

12-2017

Effects of Lower Extremity Aerobic Exercise and Conditioned Pain Modulation on Evoked Shoulder Pain

Logan Lumpkins

East Tennessee State University

Craig Wassinger

East Tennessee State University

Follow this and additional works at: <https://dc.etsu.edu/honors>

 Part of the [Anesthesia and Analgesia Commons](#), [Kinesiotherapy Commons](#), [Movement and Mind-Body Therapies Commons](#), [Musculoskeletal System Commons](#), [Nervous System Commons](#), [Physical Therapy Commons](#), [Physiotherapy Commons](#), and the [Therapeutics Commons](#)

Recommended Citation

Lumpkins, Logan and Wassinger, Craig, "Effects of Lower Extremity Aerobic Exercise and Conditioned Pain Modulation on Evoked Shoulder Pain" (2017). *Undergraduate Honors Theses*. Paper 434. <https://dc.etsu.edu/honors/434>

This Honors Thesis - Open Access is brought to you for free and open access by the Student Works at Digital Commons @ East Tennessee State University. It has been accepted for inclusion in Undergraduate Honors Theses by an authorized administrator of Digital Commons @ East Tennessee State University. For more information, please contact digilib@etsu.edu.

**EFFECTS OF LOWER EXTREMITY AEROBIC EXERCISE AND CONDITIONED PAIN
MODULATION ON EVOKED SHOULDER PAIN**

Thesis submitted in partial fulfillment of Honors

By

Logan Lumpkins
The Honors College
Midway Honors Scholar Program
East Tennessee State University

December 1, 2017

Craig Wassinger, PT, Ph. D, Faculty Mentor

Michael Bourassa, PT, DPT, OCS, FAAOMPT,
Faculty Reader

Beatrice Owens, PT, Ph. D, CHT, Faculty Reader

ORIGINAL RESEARCH
EFFECTS OF LOWER EXTREMITY AEROBIC EXERCISE
AND CONDITIONED PAIN MODULATION ON EVOKED
SHOULDER PAIN

Logan Lumpkins

Craig A. Wassinger, PT, Ph. D

ABSTRACT

Background: Emerging evidence suggests that aerobic exercise and conditioned pain modulation may be advocated in treating patients with musculoskeletal pain. The effects of lower extremity aerobic exercise and conditioned pain modulation on evoked shoulder pain are not known.

Purpose: To determine the acute effects of lower extremity aerobic exercise and conditioned pain modulation on outcomes of evoked shoulder pain from pain pressure threshold measurements.

Study Design: Repeated measures.

Methods: Thirty (30) healthy volunteers were tested over the course of two sessions. Session 1 consisted of collecting pain pressure threshold measurements over the infraspinatus before and immediately following a conditioned pain modulation with cool water. Session 2 consisted of collecting pain pressure threshold measurements over the infraspinatus before and immediately following a bout of lower extremity aerobic exercise on a recumbent stepper apparatus.

Results: Pain pressure threshold was not significantly influenced by the conditioned pain modulation using cool water ($p=0.725$). Pain pressure threshold was significantly increased immediately following the lower extremity exercise session ($P<0.001$).

Conclusion: Conditioned pain modulation with cool water did not produce any significant changes in pain pressure threshold. Lower extremity aerobic exercise acutely increased pain pressure threshold in participants with experimentally induced shoulder pain. Physical therapists may consider lower extremity aerobic exercise to produce short-term hypoalgesic effects and facilitate the application of more active interventions.

Department of Physical Therapy, East Tennessee State University, Johnson City, TN

This study was approved by the Institutional Review Board at East Tennessee State University on 01/12/2017

Financial Disclosure and Conflict of Interest: The authors of this manuscript affirm that we have no financial affiliation (including research funding) or involvement with any commercial organization that has a direct financial interest in an attachment and cited in the manuscript. Any other conflict of interest (i.e., personal associations or involvement as a director, officer, or expert witness) is also disclosed in an attachment.

