**Background**

**Conditioned Pain Modulation**

Endogenous analgesia (EA) involves multiple inhibitory and facilitatory mechanisms that modulate the perception of noxious stimuli. One of the most widely investigated EA mechanisms is diffuse noxious inhibitory control (DNIC). This is the widely recognized concept that pain inhibits pain (Reinert et al. 2000). DNIC involves a cortically influenced spinal-bulbo-spinal neural circuit acting through inhibition of wide dynamic range (WDR) neurons in the spinal dorsal horn (Le Bars et al. 1979). Yarnitsky and colleagues (2010) have recommended the use of Conditioned Pain Modulation (CPM) as a term to distinctly define the DNIC phenomenon in humans. CPM testing typically involves application of a painful ‘test stimulus’, during or after a distant noxious ‘conditioning stimulus’ (Yarnitsky 2015). CPM effect is defined as the difference between the ‘test stimulus’ values before and during or after the ‘conditioning stimulus’ application. In the case of pressure pain threshold (PPT), a positive CPM response is represented by an increase in the PPT measure (Locke et al. 2012). Many studies have demonstrated that a normal response involves a reduction in the painfulness of the test stimulus following application of the conditioning stimulus (Bouhassira et al. 2003; Graven-Nielsen et al. 2002; Reinert et al. 2000). It is proposed that this reflects a normally efficient CPM response and an efficient pain modulation system. Lewis et al. (2012a), in their systematic review and meta-analysis, concluded that several chronic pain conditions are associated with inefficient CPM. Yarnitsky (2015) acknowledges that the less efficient CPM seen in chronic pain conditions implies a dysfunctional pain modulation system. However, an alternative explanation may be that the less efficient CPM in chronic pain syndromes is instead the by-product of a pain modulatory system that is already working optimally, so that no further increase in CPM is possible (Yarnitsky 2015).

**Protocols for testing CPM**

The CPM literature has described different CPM testing protocols (Pud et al. 2009). Test stimuli modalities can include contact heat, mechanically-induced pressure (PPT), electrical stimulation or chemical stimuli (Nir & Yarnitsky 2015; Yarnitsky 2015). Different pain measurement parameters have also been used such as pain threshold, rating of supra-threshold pain and rating of temporal summation pain (Pud et al. 2009). With respect to conditioning stimuli, these may include contact heat, or the most frequently used cold water immersion, the so called cold pressor test (CPT), or hot water immersion (Nir & Yarnitsky 2015; Pud et al. 2009; Yarnitsky 2015). The most pronounced analgesic effect has been observed in CPM paradigms using cold water immersion pain to inhibit a test stimulus of PPT (Oono et al. 2011). The test stimulus is applied at an anatomically distant site from the conditioning stimulus, preferably using one upper and lower limb site, though using two upper limb sites is acceptable (Yarnitsky 2015). Lewis et al. (2012b) have shown that CPM testing is a reliable measure for evaluating EA function using cold immersion/CPT as the conditioning stimulus and PPT as the test stimulus. Similarly, Biurrun Manresa et al. (2014) have also demonstrated an acceptable CPM test/retest reliability when conducted in two separate sessions, with a period of 1-3 weeks in between. In their study, they utilised CPT as the conditioning stimulus.

**Manual therapy induced pain modulation**

Manual therapy induced pain modulation (MIPM) is a form of EA associated with manual therapy treatments. Wright (1995) has suggested that MIPM is a multifactorial phenomenon exerting its analgesic effect through several mechanisms, including activation of descending pain modulation systems, similar to DNIC/CPM. PPT has been used to measure the analgesic effects of spinal and peripheral manipulation techniques, with increased PPT values denoting a reduction in the perceived pain at the test location, or hypoalgesia. Voogt et al. (2015) have recently conducted a systematic review to study MIPM effects. Of the 13 randomized studies included in their analysis, 10 demonstrated a significant increase in PPT post manual therapy suggesting a clear MIPM effect.

