

Cuff algometry

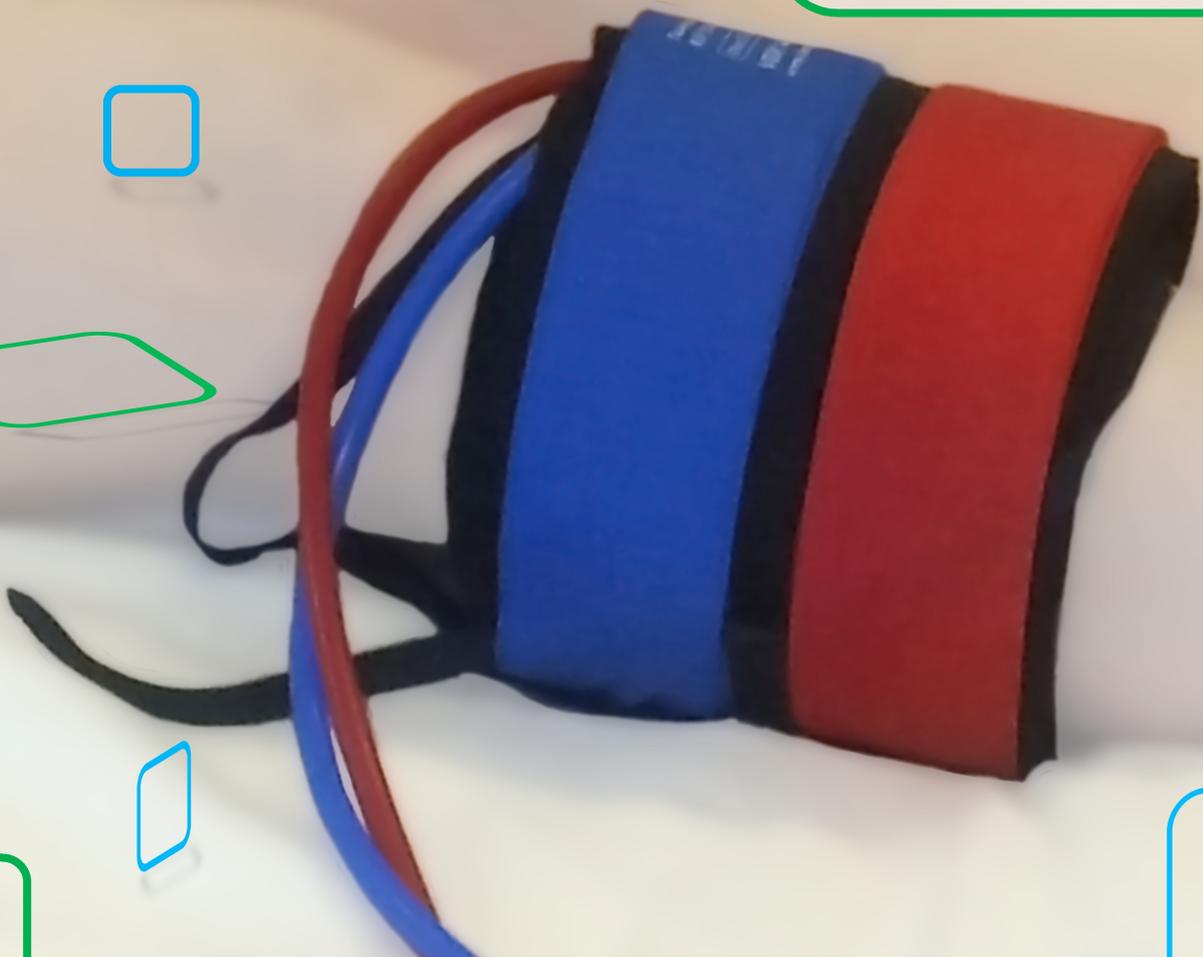
Positioning and inflation pattern

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Synopsis:

Central sensitisation contributes to several syndromes, and may be assessed by pressure algometry. Hand-held algometers have been used in previous studies, but an alternative is computer-controlled cuff pressure algometry (CPA), although the positioning in previous studies has varied, and a ramp inflation pattern has been used. The purpose of this study is to investigate the influence of positioning and inflation pattern. The study was designed as a single session randomised crossover design, with 20 volunteers. CPA measurements were conducted on 4 locations, where the pressure pain threshold, pressure pain tolerance, and spatial summation was measured. A Staircase pattern and temporal summation measurements were in addition performed at position 3. Differences between the four positions, the distal and proximal chamber, and genders were observed. Higher thresholds at position 1, and lower degree of spatial summation at position 2 were observed for the distal chamber. A significant difference between the two inflation patterns with higher staircase thresholds was observed for all measurements except temporal summation. The staircase inflation pattern was able to achieve higher thresholds than ramp inflation pattern, which could be related to the summation of pain for the ramp inflation pattern. The limited number of subjects should be taken into account for the study results and further studies with more participants would be able to identify the issues.

Resumé

Introduktion

Central sensibilisering bidrager til adskillige syndromer, og kan vurderes ved hjælp af temporal summation. Trykalgometri er blevet bredt anvendt i en lang række studier til at inducere tryksmerte og undersøge central sensibilisering, og håndholdte trykalgometre er ofte blevet anvendt. Et alternativ til disse håndholdte trykalgometre er computerstyret trykmanchet algometri som er blevet populær i den sidste tid, men målingerne med disse er blevet udført på forskellige steder på kroppen, og altid med et ramp inflationsmønster.

Formålet med dette studie er at undersøge om positionen og inflationsmønstret af trykmanchetten har indflydelse på målinger.

Metode

Studiet blev designet som et enkeltsessions randomiseret cross-over studie, 20 frivillige raske forsøgspersoner (10 mænd og 10 kvinder med en medianalder på 26 år) blev rekrutteret til studiet i et universitetsmiljø.

Forsøget blev udført ved computerstyret trykmanchet algometri målinger 4 steder på det dominante ben, hvor pressure pain threshold, pressure pain tolerance, og spatial summation blev målt. Derudover blev der målt med et staircase mønster og målt temporal summation, ved position 3. Målingerne blev foretaget ved opusting af trykmanchettens distale, proksimale og begge kamre. Derudover blev der anvendt håndholdt trykalgometer til pressure pain threshold målinger. Data blev opsamlet igennem CuffControl 1.40 og behandlet i Matlab 2014b og IBM SPSS Statistics 22.

Resultater

Der blev set forskelle både imellem de fire positioner, men også imellem det distale og proksimale kammer, derudover blev der set en indflydelse af køn. Ved brug af det distale kammer blev der set højere tærskelværdier ved position 1, og en mindre grad af spatial summation ved position 2.

For de to inflationsmønstre blev der set en væsentlig forskel med højere værdier ved brug af staircase inflationsmønsteret for alle målinger med undtagelse af temporal summation.

Derudover blev der observeret variationer imellem de fire positioner for håndholdt trykalgometri.

Diskussion

Position 1 og det distale kammer lod til at være uegnet til computerstyret trykmanchet algometri målinger. Staircase inflationsmønsteret var i stand til at opnå højere værdier end ramp inflationsmønsteret, hvilket kunne relatere til summation af smerte for ramp inflationsmønsteret. Det begrænsede antal forsøgspersoner skal dog tages i betragtning i forhold til studiets resultater, og et fremtidig studie med flere deltagere vil derfor kunne afdække disse problemstillinger.

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Preface

This Master's thesis is written by Tim Alex Lindskou, master student in Clinical Science and Technology, 4th semester at the School of Medicine and Health, Aalborg University. The thesis was written in the period February 3rd to June 3rd 2014.

The thesis concerns the anatomical variations in cuff pressure algometry. Additionally, the influence of different inflation patterns on pressure pain threshold, pressure pain tolerance threshold, spatial summation, and temporal summation.

The thesis is primarily intended for the supervisors, secondary to other interested in this field.

An accessible language is attempted to be upheld throughout the thesis, albeit specialist terms are used in certain sections. The Vancouver reference system is used, and references to the appendix, figures and tables appear throughout the thesis.

I would like to give thanks to the two supervisors, Thomas Graven-Nielsen and Steffan Wittrup Christensen. Also a special thanks to the volunteers who participated in the study.

Tim Alex Lindskou

1. Background

Knee osteoarthritis (OA) is a degenerative joint disease, causing pain in the joints and varying degrees of disability, the exact incidence and prevalence is uncertain, an estimate is 4% for males and 8% for women, with incidence rates increasing with age. (1, 2) In Denmark, an estimated 60.000 patients with OA symptoms turned to general practitioners in 2011, and approximately half were referred to hospitals. (2) Several treatments exist, including knee replacement surgery of which 8.535 and 1.291 revisions were performed in 2012 in Denmark, there is however a risk related to knee replacement surgery in the form of postoperative neuropathic pain. (3) Previously studies have indicated a possibility to anticipate the development of postoperative neuropathic pains, as well as predicting analgesic response in general by the use of quantitative sensory testing (QST) methods. (4-6) The possible prediction would help evaluating possible candidates for knee replacement and enable a more specific pain treatment for the patient, for instance oral Pregabalin could be administered perioperative as an intervention for those in risk of postoperative neuropathic pains. (7) Furthermore, several studies have shown a relation between painful OA and peripheral- and central sensitisation by using QST methods, along with the possibility to predict postoperative pain and analgesic response, this emphasises the importance of QST methods in relevance to knee OA. (8-10)

1.1. Pain

Pain is a subjective experience described by the International Association for the Study of Pain as “An unpleasant sensory and emotional experience associated with actual or potential tissue”. (11, 12) The pain process takes place when a stimulus activates a nociceptor, evoking an action potential in the afferent fibres, or first-order neurons, to the dorsal horn in medulla spinalis. From here the signal travels by second-order neurons to truncus encephalicus and thalamus which in turn via third-order neurons send the nociceptive signal to cortical areas in the brain where it is interpreted. (13, 14) It is worth noting that nociceptive signals not necessarily are perceived as pain, for example under stress or in some cases of massive trauma. Likewise the perception of pain does not necessarily derive from nociception, as in the case of allodyni, where stimuli not normally painful are perceived as pain. (11, 14-16) The nociceptive signal can be modulated by descending pain modulators, as neurons from supraspinal areas can project inhibitory or facilitating signals to the nociceptive dorsal horn neurons by the use of serotonin and noradrenalin. An ascending pain modulation can also occur, where nerve fibres from the cerebral cortex regulate the nociceptive perception process in other areas of the brain. (13) The nociceptive afferent fibres can either be myelinated A δ -fibres, or unmyelinated C-fibres.

