ORIGINAL ARTICLE

Nr 2019;9 (2):262-271

Extracorporeal Shockwave Therapy of Healthy Achilles Tendons Results in a Conditioned Pain Modulation Effect: A Randomised Exploratory Cross-Over Trial

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DOI:
10.32098/mltj.02.2019.16

LEVEL OF EVIDENCE:
1b

SUMMARY

Background. This study investigated whether ESWT applied to healthy Achilles tendons results in a conditioned pain modulation (CPM) effect. **Methods.** 3000 and 6000-shock dose radial ESWT was performed on dominant side Achilles tendon (random order over 5-9 days) among 20 healthy participants (75% male). Pressure was modulated throughout, producing >4/10 pain (10=worst imaginable). Bilateral pressure-pain thresholds (PPT) were assessed pre-post ESWT at Achilles tendon, tibialis anterior and elbow lateral epicondyle (random order). PPT change per site and PPT change scores for each site were compared between doses (repeated ANOVA), PPT reliability (intraclass correlation coefficients [ICC]), and PPT change variability (each site, coefficient of variation) were investigated. Dose order was investigated (first vs second) (t-tests, each site). **Results.** Test-retest reliability was good for all sites (ICC [3,2]=0.76-0.89). PPT increased significantly ($p<0.05$) at all sites bilaterally following 3000-shock dose, and at bilateral Achilles tendon, and left sided tibialis anterior and lateral epicondyle following 6000-shock dose (right 6000-shock tibialis anterior, lateral epicondyle $p>0.05$). Dose order wasn't associated with outcome ($p>0.05$). **Conclusion.** ESWT produces immediate CPM effect when applied to Achilles tendon in healthy populations. This appears more consistent at 3000-shock dose. Determining if this mechanism occurs in Achilles tendinopathy will inform appropriate modality use.

KEY WORDS

Extracorporeal shock wave therapy; conditioned pain modulation; endogenous pain modulation; Achilles tendon.

INTRODUCTION

Tendinopathy is overuse injury that affects athletes and sedentary people. It is characterised by localised load-related pain and reduced function. Pathoaetiology is poorly understood but is thought to involve both extrinsic factors and intrinsic factors. Tendon pathology has been extensively investigated and includes changes in cell phenotype and signalling (e.g. increased production of certain cytokines and growth factors), increased and larger molecular weight ground substance molecules that draw water into the tendon, disruption of collagen matrix and ingrowth of blood and nerve vessels. Tendon pain is thought to have a peripheral driver, with many biochemical changes in tendinopathic compared with normal tendon tissue that may be involved, including substance P and lactate changes (1,2).

A complimentary treatment for tendinopathy is extracorporeal shock wave therapy (ESWT). The non-invasive modality involves high frequency pressure wave delivery to targeted tendon through the skin. There are two types of ESWT modality, focused and radial. Radial ESWT dispers-

es energy less intensely subcutaneously (3). Although not consistently, some studies demonstrate efficacy of ESWT in managing tendinopathy. Low level evidence supports ESWT in lower limb tendinopathy for improving pain, function and patient perceived improvement (4). Long term benefit has been demonstrated following ESWT application in both midportion and insertional Achilles tendinopathy (5,6). However, some studies show ESWT has no effect when compared to placebo (7).

ESWT mechanisms are poorly understood, limiting optimal clinical use. Aside from non-specific and placebo effects, preliminary evidence supports potential biochemical and tissue remodelling mechanisms. Animal studies have shown substance P is reduced in local tissue which may alter pain perception and nervous system sensitivity (8). Further, in vitro studies report improved tendon healing, possibly related to anabolic and inflammation effects (9).

Another potential mechanism of ESWT is conditioned pain modulation (CPM). CPM involves activation of endogenous pain inhibitory pathways, primarily the diffuse noxious inhibitory control system (DNIC), a spinal-bulbo-spinal pathway, following exposure to painful stimuli. People with chronic pain states such as fibromyalgia have been shown to have impaired CPM effect to laboratory stimuli (10). Given ESWT is painful with application its possible resulting analgesic effects are partly explained by CPM. In a recent study, García et al. reported immediate and widespread analgesia after using ESWT as a conditioning stimulus at different pain intensities. This resulting effect was suggested to likely be the result of CPM (11).

The aim of the current study is to investigate whether radial ESWT has an immediate CPM effect (increase in pressure-pain thresholds (PPT)). Further, at present it is not known if there is optimal dosage for this effect. This study will investigate whether 3000 or 6000-shock dose ESWT produces greater immediate CPM effect. Radial ESWT was chosen as its painful during application, and therefore may produce a CPM effect. This study will specifically determine whether there is a CPM effect with ESWT applied to healthy Achilles tendon, and if optimal dose exists, prior to testing this mechanism among people with tendinopathy who may have more variable endogenous pain inhibitory pathways (12).

METHODS

Study Design

A randomised exploratory cross over trial was used to investigate the effect of Achilles tendon ESWT at two dose settings on PPT among healthy participants.