CORRESPONDING AUTHOR

Craig Wassinger, PT, PhD

Associate Professor

Department of Physical Therapy

East Tennessee State University

216 Charles Allen Hall PO Box 70624

Johnson City, TN 37614

Phone: 1-423-439-8295

Fax: 1-423-439-8077

Email: wassinger@etsu.edu

INTRODUCTION

Shoulder pain is among the most common pain complaints with point prevalence rates ranging from 6.9 to 26% and life-time prevalence rates ranging from 6.7 to 66.7% in the general population.¹ Given this, physical therapists have adopted several interventions directed toward reducing patients' complaints of shoulder pain. These interventions include but are not limited to: shoulder specific exercises, variations of manual therapy, joint mobilization, electrical and thermal modalities and kinesiотaping.^{2,3,4,5} Despite these established interventions, numerous studies have demonstrated the urgency for further research regarding shoulder pain reduction.^{6,7,8,9,10} It is suggested from these studies that an estimated 20 to 41% of patients who sought treatment from a physical therapist or primary care physician for their shoulder complaints were still experiencing pain at one to seven years following initial treatment.^{6,7,8,9,10} It is evident there is a need for alternative treatments regarding shoulder complaints.

Conditioned pain paradigms are typically used to assess the function of endogenous pain inhibitory pathways in humans.¹¹ In this technique, a painful test stimulus is evaluated in the absence and in the presence of a second conditioning painful stimulus applied to a remote region of the body.^{11,12} The primary purpose of this technique is not to inhibit pain

by applying another pain, but to analyze the body's ability to inhibit pain.^{11,12} In a normal functioning nociceptive system, the amount of pain experienced with the primary test stimulus will be reduced during presentation of the secondary stimulus.¹¹ In a recent study, a conditioned pain paradigm utilizing cool water was noted to cause a multi-segmental increase in pain threshold.^{13,14} It is therefore postulated that conditioned pain modulation may be advocated in treating shoulder pain.^{13,14}

In addition, numerous studies have indicated that aerobic exercise is associated with alterations in pain perception.^{15,16,17} This phenomenon has been termed exercise-induced hypoalgesia. In general, investigators have typically found diminished pain perception, or hypoalgesia, to occur during and following aerobic exercise.^{15,16} Emerging evidence from a recent meta-analytic review of exercise-induced hypoalgesia suggests that exercise of non-painful muscles for individuals with regional chronic pain conditions produces a hypoalgesic effect and may be considered an effective method to temporarily relieve pain in painful muscles;¹⁷ however, to our knowledge, the concept of aerobic exercise-induced hypoalgesia has never been explored at the shoulder.

Therefore, the aim of this investigation is to determine the impact of conditioned pain modulation with cool water and lower extremity

aerobic exercise on evoked shoulder pain in healthy adults using pain pressure threshold measures. It is hypothesized that participants will exhibit significant changes in pain perception following the conditioned pain modulation and the lower extremity aerobic exercise protocol. Outcomes of this study may help provide better understanding of conditioned pain modulation, exercise-induced hypoalgesia, and their clinical applications.

METHODS

Participants and Screening

A sample of convenience consisting of 30 healthy volunteers (20 females, 10 males) participated in this study. Participants between the ages of 18 and 30 were exclusively recruited for this study. This age group was specifically chosen to decrease the prospect of age-related degeneration of the infraspinatus and its surrounding muscles.¹⁸ Participants were considered healthy using the following criteria: denied any history of seeking medical care for shoulder or neck injuries and reported no current (within the past 6 months) shoulder or neck pain. Exclusion criteria consisted of prior shoulder surgery or fracture and inability to tolerate one minute of cool water hand immersion or performing lower extremity aerobic exercise at a moderate intensity. Participants were also excluded if they were

currently seeking treatment for any other musculoskeletal disorder. Participants who met the inclusion criteria were provided with a detailed description of the procedures, excluding the principle objectives of the study, and were instructed to wear athletic shoes, shorts, and a sleeveless shirt to each testing session. Participants were instructed to complete an individual information form which included the most recent measurements of their height and weight and their hand dominance.

All testing was completed in a university research laboratory. All procedures were approved by the Institutional Review Board at East Tennessee State University, and all participants provided written informed consent to participate.