The myelinated A δ -fibres conduct at velocities of 30-50 m/s and are the cause of first pain after tissue damage and are easily sensitised. The unmyelinated C-fibres however only conduct at velocities of 1 m/s, and are the cause of second pain after tissue damage. In both A δ - and C-fibres, sleeping nociceptors with a high activation threshold can be found; these sleeping nociceptors can be activated by inflammation or sensitisation and could be involved in increased pain perception, (hyperalgesia) in relation to tissue damage. (11, 13, 16)

1.2. Sensitisation

The mechanisms behind peripheral- or central sensitisation are complicated and diverse, as they represent a normally reversible plasticity in the nociceptive system. (11, 13, 17)

1.2.1. Peripheral sensitisation

Following tissue damage, the local phenomenon peripheral sensitisation can occur causing a decreased pain threshold and amplification of responsiveness in the primary and secondary hyperalgetic area. (13, 15, 17) This can be explained by macrophages, damaged cells, and mast cells all release inflammatory substances in the damaged area following tissue damage, activating the peripheral nociceptors which result in hyperalgesia, an increased pain from painful stimuli. (11, 13, 17) When the peripheral nociceptors are continuously activated, a change in the cell membrane occurs, causing hyperexcitability. Furthermore, phenotypic changes occur in myelinated fibres, causing A δ -fibres to behave as C-fibres, thus contributing to the mechanisms behind allodynia. (13, 17)

1.2.2. Central sensitisation

In contrast to the local peripheral sensitisation, central sensitisation occurs in the central nervous system. (15) As a result of the peripheral sensitisation, the sensitised nociceptors and activated sleeper nociceptors sends an overload of signals to the central nervous system, resulting in the release of glutamate, aspartate and substance P in the dorsal horn, and thereby depolarisation. (13, 15) A persistent depolarisation of the second-order neurons leads to the activation of the NMDA- and mGlu receptor system. This activation result in a build-up of intracellular Ca $^{2+}$ causing a number of changes leading to a potentiation of NMDA receptors, as well as a sensitisation of the neurons which fires more rapidly and independent of activation. (13, 15) The potentiation of NMDA receptors relates to temporal summation which will be described in section 1.3. (15) Furthermore, changes in inhibitory GABA interneurons can result in facilitating depolarisation rather than inhibiting, changes also appear in the neurons located in the ascending and descending pain modulators, causing decreased inhibition. (13, 15)

On a cortical level changes in the neuron organisation may occur, causing impulses from a damaged area to occupy an area not normally related to pain impulses. (13) Central sensitisation is believed to contribute to several clinical conditions including OA, fibromyalgia, neuropathic pain, as well as post-operative pain. (8)

1.3. Temporal and spatial summation

When a stimuli at the same intensity is repeated with a frequency under 0.3 Hz, i.e. under 3 seconds, an increased pain perception can be observed; this mechanism is known as temporal summation. (18, 19)

The summation derives from C-fibres evoking dorsal horn neuron responses, and as mentioned in section 1.2.2 the repeated stimuli result in a potentiation of NMDA receptors. (15, 20)

Temporal summation can be used to investigate central sensitisation, as several studies have demonstrated central sensitisation through an enhanced response to temporal summation. (9, 20, 21)

Another form of summation is spatial summation, where temporal summation relates to the stimulation frequency, spatial summation relates to the size of the stimulated area. The summation is the result of converging nociceptor inputs, resulting in a decreased pain threshold, i.e. a large stimulation area will have an increased pain perception in contrast to a smaller stimulation area. (13, 22, 23) Enhanced spatial summation has been observed in knee OA patients, indicating sensitisation of central mechanisms. (10) An example of spatial- and temporal summation can be seen in figure 1.

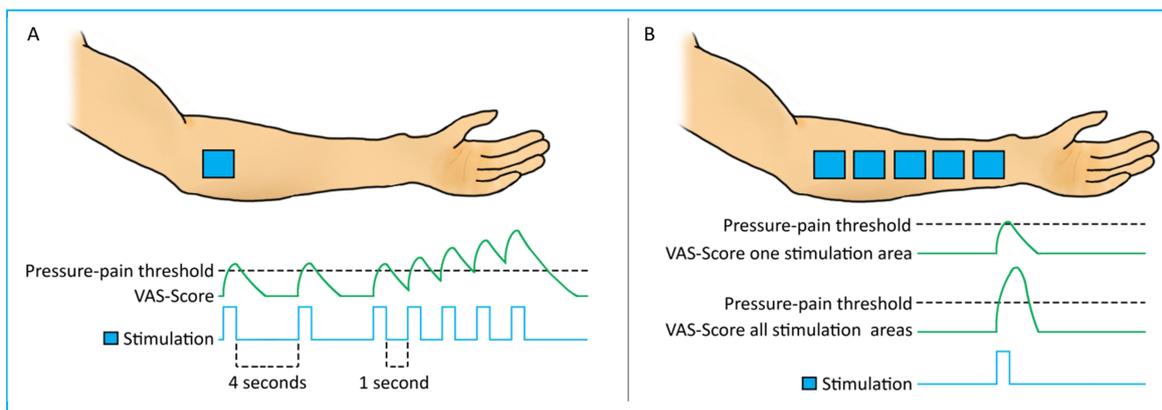


Figure 1: Illustrations of temporal- and spation summation. Temporal summation (A) 1 second interval stimulations result in a higher VAS-score, and spatial summation (B) demonstrating an increased visual analogue scale (VAS) score when a larger area is stimulated.

1.4. Quantitative sensory testing

A number of modalities have been investigated in order to evaluate sensory function; one way is by QST, which is a number of psychophysical methods applicable for both healthy persons as well as patients. (5, 24) QST is applied by giving an objective sensory stimulation and receiving a subjective response, e.g. a pressure of 50 kPa is given, to which a subject rates 3 cm on a visual analogue scale. QST is thereby able to provide information on static sensory function, but it can also give information on dynamic functions such as temporal summation. (25-27)

QST have been used in several studies, as it has the advantages of the possibility to control the intensity and duration of stimulation, as well as the affected modality by using, for example, cold and warmth thresholds, mechanical pain threshold, or vibration threshold. (5, 25, 28)

More than one test can however be applied for each modality and several QST-protocols therefore exist, one example from Rolke et al provides a somatosensory profile for one affected, and one unaffected area within one hour, by using thermal and mechanical testing. (28) For this study there will only be focused on one QST modality, namely pressure algometry.

1.5. Pressure algometry

Pressure algometry is typically used in order to assess musculoskeletal tenderness by applying pressure until pain is elicited; this change from the sensation of strong pressure to pain is the pressure pain threshold (PPT). (13, 29, 30) Another measurement used in several studies, is the pressure pain tolerance threshold (PTT), often defined as when the pain intensity becomes strong enough to make the subject feel the need to interrupt or stop the pain, i.e. where the pain becomes unbearable. (31, 32)

Pressure can be applied by several methods; one of these is the hand-held algometer which have been used in several studies and considered to be a reliable tool. (29) The hand-held algometers depend on the users own force to apply a constant rate of pressure, typically with a probe of 1 cm². (13, 29, 33) The size and shape of the probe are an important factor when assessing PPT with hand-held algometers, as well as the area where the pressure is applied. (13, 30)

Hand-held algometers have been used extensively in previous studies, but are criticised for the need for an experienced user as a constant rate of pressure has to be applied, alongside different reaction time among users, user expectancy and sensitivity of the skin despite padded probe. (29, 31)

1.5.1. Cuff pressure algometry

An alternative to hand-held algometers is computer-controlled cuff pressure algometry (CPA) which have become popular in recent years. To avoid confusion between hand-held algometer and CPA measurements, the terms cuff PDT and cuff PTT will be used for CPA throughout this study. Where hand-held algometers relies on user experience, the CPA inflation rate is controlled by a computer and therefore independent of the user, thus eliminating some of the possible bias related to hand-held algometers. (31) The pressure from CPA affects all structures under the cuff, although it is not significantly affected by skin sensitivity when measuring cuff PDT, and is therefore considered well suited for testing pain sensitivity. (13, 31, 34) The CPA size however limiting the placement options and the large stimulation area makes it unusable for some structures. (21, 32)

Studies using the CPA have, amongst others, related to the CPA itself, lateral epicondylalgia, fibromyalgia, and knee OA. (9, 21, 31, 35) Common for all the studies is the varying placement of the cuff, and the inflation rate has been constant continuously rising also known as a ramp inflation pattern. (10, 31, 32, 35)

The tonic nature of the ramp inflation pattern may however affect the measurements; previous studies have demonstrated temporal summation in the patient, but also healthy control group, by inflating the CPA to a certain pressure and maintaining it for 10. (21, 36) Although the CPA is not normally inflated for 10 minutes when determining cuff PDT and cuff PTT, it is possible that the ramp inflation pattern may be affected by summation of pain.

2. Study aims

Central sensitisation contributes to several syndromes, amongst others OA, and may be assessed by temporal summation. For knee OA patients receiving a knee replacement surgery, there is a risk of postoperative neuropathic pains, studies have however indicated a possibility to anticipate these. Both assessing central sensitisation and anticipating postoperative neuropathic pains can be achieved by the use of QST methods, such as CPA which circumvents some of the bias related to hand-held algometers. The CPA is well suited for testing pain sensitivity, but previous studies have had varying cuff placement, and only used a ramp inflation pattern. Two study aims addressing these issues were therefore formulated:

- **To determine whether the position of the cuff has an effect on cuff pressure pain threshold, cuff pressure pain tolerance, and spatial summation**
- **To evaluate whether the inflation pattern when using computer-controlled cuff algometry has an effect on cuff pressure pain threshold, cuff pressure pain tolerance, spatial summation, and temporal summation**

Four positions and two inflation patterns were used for comparison; to avoid confounding factors a population of healthy subjects were recruited.

3. Hypothesis

On the basis of the study aims, the following two hypotheses were formed, where the values relate to cuff PDT, cuff PTT, spatial summation and temporal summation.

Positions

μ_1 = Position 1

μ_2 = Position 2

μ_3 = Position 3

μ_4 = Position 4

H_0 : $\mu_1 = \mu_2 = \mu_3 = \mu_4$

H_A : $\mu_1 \neq \mu_2 \neq \mu_3 \neq \mu_4$

Rejection rule: If H_0 is not rejected, then the position has no effect on the values.