Participants

Healthy volunteers between 18 and 60 years were recruited from social media and local sporting teams. Participants were excluded if they had any painful condition at the time of testing or in the previous three months. Participants with a history or condition associated with pain perception and sensitisation such as inflammatory arthritis (e.g. Rheumatoid arthritis, gout, psoriatic arthritis), or neurological (e.g. stroke, multiple sclerosis, Parkinson's disease) or endocrine disorders (e.g. type 1 or type 2 diabetes) were excluded. Women were excluded if in different phases of their menstrual cycle (ovulation or other phase) at the two testing occasions (13). Participants who undertook vigorous activity (i.e. sport, heavy lifting, manual work) prior to one test session but not another were excluded. Providing that the level of activity was matched across both testing sessions, participation in sport or vigorous physical activity close to the time of testing was not reason for exclusion.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study meets the ethical standards of Muscles, Ligaments and Tendons Journal (14).

The Monash University Human Ethics Committee approved the study (12280), and all participants provided informed consent.

Protocol

At the baseline testing session participants completed pain and function, and physical activity questionnaires and demographic data were collected. Participants received ESWT on two separate occasions separated by 5-9 days, and baseline PPT testing at each occasion was used to evaluate reliability (**Figure 1**). The ESWT intervention was identical on each occasion aside from dose (3000 versus 6000 dose). Dose order was randomised using a computer random number generator. Immediately (within 2 minutes) before and after the ESWT intervention PPT were assessed at bilateral lateral epicondyle, tibialis anterior and Achilles tendon. The order that each site was tested was randomised.

Effort was made to ensure factors that may influence PPT were as consistent as possible across both test times. Participants were tested at approximately the same time of the day (within 2 hours) and asked to avoid fluctuations in exercise the day prior to both testing occasions. PPT and ESWT was performed in a quiet room with consistent level of lighting

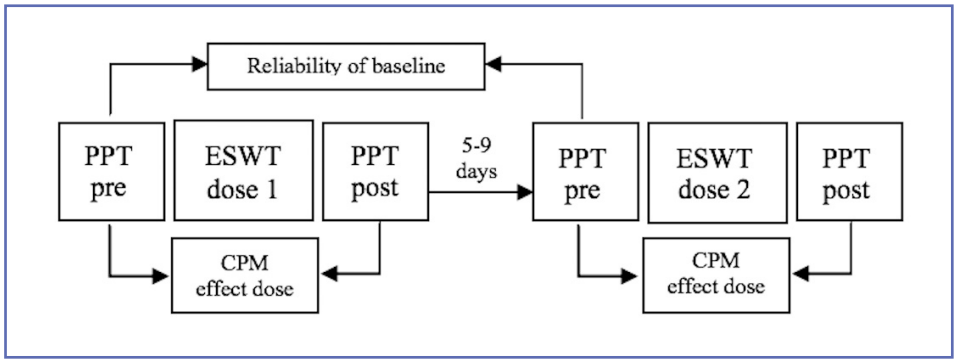


Figure 1. Evaluating reliability of PPT and CPM effect at each dose.

and we ensured there were no distractions during testing. The site of testing was consistent for sessions attended, with participants undergoing both testing sessions at Complete Sports Care, Hawthorn, Victoria, Australia or Back In Motion Ascot Vale, Ascot Vale, Victoria, Australia. Both sites are private practice clinics. Participants were asked not to consume alcohol, caffeine or nicotine products on days of testing.

Pressure-pain thresholds

PPT was measured using a digital algometer (Commander Algometer, JTECH Medical Industries, Salt Lake City, USA) with a 1cm² rubber plate. Familiarisation testing was performed on the thenar eminence on their dominant hand. Sites were marked to ensure accuracy of repeated testing. The test included the Achilles tendon (mid tendon, approximately 3cm proximal to the insertion site on the calcaneus), tibialis anterior (approximately 5cm distal to the tibial tuberosity and 3cm lateral to the limbs mid-line), and lateral epicondyle (most prominent lateral bony protuberance of the elbow confirmed with palpation) (12,15).

Participants were set in a pre-determined position for each site, and pressure applied in a pre-determined line of force (**Figure 2**) (12). Pressure was applied with a gradual increase (4N/sec), and the participant verbalised their first experienced sensation of pain. PPT measures were taken three to five times over each site bilaterally. While testing body sites, application alternated between right and left sites to allow a minimum 30 second flush-out between tests on a single site (12).

The first measurement at each site was removed to improve accuracy (16). For all subsequent trials, if recorded pressure varied by greater than 10% in comparison to the prior trial a further trial was performed. Mean of the first two trials (excluding the first measurement at each site) within 10% were averaged and used in analyses. Trials per site were limited to five. If no trials were within 10% after five trials, the closest two trials were averaged and used in analyses (this only occurred in 35/548 trials [6.4%]).

As PPT assessment of the selected sites for CPM effect with ESWT as conditioning stimulus hasn't been trialled previously, test-retest reliability was assessed to ensure protocol reliability. The PPT method used demonstrated good reliability (n=20) at the Achilles tendon (right ICC (3,2) =0.86, 95% CI=0.65-0.94; left ICC (3,2) =0.85, 95% CI=0.62-



Figure 2. Participant position and angle of force application for pressure-pain thresholds, **a)** Achilles tendon: Prone with feet over the end of the plinth and fixed against the thigh of the tester to ensure ankle is fixed in neutral; pressure applied perpendicularly.