Study Design

A repeated measures design was utilized in this study with two testing sessions occurring over the course of two days (Fig. 1). The first testing session consisted of baseline outcome measures of participants' pain pressure threshold, a fifteen-minute rest interval, one-minute of conditioned pain modulation using cool water, and a reassessment of participants' pain pressure threshold. Participants returned for the second day of testing 24–48 hours following the first session. Participants were instructed to refrain

from performing any upper body exercises between testing sessions and from participating in aerobic exercise immediately before the testing sessions as it may influence subsequent data.¹⁷ The second testing session consisted of baseline outcome measures of participants' pain pressure threshold, a fifteen-minute lower extremity aerobic exercise protocol, and a reassessment of participants' pain pressure threshold. Participants' final heart rate and rating of perceived exertion were also evaluated immediately following the exercise protocol.

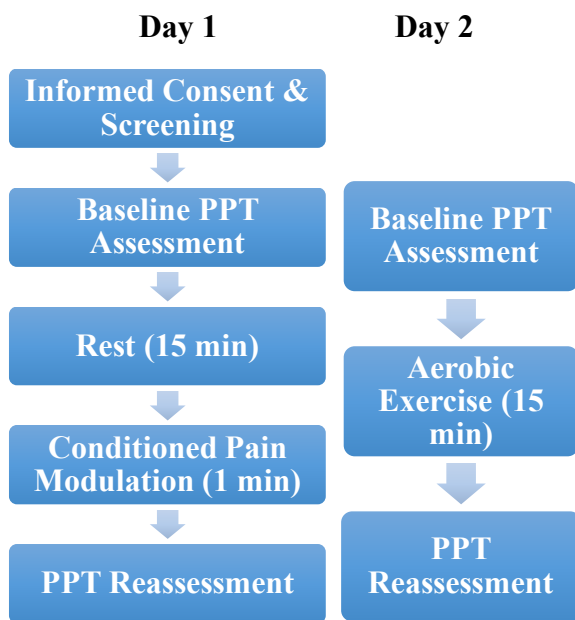


Figure 1: Participant testing outline

Pain Pressure Testing

Pain pressure threshold (PPT) is the minimal amount of force required for the sense of pressure to change to pain.¹⁹ A hand-held digital algometer (Wagner, Pain Test FP Algometer,

Greenwich, CT) with a 1 cm² blunt tip was used for testing. Pain pressure threshold was analyzed over the infraspinatus muscle belly with the participant in prone in the anatomical position. Testing occurred bilaterally as means to determine the systemic effects of the interventions. The infraspinatus muscle belly was located by palpation inferior to the approximate midpoint of the scapular spine (Fig. 2). When the participant perceived the vertical force as pain, the algometer was removed and the peak force was recorded. Standardized procedures for use of the pressure algometer were performed by the same investigator for all measures, with the average of three measurements used for analysis (Nussbaum and Downes, 1998). The time between pain pressure threshold measures was 30 seconds. Training on pain pressure threshold measurement procedures was performed prior to commencement of the study.



Figure 2: Participant position during PPT testing

Conditioned Pain Modulation

On Day 1 of testing, conditioned pain modulation was administered to all participants following baseline pain pressure threshold measurements. Procedures were administered following the recommendations of Yarnitsky et al.²⁰ The conditioned pain modulation was performed with the participant in prone in the anatomical position while immersing their non-dominant hand in a vessel of cool water at 0–7°C. The participant immersed their hand approximately 5 cm above the wrist for 1 minute. After 1 minute, the participant's hand was removed from the vessel. Pain pressure threshold of the infraspinatus on the participant's non-dominant side was measured

immediately following hand immersion in cool water.

Aerobic Exercise Protocol

On Day 2 of testing, all participants performed an aerobic exercise protocol following baseline pain pressure threshold measures on their dominant side for the duration of fifteen-minutes. This aerobic exercise protocol was completed on a recumbent stepper apparatus (NuStep TRS 400 Recumbent Cross Trainer). See figure 3 for details. Participants self-selected a “somewhat hard” intensity using the Borg Scale and were instructed to keep this intensity for the duration of the exercise protocol (Fig. 4). The level of intensity was controlled by adjusting the amount of weighted resistance applied to the foot pedals. Participants were instructed to refrain from engaging the handles by placing their hands in their lap as this exercise protocol was designed to solely target their lower extremities. Final heart rate, rating of perceived exertion, and pain pressure threshold of the infraspinatus on participants' arm-dominant side was measured immediately following the aerobic exercise protocol.

