The influence of aerobic exercise on conditioned pain modulation and manipulation induced analgesia in people with lateral epicondylalgia: a randomised controlled trial

Ahmad Muhsen
Curtin University School of Physiotherapy and Exercise Science https://orcid.org/0000-0002-3032-6410
Penny Moss
Curtin University School of Physiotherapy and Exercise Science
William Gibson
Universite Notre Dame Australia
Bruce Walker
Murdoch University
Angela Jacques
Curtin University
Stephan Schug
University of Western Australia
Anthony Wright (T.Wright@curtin.edu.au)
Curtin University https://orcid.org/0000-0002-0289-6141

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Abstract

Background: Exercise has been shown to reduce pain sensitivity. It is unclear whether exercise can also potentiate the endogenous analgesia and reduction in pain sensitivity produced by conditioned pain modulation (CPM) and manipulation induced analgesia (MIA).

Objectives: To determine whether aerobic exercise potentiates CPM and MIA and to investigate associations between exercise induced analgesia, CPM and MIA.

Design: Parallel randomised, controlled trial using computer-generated randomisation to allocate interventions.

Methods: A gender-stratified convenience sample included 68 participants with lateral epicondylalgia (LE) from Perth, Western Australia, recruited between October 2017 and June 2018. Participants were allocated to receive either moderate intensity aerobic exercise (control condition, n=34) or high intensity aerobic exercise (active condition, n=34) for 15 minutes on two separate test sessions, with a three-day rest in between. Exercise intensity was determined based on age-related target heart rate (HR) corresponding to 50% and 75% of maximum HR respectively. Following aerobic exercise, participants were immediately assessed for CPM or MIA response, one on each test day, in a random order. A blinded assessor measured pressure pain thresholds (PPT), the main outcome measure, at the elbow and ipsilateral wrist to evaluate CPM and MIA. Data were analysed using linear mixed models, partial correlations, and univariate regression.

Results: All participants showed significant increases in PPT at both test sites ($p<0.001$). The high intensity exercise group demonstrated higher levels of CPM and MIA at both test sites ($p<0.001$). There were large and positive partial correlations between CPM/MIA and the initial change in PPT following exercise (CPM (r:0.90–0.93, $p<0.001$)/MIA (r:0.68–0.86, $p<0.001$)). The change in PPT following aerobic exercise was a significant predictor of both CPM (adjusted R^2:92%-95%) and MIA (adjusted R^2:73%-93%) response.

Conclusion: An acute bout of high intensity aerobic exercise significantly enhanced the analgesic effect of CPM and MIA in people with LE. CPM and MIA may activate similar descending inhibitory mechanisms to mediate their analgesic effects.

Trial registration: Prospectively registered with the Australia New Zealand Clinical Trials Registry on 9/02/2017: ACTRN12617000219381, https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372232

1. Introduction

There is some evidence to suggest that conditioned pain modulation (CPM) and manipulation induced analgesia (MIA) may activate similar endogenous analgesic mechanisms. Serotonin has been identified as a key neurotransmitter in both CPM [1] and MIA [2]. There is some ambiguity related to the involvement of the opioid system. For CPM, some studies have shown that naloxone (an opioid antagonist) blocks CPM analgesia [3–5] while others have reported no reversal (CPM: [6–8]). For MIA, the majority of studies suggest that naloxone does not reverse its effects [2, 9–11], suggesting some potential variations in the mechanisms for CPM and MIA.

Exercise has also been shown to induce endogenous analgesia leading to a reduction of pain sensitivity [12, 13]. This response has been reported following aerobic [14], isometric [15] and resistance exercise [16] using a range of measures (e.g. pressure, thermal or electrical stimuli) [17]. In the case of aerobic exercise, a hypoalgesic response is induced when exercise is performed at moderate to high intensity [14]. Vaegter et al. [14] compared the immediate effect of high (75% VO_2max) and moderate (50% VO_2max) intensity aerobic exercise (stationary cycling) on the magnitude of hypoalgesia in healthy participants. Their results showed that high intensity exercise induced a greater response than moderate intensity exercise, suggesting a dose-response relationship.

The presence of an effective exercise analgesia response has been associated with efficient CPM analgesia [14, 18, 19]. We hypothesized that a similar association may exist between exercise analgesia and MIA so that there is potential for exercise to potentiate MIA. Therefore, the first aim of this randomized, controlled study was to determine whether aerobic exercise potentiates CPM and MIA to a similar degree. The second aim was to assess the association between exercise induced analgesia, CPM and MIA. LE was used as a clinical model as the effect of CPM and MIA in LE has been previously established [24, 25].

2. Methods

Study design

A randomised, controlled, single blind, between-group experimental design was used. Eligible participants were randomised to receive either moderate intensity aerobic exercise (control condition) or high intensity aerobic exercise (active condition), during two separate test sessions.