Figure 2. b) tibialis anterior: Supine with the lower limb internally rotated 30 degrees; pressure applied on a 45-degree downward angle; **c)** lateral epicondyle: In supine with the hand fixed on the contralateral shoulder (elbow flexed to approximately 90 degrees); pressure applied perpendicularly.

0.94), tibialis anterior (right ICC (3,2) =0.76, 95% CI 0.39-0.91; left ICC (3,2) =0.85, 95% CI=0.62-0.94) and lateral epicondyle (right ICC (3,2)=0.89, 95% CI=0.73-0.96; left ICC (3,2) =0.89, 95% CI=0.73-0.96). Confidence bands for the ICCs were high, likely reflecting the time frame (5-9 days) over which we assessed reliability.

ESWT intervention

Radial ESWT was delivered (Swiss Dolorclast Classic ESWT device and Swiss Dolorclast Evo Blue handpiece, E.M.S. Electro Medical Systems S.A., Nyon, Switzerland) to the Achilles tendon (dominant side) while positioned as described in Figure 2 for Achilles tendon PPT assessment. ESWT was applied to a 2cm^2 region of the Achilles tendon midportion (4-8cm from the proximal border of the calcaneus) (**Figure 3**). Three or six thousand shocks were delivered in randomised order (5-9 days apart). ESWT pressure was dependent on participant-reported pain. Participants were asked to rate their pain during ESWT application every 20-30 seconds. Targeted self-reported pain was >4/10 until the highest tolerable pain (numerical pain rating scale, 0=no pain, 10=worst pain imaginable). If self-reported pain dropped below 5/10 the ESWT probe was moved to a different region within the region of interest. If pain

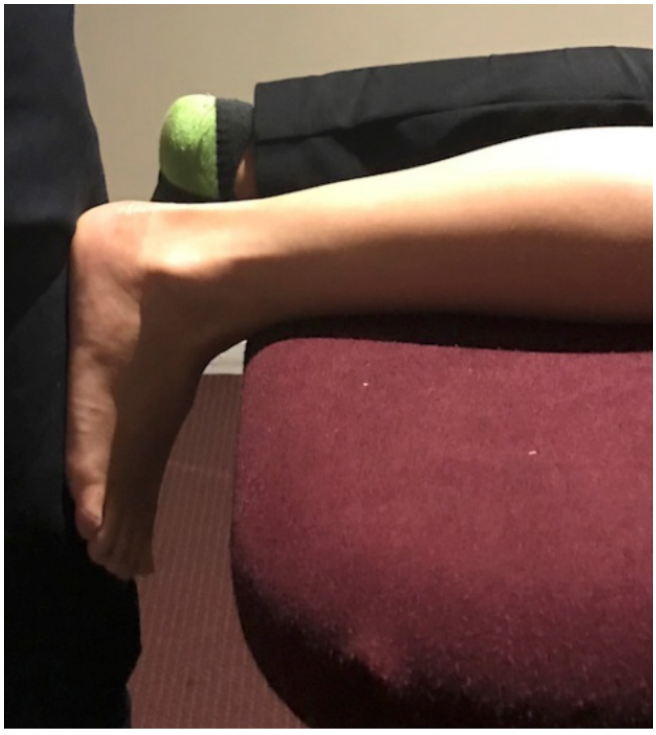


Figure 3. Participant position for application of ESWT (ankle is held in plantargrade against the thigh of the tester).

remained below 5/10 throughout the region of interest, ESWT pressure setting was progressed from two bar of pressure (always the starting point) up to and including four bar of pressure so as to achieve the target self-reported pain output.

QUESTIONNAIRE OUTCOMES

Achilles tendon pain and function

Given that participants that do not have Achilles tendinopathy may report mild discomfort and symptoms in the Achilles region, we assessed Achilles tendon symptoms with the Victoria Institute of Sport Assessment - Achilles (VISA-A) assessment. The VISA-A is a disease specific and validated tool for assessing Achilles pain and function (17).

Physical activity in the previous week

Physical activity was evaluated with the 7-day Recall Physical Activity Questionnaire. Participants were asked to recall time spent sleeping and doing physical activity (work, leisure, household activities) over the last 7-days.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc. Version 22.0, Chicago, IL, U.S.A.). Histograms were created to inspect normality of PPT outcome. Mixed two-way repeated measures ANOVA was used to analyse PPT data, whereby change in PPT per site and PPT change scores for each site were compared between doses. Dose order was investigated (first vs second) for 3000 and 6000 dose at all sites with t-tests. Intraclass correlation coefficients (ICC 3,2 [two way mixed effects, mean of k measurements, absolute agreement]) investigated baseline across testing dates (3000 and 6000-shock dose) at bilateral Achilles tendon, tibialis anterior and lateral epicondyle for test-retest reliability/intra-rater reliability (18). The variability in PPT change scores pre-post ESWT was described by reporting the coefficient of variation ([SD/mean]*100). The significance level was set at $p<0.05$ for all analyses.