Figure 3: NuStep Recumbent Cross Trainer



Figure 4: Borg Scale

6	No exertion
7	
8	
9	
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	
20	Maximal exertion

Data Analysis

Two distinct analyses were performed in this study. The first analysis aimed to determine the

role of cool water on pain perception compared to a control condition. The second analysis utilized paired t-tests to evaluate the role of lower extremity aerobic exercise on PPT. In this analysis, the PPT was measured before and immediately following the lower extremity exercise. For both analyses, paired t-tests were performed comparing the control PPT measures to either the PPT following during the cool water immersion or following the lower extremity exercise. Significance was set at $p < 0.05$ *a priori*.

Effect size and relationship to minimal clinically important differences (MCID) were calculated for significant group differences. Effect sizes (ES) were also calculated using the effect size index [(pre-intervention score – post-intervention score) / standard deviation pre-intervention score]. Further, individual changes in PPT were compared to the minimal clinically important difference previously described.²⁴

RESULTS

Thirty healthy participants (20 females, 10 males) met the inclusion criteria and completed the study protocol. Participants were between the ages of 18 and 23 years (means age 20.6 years). See table 1 for details.

Table 1: Demographic Data

Participants		Age (yrs)	Mass (kg)	Height (cm)	Right Dominant
Males	10	19.9 ± 1.89	79.7 ± 12.8	179.6 ± 5.56	10
Females	20	20.9 ± 1.77	61.6 ± 23.5	165.7 ± 9.05	16
Total	30	20.6 ± 1.59	67.1 ± 4.2	170.4 ± 10.7	26

Values are expressed as mean ± standard deviation.

Pain pressure threshold was not significantly influenced by the cool water immersion (p=0.725). See Table 2 for details.

Table 2: Results of Conditioned Pain Modulation Using Cool Water

	Baseline PPT (kg)	Post CPM PPT (kg)
Male	8.1	8.0
Female	5.1	5.0
Total	6.1	6.0

Participants rate their rate of perceived exertion (RPE) with an average of 13.3/20. The target for this exercise was 13/20. The final heart rate at the end of the exercise session was 120.6 beats per minutes (bpm). This represents approximately 60% of the participants age-predicted maximum heart rate. Pain pressure threshold was significantly increased (indicating decreased pain perception) immediately

following the lower extremity exercise session (P<0.001). See Table 3 for details.

The effect, measured by effect size, of the lower extremity exercise was 0.32 with a 95% confidence interval of -0.20 to 0.82.

Furthermore, 14/30 participants reported changes which exceeded the MCID (minimal clinically important difference) for pain pressure threshold.²⁴

Table 3: Results of Lower Extremity Aerobic Exercise

	Final RPE	Final Heart Rate (bpm)	Baseline PPT (kg)	Post Exercise PPT (kg)
Male	13.0 ± 2.3	121.0 ± 26.5	7.1	7.9 *
Female	13.4 ± 2.4	120.4 ± 23.2	5.4	6.2 *
Total	13.3 ± 2.4	120.6 ± 24.3	6.0	6.8 *

DISCUSSION

The aim of this investigation was to examine the acute influence of lower extremity aerobic exercise and conditioned pain modulation using cool water on evoked shoulder pain. This study measured the acute effects of conditioned pain modulation using cool water and a bout of lower extremity aerobic exercise by pain pressure threshold measurements. A unique aspect of this study was that the pain pressure threshold measurements immediately following the aerobic exercise protocol and cool water

immersion were obtained over the infraspinatus muscle belly, in contrast to similar studies where pain pressure threshold measurements were obtained at various areas such as the finger, hand, back, leg, or foot.^{13,17,21,22,23} Measurements were employed at this site in order to examine the immediate impact lower extremity aerobic exercise and conditioned pain modulation using cool water have on the shoulder muscles. Results indicated that pain pressure threshold measurements at the infraspinatus were significantly altered following a bout of lower extremity aerobic exercise, but did not significantly change following cool water immersion.

