The Effect of Ibuprofen and a Placebo on Conditioned Pain Modulation Among Varsity Athletes

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ABSTRACT

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In the world of athletics, the role of pain is complex. While pain-relieving medications like ibuprofen are commonly used, research on their effects on athletes remains limited in number and quality. Additionally, the influence of the placebo effect in sports remains unclear. Our study aimed to compare the impact of ibuprofen and placebos on conditioned pain modulation in athletes. We conducted a semi-randomized controlled trial involving 60 male and 60 female varsity athletes across ten sports disciplines. Participants underwent two visits and were randomly assigned to one of three groups: ibuprofen, placebo, or control. We assessed subjective pain using a numerical scale before, during, and after a cold pressor test (CPT). Conditioned pain modulation was measured via pain pressure threshold measurements before and after the cold pressor test. We monitored cardiovascular variables during-CPT which may serve as a more objective measure of pain. Surprisingly, neither the ibuprofen nor the placebo led to a significant reduction in pain during the CPT. All athletes experienced heightened pain perception, increased blood pressure, and elevated heart rate during-CPT, followed by a return to baseline post-CPT. All athletes exhibited an improved pain pressure threshold after the CPT, indicating conditioned pain modulation. Male and female athletes experienced the same pain during the CPT, however, when pain was measured a different way, via pressure algometry, males could tolerate more pressure before it became painful. This makes it more complicated to distinguish which sex feels more pain, and sex differences in pain perception require further investigation.

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LIST OF ABBREVIATIONS

CPM – conditioned pain modulation
PPT – pain pressure threshold
CPT – cold pressor test
DNIC – diffuse noxious inhibitory control system
IASP – international association for the study of pain
PCS – pain catastrophizing scale
NRS – numerical rating scale
VAS – visual analogue scale
NSAID – non-steroidal anti-inflammatory drugs
COX – cyclooxygenase

CHAPTER 1: THEORETICAL CONTEXT

1.0 Introduction

Humans have naturally occurring pain reducing mechanisms,[1] which can be seen in runner's high for example, when the body is pushed until a relaxing euphoric feeling takes over.[1] Exercise induced hypoalgesia, otherwise known as a decreased sensitivity to pain due to exercise, is the result of this natural pain relief system.[1] The body feels pain and sends appropriate signals to reduce it.[1,2] The body's capacity to reduce its own pain is at the epicenter of this multifaceted project. This study examined the mechanism of pain in athletes. There is some evidence that athletes may experience pain differently compared to non-athletes[3,4] and I wanted to delve deeper into this pain experience. The literature review will discuss pain in athletes and review medications used to manage pain; how these function, and more specifically what their effect is on athletes' pain and conditioned pain modulation. Furthermore, its crucial to discuss the placebo effect when exploring medication, given its significant connection with pain in medication studies.[5,6] Much like with medication, we wanted to know the effect of a placebo on pain and conditioned pain modulation as well as its effectiveness in athletes. Another factor of interest to us was sex differences in pain experience and conditioned pain modulation. Epidemiological studies have shown that females tend to report pain more frequently and earlier than males.[7] However, the role of sex in conditioned pain modulation remains unclear, with studies yielding inconsistent findings, some showing no difference, and others suggesting better CPM in males.[7,8] Currently, the best method we have to assess pain is the numerical rating scale, which is entirely subjective, however there is some preliminary evidence that heart rate and blood pressure may be a more objective measure of pain. Therefore, the purpose of this study was to compare the effect of ibuprofen and a placebo on conditioned pain modulation in athletes, by measuring changes in pain pressure threshold, blood pressure, heart rate, and pain intensity during a cold pressor test (CPT). We will begin by discussing pertinent information and studies, and our hypotheses will be stated at the end of the theoretical context sections.