RESULTS

Twenty-three participants were included and underwent ESWT at both doses. One male participant was excluded from analyses because they had been more active the day prior to first testing session (they played a game of Australian rules football prior to the first session and were inactive prior to the second session). Two women were excluded because they were in different phases of their menstrual cycle at the two data collection occasions. No participants experienced any harm or unintended effects as a result of their participation.

Demographic, activity and Achilles tendinopathy pain and function (VISA-A) data are presented in **Table 1**. The mean VISA-A score was 95.25/100 (SD=6.33), where 100 indicates no pain and full function.

Pressure-pain thresholds before and after ESWT

Pressure-pain thresholds increased significantly ($p<0.05$) at the right Achilles tendon (mean change 8.22N (Newtons) [16.28%], SD 10.85, p=0.00) and left Achilles tendon (mean change 8.38N [16.21%] SD 10.75, p=0.00), the right tibialis anterior (mean change 7.3N [16.88%] SD 7.3, p=0.00) and left tibialis anterior (mean change 6.74N [16.15%] SD 8.9, p=0.00), and the right lateral epicondyle (mean change 5.48N [12.75%] SD 9.72, p=0.02) and left lateral epicondyle (mean change 5.5N [13.51%] SD 10.97, p=0.04) for the 3000-shock dose.

At the 6000-shock dose, there was a significant ($p<0.05$) increase at the right Achilles tendon (mean change 8.11N [14.88%], SD 14.19, p =0.02) and left Achilles tendon (mean change 9.71N [17.94%] SD 13.01, p=0.00), the left tibialis anterior (mean change 5.04N [11.99%] SD 7.95, p =0.01), and the left lateral epicondyle (mean change 4.93N [11.27%] SD 8.56, p=0.03). The increase at the right tibialis anterior (mean change 2.52N [5.89%] SD 8, p =0.2) and right lateral epicondyle (mean change 2.19N [4.69%] SD 7.34, p=0.23) did not reach significance.

Figure 4 demonstrates mean change at each site following 3000 and 6000-shock dose.

Table 1. Descriptive data for the cohort.

	Cohort (N=20)	Male (N=15)	Female (N=5)
Age (years)	28.3 (7.2)	26.9 (6.1)	32.4 (9.1)
Height (cm)	176.2 (10.4)	181.7 (3.4)	159.7 (4.4)
Weight (Kg)	77.0 (15.3)	83.9 (9.9)	56.2 (7.4)
VISA-A	95.3/100 (6.3)	95.1/100 (6.5)	95.6/100 (6.4)
Activity	280.8 (40.8)	280.5 (44.5)	281.7 (31.2)

*Values are mean (SD)

Abbreviations: VISA-A Victorian Institute of Sport Assessment-Achilles

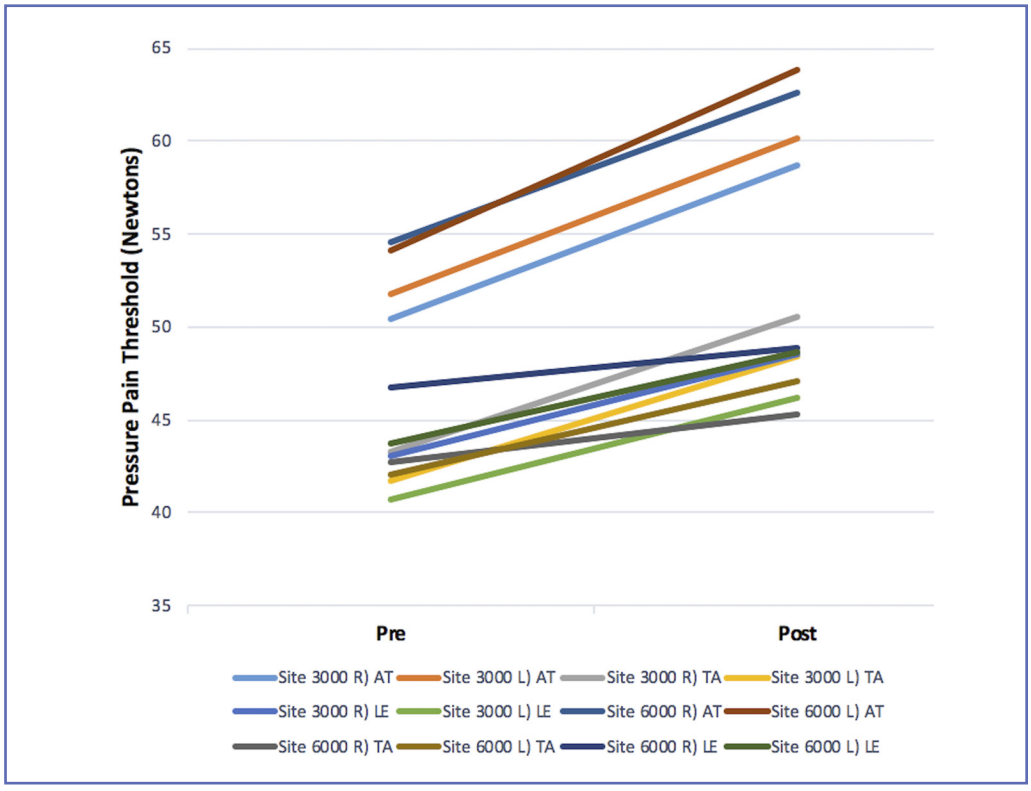


Figure 4. Mean change in PPT at all sites pre to post ESWT at 3000 and 6000-shock dose.

