuring single-point pressure pain thresholds (PPTs). The 1-cm^2 probe was directed perpendicularly to the skin and pressure was applied at 30 kPa/s until the participant identified the pressure as pain and pressed a button. Single-point algometry was performed at the tibialis anterior (TA) muscle 5 cm distal to the tibial tuberosity.

Statistics

The data are presented as mean and standard error of the mean (SEM). Data were normally distributed, confirmed by visual inspection of Q–Q plots, except for TSP which was then analyzed by non-parametric statistics. To compare demographics and clinical characteristics between same age groups, independent samples t-test was used for categorical measures (e.g. BMI and age) and the chi-squared test was used to assess significant differences in gender distribution. MPDT, PTT, CPM-effect, and PPT were analyzed by 2-way analysis of variance (ANOVA) with *group* (KOA, control) and *age* (≤ 65 years, > 65 years) as between-group factors. Post-hoc tests adjusted for Multiple comparisons (Bonferroni correction) was used in case of significant factors or interactions in the ANOVA. The Kruskal-Wallis test was used for analysis of TSP, Mann-Whitney test was applied as post-hoc analysis, and the Bonferroni correction was calculated manually. Gender differences have consistently been found when studying QST parameters[16,21,27] and thus the present study adjusted for gender differences. Pearson's product moment correlation coefficient was extracted to assess the association between age

and the QST parameters (MPDT, PTT, PPT, TSP and CPM) in KOA patients and controls. Only significant factor or interaction effects are reported. $P \leq 0.05$ was considered significant.

RESULTS

One-hundred-thirty-five patients were recruited and two patients excluded from the analysis due to technical problems resulting in 133 patients included in this analysis. Patients compared with controls had significantly higher BMI in the ≤65 age group ($P<0.05$) and the patients in the older group had higher age compared with the controls in the older group ($P<0.05$; Table 1).

Cuff MPDT and PTT assessed from the lower leg

ANOVAs of the MPDT and PTTs recorded with a single-chamber cuff showed a group effect (ANOVA: $F(1,170\text{-}172) >31.59$, $P < 0.001$) where patients showed lower MPDTs and PTTs compared with controls (Bonferroni: $P < 0.001$) and an effect of age (ANOVA: $F(1,170\text{-}172) > 9.71$, $P < 0.01$) where participants older than 65 years compared with 65 years or younger showed lower MPDTs (Bonferroni: $P < 0.01$), see figure 1A. ANOVAs of the MPDT and PTTs recorded with a double-camber cuff showed a group effect (ANOVA: $F(1,169\text{-}173) > 9.74$, $P < 0.01$) where patients showed lower MPDTs and PTTs compared with controls (Bonferroni: $P < 0.01$), see figure 1B.

-------- Figure 1 around here --------

Temporal summation of pain

Analysis of the TSP-effect showed a significant effect between groups (*Kruskal-Wallis*: $P < 0.001$). Post-hoc analysis showed that patients reported facilitated TSP compared with controls (Mann-Whitney: $P < 0.02$), see figure 2.

-------- Figure 2 around here --------

Conditioned pain modulation

The ANOVA of the CPM-effect showed a trend towards a group effect (ANOVA: $F(1,165) > 3.49$, $P = 0.06$) where patients showed impaired CPM-effect compared with controls, figure 3. The CPM-effect was not significantly different in the two age groups (ANOVA: $F(1,165) < 2.75$, $P > 0.1$).

-------- Figure 3 around here --------

Handheld PPT assessed from the tibialis anterior muscle

ANOVA of the handheld PPTs showed a group effect (ANOVA: $F(1,164) > 1.64$, $P < 0.01$) where patients showed lower PPTs at the TA muscle compared with controls (Bonferroni: $P < 0.01$), figure 4.

-------- Figure 4 around here --------

Correlations of age and mechanistic pain parameters

Correlation analysis showed that age correlated with pressure thresholds (MPDT: $R = -0.28$, $P < 0.001$, PTT: $R = -0.24$, $P < 0.01$ and PPTs: $R = -0.20$, $P < 0.05$) but not TSP or CPM.