Inflation pattern

μ_1 = Inflation pattern 1

μ_2 = Inflation pattern 2

H_0 : $\mu_1 = \mu_2$

H_A : $\mu_1 \neq \mu_2$

Rejection rule: If H_0 is not rejected, then the inflation pattern has no effect on the values.

5. Method

The study was approved by the local ethics committee (N-20140002) and followed the Helsinki declaration.

5.1. Literature search

A systematic literature search was performed in various databases, amongst others PubMed, Primo, and Web of Knowledge Google and Google Scholar were also used as resources, as well as the references from selected articles. The literature search was limited to Danish, English, Norwegian and Swedish articles, no limitations to the year of publication were made.

Each article was evaluated by reviewing the abstract and, if relevant, the entire article. The literature search was conducted from February to June 2014.

Searches were conducted using MESH terms with relevant keywords relating to the study aims. These keywords were *cuff, algometry, hand-held, pressure, pressure-pain, pain, threshold, temporal summation, spatial summation, central sensitisation, and peripheral sensitisation*. The keywords were used by themselves, and combined using AND/OR.

An example of the literature search can be seen with the keyword “Temporal summation” used in PubMed, providing 1524 hits. In order to specify the search further the keyword “cuff algometry” was added to the search, resulting in the search string “temporal summation AND cuff algometry”. As a result, 8 articles were found and, after reviewing their abstracts, four of them were determined to be of relevance. All of the four articles were then read in their entirety, and one article was selected for use in the study.

5.2. Study design

The study was conducted as a single session randomised cross-over design; every measurement was conducted on all participants. This design enabled within-subject comparison, providing an advantage in regard to the need for fewer subjects than, for example, a parallel design. Another statistical advantage is that within-subject comparisons have smaller variability than between-subject comparisons. (37)

5.3. Subjects

20 healthy subjects, 10 males and 10 females aged between 19 and 48 years with a median of 26 years, were recruited for the study from a university setting. For a full list of subject information, see appendix A. The following inclusion- and exclusion criteria were used.

Inclusion criteria

- Male and female subjects
- Age 18-80 years old

Exclusion criteria

- Inability to cooperate
- Pregnancy
- Previously or currently neurological, musculoskeletal or mental illnesses
- Past history of a chronic pain condition
- Physical training 24 hours prior to the study
- History of acute pain affecting the lower limb and/or trunk in the last 6 months
- Consumption of alcohol, caffeine, nicotine or analgesics in the morning of the study day

The exclusion criteria were formulated with the intention of creating a homogeneous group of healthy subjects, by excluding a range of elements able to affect the nervous system and pain perception.

A written informed consent was given by all subjects prior to the study.

5.4. Safety and ethical considerations

The safety features of the CPA setup consisted of a maximum pressure of 100 kPa (760 mmHg), an emergency stop button on the air compressor, and a “stop” button on the electronic visual analogue scale for immediate release of air in the cuff.

The subjects' identity and other personal information are subject to the Act on Processing of Personal Data. (38)

5.5. Protocol

A comprehensive review of the protocol will be given in the following subsection. Further subsections occur, providing relevant information and terminating in a description of the practical execution of the study.

5.5.1. Equipment and materials

The following equipment was used for the study:

- Double chamber 13-cm wide silicone high pressure tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany)
- Computer-controlled air compressor
- 10 cm electronic visual analogue scale (Aalborg University)
- CuffControl 1.40 (Knud Larsen, Aalborg University)
- Hand-held algometer equipped with a 1 cm² latex sheath covered probe (Somedic, Hörby, Sweden)

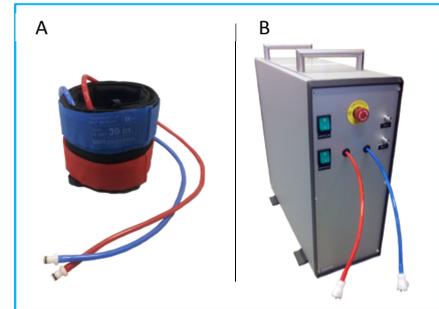


Figure 2: The tourniquet cuff (A) and computer-controlled compressor (B)

5.5.1.1. Cuff pressure algometry

The CPA was conducted using a silicone high-pressure cuff as seen in image 1 A, and a 10 cm electronic visual analogue scale (VAS) connected to a computer-controlled air compressor, (image 1 B) which itself was connected to a computer with CuffControl 1.40 installed.

5.5.1.2. Electronic visual analogue scale

The electronic VAS, which can be seen in image 2, consisted of a 10 cm adjustable scale with the extremities “0” and “10” respectively defined as “no pain” and “worst pain imaginable”. A yellow stop-button was located at the top of the VAS for immediate release of air in the tourniquet cuff.



Figure 3: Electronic visual analogue scale with yellow stop button.

5.5.1.3. CuffControl 1.40

Input parameters and data collection were completed using the CuffControl 1.40 software, which allowed full control of the compressor, and thereby the tourniquet cuff. Only three standard settings for inflation patterns were used:

- **The ramp inflation pattern**, figure 2 A, delivering a continually inflation rate of 1 kPa/s.
- **The staircase inflation pattern**, figure 2 A, delivering a repeated increasing stimuli separated by a four second interval, each stimulus increasing by 5 kPa and thereby applying the same average pressure per second as the ramp inflation pattern.
- **The repetitive inflation pattern**, figure 2 B, delivering a repetition of 10 painful stimuli of one second duration with a one second interval, in order to invoke temporal summation. The pressures of the stimulations were set as the mean of cuff PTT measurements from the same position.

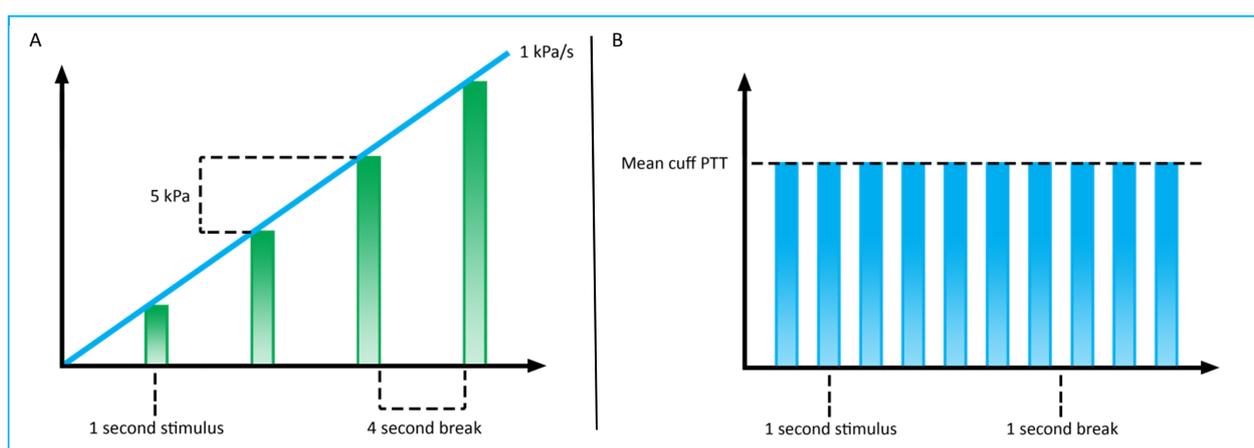


Figure 4: Ramp, staircase and repetitive inflation pattern. Ramp and staircase inflation pattern (A) The continually rising ramp inflation pattern is illustrated by the blue line, whereas the green pillars illustrates the staircase inflation pattern. Repetitive inflation pattern: (B) ten 1 second stimulations at 1 second interval with an intensity corresponding to mean cuff PTT.

5.5.1.4. Hand-held algometry

A hand-held algometer (Somedic, Hörby, Sweden) equipped with a 1 cm² probe covered by a disposable latex sheath was used in the study. A wired stop-button was attached to the algometer which, when activated, produced a beep from the algometer to notify the user in addition to display the pressure at the time the stop-button was pushed. To secure an evenly applied pressure rate, the hand-held algometer was set to guide the user via the display, to apply a force increasing with 30 kPa/s.

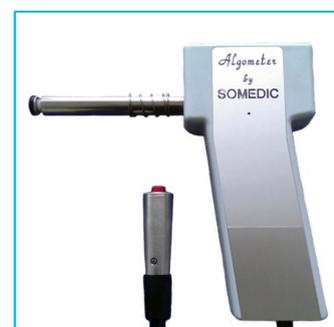


Figure 5: Hand-held algometer with wired stop-button.

5.5.2. Structure of study

To fulfil the study aims and thereby answer the two hypotheses, five elements were included in the protocol:

- **Position hypothesis**
 - Cuff- PDT, PTT, and spatial summation determined at all four positions with the distal, proximal and both chambers, using the ramp inflation pattern
 - Control measurement of PPT at all four positions using hand-held algometer

- **Inflation pattern hypothesis**
 - Cuff- PDT, PTT, and spatial summation determined at the same single position with the distal, proximal and both chambers, using the staircase and ramp inflation pattern
 - Temporal summation determined at one position using ramp inflation pattern values
 - Temporal summation determined at one position using staircase inflation pattern values

5.5.3. Randomisation

In order to avoid any systemic differences and thereby bias, a total of four randomisations were made for all 20 subjects: 1) The method sequence, i.e. CPA or hand-held algometer measurements first, 2) the position sequence, 3) the chamber sequence, i.e. distal or proximal, and 4) the inflation patterns, i.e. ramp or staircase first. (37) The randomisations were conducted by using the random integer generator and list function on www.random.org. (39) As temporal summation could not be measured before PTT values had been obtained, it was omitted from the method sequence randomisation.

The randomisations were contained within 20 envelopes; at the start of their session each subject was asked to choose an envelope at random, in order to further randomise the study. The randomisation for each subject can be seen in appendix A.

5.5.4. Cuff pressure algometry and hand-held algometry positions

The specific sites for the positions of the tourniquet cuff were chosen with the intent of covering as much of the leg as possible, without the positions overlapping each other. With this in mind, four positions were chosen based on pilot studies revealing that additional positions would overlap. Both the distal, proximal and both chambers were used in order to determine spatial summation.

Starting from a prominent structure, all positions were measured to the lowest part of the tourniquet cuff, see figure 3. If any position was not accessible due to the length of leg etc., the tourniquet cuff was placed as high as possible regardless of overlap with the nearby position. For position 2 any overlap with the patella was avoided.

Position 1: 10 cm from the lateral malleolus.