Pain pressure threshold measures were found to improve immediately following lower extremity aerobic exercise. These findings indicate lower extremity aerobic exercise has an immediate systemic hypoalgesic effect on shoulder pain evoked by pain pressure threshold measurements in healthy individuals. The increase in pain threshold was approximately 13% with small to moderate effect sizes near 0.32. Increases in pain pressure threshold greater than 15% have been reported to be clinically meaningful.²⁴ Thus, both statistical and clinically significant changes in pain pressure threshold were noted for 47% of the demographic immediately following the bout of

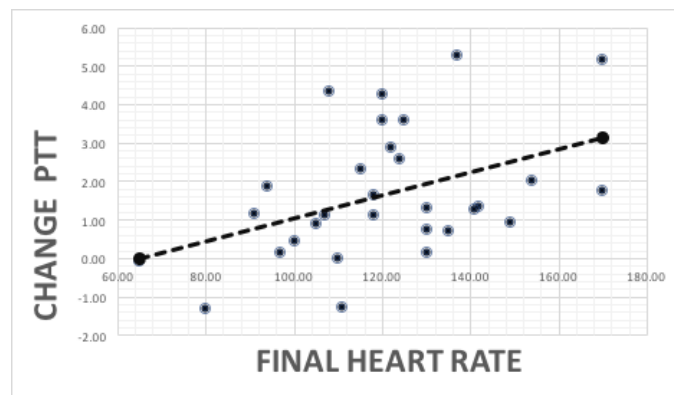
lower extremity aerobic exercise performed in this study. Thus, lower extremity aerobic exercise at moderate intensity (approximately 60% of HR_{max}) was associated with higher pain pressure threshold at the infraspinatus and ultimately decreased pain perception following exercise. Therefore, the results of this study indicate and suggest that a single bout of moderate intensity lower extremity exercise may serve as an appropriate intervention or “warm-up” for patients suffering with shoulder pain, as it may increase patients’ pain tolerance and allow for more aggressive participation in a standard multimodal treatment approach.

The increased pain pressure threshold findings following aerobic exercise are in accordance with conclusions from recent systematic and meta-analytic reviews regarding exercise-induced hypoalgesia.^{17,25} However, as previously noted, this is the first study to analyze the immediate effects of aerobic exercise on evoked shoulder pain; therefore, direct comparisons are difficult. Numerous studies have been conducted examining whether pain perception is altered during and following aerobic exercise, and several review articles have been published regarding this topic.^{17,25,26,27,28} These studies have included a variety of population criteria, aerobic exercise modalities, prescribed intensities, as well as a

variety of pain induction techniques and measurement procedures.^{17,25,26,27,28} In line with this study, it has been shown in previous investigations that aerobic exercise reduces perception of experimentally evoked pain in healthy participants, with effect sizes ranging from moderate to large depending on pain induction technique and exercise protocol.^{17,25} It has also been suggested from previous studies that the magnitude and direction of the effect sizes of aerobic exercise-induced hypoalgesia were highly variable and appeared to depend on the intensity of the aerobic exercise.^{17,25} Naugle et al.¹⁷ noted the largest effect sizes when assessing pain perception in healthy individuals were found when aerobic exercise was performed at a high intensity (ie, 75% of maximal oxygen uptake [VO_{2max}]; 70–80% of maximal heart rate [HR_{max}]) and relatively longer duration (>10 minutes). Naugle et al.¹⁷ further hypothesized that there may be a dose-response relationship between the intensity and duration of exercise and its hypoalgesic effect. A similar dose-response relationship between aerobic exercise intensity and its hypoalgesic effect in healthy individuals is evident within this study and can be seen in Fig. 5 when comparing participants' final heart rate and change in pain pressure threshold. The results from the present study suggest that exercise-induced hypoalgesia in a healthy population

with evoked shoulder pain may only be elicited in response to moderate-to-high intensity aerobic exercise, with the higher intensity values generating a greater reduction in pain perception.

Figure 5 – Dose Response Relationship



In addition to the aforementioned studies, several investigations have been conducted examining the effects of aerobic exercise in chronic pain populations, and exercise-induced hypoalgesia has been exhibited in a number of these studies; however, the effect sizes for pain threshold and intensity measures were highly variable.^{17,25} It was postulated by investigators that this was due in part to the various types of chronic pain conditions being assessed and the intensity in which the exercise was prescribed.^{17,25} For example, several studies indicated that vigorous aerobic exercise had a moderate-to-large hyperalgesic effect, exacerbating pain levels, on experimentally

evoked pain in participants with fibromyalgia;^{29,30,31} whereas, aerobic exercise performed at a prescribed moderate intensity elicited exercise-induced hypoalgesia with large-to-moderate effects in participants with fibromyalgia.²³ These results have led investigators to believe that exercise-induced hypoalgesia in chronic pain populations may only be elicited in response to low-to-moderate intensity aerobic exercise, which is in contrast to the results for healthy adults.¹⁷ However, further research is needed to confirm this hypothesis.