**Evidence of central mechanisms**

In patients with chronic lateral epicondylalgia (LE), Vicenzino et al. (1998) examined the close link between the immediate analgesia post mobilization and centrally-driven sympathoexcitation. This study showed that cervical mobilization induced analgesia at the elbow together with sympathoexcitation changes, such as an increase in skin conductance in the upper limb. This close association between theMIPM and sympathoexcitation responses suggests a role for descending pain modulation systems (similar to DNIC/CPM) in producing the pain relief associated with manual therapy. Animal studies similarly suggest involvement of central spinal-bulbo-spinal pathways in the pain inhibition produced by manual therapy, as similarly shown for the DNIC/CPM phenomena. Sluka and Wright (2001) showed that knee joint mobilisation decreased ankle hyperalgesia induced by joint inflammation in an animal model of articular pain. Further, Skyba et al. (2003) used the same pain model and reported that intrathecal administration of the α2-adrenergic receptor antagonist, yohimbine partially blocked and the 5-HT receptor antagonist, methysergide completely blocked the analgesic effect of joint manipulation. They concluded that spinal serotonergic and noradrenergic receptors linked to descending serotonergic and noradrenergic neurons play a key role in mediating MIPM**.** This suggests that there may be a considerable overlap between the neurophysiological mechanisms responsible for DNIC/CPM and those responsible for MIPM.

**Aerobic exercise**

There is evidence from previous studies that strong hypoalgesic responses are observed after moderate intensity aerobic exercise (Koltyn et al. 1996; Naugle et al. 2014; Vaegter et al. 2014, 2016). Naugle et al. (2014) compared the hypoalgesic effects of stationary cycling at 70% VO2max and 50% VO2max among 27 healthy volunteers. Both intensities of aerobic exercise induced significant hypoalgesic effects, with a greater hypoalgesia effect after cycling at 70% VO2max. Further, Vaegter et al. (2015) examined the hypoalgesic effects of 15mins of bicycling exercise at an intensity of 75% VO2max and cold immersion/CPT among active and inactive healthy participants. While the active group showed higher levels of exercise induced hypoalgesia (EIH) and more efficient CPM effect, as measured by PPT than the inactive group, the extent of analgesia induced by CPM and aerobic exercise in both groups was positively correlated. This indicates that EIH and CPM analgesia are likely mediated by common mechanisms. This in turn suggests that a period of aerobic exercise may similarly potentiate the MIPM analgesic responses.

Given the apparent link between the neurophysiological mechanisms responsible for CPM and MIPM analgesic effects, this raises the possibility that either CPM or MIPM analgesia might be enhanced in combination with aerobic physical exercise.

**Summary**

The available research evidence suggests that CPM and MIPM induce natural forms of analgesia. They appear to share similar neuro-physiological mechanisms involving activation of endogenous descending pain inhibitory systems. There is also an overlap with EIA. This raises questions as to whether they activate the same or different mechanisms, whether people who show a good response to CPM will also respond well to MPIM and whether combining two or more modalities might produce an increased analgesic effect. In particular, does the addition of aerobic exercise potentiate the CPM and MIPM effects.

**Objective**

The overall objective of the proposed research is to investigate whether there are similar patterns in the way that each form of endogenous analgesia (CPM and MIPM) varies in response to an experimental paradigm designed to enhance the activity of the descending pain modulation systems. The paradigm we propose to use to enhance the EA system function is a period of aerobic physical exercise. If the change in response to CPM and MIPM is the same following aerobic exercise we would suggest that both forms of analgesia are accessing essentially the same pain modulation pathways in the central nervous system. This will greatly enhance our understanding of manual therapy analgesia.

**Experimental Study**

**Sample size calculations**

Sample size calculation has been madebased on estimated differences in CPM effect between active and control groups**.** 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.