Variability in pressure-pain threshold response after ESWT

There was substantial inter-subject variability in PPT change pre-post ESWT. **Figure 5** shows individual participant change in PPT at the right Achilles tendon pre-post ESWT at 3000-shocks. The coefficient of variation for change scores at Achilles tendon (128.3-174.9%), tibialis anterior (132.2-317.3%) and lateral epicondyle (173.5-334.7%) indicated that the change scores standard deviation was at least 1.3 and up to 3.3 times greater than the mean PPT.

Factors related to pressure-pain threshold response following ESWT

The order of dose application (3000 vs 6000) was not associated with outcome at any site ($p>0.05$), however, there was a significant dose effect (greater effect with low dose) but only at the right tibialis anterior ($p<0.05$).

DISCUSSION

The main finding of this study is that application of 3000 shocks of painful ESWT to healthy Achilles tendon results in significantly increased PPT. Increase in PPT occurred consistently at the site of application, the opposite Achilles tendon, as well as the tibialis anterior and lateral epicondyle bilaterally. At the higher dose of 6000 shocks, findings were similar but did not reach significance for the right tibialis anterior and right lateral epicondyle. The diffuse and consistent (at 3000 shocks) reduction in pain sensitivity observed after application of painful ESWT may be explained by CPM. CPM is a dynamic psychophysical protocol used to explore DNIC mechanisms (19,20,21). In CPM, peripheral nociceptive stimuli activate a spino-bulbar-spinal loop that inhibits pain via descending adrenoreceptors and serotonergic inhibitory pathways mechanisms (19,21). This novel potential mechanism of ESWT can be used to develop and test new treatment paradigms for this modality.

PPT change observed after ESWT in the current study was comparable to CPM effects in the literature among healthy participants and at similar sites. Tompra et al. compared healthy participants and people with Achilles tendinopathy, reporting a 24% PPT increase at the Achilles tendon in the healthy participant group following cold water immersion of the contralateral hand (12). Studies in the literature use various methods to provide a painful conditioning stimulus (22). The only other study to date we are aware

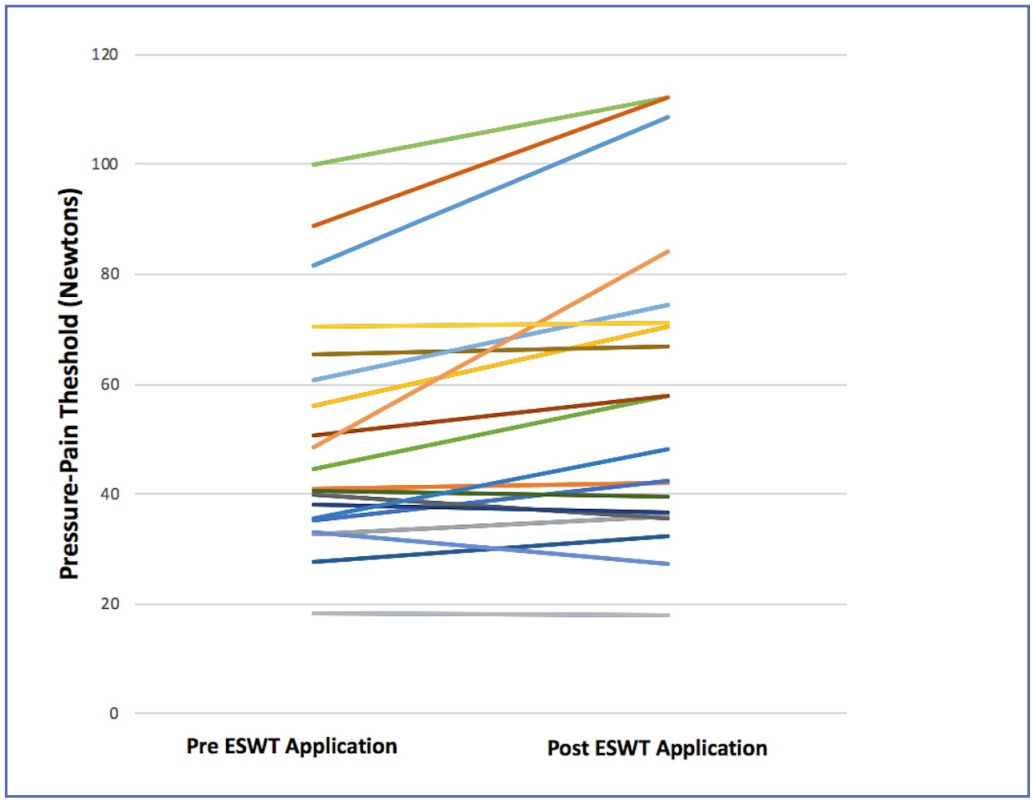


Figure 5. Individual pressure-pain thresholds change at the right Achilles tendon from pre to post ESWT application on low (3000 shock) dose.

of that utilises ESWT as a conditioning stimulus applied ESWT at varied pain intensities to the dominant sided lateral epicondyle of healthy participants. At a moderate pain intensity that most closely replicates our protocol, it was reported 29% PPT increase at the dominant lateral epicondyle, 27% increase at non-dominant lateral epicondyle and 12% increase at combined tibialis anterior (11).