Randomisation

A randomisation sequence was computer-generated and held by the Physiotherapy Clinic supervisor at Curtin University. Randomisation was stratified for males and females. Prior to commencing each testing session, the research assistant contacted the holder of the allocation schedule to ascertain group allocation for each participant. This research assistant conducted the aerobic exercise sessions. The primary investigator (PI) (AM) who undertook all testing remained blind to group allocation.

Participants

A gender-stratified convenience sample of 68 participants with LE, aged between 18 and 60 years, was recruited from Perth, Western Australia. Recruitment took place from October 2017 until June 2018 through radio advertisements and a clinical trials recruitment agency. LE was diagnosed based on the criteria established by Haker and Lundeberg [18] (unilateral lateral elbow pain for a duration of at least 6 weeks reproduced on at least two of the following: palpation of the lateral epicondyle, isometric testing of the wrist extensors, middle finger extension test, passive stretch of wrist extensors, resisted hand gripping using a dynamometer, and upper limb neurodynamic test with radial nerve bias (ULNDT-RN)). Exclusion criteria included history of surgery/fracture (past 2 years), history of neurological/radicular dysfunctions, steroid injection (preceding 6 weeks), contraindication to cold application, current use of antidepressants for > 12 weeks, and the presence of widespread arthritis.

Prior to commencing the study, each participant underwent a thorough clinical examination by an experienced musculoskeletal physiotherapist, to confirm eligibility. Participants were also required to complete the Adult Pre-exercise Screening System (APSS) tool [26] to ensure they were eligible for the aerobic exercise intervention. Participants were asked to abstain from taking pain medications 24 hours prior to testing and to avoid any additional physical treatment 3 days before and on the testing day. Written informed consent was obtained from all participants.

Curtin University Human Research Ethics Committee approved the study (HRE2017-0198-02). The study was also prospectively registered on 9/2/2017 with the Australia New Zealand Clinical Trials Registry (ACTRN12617000219381). Further, the study adheres to CONSORT guidelines (http://www.consort-statement.org/) for reporting clinical trials.

Procedure

After confirming eligibility, the PI tested all participants for PPT at the affected elbow and at a site just proximal to the wrist [24]. These PPT values were used as the baseline value for the initial aerobic exercise response (Baseline 1). Following initial baseline PPT measurement, the PI left the laboratory and the aerobic exercise session was conducted

under the supervision of a research assistant who had received training in the exercise protocol. Participants were allocated to receive either moderate (50% maximum heart rate (HRmax)) or high intensity (75% HRmax) aerobic exercise based on the randomisation schedule. Each participant completed two sessions, both at the same exercise intensity, three days apart. Following completion of the cycling exercise, the PI re-entered the laboratory and conducted either a CPM or a MIA assessment protocol (order randomised). In both cases, a second set of PPT measures (Baseline 2) were taken before the CPM or MIA intervention was applied. Additional PPT measures were then taken during and post the CPM and MIA protocols, as described below. All PPT assessments were performed by the PI, who remained blind to the experimental group assignment of each participant (Fig. 1).

Pain-related outcome measures

Pain-related measures of PPT, pain free grip (PFG) and ULNDT-RN were completed using previously reported methodology [24]. These were measured by an electronic digital algometer in kPa, an electronic digital dynamometer in N, and an M180 twin axis electrogoniometer in degrees, respectively. PFG and ULNDT-RN were used as secondary measures of the analgesic effect of the cervical lateral glide mobilisation. All measures were obtained in triplicate. Mean values were used in the analysis. PPT measures were assessed at wrist and elbow test sites.

CPM and MIA assessment protocols

CPM and MIA were assessed using the same protocols as reported in a previous publication [24]. Immersion in cold water (10 °C) was used as the conditioning stimulus for CPM and a cervical contralateral lateral glide mobilisation of the C5/6 motion segment was used to induce MIA. PPT was tested in the affected arm at baseline prior to, at 1 minute during, and at 1 minute post cold water immersion or cervical glide mobilisation, respectively. At each time point, PPT was measured three times. The mean value of the three measurements at each time point was used for analysis. The relative change in PPT at each test site from Baseline 2 to during and post cold water immersion and cervical mobilisation was considered as the CPM and MIA effects, respectively.

Tennis Elbow specific assessment

Before physical testing, all participants were asked to complete the Patient Rated Tennis Elbow Evaluation (PRTEE), which evaluates pain and function over the preceding week [27].

Physical activity assessment

Participants also completed the Global Physical Activity Questionnaire (GPAQ) [28] to evaluate their physical activity levels. The total GPAQ score was calculated using the GPAQ guidelines [28] and expressed as Metabolic Equivalents (MET)-minute/week. The GPAQ is a reliable measure of physical activity with moderate to strong concurrent validity [29].

Experimental conditions

The method described here is based on a study by Naugle et al. [30]. Participants completed both stationary cycling sessions at either high or moderate intensity (randomly allocated) for 15 minutes. The PI was not present in the laboratory at any time during the exercise sessions. Before starting the first session, a target heart rate (THR) was calculated for each participant by the research assistant, based on age-predicted maximum heart rate (HRmax), where maximum HR = 220-age [31]. THR for those in the high intensity group was determined using the formula HRmax × 0.75 and for the moderate intensity group it was calculated as HRmax × 0.50.

