**Introduction**

The proposed research is part of a PhD project that will evaluate the analgesic responses induced by two specific forms of endogenous analgesia: manual therapy induced pain modulation (MIPM) and conditioned pain modulation (CPM). The research will help determine if both forms of analgesia share similar neurophysiological mechanisms.

For the proposed research study, the CPM and manual therapy analgesic responses will be assessed using CPM and MIPM assessment protocols, respectively, after a 15mins session of low and moderate aerobic physical exercise intensities (i.e. 50% VO2max and 75% VO2max, respectively) on a cycle ergometer. There is evidence from previous studies that strong hypoalgesic responses are observed after the higher intensity aerobic exercise (Koltyn et al. 1996; Naugle et al. 2014; Vaegter et al. 2014, 2016). It is thought that a period of aerobic exercise will potentiate the MIPM and CPM analgesic responses.

Both assessment protocols will use pressure pain threshold (PPT) as the main outcome measure to quantify the analgesic changes in response to the proposed experimental interventions in a patient population with lateral epicondylalgia (LE). CPM and MIPM responses will be assessed on two study days, with a rest period of three days in between. The PPT values will then be analysed to determine if there is a difference in the CPM and MIPM responses for the low intensity and moderate intensity aerobic exercise groups. If both forms of pain modulation demonstrate a similar pattern of response, this would suggest a common underlying mechanism of action. This research may provide a base from which to investigate the possibility of enhancing MIPM effects by combining manual therapy with other treatment modalities. It will therefore extend our knowledge of manual therapy induced analgesia.

**Study protocol**:***The influence of aerobic exercise on CPM and MIPM***

**Aim**

To determine the effect of moderate and low intensity aerobic exercise on a cycle ergometer on CPM and MIPM responses as measured by percentage change in PPT in a patient population with Lateral Epicondylalgia.

**Null hypothesis**

There will be no difference in the level of CPM and MIPM analgesia between participants who receive moderate intensity aerobic exercise and those who receive low intensity aerobic exercise.

**Methods**

**Subjects**

Participants with LE will be recruited through Curtin radio advertisements, and adverts in sports clubs and a range of musculoskeletal and sports physiotherapy clinics in Perth. Using data from previous CPM studies, it is estimated that there would be a difference in percentage change in PPT of approximately 20% between active intervention and control groups. Assuming power of 0.80 and alpha set at 0.05, this would require 26-30 subjects per group. Inclusion criteria (Haker & Lundeberg 1990) and exclusion criteria are as follows:

***Inclusion criteria***

|  |
| --- |
| Unilateral elbow pain > 6 weeks reproduced on **at least 2** of the following tests:  |
| Palpation of the lateral epicondyle | Passive stretch of wrist extensors |
| Isometric testing of the wrist extensors | Resisted hand gripping using a dynamometer |
| Middle finger extension test | Upper limb neurodynamic test-radial nerve bias |

***Exclusion criteria***

|  |  |
| --- | --- |
| Neurological and radicular dysfunctions | Steroid injection into the elbow (previous 1 month)  |
| History of fracture/surgery in the forequarter (past 2 y) | Contraindications to cold applicationInability to communicate in English |
| History of generalized arthritis |  |
| Present or chronic use of anti-depressants |  |

To confirm that the eligibility criteria are met, a thorough clinical examination of all subjects will be carried out prior to commencing the study (i.e. in study one). All testing will be carried out at the Physiotherapy Clinic, School of Physiotherapy and Exercise Science, Curtin University. Subjects will be asked to avoid taking pain medications 24 hours prior to initial testing.

**Pain-related outcome measures**

**Pressure pain threshold (PPT)**

PPT will be measured using an electronic digital algometer (Somedic AB, Sweden) with standard methodology ([Coombes](http://www.ncbi.nlm.nih.gov/pubmed/?term=Coombes%20BK%5BAuthor%5D&cauthor=true&cauthor_uid=24480912) et al. 2015). PPT is a highly reliable measure for assessment of pain in LE (ICC > 0.86) (Fernández-Carnero et al. 2009). The assessor will identify the most tender point at the lateral aspect of the affected elbow by palpation. He will also identify a mid-point on the posterior aspect of the wrist, 2 cm proximal to the wrist crease. These measurement sites will then be marked. The participant will be sitting on a chair of adjustable height so the forearm is comfortably positioned in pronation on a table. A 1 cm² algometer tip will be applied perpendicularly over each marked site by the assessor and the pressure stimulus applied at a standard rate of 40 kPa/s. The participant will be instructed to push a control switch at the moment they perceive the pressure becoming painful. PPT measures are the pressure value (kPa) recorded from the algometer. The test procedure will first be conducted at the unaffected forearm for familiarization. Three PPT measurements will be taken at each site on the symptomatic side with 10-15 s intervals between each. Mean values will be used in analysis.