As CPM magnitude is dependent on both type of conditioning stimulus used and site of application relative to testing (PPT), difference in size of PPT change between the García et al. study and the current study may be explained by site of ESWT application (23).

There was no placebo control group in this study because our aim was to investigate whether ESWT has a dose-dependent CPM effect. A limitation of this design is that placebo effect may have influenced our findings. Prior studies have reported 7% to 15% increases in PPT at the tibialis anterior muscle with placebo transcutaneous electrical stimulation (24,25). Schliessbach et al. compared CPM effect from acupuncture, placebo acupuncture and cold water immersion and found a similar response from acupuncture and placebo acupuncture (lower than cold water immersion), highlighting the potential contextual effects from clinical interventions such as acupuncture (26).

To minimise expectation-based placebo effects we did not inform participants of potential for a CPM response following ESWT. Further, the differential effects from 3000 and 6000 shock dose are not consistent with placebo being the main mechanism. The change in PPT consistently reached significance for 3000-shock dose and were generally larger than 6000-shock dose although this difference was only significant at one site. In contrast for the 6000-shocks dose, two remote sites did not reach significance. The time taken to complete the 6000 dose was approximately twice that of the 3000 dose. Our findings appear to suggest that the CPM effect of ESWT may be dependent on time of application.

It is plausible that longer ESWT may negatively affect the CPM effect. Although it has been reported that CPM effect appears to be sustained for the duration of painful conditioning stimulus irrespective of application length (27). However, the protocol used in the present study produced a fluctuating rather than stable pain stimulus. Standard temporal summation protocol requires the painful stimuli is applied at intermittent interval, with consistent pain intensity (28). While differences exist, the current study overlapped with this protocol when ESWT pressure was increased incrementally throughout dose administration as required to increase

pain intensity above 4/10. Often as a result of this increase, pain would increase >7/10 (peak pain measured was 10/10), potentially mimicking standard temporal summation protocol where increases to peak pain may have acted as intermittently applied painful stimuli. Therefore, it is possible that our ESWT protocol stimulated both CPM and temporal summation pathways. Given temporal summation is time dependent, whereby pain sensitivity is described to 'wind up' with repeated painful stimuli (29), this may have diluted the CPM effect of the 6000-shock dose. Alternatively, cortical influences may influence the CPM effect, for example, it may be impaired by higher brain centre hyper-vigilance, and this may also be dose dependent (30).

A common ESWT mechanism discussed in the literature is increase and subsequent decrease in substance P concentration. This has been argued to be a potential explanation for the latent (sometimes lasting weeks) analgesic effect following ESWT. Interestingly, substance P and antinociceptive pathways are triggered simultaneously following painful stimulus (1,2,31,22). It's possible that immediate CPM effects function in series with longer term local biochemical effects to explain reported sustained analgesic effects of ESWT in painful tendinopathy. Alternatively, short-term CPM-related analgesic effects (usually lasting no longer than 15 minutes) may result in altered top-down anti-nociceptive drivers that explain the sustained benefits of ESWT (32). To date, there has been only one study investigating local biochemical changes following ESWT application in humans. Waugh et al. used microdialysis to sample local biochemical environment before and after application of ESWT to painful Achilles tendon (33). They reported increased IL-6 and IL-8 concentrations and 5-fold increase in inflammatory MMP markers related to reduction in pain following ESWT. Further work is needed to understand how local tissue-mediated biochemical factors may influence tendon pain perception and how this interacts with CPM mechanisms following ESWT.

An important finding from the current study is that the CPM effect following ESWT among healthy participants is highly variable. The coefficient of variation indicated that the change score standard deviation was varying between 1.3 and up to 3.3 times the size of PPT change scores, with greater variation at the tibialis anterior and lateral epicondyle compared to the Achilles tendon. The percentage PPT change at any site varied between 4.5%-16.9% (entire cohort). Some participants experienced increased pain sensitivity (decreased PPT) following ESWT, although this occurred much less frequently (approximately 25% of the time) than PPT increase. Increased pain sensitivity following ESWT may be explained by activation of pro-nociceptive pathways, highlighting individual endogenous response variability.