Although the causal mechanisms underlying the positive effect of lower extremity aerobic exercise were not addressed directly in this study, some discussion is warranted. Perhaps the most widely considered mechanism for exercise-induced hypoalgesia is that exercise creates an internal stimulus causing activation of descending inhibitory pain systems such as autonomic and endogenous opioid systems which reduce pain perception during and following exercise.^{17,32} It has been noted that exercise of sufficient intensity and duration results in the release of opioids, beta-endorphins, norepinephrine, and serotonin, which have been associated with changes in pain sensitivity.^{17,32} However, the conflicting evidence surrounding the causal mechanisms of

exercise-induced hypoalgesia suggest it is a result of a combination of varying factors.

This study also measured the acute effects of conditioned pain modulation on measure of pain pressure threshold. Pain pressure threshold measurements did not increase immediately following conditioned pain modulation with cool water. This finding was unexpected as previous investigations have suggested that the effect of conditioned pain modulation is comparable to exercise-induced hypoalgesia and that conditioned pain modulation can be utilized to predict exercise-induced hypoalgesic effects in healthy adults.^{13,33} Conditioned pain modulation has been investigated extensively in healthy volunteers over the past several decades. Currently, there is considerable interest in the science and conduct of conditioned pain modulation testing as there is a growing body of evidence suggesting that conditioned pain modulation may be an important biomarker of chronic pain and a predictor of treatment response.³⁴ Numerous investigations have been conducted examining changes in pain perception during, as well as following, variations of conditioned pain modulation, and several systematic reviews have been published concerning this phenomenon.^{33,35,36} It has been indicated from these studies that conditioned pain modulation utilizing cool water has the

potential to significantly reduce pain pressure thresholds at various measurement sites in both healthy and chronic pain populations;^{37,38,39,40,41} however, it has been shown that the hypoalgesic effect is dependent upon the temperature and duration of the conditioning stimulus.⁴² Therefore, it is postulated that the temperature and duration parameters of the current study were insufficient to elicit a hypoalgesic response. Furthermore, it has been indicated that there are a variety of psychological factors which may influence the results of conditioned pain modulation; these include but are not limited to: pain catastrophizing beliefs, analgesia expectation, depression, distraction, and impaired sleep.^{43,44,45,46,47} Therefore, it is possible any number or combination of these variables may have influenced study outcomes.

Although the causal mechanisms underlying the hypoalgesic effects of conditioned pain modulation were not addressed directly in this study, some discussion is warranted. The most prominent theory behind this “pain inhibits pain” phenomenon is the activation of “diffuse noxious inhibitory controls” (DNIC) – a spino-bulbo-spinal loop leading to an inhibition of wide-dynamic-range neurons in the spinal cord dorsal horn.^{12,48,49,50} It has also been postulated that activation of the descending pain-

modulating system may contribute to this phenomenon.^{12,49}

Limitations

There are some limitations to this study which should be noted. First, the sample was selected based on convenience and was further limited to young and healthy volunteers with evoked shoulder pain. The response of shoulder patients of various conditions, and preexisting higher pain levels, may differ from the outcomes reported in this experiment. However, aerobic exercise at low-to-moderate intensity has been noted to activate the endogenous opioid system and produce hypoalgesic effects in a chronic pain population with fibromyalgia.²³ Furthermore, the sample size used in this study was relatively small, which inadvertently decreases the statistical power of the results and increases the study’s margin of error.⁵¹ Moreover, evoked pain from activity or exercise may differ from pain pressure threshold measurements. Lastly, only the acute effects of the aerobic exercise protocol were evaluated. Observing the duration of these hypoalgesic effects was beyond the scope of this study but is a topic which needs to be explored in future studies.

CONCLUSIONS

This study demonstrated significant acute pain reduction in healthy participants with pressure induced shoulder pain following a bout of lower extremity aerobic exercise. Both statistical and clinically significant changes in pain pressure threshold were noted for 47% of the demographic immediately following the exercise bout. No significant changes in pain pressure threshold were indicated following conditioned pain modulation using cool water. Further research is needed to determine if the use of moderate intensity lower extremity exercise may be considered an appropriate intervention by physical therapists for treating patients with painful shoulder conditions, where such treatments are otherwise contraindicated.