**Part One: *Association between the analgesic effects of CPM and MIPM***

This is a two-part study protocol and it is envisaged that subjects who complete the first part of the study will then proceed to the second stage of the study.

**Aims**

* To assess CPM and MIPM in a patient population with Lateral Epicondylalgia (LE) to determine if there is a correlation between the induced analgesic responses in this patient population.
* To determine whether there is a difference in the level of MIPM analgesia between those who exhibit a CPM effect (CPM responders) and those who do not demonstrate a CPM effect (CPM non-responders).

**Null hypotheses**

1. There will be no correlation between the level of MIPM and CPM analgesia as detected by PPT.
2. There will be no difference in the level of MIPM analgesia between those subjects who do and those who do not exhibit a CPM effect (CPM responders vs non-responders).

**Methods**

**Subjects**

60 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. 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. Subjects will also be required to initially complete the Adult Pre-exercise Screening System (APSS) tool, which is an Australian screening tool developed by Exercise and Sport Science Australia (ESSA), Fitness Australia (FA), and Sports Medicine Australia (SMA) to examine participants’ eligibility and safety for aerobic exercise testing (Norton & Norton 2011). All testing will be carried out at the Physiotherapy Clinic (Building 404), School of Physiotherapy and Exercise Science, Curtin University. Subjects will be asked to avoid taking pain medications 24 hours prior to initial testing.

**Physical activity level outcome measure**

All eligible participants will need to report their typical weekly physical activity level using the Global Physical Activity Questionnaire (GPAQ) (WHO 2005). It is a 16-question self-report questionnaires measuring physical activity levels in three main areas: work, transport and recreation. The GPAQ is shown to be an adequately reliable measure of physical activity, with a low-to-moderate validity (Herrmann et al. 2013).

**Pain-related outcome measures**

**Pressure pain threshold (PPT)**

PPT will be measured by using an electronic digital algometer (Somedic AB, Sweden) using 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 scapula 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**.**

**Procedure**

Once eligibility criteria are confirmed, each participant will be asked to attend for a preliminary baseline assessment with CPM and MIPM assessment protocols in a single session (see Fig. 1). The CPM assessment protocol will be followed by the MIPM assessment protocol with a rest period of 15 min in between (subject to the findings from Pilot Study: HRE2016-0181). All outcome measures will be performed by the same researcher applying the CPT and CLG stimuli. All instructions will be standardized. Subjects will be asked to avoid physiotherapy treatment and other forms of physical exercise on the study days. They will also be asked to avoid taking pain medications on the study days.

**Analysis**

Measures of CPM effect (% change PPT) and MIPM effect (% change PPT) will be obtained for the wrist and elbow sites. Null hypothesis 1 (i.e. no correlation between MIPM and CPM analgesic effects) will be tested using a Pearson’s correlation test to evaluate the association between change in PPT at both test sites during CPM and MIPM assessment protocols.

To test ‘null hypothesis2’subjects will be assigned post hoc into two groups, based on whether or not they demonstrate a meaningful CPM effect at the wrist test site. The assessment of meaningful CPM effect will be determined based on the criteria described by Locke et al. (2014). CPM effect will be considered meaningful if the percentage increase in wrist PPT from baseline is greater than the standard error of measurement (SEM) for repeated PPT measures. To compute the SEM, a pilot study (HRE2016-0181) of 10 participants will be conducted following the same PPT test-retest protocol (baseline, at 1 minute and at 2 mins) but without applying CPT. The SEM will then be calculated for each time point using the formula SD x √(1-ICC), where ICC represents the interclass correlation coefficient of the mean value for each time point. The SEM value will then be added to the PPT mean value to indicate the maximum upper value of normal variation in repeated PPT measures (Lock et al. 2014). This value will then be represented as a percentage change value. Therefore, any PPT percentage value above this percentage change value will indicate a meaningful CPM effect, greater than the normal measurement error. Subjects with a CPM effect above this percentage will be classified as CPM responders and those with a CPM effect below this percentage will be classified as CPM non-responders. In the study by Locke et al (2014) the meaningful CPM cut-off value was 5.3%, with approximately 10% of subjects found to be non-responders. It is anticipated that in this patient population this percentage of non-responders will be higher.