Position 2: 1 cm above the top part of the tourniquet cuff in position 1.

Position 3: 5 cm above patella.

Position 4: 1 cm above the top part of the tourniquet cuff in position 3.

For the hand-held algometry, positions located approximately at the middle of the corresponding tourniquet cuff positions were chosen, see figure 3. All positions were located on muscle sites used in previous studies measuring PPT with hand-held pressure algometers (40, 41)

Position 1: Tibialis anterior, approximately 20 cm from the lateral malleolus.

Position 2: Gastrocnemius medialis, approximately 8 cm from the lower part of the patella.

Position 3: Vastus lateralis, approximately 9 cm from the upper part of the patella.

Position 4: Rectus femoris, approximately 22 cm from upper part of the patella.

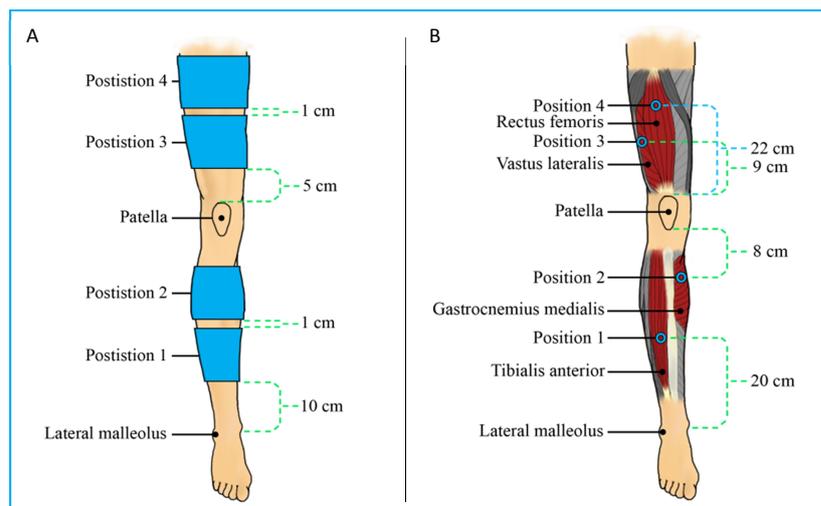


Figure 6: Tourniquet and hand-held algometer positions. The positions and distances of measuring sites for tourniquet cuff (A) and Hand held algometer (B).

5.5.5. Practical execution

For the sake of clarity the practical execution is described chronological in figure 4, although randomisations were applied. The subject was placed in a comfortable and relaxed supine position, see image 3, lying on a bed with a pillow to support the head during all measurements, which were carried out on the dominant leg.



Figure 7: Subject with cuff tourniquet and VAS. Subject in the supine position holding the VAS, with the tourniquet cuff placed on the right leg in position 2.

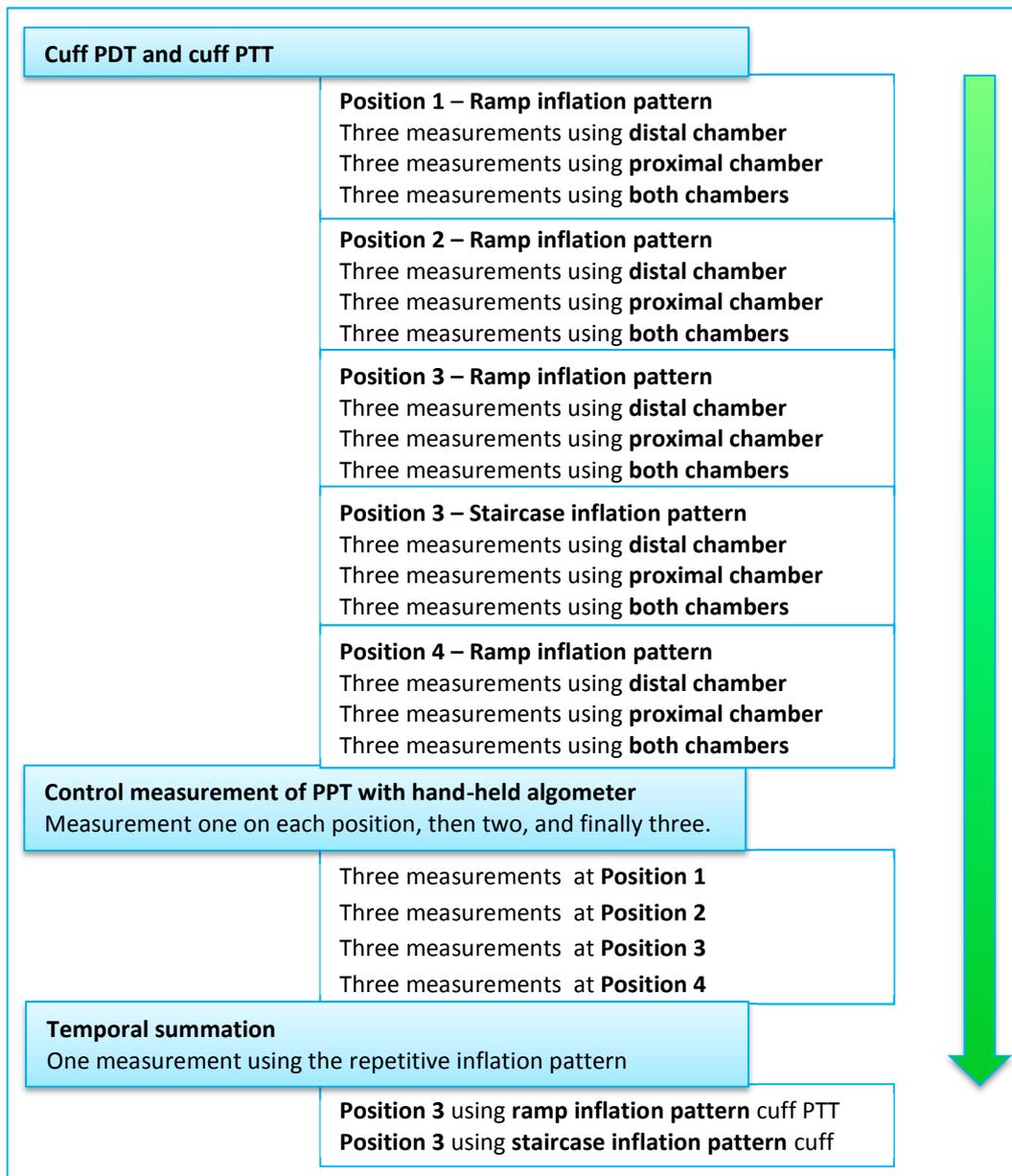


Figure 8: Practical execution of the study. All measurements carried out in each session in chronological order.

Cuff PDT, cuff PTT and spatial summation measurements for both inflation patterns

The tourniquet cuff positions were marked by drawing a line on the skin at the bottom and upper edge of the cuff for each position, in order to secure a starting point for the rest of the positions as well as to ensure that the cuff did not move during the measurements.

To minimise the risk of bias when conducting the CPA measurements, precautions were made by ensuring that the cuff fitted tightly around the leg with no other material between the cuff and the skin.

Starting with the VAS in the “0” position, the subject was instructed to continuously rate pain intensity on the VAS, starting from the first sensation of pain defined as the moment where the pressure was perceived as painful, i.e. the cuff PDT. Furthermore, the subject was instructed to press the stop-button when the pain intensity was strong enough to make them feel the need to interrupt or stop it, i.e. the cuff PTT.

The double chamber cuff PTT divided with either the proximal or distal chamber cuff PTT was used as an index for spatial summation.

Temporal summation measurements

Again starting with the VAS in the “0” position, the subject was instructed to continuously rate pain intensity on the VAS during the ten stimulations. It was emphasised that the subject should attempt to rate the pain intensity continuously, rather than after each stimulation.

PPT with hand-held algometer

All positions were marked on the skin to ensure the measurements would be carried out on the same position. The subject was handed the wired stop-button and instructed to press it at the first sensation of pain, described as the moment where the pressure was perceived as painful.

Measurement intervals

In previous studies, intervals between measurements for CPA vary with a range of 60 seconds to 5 minutes. (31, 35, 42) For this experiment the interval was therefore based on the most recent described interval in a study, namely at least 60 seconds. (42) For hand-held algometry the same interval was selected so only the method of the measurements was different from the CPA measurements.

Hand-held algometer measurements were conducted in triplets starting with measurement one on each position, then two, and finally measurement three. The decision to not obtain all three measurements for each position and then move on to the next was made in order to avoid sensitising the skin.

5.6. Data processing

Data obtained during the study was saved directly from the CuffControl 1.40 software into txt files, or handheld PPT data was typed into an excel sheet (Microsoft Excel 2010). A custom script was made for the Mathworks MATLAB r2014a software to extract data from the txt files, the full script can be seen in appendix B.

The data was initially converted to a readable format, imported, and sorted by the script.

For measurements using the ramp inflation pattern, the pressure for the first time VAS exceeded 0.1, and the last measured pressure was located and extracted, providing the cuff PDT and PTT respectively. Measurement obtained using the staircase inflation pattern required a somewhat different processing. Cuff PDT values were located as with the ramp inflation pattern and PTT was located by finding the maximum pressure, both of these values were however adjusted to fit to the nearest 5 (e.g 10,2 adjusted to 10, and 85,34 adjusted to 85) as the staircase inflation pattern increased with 5 kPa per burst.

In regard to temporal summation, sample numbers for each stimulation start and end were located using the stimulation pressure, and the corresponding VAS scores were obtained. A mean of the start and end VAS score was then calculated, and the total ten VAS scores were normalised by subtracting the first stimulation score from all of the stimulation scores. The ten VAS scores, along cuff PDT, cuff PTT, and spatial summation were then exported to excel files.

To reduce possible input bias, the script was designed as a function; requiring only 1 input, namely the subject number.

When a subjected pressed the stop-button at 100 kPa, which was the maximum pressure for the CPA setup, an error occurred causing the CuffControl 1.40 software to prompt a negative cuff PTT value far lower than the correct 100 kPa value. A function to control and correct this error was implemented in the Matlab r2014a script, eliminating the error for all data. A similar miscalculation occurred for cuff PDT when the VAS was not set in the "0" position at the start of each measurement, resulting in a cuff PDT of 0 kPa. This error was reduced by both controlling the CuffControl 1.40 software for the VAS position, and verbally confirming with the subject that the VAS was in the "0" position before the start of each measurement. The few occurring cuff PDT errors were noted and corrected during the data processing, where all data also was visually inspected.