All participants completed their exercise sessions using a cycle ergometer (828E Ergometer, Monark, Vansbro, Sweden). Heart rate was monitored during exercise using a chest heart rate monitor (Monark Heart Rate Monitor, Monark Exercise AB). The targeted exercise intensity level was achieved through adjusting the speed and the resistance of the cycle

ergometer. Participants started the exercise session by cycling at low intensity (HR = 40% HRmax) for two minutes to familiarise themselves with their preferred cadence. The resistance was then gradually increased over the next three minutes (i.e. HR was elevated by an average of 10% and 3% per minute for high and moderate intensity exercise, respectively) to reach the desired target heart rate by the end of the first 5 minutes. Participants then continued cycling for the following 10 minutes, while maintaining the THR. Heart rate was continuously monitored to stay within a range of 10% above and 5% below the THR. Every five minutes during the cycling session participants were instructed to rate their perceived exertion (RPE) using the Borg-Scale (6–20) [32]. Heart rate (beats/minute) and workload (watts) were recorded every minute during the first five minutes and every 30 seconds and one minute, respectively, during the main exercise session. Mean RPE, HR and workload data collected during the 10 minutes of cycling at the THR were used for analysis.

Sample Size calculation

Sample size calculations were conducted using Stata/IC (version 15.0: StataCorp LLC, TX). Based on data from a large clinical trial comparing corticosteroid injections and physiotherapy management of tennis elbow [33] the minimal clinically important difference (MCID) in pressure pain threshold at the elbow was considered to be 88 kPa [34]. In determining our sample size, we used a more conservative difference value of 50 kPa (just above half of the MCID), as we expected that the influence of the aerobic exercise intervention assessed in this study would be more subtle than the influence of a corticosteroid injection, with a pooled standard deviation of 73.22 kPa resulting in an effect size difference of 0.68. An a priori power analysis (alpha = 0.05, beta = 0.80) indicated a required sample size of 68 (34 per group).

Statistical analysis

Data were analysed using Stata/IC (version 15.0: StataCorp LLC, TX). For all analyses, $P < 0.05$ was considered statistically significant. Descriptive statistics were based on frequency distributions for categorical data (gender and elbow tested) and means and standard deviations (SD) (age, PRTEE and RPE) or medians and interquartile ranges (IQR) for continuous data (duration of LE, GPAQ, HR, workload). Univariate group comparisons between intervention groups at baseline and during exercise sessions included χ^2 and Fisher exact tests for categorical comparisons, and independent t-tests or Mann-Whitney U tests for continuous outcomes, as appropriate.

All outcome data were evaluated for normality using Shapiro-Wilk tests and graphical review. Non-normally distributed data (PPT, PFG, ULNDT-RN) were transformed using natural logarithms.

Linear mixed models with random subject effects were used to evaluate differences (relative to baseline measures) between time points (all participants) and between exercise groups over time for CPM and MIA measures for all outcome variables (PPT, PFG and ULNDT-RN). The respective marginal means, 95% confidence intervals (CI), and p-values of these differences were calculated. The analysis was controlled for PRTEE, GPAQ and sex.

Partial correlations and univariate regression models were used to determine the relationships between exercise induced analgesia and CPM and MIA, measured both during and post cold water immersion / cervical mobilisation at both test sites. The strength of the correlations were interpreted according to the guidelines defined by Cohen [35]: (small: $0.10 \leq r \leq 0.29$; medium: $0.30 \leq r \leq 0.49$; large: $0.50 \leq r \leq 1.0$). Univariate regression models were used to calculate regression coefficients (B), and their 95% CI and p-values. The adjusted coefficients of determination (adj. R^2) were also calculated in order to determine the proportion of variability in CPM /MIA PPT (dependent variable) that was explained by post cycling PPT. Due to the anticipated between-individual variability in PPT, baseline PPT (Baseline 1) was identified as a potential confounder for the association and therefore it was adjusted for in the partial correlations and regression analyses.

3. Results

A total of 68 participants met the eligibility criteria and participated in the study. There were no drop outs and all volunteers were randomised, received the intended aerobic exercise interventions, completed the CPM and MIA assessment sessions, and were analysed with regards to outcomes (Fig. 2).

Table 1
Descriptive summaries for the research sample by intervention groups.