DISCUSSION

The current study found that KOA patients showed hyperalgesia at the lower leg detected as lower cuff algometry MPDT, cuff algometry PTT and handheld algometry PPTs, facilitated TSP, and impaired CPM-effect when compared to controls. Age was found to be associated with pressure pain thresholds from cuff algometry MPDT, cuff algometry PTT and handheld algometry PPT but the methodology applied in the current study found no association between age and TSP or CPM.

Associations between age and pain sensitivity

The major part of age-related research have focused on pain thresholds[17–19,28,29], whereas central pain mechanisms such as CPM[30] and TSP[28,31] have been less investigated. Studies have suggested that increased clinical pain intensity and pain sensitivity in the elderly could be due to plasticity in the central nervous system[31,32], and animal studies have suggested that multiple neural and hormonal pain modulating systems become less functional with increasing age[33]. Interestingly, the current study found correlations showing that the pressure pain sensitivity decreased with aging, whereas no association was found for CPM. Pain sensitivity based on pain thresholds is a mixed measure of peripheral and central nociceptive mechanisms whereas CPM is believed to reflect a central nociceptive mechanism[3,34], why the results from the current study may suggest that increasing age mainly affect the peripheral nociceptive system and to a less extent the central nociceptive mechanisms.

In the general population, aging decreased pain sensitivity to single-point pressure algometry have been shown [18,28] although Graven-Nielsen et al., 2015[19] showed increased sensitivity to cuff pressure algometry. In line, the current study found increased sensitivity to single chamber cuff MPDTs. In contrast to previously, the current study did not find age to interfere with single-chambered cuff PTT, double-chamber cuff MPDT and PTT, and handheld PPT. As suggested by Gibson et al., 2004[17] the age interference with pain mechanistic measure are mixed and could be due to assessment modality, stimulus duration and stimulus area, which could explain difference from the current study and the previous literature. Further, Gibson et al. 2004[17] state that structural and biochemical changes occurs in the peripheral nervous system but difference in single-point versus cuff algometry in the elderly are unknown.

Mixed results are found in the literature regarding age-related interactions on TSP and CPM. Previous studies have found facilitated temporal pain summation to heat[31] and CPM to be reduced[30,35] in elderly. TSP is believed to be modulated by endogenous pain inhibitory systems[36], which have previously been used to explain why temporal pain summation is enhanced in elderly. In contrast,

Lautenbacher et al., 2005[28] found no age-related changes in pressure-induced TSP, which is similar to the current study. Future studies are needed to investigate if TSP is facilitated with increasing age.

Pain sensitivity difference between patients and controls

Handheld pressure algometry has been widely used to assess pain sensitivity in patients with KOA[3]. Several studies have found lower PPTs in patients compared with healthy controls[4,5], which is in accord with the current study. As confirmed by the present data several studies have shown that patients with KOA demonstrate hyperalgesia at the lower leg compared with healthy controls using both single-point and cuff algometry[4,5]. Likewise, facilitated TSP has been well documented in KOA[3] but also shown in e.g. fibromyalgia[37] and low back pain[38] as well as in the current study. Conflicting findings suggest that patients with KOA have impaired CPM compared with healthy controls. Arendt-Nielsen et al. 2010[5] and Graven-Nielsen et al., 2012[4] found that patients with KOA have impaired CPM compared with healthy controls, whereas King et al.2013[39] and Egsgaard et al., 2015[40] found no differences. Edwards et al. 2003[30] reported that older healthy controls showed facilitated pain response to a thermal stimulus during the cold pressor test, while younger healthy controls showed the usual CPM effect with reduced pain intensity. Several CPM models have been suggested with different test stimuli e.g. mechanical[5], electrical[41], and thermal[42] and different conditioning stimuli e.g. cold pressor test[43], ischemic pain[5] or chemical[44], which could explain these inconsistent results in KOA patients compared with healthy controls. To improve this, recent recommendations have been proposed to standardize the CPM paradigms[10,11] and a user-independent cuff-algometry approach have recently been demonstrated with good test-retest reliability[45]. Approximately 15% of KOA patients are categorized by impaired CPM and facilitated TSP while other patients were only categorized by either impaired CPM and normal TSP (43%), normal CPM and facilitated TSP (15%) or even normal CPM and normal TSP (27 %) [9]. Based on these previous findings less than 58 % of KOA patients presents with impaired CPM and this could be an explanation for the inconsistent CPM findings in KOA patients compared with controls and