Data from the MATLAB r2014a produced XLS files and the subject pages were loaded into IBM SPSS statistics 22 for statistical calculations.

5.7. Statistics

All statistical analyses were performed using IBM SPSS Statistics 22.

Data was initially controlled for normal distribution and homogeneity of variance, the Shapiro-Wilk test of normality was chosen as it is able to handle small sample sizes (43)

The data for positions were not normally distributed, Kruskal-Wallis (KW) tests with Bonferroni post hoc tests were therefore applied to determine differences between positions, and Wilcoxon signed-rank (WS) tests were used for determining differences between chambers. All position data was controlled for influence of gender, coefficients of variance expressed in percentage (CV) were furthermore used to determine the variability of the measurements, using WS and KW tests.

For comparisons between the two inflation patterns, WS tests were used for cuff PDT, cuff PTT and spatial summation, as the data for these measurements also was not normally distributed. CV was also used to determine variability between the two patterns by applying WS tests.

For temporal summation the majority of data was normal distributed, and a repeated measures ANOVA (RM) with Bonferroni post hoc tests were therefore applied. Data did however not have the same variance and the greenhouse-geisser correction where therefore used, as the assumption of sphericity, alongside normal distribution and homogeneity, have to be satisfied for the RM. (44). As with position data, all inflation pattern data was also controlled for influence of gender.

6. Results

Several tests were conducted for the study, and the results will be presented in this section with all values expressed as mean and the standard error of the mean (SEM).

6.1. Positions

For cuff PDT at all four positions, no significant differences were observed between the positions for each of the chambers. Significantly higher cuff PTT between the proximal and distal chamber were observed for the distal chamber ($WS, P<0.05$) at position 1 and 3. (Figure 9)

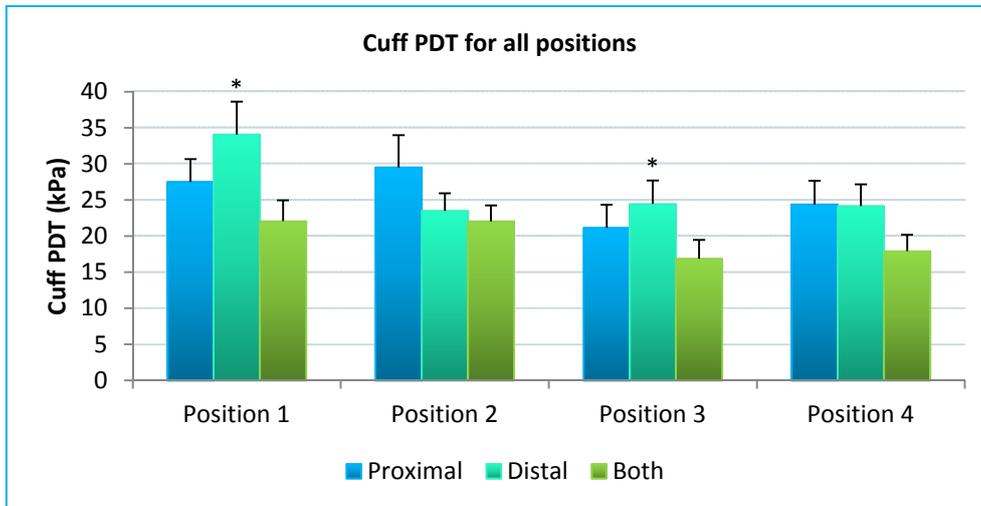


Figure 9: Positions cuff PDT. Mean (+SEM, n=20) cuff PDT for all four positions using the proximal, distal and both chambers. Significant different compared with proximal values (*, $WS, P<0.05$).

For cuff PDT CV, a significant lower CV for both chambers ($WS, P<0.001$) were observed at all positions. (Table 1)

	Proximal	Distal	Both
Position 1	24.45 (+/- 4.38)	23.44 (+/- 3.49)	0.24 (+/- 0.04)*
Position 2	24.96 (+/- 3.07)	19.98 (+/- 3.19)	0.22 (+/- 0.02)*
Position 3	24.21 (+/- 4.91)	25.86 (+/- 3.81)	0.19 (+/- 0.03)*
Position 4	22.93 (+/- 2.90)	20.38 (+/- 3.52)	0.22 (+/- 0.02)*

Table 1: Cuff PDT CV. Mean (+/-SEM, n=20) CV expressed in percentage at all positions, using the proximal, distal and both chambers. Significant different compared with proximal and distal values (*, $WS, P<0.001$).

Cuff PTT at all four positions showed significantly difference between the positions for the distal and both chambers (*KW*, $P < 0.05$). Significantly higher cuff PTT between the proximal and distal chamber were observed for the distal chamber (*WS*, $P < 0.01$) and the proximal chamber (*WS*, $P < 0.001$). (Figure 10)

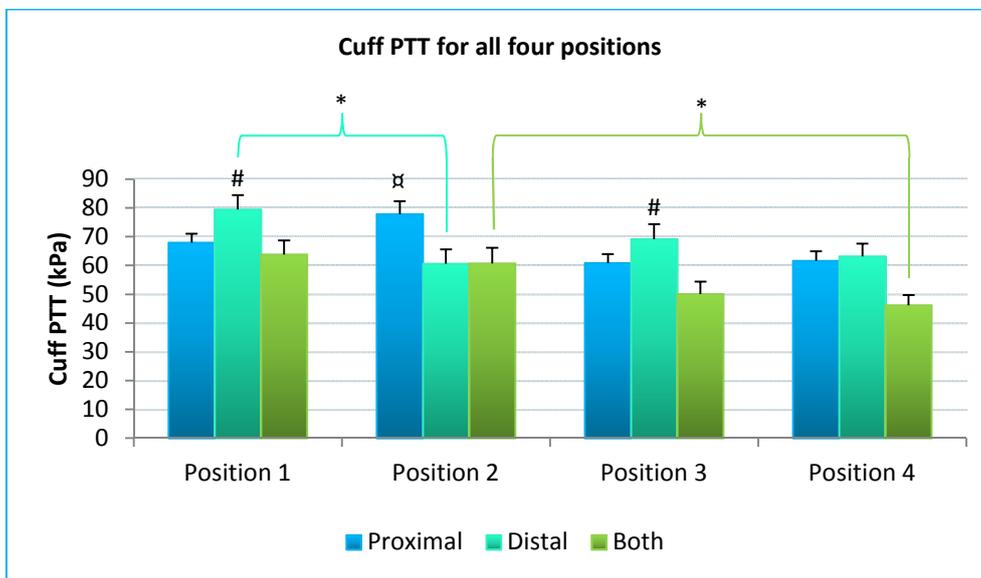


Figure 10: Positions cuff PTT. Mean (+SEM, n=20) cuff PTT for all four positions using the proximal, distal and both chambers. Significant different values between positions (*, *KW*, $P < 0.05$). Significant different compared with proximal values (#, *WS*, $P < 0.01$) or distal values (α, *WS*, $P < 0.001$)

The cuff PTT CV showed significantly different CV values between the positions for the distal chamber (*KW*, $P = 0.034$). A distal CV significantly higher (*WS*, $P = 0.031$) than the proximal CV were observed at position 2. Finally significantly lower CV were observed for both chambers at all positions when comparing all three chambers for each position (*WS*, $P < 0.002$). (Table 2)

	Proximal	Distal	Both
Position 1	5.28 (+/- 1.18)	4.33 (+/- 1.24)	0.07(+/- 0.02) ^α
Position 2	4.80(+/- 1.07)	10.19 (+/- 3.05) [#]	0.09(+/- 0.03) ^α
Position 3	5.17 (+/- 0.84)	9.30(+/- 3.33)	0.07(+/- 0.01) ^α
Position 4	6.91 (+/- 1.84)	4.47(+/- 0.7)	0.08(+/- 0.03) ^α

Table 2: Cuff PTT CV. Mean (+/-SEM, n=20) CV expressed in percentage at all positions, using the proximal, distal and both chambers. Significant different values between positions (*, *KW*, $P < 0.002$). Significant different compared with proximal and distal values (#, *WS*, $P = 0.031$) and significant different compared with proximal and distal (α, *KW*, $P < 0.002$).

Spatial summation using the cuff PDT showed significantly difference between the positions for when using the distal chamber ($KW, P<0.002$). A significant higher degree of spatial summation were observed at position 1 and 3 when using the distal chamber ($WS, P<0,045$). (Figure 11)

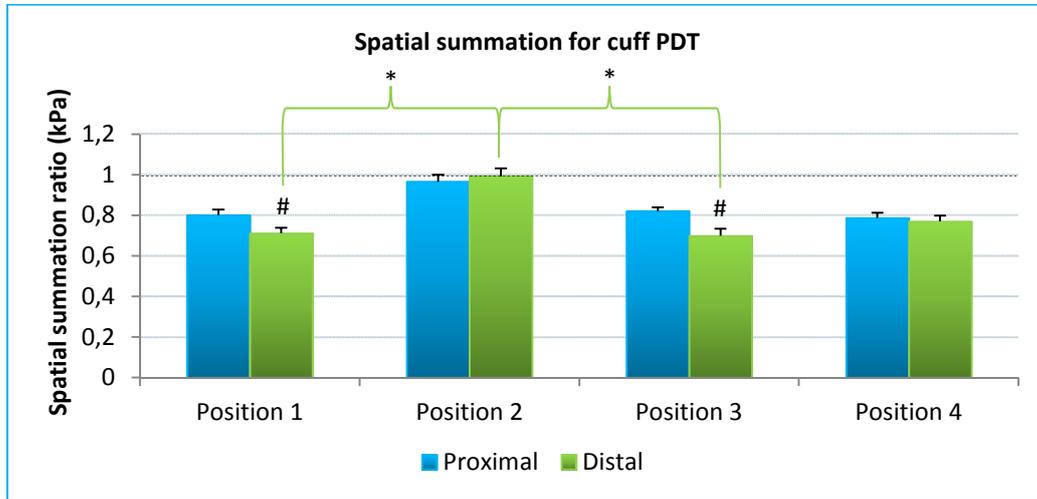


Figure 11: Spatial summation for cuff PDT. Mean (+SEM, n=20) spatial summation ratio for all four positions using the proximal and distal chambers. No spatial summation (dotted line) Significant different values between positions (*, $KW, P<0.002$). Significant different compared with proximal values (#, $WS, P<0.045$).