		Sample (N = 68)	Moderate intensity (n = 34)	High intensity (n = 34)	p
Gender *n (%)**	F	24 (35.29)	12 (35.29)	12 (35.29)	1.000
	M	44 (64.71)	22 (64.71)	22 (64.71)	
Elbow tested *n (%)**	L	29 (42.65)	15 (44.12)	14 (41.18)	1.000
	R	39 (57.35)	19 (55.88)	20 (58.82)	
Age *(year)*		46.47 (9.62)	45.80 (9.57)	47.14 (9.77)	0.571
Duration* *Median (IQR) (year)**		0.67 (0.42, 1.5)	0.58 (0.38, 2)	0.67 (0.50, 1.50)	0.551
PRTEE		37.68 (15.54)	37.59 (14.44)	37.78 (16.79)	0.960
GPAQ *Median (IQR)** *(MET-min/week)*		3090 (1650, 5740)	3090 (1660, 5760)	2960 (1440, 5720)	0.883
Level of significance p < 0.05 (Bold values indicate statistical significance)					
Data are presented as mean and standard deviation (SD) unless otherwise specified					
F: female, M: male, L: left, R: right, PRTEE: patients rated tennis elbow evaluation, GPAQ: general physical activity questionnaire, MET: metabolic equivalent. IQR: interquartile range, SD: standard deviation. *Level of significance, P < 0.05*					

Demographics

There were no significant differences between exercise groups ($p > 0.05$) in demographic characteristics and there were equal numbers of females and males in each aerobic exercise group (Table 1).

Exercise intensity measurements during cycling tasks

There were statistically significant differences in exercise intensity between the groups during the two cycling sessions (Table 2). As anticipated, the high intensity exercise group maintained significantly higher HR and workload, and reported significantly higher perceived exertion.

Table 2
Exercise intensity measurements for each exercise group during CPM and MIA assessment sessions.

Exercise descriptor	Moderate intensity (n = 34)	High intensity (n = 34)	*p*
CPM cycling			
HR	89.65 (85.9, 95.3)	134.75 (126, 144.2)	< 0.001
Workload	31.6 (21, 55.8)	112.6 (83.8, 158.7)	< 0.001
RPE (6–20)	9.68 (2.15)	13.29 (1.79)	< 0.001
MIA cycling			
HR	89.95 (84.8, 97.4)	134.65 (126.9, 140.9)	< 0.001
Workload	39.55 (59.2, 23.6)	104.45 (73.8, 154.7)	< 0.001
RPE (6–20)	10.26 (1.82)	13.34 (1.81)	< 0.001
Level of significance p < 0.05 (Bold values indicate statistical significance)			
Data summarised as median (IQR) (except RPE data summarised as mean (SD))			
HR: heart rate (beats/minute), workload (watt), RPE: rating of perceived exertion (Borg), IQR: interquartile range,			
SD: standard deviation.			

Between time points differences (all participants)

There was a significant ($p < 0.001$) increase in PPT measures for both exercise protocols and both CPM and MIA protocols at the wrist and elbow sites: from pre to post cycling, during CPM, during MIA; and immediately post both CPM and MIA (Table 3).

PFG and ULNDT-RN were used as secondary measures of the analgesic effect for the cervical lateral glide mobilisation. There was a significant ($p < 0.001$) increase in both PFG and ULNDT-RN from pre to post MIA (Table 3).

Table 3: Linear mixed regression models for CPM and MIA responses: between time points differences (all participants).

	Baseline 1 (pre-cycling)		Baseline 2 (pre CPM/MIA)		During CPM/MIA		Post CPM/MIA		Baseline 1 to Baseline 2 (EIA effect)	Baseline 1 to During CPM/ MIA	Baseline 1 to Post CPM/ MIA *pre-post MIA
	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*	*p*
CPM Wrist PPT	494.48	*463.60 - 527.42*	609.44	*571.38 - 650.04*	731.70	*686.00 - 780.44*	671.62	*629.68 - 716.36*	**<0.001**	**<0.001**	**<0.001**
CPM Elbow PPT	274.91	*255.48 - 295.83*	390.16	*362.58 - 419.83*	502.50	*466.98 - 540.73*	446.02	*414.49 - 479.95*	**<0.001**	**<0.001**	**<0.001**
MIA Wrist PPT	490.32	*458.38 - 524.48*	590.88	*552.39 - 632.05*	665.31	*621.97 - 711.66*	682.20	*637.76 - 729.73*	**<0.001**	**<0.001**	**<0.001**
MIA Elbow PPT	270.36	*248.64 - 293.97*	382.17	*351.47 - 415.54*	469.71	*431.99 - 510.74*	479.45	*440.94 - 521.32*	**<0.001**	**<0.001**	**<0.001**
PFG			216.72	*201.52 - 233.08*			255.71	*237.77 - 275.00*			**<0.001***
ULNDT-RN			13.27	*12.08 - 14.58*			20.16	*18.36 - 22.15*			**<0.001***

Level of significance p<0.05 (Bold values indicate statistical significance)
Mixed regression models for CPM and MIA predicted marginal means, adjusted for PRTEE, GPAQ and sex
CPM: conditioned pain modulation, MIA: manipulation induced analgesia, PPT: pressure pain threshold, PFG: pain free grip, ULNI limb neurodynamic test-radial nerve bias,
95%CI: 95% confidence interval.

Between-group differences over time (group x time interaction effect)

There were significant ($p < 0.001$) group x time interaction effects for PPT both at the elbow and the wrist sites during CPM, during MIA, post CPM and post MIA. Significantly higher PPT values were measured for the high intensity exercise group at both sites across all time-points (Table 4). There was a clear additive analgesic effect for both CPM and MIA after exercise. For example, for the high intensity group, the percentage increase in PPT at the elbow improved from 72.70% immediately following exercise to 125.50% during cold immersion, and to 119.60% during mobilisation. There was a significant group x time interaction effect for change in ULNDT-RN but this did not reach significance for PFG.