why the current study only found a statistical trend for impaired CPM in patients compared with controls. Furthermore, the current study applied a CPM model with fixed conditioning intensity not adjusting for individual sensitivity differences in line with previous studies[9,46]. However, a recent study showed that the CPM-effect assessed by cuff algometry was associated with the conditioning pain intensity[45], which could explain the trend for impaired CPM in patients compared with controls in case the controls should have received a stronger conditioning stimulus. There is an ongoing debate regarding optimal CPM assessment and whether parallel or sequential paradigms are the most appropriate. The latest recommendation from the CPM consensus group recommended sequential paradigms[47], which was not used in the current study. Recent studies have however found that CPM can be assessed using parallel mechanical stimuli applied by a cuff algometer in both healthy controls[48,49] and patients with chronic pain[19,46].

One of the limitations of the present study was the explorative study design and as such no firm à priori statistical plan was formulated which further highlight the preliminary nature at the study. Further, the CPM paradigm applied in the current study was exploratory and more robust CPM paradigms have been suggested[45] after the initiation of the study, which should be accounted for when interpreting the CPM results. In regards to the conditioning stimulus intensity, participants who could not tolerate 60 kPa, due to high intensity pain, had the conditioning intensity reduced to 30 kPa, which was considered less painful but the pain intensity was not recorded. A recent study have found an association between higher conditioning stimulus intensity and higher CPM effect[45], why this is considered a limitation.

Conclusion

The current study found that KOA patients showed hyperalgesia at the lower leg detected as lower cuff algometry MPDT, cuff algometry PTT and handheld algometry PPTs, facilitated TSP, and impaired CPM-effect when compared to controls. Further, age-related associations were found for pressure pain thresholds assessed by cuff algometry and pressure algometry, but not temporal summation of pain or CPM recorded by cuff algometry, indicating that temporal summation of pain and CPM assessed with the methodologies applied in the current study were unaffected by age.

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FIGURE LEGENDS

Figure 1: Mean (+SEM) of mild pain pressure detection thresholds (MPDT, black bars) and pressure tolerance thresholds (PTT, grey bars) for knee osteoarthritis patients (N=133) and controls (N=50). Measurements from single-cuff (A) and double-chamber cuff (B) are presented. Significant differences comparing patients and controls are indicated as * ($P < 0.01$) and ** ($P < 0.001$). Significant differences between age groups are indicated as # ($P < 0.01$).

Figure 2: Mean (+ SEM) temporal summation of pain for **(A)** normalized VAS values, and **(B)** TSP-effect from knee osteoarthritis patients (N=133) and controls (N=50). Significant differences in the TSP-effect between patient and controls are indicated as * ($P < 0.01$).

Figure 3: Mean (+SEM) pressure difference (CPM-effect) between PTTs measures at during conditioning pain stimulation (constant cuff stimulation around the arm) and PTT without conditioning stimulation of knee osteoarthritis (KOA) patients (N=133) and controls (N=50). A tendency towards a reduced CPM-effect was found for patients compared with controls.

Figure 4: Mean (+SEM) pressure pain thresholds recorded at the tibialis anterior muscle for knee osteoarthritis patients (N=133) and controls (N=50). Significant differences comparing patients and controls are indicated as * ($P < 0.01$).

TABLES

Table 1: Demographics of study participants. Mean (SEM), median [range] or fractions. NS indicates non-significant.