**Pain free grip (PFG)**

Pain on gripping is a clinical sign of LE (Vicenzino et al. 1998). Pain free grip (PFG) refers to the amount of grip force that can be applied prior to the onset of pain (Paungmali et al. 2003). PFG will be measured with an electronic digital dynamometer (MIE, Medical Research Ltd.) using standard methodology ([Coombes](http://www.ncbi.nlm.nih.gov/pubmed/?term=Coombes%20BK%5BAuthor%5D&cauthor=true&cauthor_uid=24480912) et al. 2015). It is both a reliable (ICC > 0.97) (Smidt et al. 2002) and valid (Paungmali et al. 2003) measure used in patients with LE. The participant will be lying supine with the arm by their side positioned in elbow extension and forearm pronation. They will then be requested to squeeze the dynamometer handles until they first feel their lateral elbow pain, and then to stop the squeezing action. The PFG force value is then recorded from the digital display. The PFG test will be performed three times with 10-20 s rest intervals in between. The average value will then be used for analysis.

**Upper limb neurodynamic test (ULNDT) with radial nerve bias**

The upper limb neurodynamic test (ULNDT) with radial nerve bias will be used to assess primarily neural mobility of the forequarter (Butler 2000). Painfree range of motion in the test is restricted in patients with LE (Yaxley & Jull 1993). The participant’s arm will be progressively positioned in scapular depression and protraction, elbow extension, internal rotation, forearm pronation, wrist and finger flexion. Scapular depression will be sustained while performing the test. The shoulder will then be slowly taken into abduction. The participant will be instructed to depress a switch at the onset of pain with this movement and the arm will be returned to the start position. The shoulder abduction range at the onset of pain will be measured using an M180 twin axis electrogoniometer (Penny & Giles, United Kingdom) positioned over the anterior shoulder (Vicenzino et al. 1996). Three readings will be taken with 20-30 s intervals in between. The average of these readings will be used for analysis.

**Assessment protocols**

**Conditioned pain modulation (CPM) assessment protocol**

***Test stimulus:***PPT will be used as the test stimulus, using an electronic digital algometer (Somedic AB, Sweden) as outlined above. It has been shown that PPT has a high intrarater reliability with excellent intraclass correlation coefficient (ICCs: 0.81-0.99) when measured at 4 different body sites (Waller et al. 2015). Participants will sit on a chair of adjustable height so the forearm is comfortably supported. PPT will be performed as outlined above on the two marked locations of the affected arm, which will be positioned in pronation on a table. PPT will be tested at baseline prior to cold water immersion, after 1 min during immersion, and 1 min post immersion. At each time point, PPT will be measured three times with 10-15 s rest intervals in between. The mean value of the three measurements at each point will be used for analysis.

***Conditioning stimulus****:* The Cold Pressor Test (CPT) will be used as a conditioning stimulus to elicit the CPM response. The unaffected hand will be submerged 4 inches above the wrist crease in a cold water bath, with a temperature maintained at 7°C for a period of 2 min (Locke et al. 2014). The water bath contains a mix of water and ice and it is supplied with a circulating pump to ensure uniformity of water temperature at the skin. The difference between PPT measurements taken before and after water immersion represents the CPM effect. This will be quantified as the percentage change in PPT relative to the baseline measure. Separate percentage change measures will be obtained for the wrist and elbow sites.

**Manipulation induced pain modulation (MIPM) assessment protocol**

The existence of a MIPM effect will be assessed using a very similar protocol to CPM testing.