1.1 Conditioned pain Modulation

1.0.1 What is conditioned pain modulation?

Conditioned pain modulation (CPM) is a commonly used method to assess pain inhibition.[2] CPM involves two painful stimuli(i: a primary test stimulus and ii: a secondary conditioning stimulus.)[2] When testing for conditioned pain modulation, the test stimulus is applied, causing a pain response (for example on the tibialis anterior muscle on the shin), then the conditioning stimulus is applied at another location on the body (for example the hand). When the test stimulus is then repeated by inducing pain on the tibialis anterior in the case of this example, pain inhibition should be seen as perceived pain scores lower or the individual is able to tolerate more pain.[2] The test stimulus is often pressure algometry, a reliable and valid approach to assess pressure pain sensitivity.[2] Using a handheld pressure algometer, pressure is applied to a specific point by the researcher, for example the thenar eminence of the hand, and the participant says,

"now" when the pressure becomes pain. Individuals with chronic pain often show increased pain facilitation and diminished pain inhibition, therefore have weaker conditioned pain modulation.[2]

1.0.2 The physiology of conditioned pain modulation

Conditioned pain modulation (CPM) is defined as, "the net effect of the endogenous pathways that enhance or diminish the effects of afferent noxious stimuli."[9] This means that CPM looks at how effective descending pain pathways are at preventing the development of pain conditions,[1,9] hence why it is the most used method to assess pain inhibition.[2]

Conditioned pain modulation involves the central nervous system and opioidergic pathways that influence pain modulation.[9] In individuals with a functional nociceptive system, the experience of a conditioning stimulus typically leads to a reduction in pain reported during the subsequent primary test stimulus.[1] To help explain how CPM works, here is an example of its effect. In a study by Peterson et al., conditioned pain modulation was tested with 26 participants. The test stimulus was pain pressure threshold at the brachioradialis while the conditioning stimulus was a 60 second cold pressor test.[10] Prior to the cold pressor test, the baseline average PPT was 517.9 kPa.[10] This is a measure of the pressure or force needed for pressure to become pain. After this first PPT measure was recorded, participants completed the cold pressor test and the PPT was recorded once again.[10] The average PPT post-CPT was 605.3 kPa. This means that after the conditioning stimulus, it now takes more force for the pressure to become painful, and that participants now have a higher pain threshold. The noxious stimuli from the CPT stimulated the bodies natural pain-relieving mechanism, which is demonstrated by needing more pressure to reach the pain threshold compared to before the CPT.[10] This increase in threshold is what is expected when measuring conditioned pain modulation, but in cases where CPM is impaired this is not the outcome. Central sensitization, which leads to the development of pain conditions, occurs when descending pain modulatory pathways are impaired.[9] In those with pain conditions, the effect of CPM will be diminished, and less pain relief will be felt.[1,9] Pain inhibition is thought to occur primarily because of the diffuse noxious inhibitory control system (DNIC).[1] When a new pain is introduced, the DNIC is said to inhibit previous pain in distant areas,[1] explaining why repeating the test stimulus after a conditioning stimulus reduces perceived pain.

1.0.3 Test and conditioning Stimuli to measure CPM

A painful test and conditioning stimulus is crucial to see the effect of conditioned pain modulation, and there are a variety of methods for testing either.[1,9] The test stimulus could be thermal (hot or cold), mechanical (pressure), electrical or chemical.[9] The conditioning stimulus could include a cold pressor test (the most common method) involving limb immersion in cold water, noxious heat stimulation using a contact thermode or hot water bath, or ischemic techniques using mechanical stimulation or pain pressure threshold.[9] Regardless of the methods chosen, there are two ways that the test stimulus can be applied regarding the conditioning stimulus; either in parallel (at the same time), or sequentially (immediately after). The sequential method is preferred since it prevents bias due to distractions that may occur when experiencing both the conditioning and test stimuli at the same time.[9] Conditioned pain modulation is calculated as the difference between pre and post test stimulus measures, and has become an

important biomarker for pain outcomes.[9] Regardless, there is a lack of standardization when it comes to CPM research regarding the technique which makes pooled data difficult to interpret.[9]