Table 4: Linear mixed regression models for CPM and MIA responses: between-group differences over time

Measurement	Exercise group	Baseline 1 (pre-cycling)		Baseline 2 (pre CPM/MIA)		During CPM/MIA		Post CPM/MIA		Baseline 1 to Baseline 2 (EIA effect)	Baseline 1 to During CPM/MIA	Baseline 1 to Post CPM/MIA (*pre-post MIA)
		Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*	*p*
CPM Wrist PPT	Moderate	508.02	*468.15 - 551.28*	544.29	*501.58 - 590.65*	629.67	*580.25 - 683.29*	579.15	*533.70 - 628.47*	**<0.001** (EIA)	**<0.001**	**<0.001**
	High	481.31	*443.54 - 522.30*	682.39	*628.83 - 740.50*	850.27	*783.55 - 922.69*	778.86	*717.74 - 845.19*			
CPM Elbow PPT	Moderate	286.16	*260.51 - 314.34*	340.80	*310.25 - 374.37*	433.97	*395.06 - 476.70*	378.63	*344.69 - 415.92*	**<0.001** (EIA)	**<0.001**	**<0.001**
	High	264.11	*240.43 - 290.12*	446.66	*406.61 - 490.64*	581.86	*529.70 - 639.16*	525.40	*478.30 - 577.14*			
MIA Wrist PPT	Moderate	498.29	*457.13 - 543.15*	541.02	*496.34 - 589.73*	571.79	*524.57 - 623.27*	578.57	*530.78 - 630.66*	**<0.001** (EIA)	**<0.001**	**<0.001**
	High	482.48	*442.63 - 525.92*	645.33	*592.03 - 703.43*	774.11	*710.18 - 843.81*	804.38	*737.95 - 876.80*			
MIA Elbow PPT	Moderate	271.23	*244.06 - 301.43*	325.75	*293.11 - 362.02*	387.81	*348.96 - 430.99*	392.90	*353.54 - 436.65*	**<0.001** (EIA)	**<0.001**	**<0.001**
	High	269.48	*242.49 - 299.49*	448.36	*403.44 - 498.28*	568.91	*511.91 - 632.25*	585.07	*526.45 - 650.21*			
PFG	Moderate			212.30	*191.71 - 235.11*			243.09	*219.51 - 269.21*			**0.052***
	High			221.24	*199.77 - 245.00*			268.99	*242.90 - 297.89*			
ULNDT-RN	Moderate			12.05	*10.67 - 13.63*			16.70	*14.77 - 18.88*			**<0.001***
	High			14.62	*12.93 - 16.52*			24.35	*21.54 - 27.53*			

Level of significance p<0.05 (Bold values indicate statistical significance)
Models for CPM and MIA predicted marginal means, adjusted for PRTEE, GPAQ and sex
CPM: conditioned pain modulation, MIA: manipulation induced analgesia, PPT: pressure pain threshold, PFG: pain free grip, ULNI
limb neurodynamic test- radial
nerve bias, 95%CI: 95% confidence interval.

Between-group differences over time (group x time interaction effect) controlling for Baseline 2

Controlling for differences in Baseline 2 data, there were significant ($p < 0.001$) group x time interaction effects for PPT at the wrist test site both during and post CPM and MIA (Table 5). While the differences between both groups for PPT at the

elbow region were significant post CPM (p = 0.016), during MIA (p = 0.037) and post MIA (p = 0.010), the difference was not significant during CPM (p = 0.335). The high intensity group demonstrated significantly higher levels of CPM and MIA analgesia at both test sites across all time points, except for PPT measured during CPM at the elbow region. When controlling for Baseline 2 in this analysis, the analgesic responses were more variable at the elbow compared to those at the wrist.

Table 5: Linear mixed regression models for CPM and MIA responses: between-group differences over time controlling for Baseline 2