Limitations

There are several limitations that need to be declared. First, we did not include a control group and this should be considered to differentiate placebo mechanisms. Further, familiarisation with PPT may explain our findings but there was no observed effect of order which refutes this hypothesis. Second, we reached the maximum load sensing capacity of our algometer (112 newtons) among three participants, meaning our estimated PPT increase following ESWT may have been reduced among these participants. Third, we undertook multiple tests and did not adjust the alpha level because this is an exploratory study and the second to knowledge to investigate a potential CPM effect following ESWT. Fourth, a lack of inclusion of standard CPM paradigm limits insight into mechanism of change. If included it would have allowed for comparison between CPM response and ESWT-induced change, where similar participant response with both would strengthen argument for the proposed mechanism of CPM. However, a comparison of magnitude of ESWT-induced effect was made to CPM effect in literature. Fifth, as study design was exploratory, confounding variables were not analysed in depth. Therefore, the findings of this study should be hypothesis generating and used to inform future studies.

CONCLUSION

Our findings suggest that CPM effect contributes to the immediate short-term pain reduction experienced with ESWT application. While significant dose effect (3000 or 6000) was not found, CPM effect across sites was more consistently achieved at 3000 dose. Further research is required to find if this effect occurs in populations with Achilles tendinopathy. Additionally, research into strength of effect and optimal dosage would provide greater insight, ultimately improving effectiveness of ESWT among people with chronic pain.

ACKNOWLEDGMENTS

This research is supported by an Australian Government Research Training Program (RTP) Scholarship.

Conflict of Interest

The authors declare that they have no conflict of interest (34)

REFERENCES

1. P. Sharma and N. Maffulli, "Biology of tendon injury: healing, modeling and remodeling," Journal Of Musculoskeletal And Neuronal Interactions, vol. 6, no. 2, pp. 181-190, 2006.
2. H. Alfredson, D. Bjur, K. Thorsen, R. Lorentzon and P. Sandstrom, "High intratendinous lactate levels in painful chronic Achilles tendinosis. An investigation using microdialysis technique," Journal Of Orthopaedic Research, vol. 20, no. 5, pp. 934-938, 2002.
3. H. van der Worp, I. van den Akker-Scheek, H. van Schie and J. Zwerver, "ESWT for tendinopathy: technology and clinical implications," Knee Surgery, Sports Traumatology, Arthroscopy, vol. 21, no. 6, pp. 1451-1458, 2013.
4. V. Korakakis, R. Whiteley, A. Tzavara and N. Malliaropoulos, "The effectiveness of extracorporeal shockwave therapy in common lower limb conditions: a systematic review including quantification of patient-rated pain reduction," British Journal Of Sports Medicine, vol. 52, no. 6, pp. 387-407, 2018.
5. G. Maffulli, J. Padulo, E. Iuliano, A. Saxena, J. Rompe and N. Maffulli, "Extracorporeal shcok wave therapy in the management of insertional Achilles tendinopathy: the ASSERT database," Muscles, Ligaments and Tendons Journal, vol. 8, no. 3, pp. 416-422, 2018.
6. G. Maffulli, J. Padulo, E. Iuliano, A. Saxena, J. Rompe and N. Maffulli, "Extracorporeal shockwave therapy in the management of midsubstance Achilles tendinopathy: the ASSERT database," Muscles, Ligaments and Tendons Journal , vol. 8, no. 3, pp. 409-415, 2018.
7. J. Zwerver, F. Hartgens, E. Verhagen, H. van der Worp, I. van den Akker-Scheek and R. Diercks, "No effect of extracorporeal shockwave therapy on patellar tendinopathy in jumping athletes during the competitive season: a randomized clinical trial," The American Journal Of Sports Medicine, vol. 39, no. 6, pp. 1191-1199, 2011.
8. J. Hausdorf, M. Lemmens, S. Kaplan, C. Marangoz, S. Milz, E. Odaci, H. Korr, C. Schmitz and M. Maier, "Extracorporeal shockwave application to the distal femur of rabbits diminishes the number of neurons immunoreactive for substance P in dorsal root ganglia L5," Brain Research, vol. 1207, pp. 96-101, 2008.
9. T. Hochstrasser, H. Frank and C. Schmitz, "Dose dependent and cell type-specific cell death and proliferation following in vitro exposure to radial extracorporeal shock waves," Scientific Resports, vol. 6, 2016.
10. H. Vaegter, G. Handberg and T. Graven-Nielsen, "Hypoalgesia after exercise and the cold pressor test is reduced in chronic musculoskeletal pain patients with high pain sensitivity," The Clinical Journal Of Pain, vol. 32, no. 1, pp. 58-69, 2016.
11. A. García-Muntión, L. Godefroy, H. Robert, D. Muñoz-García, C. Calvo-Lobo and I. López-de-Uralde-Villanueva, "Study of the mechanisms of action of the hypoalgesic effect of pressure under shock waves application: A randomised controlled trial," Complementary Therapies in Medicine, vol. 42, pp. 332-229, 2019.
12. N. Tompra, J. van Dieen and M. Coppieters, "Central pain processing is altered in people with Achilles tendinopathy," British Journal Of Sports Medicine, vol. 50, no. 16, pp. 1004-1007, 2016.
13. A. Stubhaug and H. Breivik, "Conditioned pain modulation: A useful test paradigm in research and in clinical practice," Scandinavian Journal Of Pain, vol. 4, no. 2, pp. 101-102, 2013.
14. J. Padulo, F. Oliva, A. Frizziero and N. Maffulli, "Basic principles and recommendations in clinical and field Science Research: 2016 Update," Muscles, Ligaments and Tendons Journal, vol. 6, no. 1, pp. 1-5, 2016.
15. A. Stubhaug, "Pressure pain algometry - A call for standardisation of methods," Scandinavian Journal Of Pain, vol. 3, no. 1, p. 30, 2012.
16. T. Lacourt, J. Houtveen and L. van Doornen, "Experimental pressure-pain assessments: Test-retrest reliability, convergence and dimensionality," Scandinavian Journal Of Pain, vol. 3, no. 1, pp. 31-37, 2012.
17. J. Robinson, J. Cook, C. Purdam, P. Visentini, J. Ross, N. Maffulli, J. Taunton and K. Khan, "The VISA-A questionnaire: a valid and reliable index of the clinical severity of Achilles tendinopathy," British Journal Of Sports Medicine, vol. 35, no. 5, pp. 335-341, 2001.
18. T. Koo and M. Li, "A guideline of selecting and reporting intraclass correlation coefficients for reliability research," Journal of Chiropractic Medicine, vol. 15, no. 2, pp. 155-163, 2016.
19. Y. Granovsky and D. Yarnitsky, "Personalized pain medicine: the clinical value in psychophysical assessment of pain modulation profile," Rambam Maimonides Medical Journal, vol. 4, no. 4, 2013.
20. D. Yarnitsky, M. Granot and Y. Granovsky, "Pain modulation profile and pain therapy: between pro - and antinociception," Pain, vol. 155, no. 4, pp. 663-665, 2014.
21. D. Yarnitsky, "Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states," Current Opinion In Anaesthesiology, vol. 23, no. 5, pp. 611-615, 2010.
22. G. Lewis, D. Rice and P. McNair, "Conditioned pain modulation in populations with chronic pain: A systematic review and meta-analysis," The Journal Of Pain, vol. 13, no. 10, pp. 936-944, 2012.
23. P. Svensson, C. Hashikawa and K. Casey, "Site- and modality-specific modulation of experimental muscle pain in humans," Brain Research, vol. 851, no. 1-2, pp. 32-38, 1999.
24. D. Dailey, B. Rakel, C. Vance, R. Liebano, A. Amrit, H. Bush, K. Lee, J. Lee and K. Sluka, "Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia," Pain, vol. 154, no. 11, pp. 2554-2562, 2013.
25. C. Vance, B. Rakel, N. Blodgett, J. DeSantana, A. Amendola, M. Zimmerman, D. Walsh and K. Sluka, "Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial," Physical Therapy, vol. 92, no. 7, pp. 898-910, 2012.
26. J. Schliessbach, E. van der Klift, A. Siegenthaler, L. Arendt-Nielsen, M. Curatolo and K. Streitberger, "Does acupuncture needling induce analgesic effects comparable to diffuse noxious inhibitory controls?," Evidence-Based Complementary And Alternative Medicine, vol. 2012, 2012.
27. M. Razavi, P. Hansson, B. Johansson and A. Leffler, "The influence of intensity and duration of a painful conditioning stimu-