Once CPM effect groups have been determined, differences between the two groups for MIPM measures will be analysed. Percentage change in PPT at the elbow, PFG, and ULNDT (shoulder abduction), will be used to compare the MIPM effect between the CPM groups (i.e. CPM responder and CPM non-responder) using independent t-tests.

**Part Two**:***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**

60 participants diagnosed with LE will be recruited from the community and will meet the same eligibility criteria outlined in Study One above.

**Procedure**

A randomized between-group design will be used in this study. Three days subsequent to Study One, eligible subjects will be randomized to receive either low (50% VO2 max) or moderate intensity (75% VO2 max) aerobic exercise on a cycle ergometer. 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 CPM assessment protocol or an MIPM assessment protocol, in two separate test sessions (i.e. two study days) separated by three days (see Fig. 1). The randomisation process will be managed by the Physiotherapy Clinic supervisor (Mr John Watson). 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 assessed for either CPM or MIPM effect by the assessor who will remain blinded to the level of aerobic exercise that the subjects have completed. Subjects will be asked to avoid physiotherapy treatment and other forms of physical exercise during the study.

**Pain-related outcome measures**

On each test occasion, pressure pain threshold at the lateral elbow and the wrist will be measured before aerobic exercise, before and after cold water immersion (for CPM assessment), or before and after CLG (for MIPM assessment) based on the randomization schedule. The mean of three trials at each site will be used for analysis for each protocol. PFG and ULNDT with radial nerve bias will also be assessed before and after CLG for MIPM assessment. All procedures are described above in Part One. Eligible subjects randomly allocated to moderate and low intensity aerobic exercise groups will attend the Curtin University Physiotherapy Clinic for aerobic physical exercise testing, as described below. Subjects in both groups will be asked to avoid any additional physiotherapy treatment or other physical treatment during the course of the experiment. They will also be asked to avoid taking pain medications on the study days. CPM or MIPM responses will be reassessed in each subject immediately after the aerobic exercise sessions on the cycle ergometer.

**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 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. Participants 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 a level that will enable them to achieve the target exercise intensity of 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 final year physiotherapy student, who is under the supervision of senior physiotherapy staff at Curtin University Physiotherapy Clinic (Mr John Watson).

**Low intensity aerobic exercise:**Participants in this condition will undergo the same experimental procedure defined in the moderate intensity aerobic exercise, but at a cycle ergometer resistance level that enables them to achieve a target exercise intensity of 50% VO2 max instead of 75% VO2 max.

**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 aerobic exercise hypolagesia (EIH) effect (% change PPT) will be also obtained for the wrist and elbow sites based on the pre to post exercise PPT measures. 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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**Fig. 1: Aerobic exercise study: Part 1 and 2 with testing protocols**

 ***Day 1***

**CPM**

**Assessment Protocol**

**MIPM**

**Assessment Protocol**

**15 min Rest**

**Clinical Exam**

**LE**

**N=60**

**3 Days Rest**

**Part 1**

**Part 2**

Randomised assignment to 50% or 75% VO2 max groups. Randomised testing of MIPM or CPM assessment protocols between days.

 ***Day 2 Day 3***

**Group 1**

**n=30**

 **50% VO2max**

**Group 2**

**n=30**

 **75% VO2max**

PPT

PPT

**CPM**

**Assessment Protocol**

**CPM**

**Assessment Protocol**

**Group 1**

**n=30**

 **50% VO2max**

**Group 2**

**n=30**

 **75% VO2max**

PPT

PPT

**MIPM**

**Assessment Protocol**

**MIPM**

**Assessment Protocol**

**3 Days Rest**