	Exercise intensity group	Baseline 2 (pre CPM/MIA)		During CPM/MIA		Post CPM/MIA		Baseline 2 to During CPM/ MIA	Baseline 2 to Post CPM/ MIA *pre-post MIA
		Mean	*95%CI*	Mean	*95%CI*	Mean	*95%CI*	*p*	*p*
CPM Wrist PPT	Moderate	544.30	*502.32 - 589.79*	629.67	*581.10 - 682.29*	579.15	*534.48 - 627.55*	**<0.001**	**<0.001**
	High	682.38	*629.75 - 739.41*	850.27	*784.69 - 921.33*	778.86	*718.79 - 843.95*		
CPM Elbow PPT	Moderate	340.83	*310.58 - 374.02*	434.00	*395.49 - 476.26*	378.66	*345.06 - 415.54*	0.335	**0.016**
	High	446.62	*406.99 - 490.11*	581.82	*530.19 - 638.48*	525.36	*478.74 - 576.52*		
MIPM Wrist PPT	Moderate	541.02	*497.58 - 588.25*	571.79	*525.88 - 621.71*	578.57	*532.11 - 629.07*	**<0.001**	**<0.001**
	High	645.33	*593.52 - 701.67*	774.11	*711.97 - 841.70*	804.34	*739.80 - 874.61*		
MIPM Elbow PPT	Moderate	325.76	*294.68 - 360.13*	387.83	*350.81 - 428.75*	392.92	*355.42 - 434.37*	**0.037**	**0.010**
	High	448.34	*405.55 - 495.65*	568.89	*514.60 - 628.92*	585.05	*529.21 - 646.78*		
PFG	Moderate	212.30	*191.71 - 235.11*	-	-	243.09	*219.51 - 269.21*		0.520
	High	221.23	*199.77 - 245.00*	-	-	269.00	*242.90 - 297.89*	-	
ULNDT-RN	Moderate	12.05	*10.66 - 13.63*			16.70	*14.77 - 18.88*		**<0.001**
	High	14.62	*12.93 - 16.52*			24.35	*21.54 – 27.53*		

Level of significance, P<0.05 (Bold values indicate statistical significance)
Models for CPM and MIA predicted marginal means, adjusted for Baseline 2 (dropping Baseline 1), PRTEE, GPAQ and sex
CPM: conditioned pain modulation, MIA: manipulation induced analgesia, PPT: pressure pain threshold, PFG: pain free grip, ULNDT: upper limb neurodynamic test- radial nerve bias 95%CI: 95% confidence interval.

Correlation between post exercise PPT values and CPM

There were significant (p < 0.001) large, positive partial correlations between PPT values measured post aerobic exercise (exercise induced analgesia response) and PPT values during and post cold water immersion (CPM), with Pearson correlation coefficients (r) ranging between 0.90 and 0.93 (Table 6). The subsequent regression analyses, adjusting for baseline PPT, showed that post exercise PPT is a significant (p < 0.001) predictor of CPM-induced PPT at both test sites

during and post cold water immersion. The adjusted coefficient of determination (adj. R^2) values ranged between 0.92 and 0.95.

Table 6: Correlation between exercise PPT values and CPM: Partial correlations and regression models controlling for Baseline 1

^{EIA} PPT (time point) vs. ^{CPM} PPT (time point)	Partial correlation coefficient (r)	Regression coefficient B	Standard error (B)	95%CI (B)	Adjusted R^2	p (r)	p (B)	p (F-test)
^{EIA} PPT Wrist vs. ^{CPM}PPT Wrist During	0.90	0.70	0.04	0.62 - 0.79	0.94	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Elbow vs. ^{CPM} PPT Elbow During	0.92	0.88	0.05	0.79 - 0.98	0.92	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Wrist vs. ^{CPM} PPT Wrist Post	0.90	0.72	0.04	0.63 - 0.80	0.95	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Elbow vs. ^{CPM} PPT Elbow Post	0.93	0.86	0.04	0.77 - 0.94	0.93	**<0.001**	**<0.001**	**<0.001**

Level of significance, P<0.05 *(Bold values indicate statistical significance)*
CPM: conditioned pain modulation, MIA: manipulation induced analgesia, PPT: pressure pain threshold, 95%CI: 95% confidence interval.

Correlation between post exercise PPT values and MIA

The partial correlation and regression analyses for the association between PPT values measured post aerobic exercise and PPT measured during and post cervical mobilisation (MIA) are presented in Table 7. Significant ($p < 0.001$) large, positive partial correlations were seen between post exercise PPT and MIA analgesia measured during and post the cervical mobilisation (r values ranged between 0.68 and 0.86). The regression analyses, adjusting for baseline PPT, showed that post exercise PPT is a significant ($p < 0.001$) predictor of MIA-induced PPT, measured at both sites during and post mobilisation. The adjusted coefficient of determination (adj. R^2) values ranged between 0.73 and 0.93.

Table 7: Correlation between exercise PPT values and MIA: Partial correlations and regression models controlling for Baseline 1

^{EIA} PPT (time point) vs. ^{MIA} PPT (time point)	Partial correlation coefficient (r)	Regression coefficient B	Standard error (B)	95%CI (B)	Adjusted R^2 (adj. R^2)	p (r)	p (B)	p (F-test)
^{EIA} PPT Wrist vs. ^{MIA} PPT Wrist During	0.86	0.60	0.05	0.51 - 0.69	0.93	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Elbow vs. ^{MIA} PPT Elbow During	0.68	0.58	0.08	0.42 - 0.73	0.73	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Wrist vs. ^{MIA} PPT Wrist Post	0.86	0.59	0.04	0.51 - 0.68	0.93	**<0.001**	**<0.001**	**<0.001**
^{EIA} PPT Elbow vs. ^{MIA} PPT Elbow Post	0.86	0.75	0.05	0.64 - 0.85	0.89	**<0.001**	**<0.001**	**<0.001**

Level of significance, P<0.05 *(Bold values indicate statistical significance)*
CPM: conditioned pain modulation, MIA: manipulation induced analgesia, PPT: pressure pain threshold, 95%CI: 95% confidence interval.