lation on conditioned pain modulation in volunteers," European Journal of Pain, vol. 18, no. 6, pp. 853-861, 2014.
28. R. Anderson, J. Craggs, J. Bialosky, M. Bishop, S. George, R. Staud and M. Robinson, "Temporal summation of second pain: Variability in responses to a fixed protocol," European Journal of Pain, vol. 17, no. 1, pp. 67-74, 2013.
29. R. Staud, C. Vierck, R. Cannon, A. Mauderli and D. Price, "Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome," Pain, vol. 91, no. 1-2, pp. 165-175, 2001.
30. I. Tracey and P. Dunkley, "Importance of anti- and pro-nociceptive mechanisms in human disease," Gut, vol. 53, no. 11, pp. 1553-1555, 2004.
31. J. Hausdorf, M. Lemmens, K. Heck, N. Grolms, H. Korr, S. Kertschanska, H. Steinbusch, C. Schmitz and M. Maier, "Selective loss of unmyelinated nerve fibres after extracorporeal shockwave application to the musculoskeletal system," Neuroscience, vol. 155, no. 1, pp. 138-144, 2008.
32. G. Lewis, L. Heales, D. Rice, K. Rome and P. McNair, "Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways," Pain Research And Management, vol. 17, no. 2, pp. 98-102, 2012.
33. C. Waugh, D. Morrissey, E. Jones, G. Riley, H. Langberg and H. Screen, "In vivo biological response to extracorporeal shockwave therapy in human tendinopathy," European Cells and Materials, vol. 29, pp. 268-280, 2015.
34. Padulo J., Oliva F., Frizziero A., Maffulli N. Muscles, Ligaments and Tendons Journal – Basic principles and recommendations in clinical and field Science Research: 2018 update. MLTJ 2018; 8(3): 305 – 307