Demographic variable	Age group	Patients (n=133)	Controls (n=50)	P-value
Age (years)	≤ 65 years	57.3 (0.8)	58.5 (0.7)	NS
	> 65 years	73.6 (0.6)	70.4 (0.8)	P < 0.05
Body Mass Index (kg/m^2)	≤ 65 years	32.9 (1.0)	27.0 (1.1)	P < 0.001
	> 65 years	28.6 (0.4)	25.8 (1.1)	NS
Gender (male/female)	≤ 65 years	16/33	11/15	NS
	> 65 years	33/51	14/10	NS
KL scores [range]	≤ 65 years	3.7 [2-4]		
	> 65 years	3.8 [2-4]		
VAS Pain (cm)	≤ 65 years	6.4 (0.3)		
	> 65 years	6.5 (0.2)		

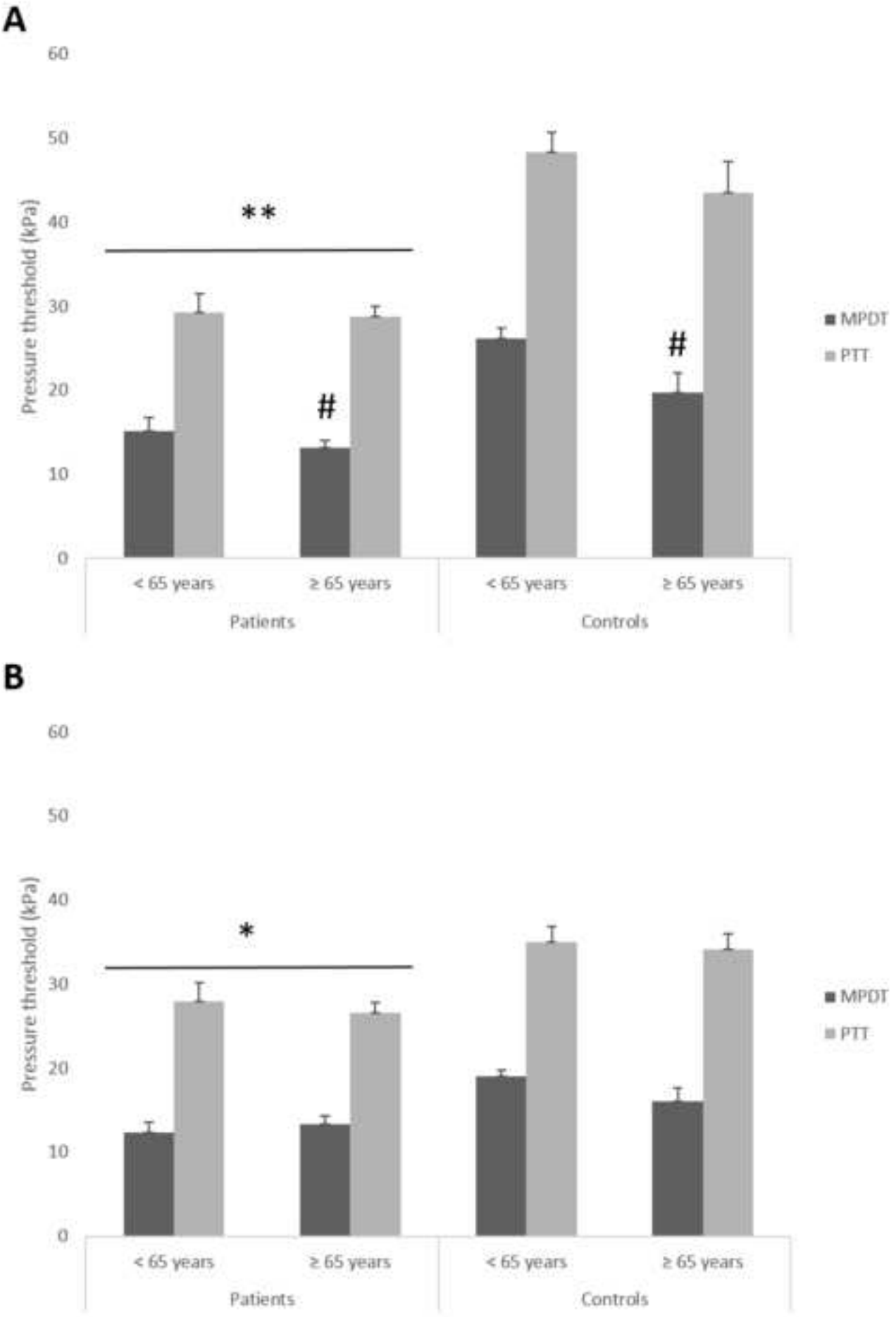

Figure 2

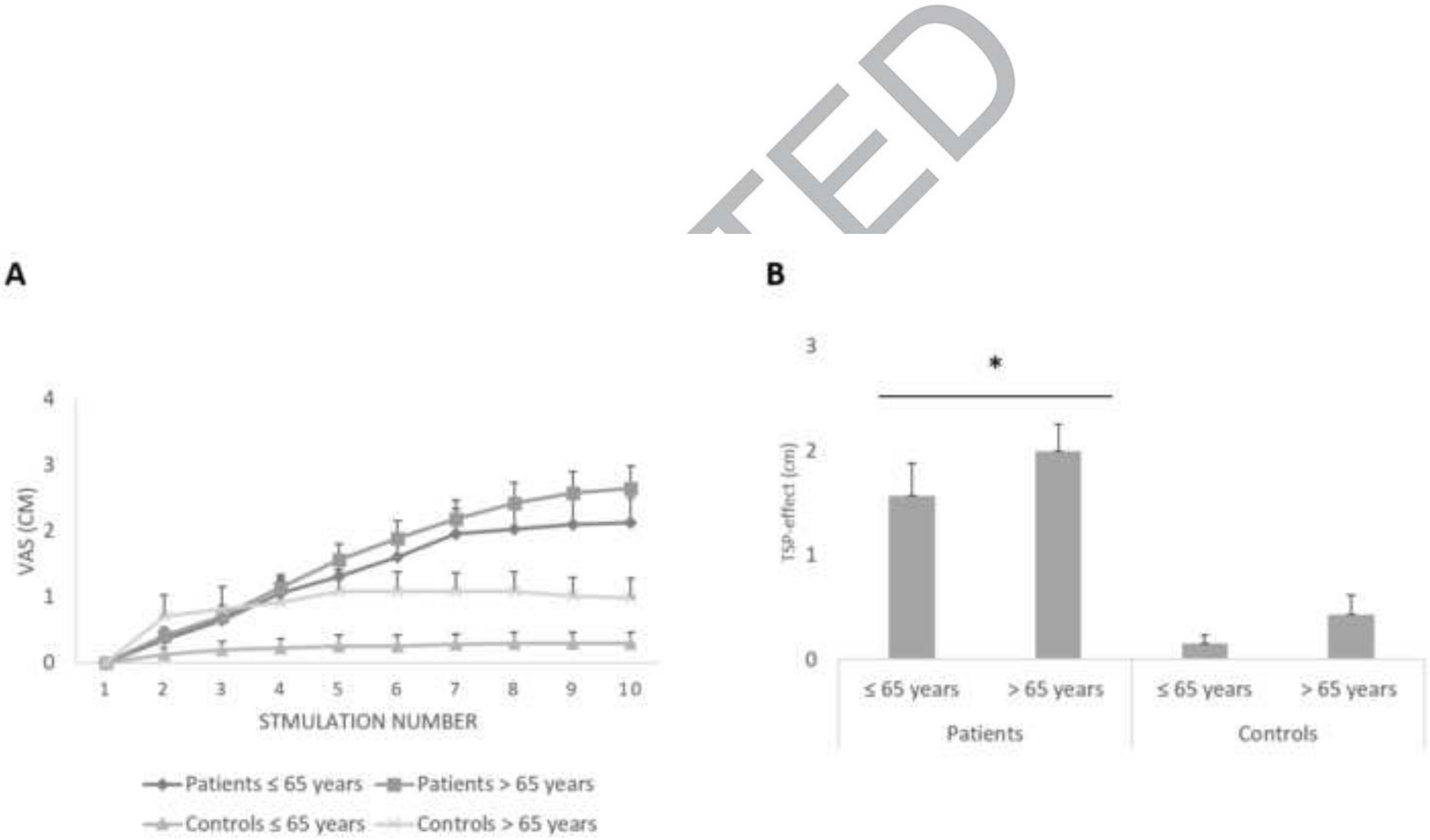

Figure 3

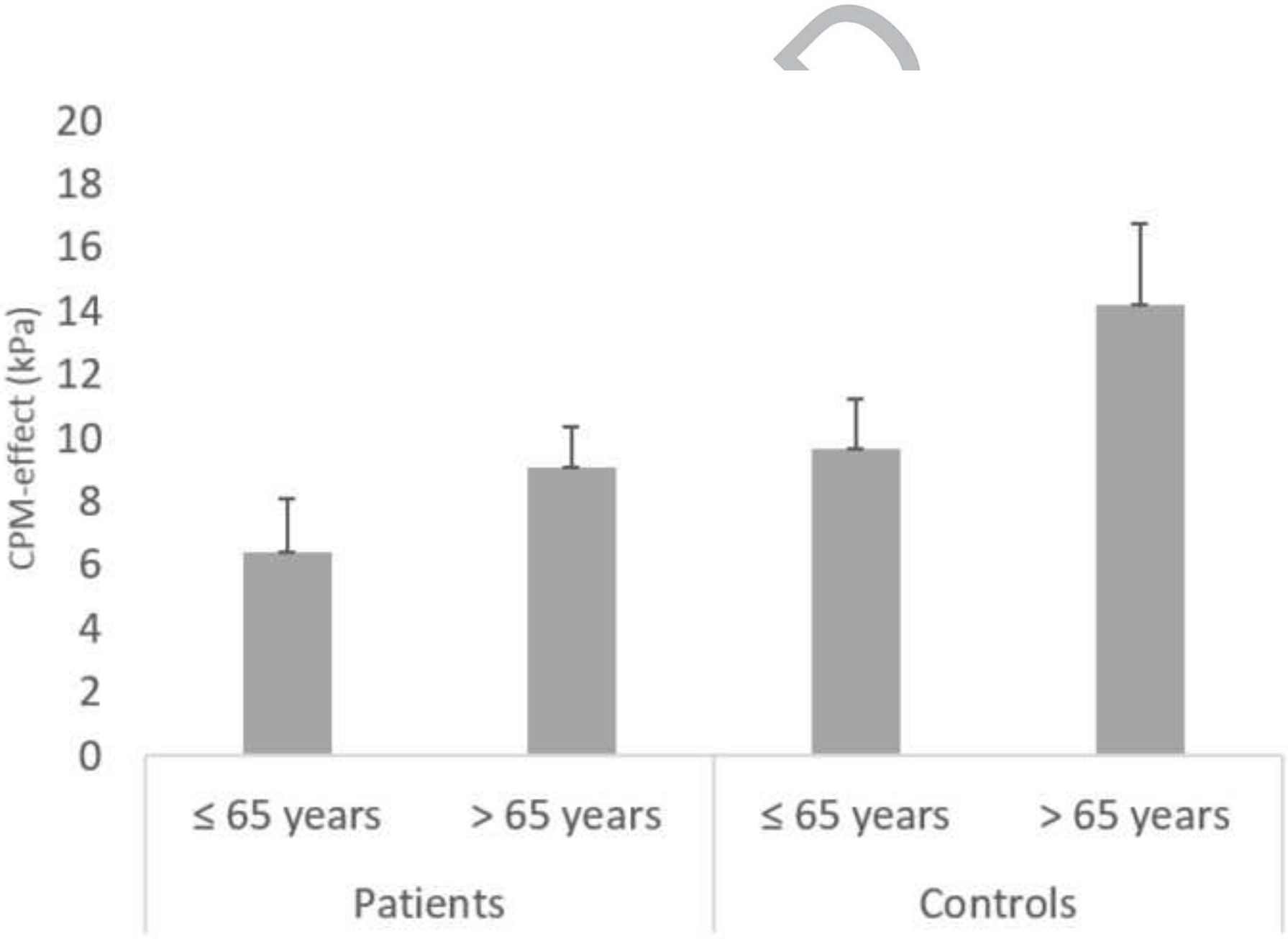

Figure 4