4. Discussion

This study showed that participants with LE showed a significant CPM and MIA response immediately following both moderate and high intensity aerobic exercise. Higher levels of analgesia, as indicated by a greater increase in PPT measures, were seen for the high intensity aerobic exercise group at each time-point, suggesting an additive effect with higher exercise dosage. The study also showed that post exercise PPT was significantly correlated with the analgesic response induced by both CPM and MIA.

The finding of a strong positive correlation between MIA and PPT post exercise in individuals with LE has not been previously reported. However, this effect is in agreement with recent findings in pain-free individuals [18, 19]. Although CPM analgesia has previously been found to predict exercise analgesia [19, 36, 37], our study appears to be the first to use aerobic exercise induced analgesia response as a predictor of both CPM and MIA analgesia. This implies that participants who exhibited greater changes in PPT post exercise demonstrated greater analgesia during and post CPM and MIA.

Significantly stronger CPM and MIA effects were induced in the current study after high intensity exercise compared with moderate intensity exercise, suggesting a greater additive effect of exercise on CPM and MIA when the exercise is more strenuous. Previous research, using a similar protocol, has also demonstrated that CPM and MIA can be enhanced when they are preceded by a period of positive, supportive therapeutic interaction, suggesting that the nature and structure of the treatment session can influence the level of analgesia perceived by patients [25]. This supports the combination of exercise and manual therapy treatments to manage musculoskeletal pain.

The comparable multi-segmental pain modulatory effects of cold water immersion and joint mobilisation suggest a potential overlap in the neurophysiological mechanisms responsible for these effects. Serotonin is a key neurotransmitter for both CPM [1], and MIA [2]. Administration of naloxone (an opioid antagonist) has been shown not to reverse the analgesia induced by CPM [6–8] or MIA [2, 9–11], suggesting a non-opioid analgesic mechanism. However, other studies

have reported that naloxone did reverse the analgesia induced by CPM [3–5], suggesting a possible role for the endogenous opioid system.

There are some limitations of this study. The intensity of aerobic cycling sessions was not assessed using a laboratory fitness test (such as VO_2max) but was estimated using an age-predicted HRmax calculation. In addition, the study only measured the immediate effects of a single session of aerobic exercise on CPM and MIA. Therefore, there is uncertainty about whether similar results would be demonstrated over longer follow-up.

5. Conclusion

The study demonstrated that high intensity aerobic exercise enhanced CPM and MIA responses in people with LE. Further, the exercise induced analgesia response was significantly correlated with CPM and MIA responses in this group and the level of exercise induced analgesia response was predictive of the subsequent level of both CPM and MIA response. This suggests that there may be an overlap in the neurophysiological mechanisms mediating CPM and MIA.

List Of Abbreviations

Adj.R2 The adjusted coefficient of determination

APSS Adult Pre-exercise Screening System

CI Confidence Interval

CPM Conditioned Pain Modulation

GPAQ Global Physical Activity Questionnaire

HRmax Maximal Heart Rate

IQR Interquartile Range

LE Lateral Epicondylalgia

MCID Minimal Clinically Important Difference

MET Metabolic Equivalent

MIA Manipulation Induced Analgesia

PFG Pain Free Grip

PI Primary Investigator

PPT Pressure Pain Thresholds

PRTEE Patient Rated Tennis Elbow Evaluation

RPE Rating of Perceived Exertion

SD Standard Deviation

THR Target Heart Rate

ULNDT-RN Upper Limb Neurodynamic Test with Radial Nerve bias

Declarations

Ethics approval

Curtin University Human Research Ethics Committee (HREC) approved the study on 12/07/2017.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding

Competing interests

The authors have no competing interests.

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Authors' contributions

This research was part of a thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD). AM was a PhD candidate who was responsible for the conception and design, data collection and analysis, interpretation of data and drafting the manuscript. AW and PM contributed to conception and design, supervised the project, interpretation of the data, reviewed and edited the manuscript. WG, BW and SS contributed to conception and design and reviewed and edited the manuscript. AJ reviewed the data, contributed to data analysis, and reviewed and edited the manuscript. All authors read and approved the manuscript.