For spatial summation using cuff PTT, a significant difference between the positions were observed ($KW, P<0.009$). A significant higher degree of spatial summation were observed using the distal chamber at position 3, ($WS, P<0.007$) and the proximal chamber at position 2 ($WS, P=0.00$). (Figure 12)

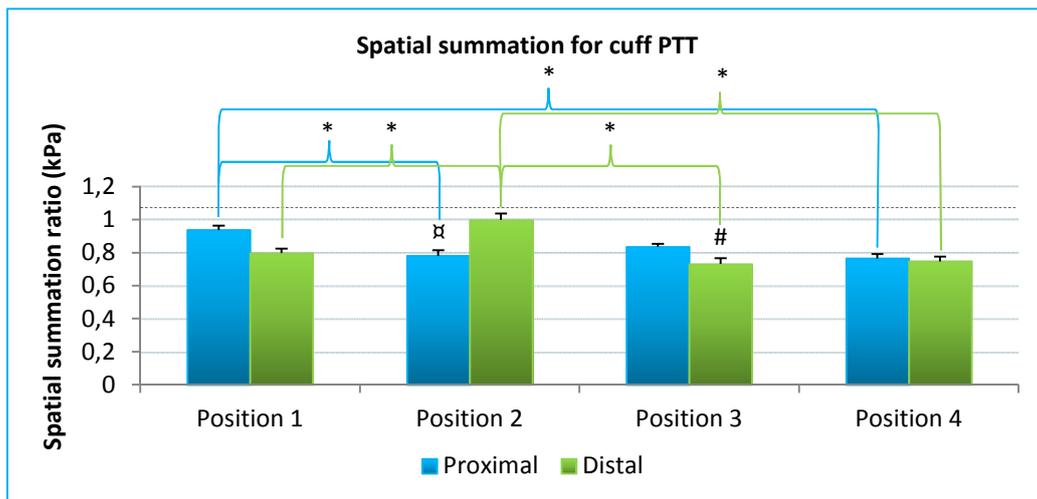


Figure 12: Spatial summation for cuff PTT. Mean (+SEM, n=20) spatial summation ratio for all four positions using the proximal and distal chambers. No spatial summation (dotted line) Significant different values between positions (*, $KW, P<0.009$). Significant different compared with proximal values (#, $WS, P=0.007$) and compared with distal values (⌘, $WS, P<0.001$).

For all positions men in general showed higher cuff PTT this was however only significant (*WS*, $P=0.04$) at position 1 and 4 when using the proximal chamber as well as position 4 when using both chambers. (Figure 13)

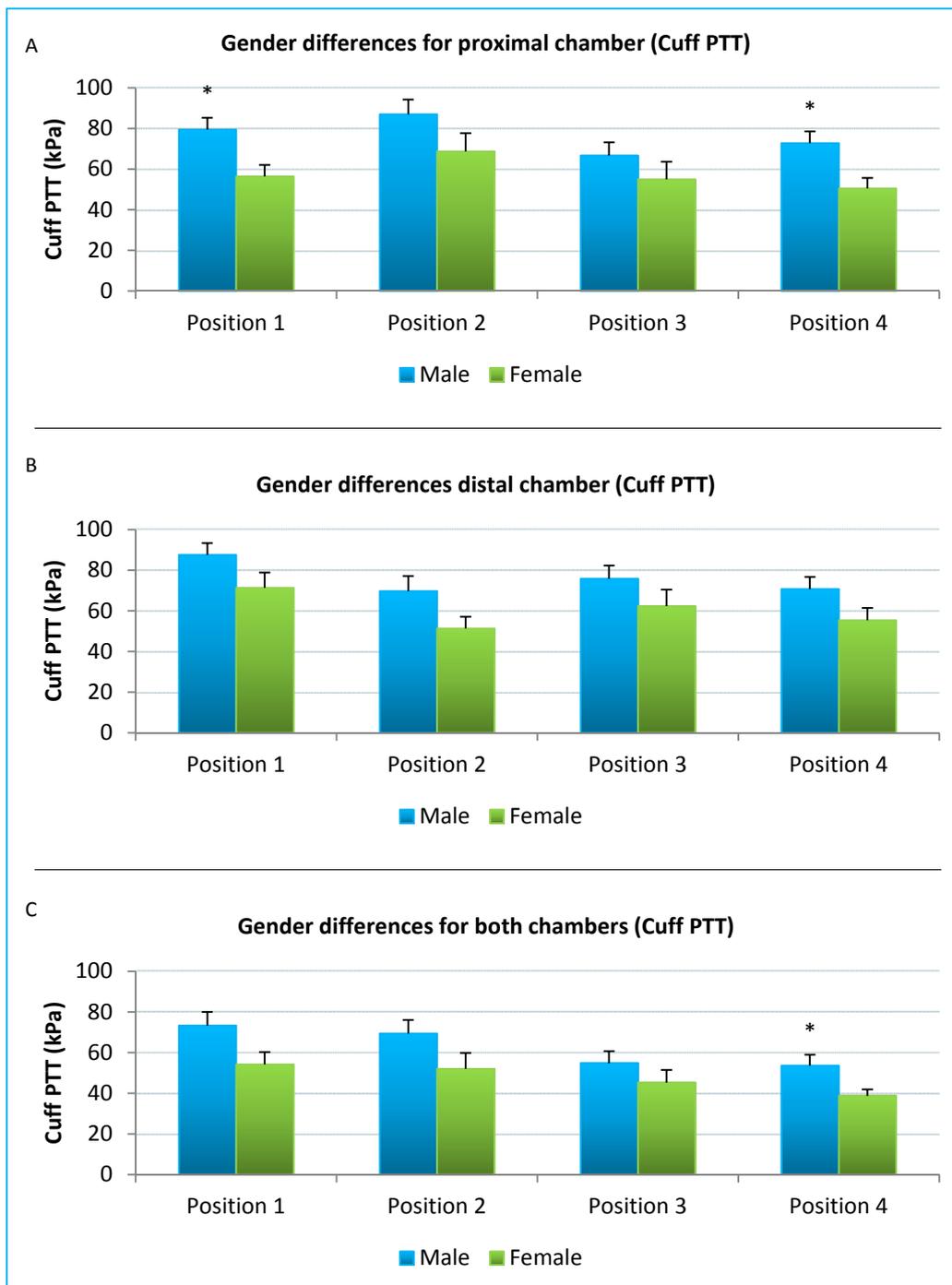


Figure 13: Gender differences in cuff PTT for all three chambers. Mean (+SEM, n=20) gender differences in cuff PTT when using the proximal, (A) distal, (B) and both chambers (C). Significant different compared with females values (*, *WS*, $P<0.04$)

6.2. Inflation patterns

For cuff PDT between the two inflation patterns, significantly higher cuff PDTs were observed for the staircase pattern for all chambers ($WS, P < 0.005$). (Figure 14)

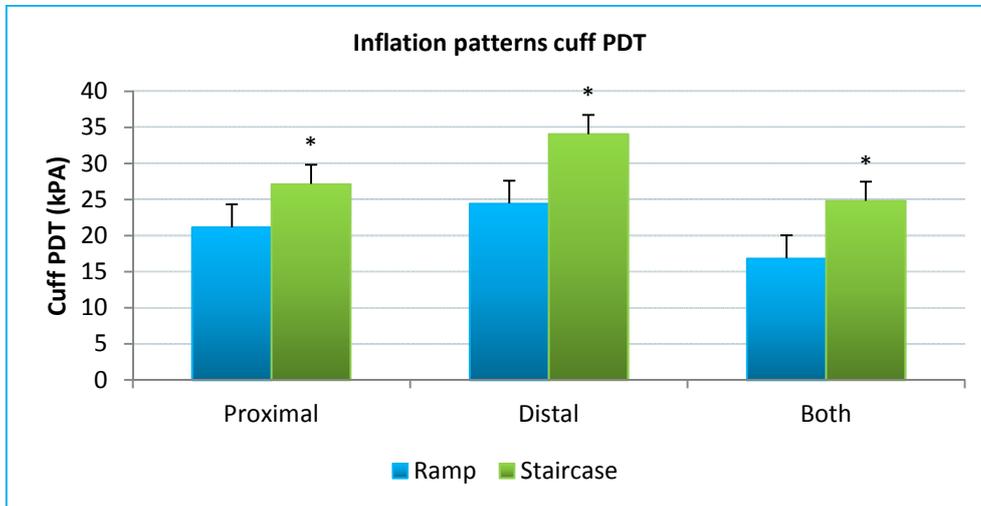


Figure 14: Inflation patterns cuff PDT. Mean (+SEM, n=20) cuff PDT for the staircase- and ramp inflation pattern at position 3, using the proximal, distal and both chambers. Significant different compared with ramp values (*, $WS, P < 0.05$).

For cuff PTT between the two inflation patterns, a significantly higher cuff PDT were observed for the staircase pattern for all chambers ($WS, P < 0.001$). (Figure 15)

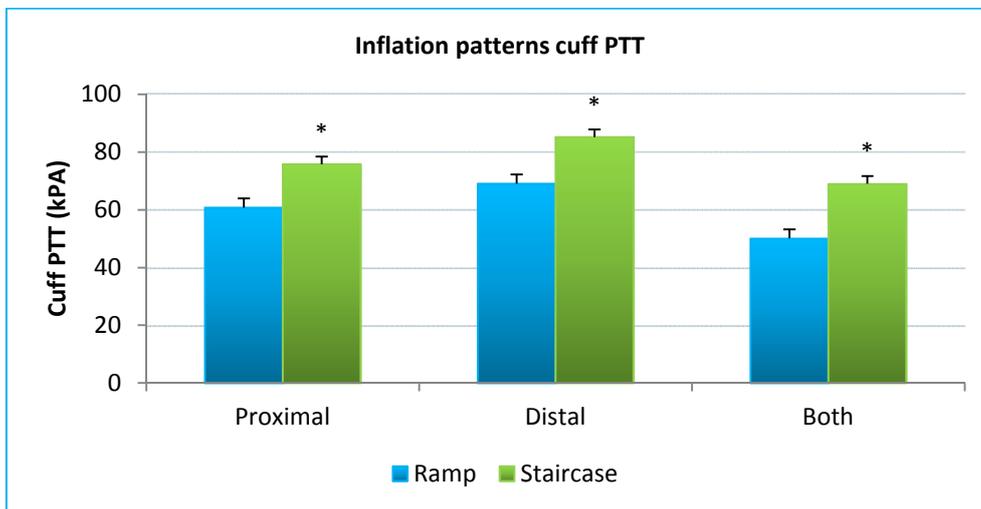


Figure 15: Inflation patterns cuff PTT. Mean (+SEM, n=20) cuff PTT for the staircase- and ramp inflation pattern at position 3, using the proximal, distal and both chambers. Significant different compared with ramp values (*, $WS, P < 0.001$).