***Test stimulus****:* PPT will be the test stimulus. The PFG test, ULNDT with radial nerve bias and measures of PPT at both test sites will be carried out at baseline and then repeated immediately after the conditioning stimulus (C5/6 contralateral lateral glide mobilisation). Testing will be performed with the participants lying supine on a plinth. PFG and UNLDT will provide additional measures of the MIPM effect.

***Conditioning stimulus*:**a grade III passive oscillatory, contralateral lateral glide (CLG) mobilisation of the C5/6 motion segment of the cervical spine will be used to induce MIPM (Vicenzino et al. 1996). The participant will be comfortably lying supine with arms by their side and instructed to report if they feel any discomfort or pain during execution of the mobilisation. In contrast to CPM this conditioning stimulus should be painless. The therapist will depress the scapulae with one hand, while the other hand cradles the occiput and neck above the C5/6 segment. Using the cradling hand, the therapist will apply a grade III passive oscillatory CLG directed towards the unaffected upper limb. The CLG stimulus will be performed for 60 s, and will be repeated three times, with 60-s rest periods in between (5 min total) (Vicenzino et al. 1996). The difference between PTT measurements taken before and after CLG mobilisation represents the MIPM effect. This will be quantified as the percentage change in PPT relative to the baseline measure. Separate percentage change measures will be obtained for the wrist and elbow sites and the PFG and ULNDT measures**.**

**Experimental conditions**

Several studies have shown strong analgesic responses induced post aerobic exercise at low and moderate intensities (Koltyn et al. 1996; Naugle et al. 2014; Vaegter et al. 2014, 2016), therefore these intensities are selected for this study. The method mentioned here is based on a study by Naugle et al. (2014).

**Moderate intensity aerobic exercise:**Participants in this condition willundergo a 15 min session of stationary cycling at an intensity of 75% VO2 heart rate reserve (HRR). Prior to beginning of the session, the target heart rate (THR) matching 75% VO2 max will be determined using the Karvonen formula (Swain et al. 1994). THR = ((maximal HR − resting HR) × %Intensity) + resting HR), where maximal HR = 220-age. Heart rate will be regularly observed during rest and exercise using a heart rate monitor, which will be fitted at the start of the session. The targeted exercise intensity level will be achieved through controlling the speed and the resistance of the cycle ergometer. Participant will initially start warming up by cycling gradually to reach the desired exercise intensity during the first 5mins, they will then continue cycling for the following 10mins while maintaining the exercise intensity at 75%Vo2max. The heart rate will be continuously monitored to ensure that the exercise intensity is achieved and adequately maintained during the session. This intervention will be conducted under standardized conditions by a physiotherapy student, who is under the supervision of senior physiotherapy staff at Curtin University Physiotherapy Clinic.

**Low intensity aerobic exercise:**Participants in this condition will undergo the same experimental procedure defined in the moderate intensity aerobic exercise, but with an intensity of 50% VO2 max instead of 75% VO2 max.

**Procedure**

A randomized between-group design will be used in this study. Three days subsequent to Part One of the study,eligible subjects will be first randomized to receive either low (50% VO2 max) or moderate intensity (75% VO2 max) aerobic exercise as described above. Participants in each group will be initially tested for PPT at both elbow and wrist measurement sites. They will then be randomized to undergo a precondition CPM assessment protocol and an MIPM assessment protocol, in two separate test sessions (i.e. two study days) separated by three days. All CPM and MIPM protocols will be performed by the same assessor who will remain blinded to the level of aerobic exercise subjects are completing. Following completion of the aerobic exercise, all subjects will be reassessed for CPM and MIPM by the blinded assessor. Subjects will be asked to avoid physiotherapy and other forms of physical exercise and coffee on the days of assessment.

**Analysis**

Measures of CPM effect (% change PPT) and MIPM effect (% change PPT) will be obtained for the wrist and elbow sites. Independent groups t-tests will be performed to evaluate differences in CPM and MIPM effects (% change in PPT) between the group receiving the moderate intensity aerobic exercise and the group receiving the low intensity aerobic exercise.

Measures of exercise induced hypoalgesia (EIH) effect (% change PPT) will also be obtained for the wrist and elbow sites. Independent groups t-tests will be performed to evaluate differences in EIH effect (% change in PPT) between the group receiving the moderate intensity aerobic exercise and the group receiving the low intensity aerobic exercise.

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