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Figures

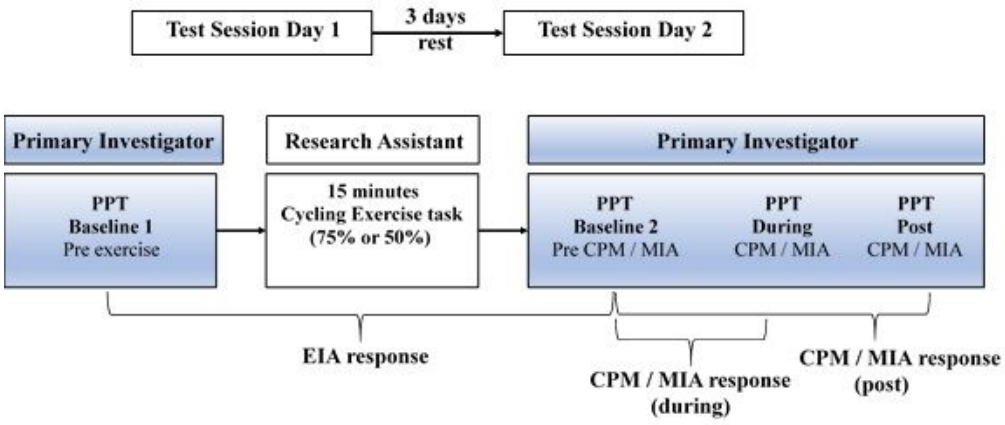

Figure 1

Testing session with inhibitory assessment protocols. PPT: pressure pain threshold, CPM: conditioned pain modulation, MIA: manipulation induced analgesia, EIA: exercise induced analgesia

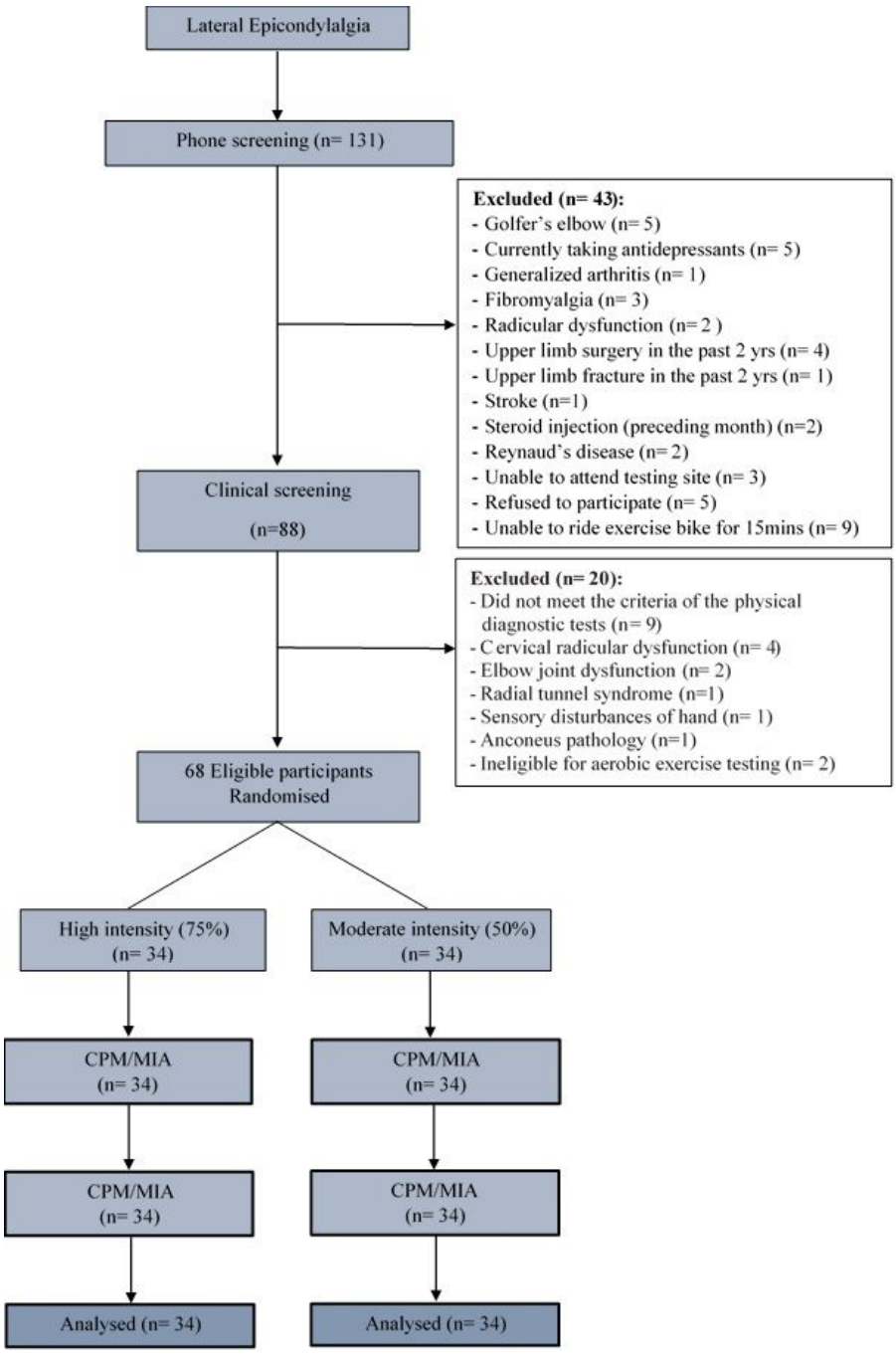

Figure 2

Consort diagram illustrating overall experimental procedure. CPM: Conditioned Pain Modulation, MIA: Manipulation Induced Analgesia

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