The cuff PDT CV when comparing patterns, showed a significantly lesser CV for staircase inflation pattern using the distal chamber, but a significantly higher CV when using both chambers (*WS*, $P<0.01$) For the staircase pattern a lesser CV for both chambers (*WS*, $P<0.05$) were observed when compared to the proximal chamber. (Table 3)

	Proximal	Distal	Both
Ramp	24.21 (+/- 4.91)	25.86 (+/- 3.81)	0.19 (+/- 0.03)
Staircase	15.49 (+/- 2.92) #	14 (+/- 2.82) *	10.43 (+/- 2.61) *

Table 3: Cuff PDT CV for both patterns. Mean (+/-SEM, n=20) ramp- and staircase inflation pattern CV expressed in percentage, at position 3, for cuff PDT using the proximal, distal and both chambers. Significant different compared with ramp chamber values (*, *WS*, $P<0.01$). Significant different compared with staircase both chambers (#, *WS*, $P<0.05$).

The cuff PTT CV when comparing patterns, also showed a significantly lesser CV for staircase inflation pattern using the distal chamber, but a significantly higher CV when using both chambers (*WS*, $P<0.03$) For the staircase pattern a lesser CV for both chambers (*WS*, $P<0.01$) were observed when compared to the proximal chamber. (Table 4)

	Proximal	Distal	Both
Ramp	5.17 (+/- 0.84)	9.3 (+/- 3.33)	0.07 (+/- 0.01)
Staircase	5.47 (+/- 1.14)	2.48 (+/- 0.65) * #	7.04 (+/- 1.1) *

Table 4: Cuff PTT CV for both patterns. Mean (+/-SEM, n=20) ramp- and staircase inflation pattern CV expressed in percentage, at position 3, for cuff PTT using the proximal, distal and both chambers. Significant different compared with ramp chamber values (*, *WS*, $P<0.03$). Significant different compared with staircase both chambers (#, *WS*, $P=0.01$).

Spatial summation for the inflation patterns using the cuff PDT, show a significant higher degree of spatial summation for the ramp inflation pattern using the distal chamber ($WS, P=0,037$). (Figure 16)

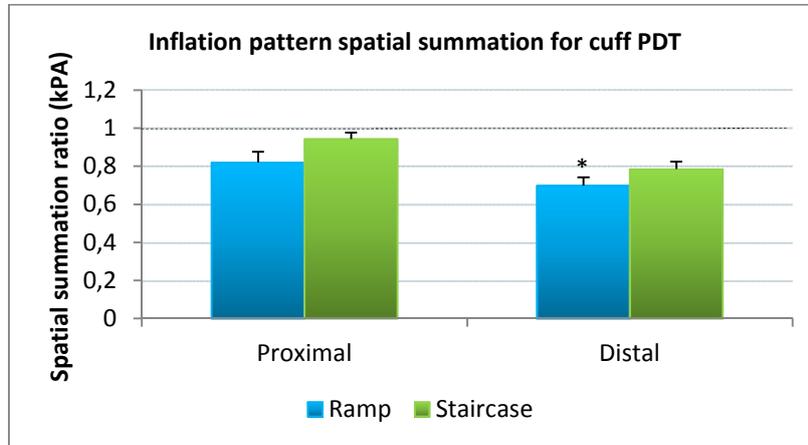


Figure 16: Inflation pattern spatial summation for cuff PDT. Mean (+SEM, n=20) spatial summation ratio for the ramp- and staircase inflation pattern using the proximal and distal chambers. No spatial summation (dotted line) Significant different compared with staircase values (*, $WS, P=0.037$).

Spatial summation for the inflation patterns using the cuff PTT, shows a significant higher degree of spatial summation for the ramp inflation pattern ($WS, P<0,012$). (Figure 17)

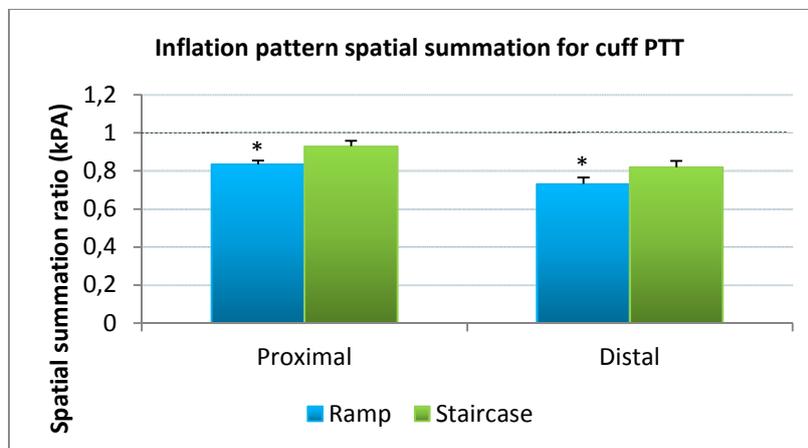


Figure 17: Inflation pattern spatial summation for cuff PTT. Mean (+SEM, n=20) spatial summation ratio for the ramp- and staircase inflation pattern using the proximal and distal chambers. No spatial summation (dotted line) Significant different compared with staircase values (*, $WS, P<0.012$).

Temporal summation showed significant difference in stimulations ($RM, P<0.001$), as well as interaction between inflation patterns and stimulations ($RM, P=0.016$). No significant difference in stimulation patterns and AUC were observed, furthermore post hoc showed no significant difference between ramp- and staircase inflation pattern for each of the ten stimulations. (Figure 18)

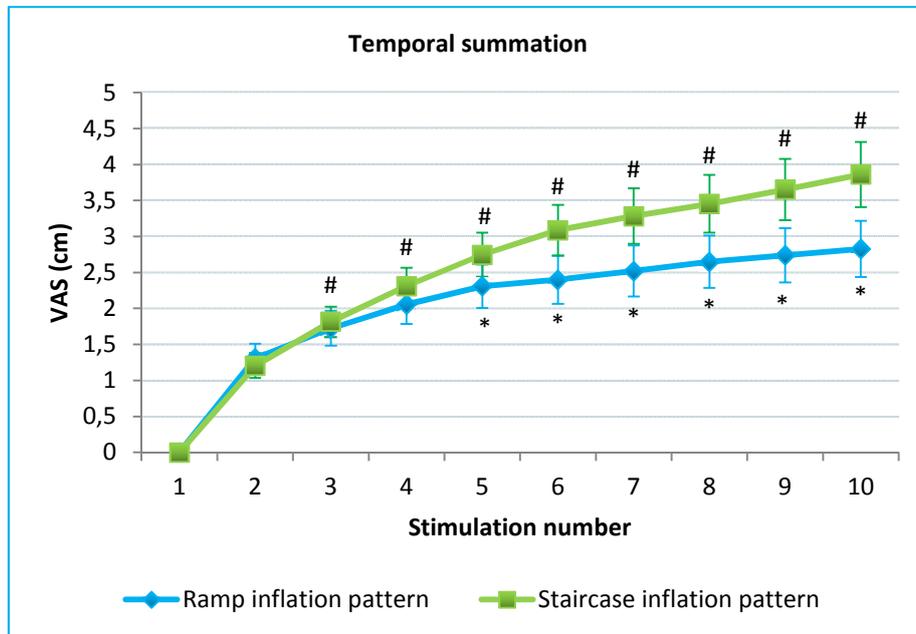


Figure 18: Temporal summation. Mean (+SEM, n=20) normalised VAS-scores for temporal summation using the ramp- and staircase inflation pattern. Significant different compared with stimulation 2 for ramp inflation pattern (*, $RM, P<0.004$) and for staircase pattern (#, $RM, P<0.001$).

6.3. Hand-held algometer

Hand held algometer PPT measurements show a significant difference between position 1 and 2 ($KW, P=0.028$). (Figure 19)

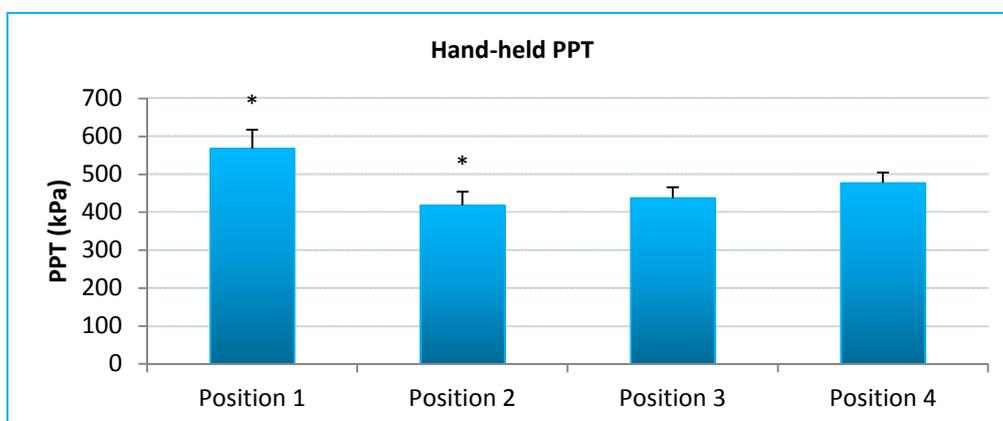


Figure 19: Hand-held PPT. Mean (+SEM, n=20) PPT for all four positions using the hand-held algometer. Significant different values between positions (*, $KW, P=0.028$).

7. Discussion

The aims of this study was to determine whether the position of the cuff has an effect on cuff PDT, cuff PTT, and spatial summation, as well as to evaluate whether the inflation pattern has an effect on cuff PDT, cuff PTT, spatial summation, and temporal summation.