REFERENCES

1. Luime JJ, Koes BW, Hendrikson IJM, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. *Scandinavian Journal of Rheumatology*. 2004;33(2):73-81.
2. Green S, Buchbinder R, Hetrick SE. Physiotherapy interventions for shoulder pain (Review). *Cochrane Database System Review* 2003;2.
3. Sluka KA. *Mechanisms and management of pain for the physical therapist*. Lippincott Williams & Wilkins. 2016.
4. Wassinger CA, Rich D, Cameron N, et al. Cervical & thoracic manipulations: acute effects upon pain pressure threshold and self-reported pain in experimentally induced shoulder pain. *Manual therapy*. 2016;21:227-232.
5. Kneeshaw D. Shoulder taping in the clinical setting. *Journal of bodywork and movement therapies*. 2002;6(1)2-8.
6. Bjornholdt KT, Brandsborg B, Soballe K, et al. Persistent pain is common 1-2 years after shoulder replacement. *Acta Orthopaedica*. 2015;86(1):71-77.
7. Valkering KP, Stokman RD, Bilsma TS, et al. Prevalence of symptomatic rotator cuff ruptures after shoulder trauma: a prospective cohort study. *European Journal of Emergency Medicine*. 2014;21(5):349-353.
8. Dawson J, Fitzpatrick R, Carr A. Questionnaire on the perceptions of patients about shoulder surgery. *British Editorial Society of Bone and Joint Surgery*. 1996;78(4):593-600.
9. Bokor DJ, Hawkins RJ, Huckell GH, et al. Results of nonoperative management of full-thickness tears of the rotator cuff. *Clinical Orthopaedics & Related Research*. 1993;Sep(294):103-110.
10. van der Windt DA, Koes B, Boeke AJ, et al. Shoulder disorders in general practice: prognostic indicators of outcome. *British Journal of General Practice*. 1996;46(410):519-523.
11. Lewis GN, Luke H, Rice DA, Rome K. Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Research and Management*. 2012;17(2):98-102.
12. Sprenger C, Bingel U, Büchel C. Treating pain with pain: supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimuli. *Pain*. 2011;152(2):428-439.
13. Vaegter HB, Handberg G, Graven-Nielson T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain*. 2014;155(1):155-167.

14. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Current Opinion in Anesthesiology*. 2010;23(5):611-615.
15. Koltyn KF, Garvin AW, Gardiner RL, et al. Perception of pain following aerobic exercise. *Medicine & Science in Sports & Exercise*. 1996;28(11):1418-1421.
16. Koltyn KF, Umeda M. Exercise, Hypoalgesia and Blood Pressure. *Sports Medicine*. 2006;36(3):207-214.
17. Naugle KM, Fillingim RB, Riley JL. A meta-analytic review of the hypoalgesic effects of exercise. *The Journal of Pain*. 2012;13(12):1139-1150.
18. Milogram C, Schaffler M, Gilbert S, et al. Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. *The Journal of Bone and Joint Surgery*. 1995;77(2):296-298.
19. Nussbaum EL, Downes L. Reliability of clinical pressure-pain algometric measurements obtained on consecutive days. *Physical Therapy*. 1998;78(2):160-169.
20. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. *European Journal of Pain*. 2014;19(6):805-806.
21. Cook DB, Stegner AJ, Ellingson LD. Exercise alters pain sensitivity in Gulf War veterans with chronic musculoskeletal pain. *The Journal of Pain*. 2010;11(8):764-772.
22. Meeus M, Roussel N, Truijten S, et al. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: An experimental study. *Journal of Rehabilitation Medicine*. 2010;42(9):884-890.
23. Newcomb LW, Koltyn K, Morgan WP, et al. Influence of preferred versus prescribed exercise on pain in fibromyalgia. *Medicine and Science in Sports and Exercise*. 2011;43(6):1106-1113.
24. Chesterton LS, Sim J, Wright CC, Foster NE. Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *The Clinical Journal of Pain*. 2007;23(9):760-766.
25. Koltyn KF. Exercise-Induced Hypoalgesia and Intensity of Exercise. *Sports Medicine*. 2002; 32(8):477-487.
26. Koltyn KF. Analgesia Following Exercise. *Sports Medicine*. 2000;29(2):85-98.
27. Janal MN. Pain sensitivity, exercise and stoicism. *Journal of the Royal Society of Medicine*. 1996;89(7):376-381.

28. O'Connor PJ, Cook DB. Exercise and pain: the neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. *Exercise and Sport Sciences Reviews*. 1999;27:119-166.
29. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain*. 2010;151:77-86.
30. Staud R, Robinson M, Price D. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. *Pain*. 2005;118:176-184.
31. Vierck C, Staud R, Price D, et al. The effect of maximal exercise on temporal summation of second pain (windup) in patients with fibromyalgia syndrome. *The Journal of Pain*. 2001;2:334-344.
32. Brito RG, Rasmussen LA, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. *Pain Reports*. 2017;2(5):e618.
33. Lemley KJ, Hunter SK, Hoeger Bement MK. Conditioned Pain Modulation Predicts Exercise-Induced Hypoalgesia in Healthy Adults. *Medicine & Science in Sport & Exercise*. 2015;47(1):176-184.
34. Kennedy DL, Kemp HI, Ridout D, et al. Reliability of conditioned pain modulation: a systematic review. *Pain*. 2016;157(11):2410-2419.
35. Lewis GN, Rice DA, McNair PJ. Conditioned Pain Modulation in Populations with Chronic Pain: A Systematic Review and Meta-Analysis. *The Journal of Pain*. 2012; 13(10):936-944.
36. Lewis GN, Luke H, Rice DA, et al. Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Research and Management*. 2012;17(2):98-102.
37. Drummond PD, Knudsen L. Central pain modulation and scalp tenderness in frequent episodic tension-type headache. *Headache*. 2011; 51:375-383.
38. Johannesson U, de Boussard CN, Brodda G, et al. Evidence of diffuse noxious inhibitory controls (DNIC) elicited by cold noxious stimulation in patients with provoked vestibulodynia. *Pain*. 2007;130:31-39.
39. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. *Clinical Journal of Pain*. 1997; 13:189-196.
40. Olesen SS, Brock C, Krarup AL, et al. Descending inhibitory pain modulation is impaired in patients with chronic

- pancreatitis. *Clinical Gastroenterology and Hepatology*. 2010;8:724-730.
41. Roosink M, Renzenbrink GJ, Buitenweg JR, et al. Somatosensory symptoms and signs and conditioned pain modulation in chronic post-stroke shoulder pain. *The Journal of Pain*. 2011;12:476-485.
42. Granot M, Weissman-Fogel I, Crispel Y, et al. Determinants of endogenous analgesia magnitude in diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter?. *Pain*. 2008;136(1-2):142-149.
43. Goodin BR, McGuire L, Allshouse M, et al. Associations between catastrophizing and endogenous pain-inhibitory processes: Sex differences. *The Journal of Pain*. 2009;10:180-190.
44. Goffaux P, Redmond WJ, Rainville P, et al. Descending analgesia—When the spine echoes what the brain expects. *Pain*. 2007;130:137-143.
45. de Souza JB, Potvin S, Goffaux P, et al. The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. *Clinical Journal of Pain*. 2009;25:123-127.
46. Moont R, Pud D, Sprecher E, et al. ‘Pain inhibits pain’ mechanisms: Is pain modulation simply due to distraction? *Pain*. 2010;150:113-120.
47. Edwards RR, Grace E, Peterson S, et al. Sleep continuity and architecture: Associations with pain inhibitory processes in patients with temporomandibular joint disorder. *European Journal of Pain*. 2009;13:1043-1047.
48. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurons in the rat. *Pain*. 1979;6(3):283-304.
49. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurons, supraspinal involvement and theoretical implications. *Pain*. 1979;6(3):305-327.
50. Sparling PB, Giuffrida A, Piomelli D, et al. Exercise activates the endocannabinoid system. *Cognitive Neuroscience and Neuropsychology*. 2003;14(17):2209-2211.
51. Raudys SJ, Jain AK, et al. Small Sample Size Effects in Statistical Pattern Recognition: Recommendations for Practitioners. *Transactions on Pattern Analysis and Machine Intelligence*. 1991;13(3):252-264.