7.1. Subjects

A recent meta-analysis found a moderate to large effect of exercise-induced hypoalgesia when measuring experimental induced heat- and pressure pain, although dependant of the exercise and induced pain, any physical training 24 hours prior to the study was set as an exclusion criterion, in order to avoid exercise-induced hypoalgesia. (45) This criterion did however not rule out the possibility of delayed onset muscle which usually occurs 24 to 72 hours after exercise, all subjects were therefore asked about soreness at the beginning of their session. (46) None of the subjects reported soreness, and the presence of delayed onset muscle soreness therefore seems unlikely. Several elements were not taken into account in this study, such as the circadian rhythm. Pain perception and reactions have been demonstrated to be dependent of the time of day, although the rhythm varies between types of pain and tissue. (47) The menstrual cycle was also not taken into account in this study, although it may influence pain perception. Despite inconsistencies occurs in the literature a recent study demonstrated pain modulation to be more effective in the ovulatory phase. (48, 49)

7.3. Positions

As seen in section 5.5.4, the positions of the tourniquet cuff were determined by measuring from prominent structures and the cuff itself, however due to the subjects' different leg length, one or more positions overlapped for eight of the subjects, and it can be speculated whether these overlapping positions have influenced the obtained values due to summation of pain. However due to measurement intervals of 60 seconds, as well as the randomised position sequence the possible bias related to overlapping positions is thought to be reduced to a minimum.

7.4. Visual analogue scale

All subjects received the same oral information regarding the use of the VAS and they were asked several times during the session to confirm this information. Variations however occurred throughout the study, as pain is a subjective sensation it is possible that subjects used the VAS correctly and therefore simply displayed different pain thresholds, previous studies however display a discrepancy in the reliability of the VAS, and a recent study using experimental thermal pain have indicated that subjects may redefine or reinterpret the "0" position of the VAS (indicating "no pain") by rating stimulus intensity rather than pain perception. (12, 50, 51)

In this study, several of the subjects reported the first stimulation in the temporal summation measurements to come as a shock, and that they may have rated it higher than intended. The normalisation of the temporal summation stimulations, as well as the randomised sequence of ramp- and staircase inflation pattern measurements, it thought to have reduced this possible bias.

7.5. Data collection and processing

The majority of data was obtained by the CuffControl 1.40 software, and extracted through the use of the Mathworks MATLAB r2014a custom script.

Cuff PDT was defined as when the VAS score was equal to or greater than “0.1”, in order to correctly display when the subject experienced pain, this definition however made the VAS score sensitive to any unintended manipulations from the subject. The full data set was visual inspected to ensure no occurrences of false cuff PDT values. Alternatively the cuff PDT could have been defined as VAS score equal to, or greater than “1”. This would however have resulted in some subjects having VAS score above “0” but below “1” for several seconds during their measurements, and thereby providing a false cuff PDT value for these subjects.

For 9 of the 20 subjects, one or more cuff PTT measurement reached the maximum pressure of 100 kPa during their session; as such these values were therefore at least 100 kPa but may in reality be higher. The measurements reaching the maximum pressure was however set as 100 kPa for the data processing and statistical analysis, and it can therefore be speculated whether a correct value would have resulted in other significant p-values. It is also worth noting that this study was conducted on healthy subjects, previous studies have demonstrated a reduced cuff PTT for people suffering from chronic whiplash associated disorder as well as patients suffering from on-going pain following a total knee replacement. (32, 36)

7.6. Results

A brief summary of the results show that differences occur between the positions, and the distal and proximal chamber are significantly different at some positions, furthermore gender has an influence on some of the measurements. For the inflation patterns a significant difference is observed, although not for temporal summation. Lastly, hand-held algometer PPT vary between the four positions.

Positions cuff PDT

The higher cuff PDT using the distal chamber at position 1 could be explained by the underlying structures here having less soft tissue compared to higher up the leg and therefore are able to obtain higher cuff PTT values. This explanation falls in line with a previous study indicating that the CPA assesses muscle and deep tissue sensitivity. (52) Furthermore previous studies have demonstrated muscle pain to be related to the hardness of the muscle, as well as the muscle strain which is induced more effectively by larger probes, which also could explain the higher cuff

PDT when using the distal chamber. (53, 54) The significant lower CV when using both chambers may relate to the converging nociceptor input and increased intensity of pain in spatial summation. (23, 55)

Positions cuff PTT

As with cuff PDT, a significant higher cuff PTT value was observed at position 1 using the distal chamber, further supporting the discussion regarding CPA assessment.

The significant higher distal CV is observed at position 2; combined with the higher distal values at position 1, could indicate that the distal chamber is not optimal for use on position 1 and 2. This study is however limited in having only 20 subjects, and future studies may therefore be necessary to determine the usability of the distal chamber. As with cuff PDT, a significant lower CV is observed when using both chambers, which again could relate to spatial summation.

Position spatial summation for cuff PDT

The significant higher degree of spatial summation using the distal chamber is a reflection of the cuff PDT results, however as observed in figure 10, position 2 have a significantly lower degree of spatial summation than position 1 and 3, when using the distal chamber. Furthermore, although not significant, a visual inspection of figure 11 shows position 2 to also have the least amount of spatial summation using the proximal chamber. This could indicate that position 2 might not be suited for spatial summation measurements.

Position spatial summation for cuff PTT

Position 2 using the distal chamber differed from all other positions, and had the least degree of spatial summation, contributing to the indication that the distal chamber might not be suited for spatial summation measurements at position 2.

Position gender differences

For all three significant differences, males had a higher cuff PTT value compared to females which corresponds with a recent review finding, although discrepancies occur, higher pain sensitivity for females. (56)

Inflation patterns cuff PDT and cuff PTT

The results showed significant higher thresholds when using the staircase inflation pattern, which could indicate that the staircase inflation pattern is not, or to a lesser extent, affected by summation perhaps due its phasic nature, unlike the ramp inflation pattern with a more tonic nature as mentioned in section 1.6.

The higher variability in ramp inflation pattern could indicate that the staircase inflation pattern is more precise when using the distal chamber, when using both chambers however the staircase inflation pattern have a higher variability than the ramp inflation pattern. This variability may stem

from the nature of the staircase inflation pattern as a 5 kPa increase occurs between each inflation, a graduation of the interval steps could therefore reduce the variability for all chambers. Future studies with a larger population may furthermore determine if this variability is consistent.

Inflation patterns spatial summation

The significant differences between the ramp- and staircase inflation pattern indicate that the ramp inflation pattern is better suited for measuring spatial summation. The significant higher staircase inflation pattern variability for both chambers however has to be taken into account, as this may explain the significant different degrees of spatial summations.

Inflation patterns temporal summation.

Despite the significant interaction between inflation patterns and stimulations, the post hoc test showed no significant differences between the two patterns at each of the ten stimulations. There was therefore no significant difference between applying the ramp- or staircase inflation pattern when measuring temporal summation. When looking at this lack of significant difference, it is important to notice that this study used a mean of the PTT measurements using both chambers at position 3 for the temporal summation pressure. In previous studies mean of cuff- PDT and PTT delivered as 10 stimuli within a short time span or as a constant pressure, have been used. (32, 36) It is therefore uncertain if the staircase inflation pattern could influence temporal summation if another measurement is used to determine the temporal summation pressure.

Hand held algometer

The significant difference between position 1 and 2 for the hand-held algometer measurements stands in contrast to the cuff PDT where no significant differences were found. The two methods are vastly different and these results could be said to indicate that no correlation exists between the two; however future studies with several more hand-held algometer measurement sites may clarify the correlation between hand-held algometer and CPA measurements.

7.7. Result summary

The significantly higher values obtained at position 1 indicates that this position might not be well suited when measuring with CPA. The distal chamber exhibiting higher cuff PDT and cuff PTT, a lesser degree of spatial summation using cuff PTT, and finally a higher variability, indicates that the distal chamber might not be optimal for CPA measurements. Exhibiting the least amount of spatial summation for cuff PDT, could indicate position 2 may not be suited for spatial summation measurements.

Despite higher variability when using both chambers and lack of difference for temporal summation, the staircase inflation pattern seems to be lesser influenced by summation of pain, and may therefore be beneficial to use when conduction CPA measurements.

8. Conclusion

In this section the study aims alongside the two hypotheses will be evaluated in relation to the results.

Positions

To determine whether the position of the cuff has an effect on cuff pressure pain threshold, cuff pressure pain tolerance, and spatial summation

$$H_0: \mu_1 = \mu_2 = \mu_3 = \mu_4$$

$$H_A: \mu_1 \neq \mu_2 \neq \mu_3 \neq \mu_4$$

For cuff PTT, the distal chamber significantly differed between position 1 and 2, and both chambers between position 1 and 4, furthermore spatial summation showed several differences between positions, and the null hypothesis is therefore rejected.

Inflation Patterns

To evaluate whether the inflation pattern when using computer-controlled cuff algometry has an effect on cuff pressure pain threshold, cuff pressure pain tolerance, spatial summation, and temporal summation

$$H_0: \mu_1 = \mu_2$$

$$H_A: \mu_1 \neq \mu_2$$

Cuff PDT, cuff PTT, and spatial summation showed a significant difference between the staircase and ramp inflation pattern, and the null hypothesis are therefore rejected. However for temporal summation no significant differences were observed and the null hypothesis for this measurement can therefore not be rejected.

With the discussion in mind, such as the small sample size and use of healthy subjects, a suggestion for a future CPA protocol can be given; position 3 or 4 should be used for cuff placement, and only the proximal and both chambers should be inflated. In addition, the staircase inflation pattern should be used to inflate the tourniquet cuff.

9. Future prospects

This study has unveiled new details in regard the CPA which may be of use for future studies, further testing the ramp inflation pattern and temporal summation measurements at other locations than position 3, as well as with a larger group of subjects, would however complement this study further.

The CPA was demonstrated to provoke spatial- and temporal summation as previous studies also have, revealing the potential of the CPA for experimental as well as clinical settings, such as in the prediction of postoperative pain. The drafting of a standardised protocol, to which this study have provided a suggestion, as well as an implementation strategy, could therefore be of great interest for the future prospects of the CPA.

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Images and figures

Lindskou TA. Cover page. 2014. PNG file.

Lindskou TA. "Illustrations of temporal- and spation summation". 2014. PNG file.

Lindskou TA. "The tourniquet cuff and computer-controlled compressor". 2014. PNG file.

Lindskou TA. "Electronic visual analogue scale with yellow stop button". 2014. PNG file.

Lindskou TA. "Ramp, staircase and repetitive inflation pattern". 2014. PNG file.

Badsberg S, Lindskou TA, Srimurugan N. "Hand-held algometer with wired stop-button". 2014. PNG file

Lindskou TA. "Tourniquet and hand-held algometer postions". 2014. PNG file.

Lindskou TA. "Subject with cuff tourniquet and VAS". 2014. PNG file.

11. Appendices

Appendix A: Subject information and randomization sequence.....1

Appendix B: Script.....2