1.0.4 The cold pressor test

The most frequently used conditioning stimulus is the CPT[1,9] which is often used to study pain, in a noninvasive manner.[11] When a body part is exposed to cold, which is a noxious stimulus, the sympathetic nervous system is activated and a change in cardiovascular activity is observed due to a stress response to the stimulus.[11] The CPT is frequently used to induce experimental pain because it is thought to effectively mimic the effects of chronic pain conditions.[12] This test involves the submersion of a limb in cold water for a maximum amount of time.[12] Noxious stimulation from the cold-water immersion can lead to reliable peak response within 90-120 seconds,[13] but the water temperature during the test is important to consider. Mitchel et al., looked at the effect of the water temperature on the results of the cold pressor test with a sample of 26 participants who underwent 4 cold pressor trials at 1, 3, 5 and 7 degrees Celsius.[12] They found that men tolerated the stimuli longer than women, and that small differences in water temperature have significant impact on the reported pain intensity.[12] The tolerance times were significantly longer with a difference of 4° Celsius, while the pain ratings were significantly higher with a difference of 2° Celsius.[12] This is important to note because it emphasizes the importance of controlling the water temperature both throughout each cold pressor test, and between each participant.

1.0.5 Factors affecting CPM

CPM can be affected by various factors such as age, gender, hormones, race, and psychological factors such as anxiety, depression, and catastrophizing.[1,9] Participants who are high catastrophizers report higher subjective pain intensity scores and have less effective CPM.[9] Conditioned pain modulation is also affected by the testing procedure, including the type of conditioning and test stimuli.[1,9] In terms of demographics, younger male adults with positive expectations who also pay attention to the conditioning stimulus tend to have more efficient CPM, and non-Hispanic white individuals tend to have greater CPM than African-Americans.[9] Additionally, the menstrual cycle seems to lead to inconsistent CPM effects, sometimes rendering CPM less effective, while exercise influences the descending pain pathways and often leads to hypoalgesia or a decrease in pain sensation.[9] Although we will not be measuring exercise induce hypoalgesia, athletes experience it while training which may improve their CPM compared to non-athletes.

1.0.6 Sex differences in CPM

Vaegter et al., conducted a study looking at conditioned pain modulation in 56 healthy individuals. The researchers used a cold pressor test and pain pressure threshold to assess CPM. They found a significant interaction between gender and physical activity for baseline PPTs. Baseline pain pressure thresholds are significantly higher in inactive men (485.8 ± 237.0 KPa) compared to inactive women (316.1 ± 95.9 KPa).[14] At both the bicep and quad tendons females showed consistently lower PPT values than males. [14] Conditioned pain modulation was maintained in women immediately after the cold pressor test but not in males and was not

present 15 minutes after the CPT for either sex.[14] Since there is some evidence to show a sex difference in pain perception and CPM, we analyzed data from both sexes separately in order to compare the outcomes and to look for similarities and differences, but also to make sure that the overall results are not skewed by lumping both sexes into one group. We recognize other communities (2SLGBTQI+), however as of now there are very limited studies on other members of this population, future studies are needed to examine pain in a more diverse and inclusive environment.

1.0.7 Conditioned pain modulation and chronic pain

Populations with chronic pain may exhibit impaired conditioned pain modulation. Lewis et al., conducted a meta-analytic review to inquire whether chronic pain populations have impaired CPM.[1] The authors included 30 studies in their review, which included a total of 42 comparisons of CPM between a patient (pain) and a control group. 69% of those comparisons resulted in significantly greater modulation in the control group.[1] Their analysis suggests that across all studies, the groups with pain conditions showed reduced conditioned pain modulation, with a large effect size of 0.78 at a 95% confidence interval.[1] This is important because they discussed the findings of the articles and suggested a distinction in the CPM between both groups, and their meta-analysis also provided the first quantification of this impairment. They found that the most influential factor on effect size was the age of the participants, with studies including older populations showing a smaller effect[1], therefore considering that we are looking at athletes between the ages of 18-35 we may be more likely to see CPM.

Conditioned pain modulation is the human body's naturally occurring pain reducing mechanism, though chronic pain, psychological and demographic factors, and exercise are a few variables that may impair this mechanism. Since exercise may lead to hypoalgesia or reduced pain sensitivity, this opens a door to question the effect of pain and conditioned pain modulation in athletes who are frequently pushing their bodies physically. Though research has been conducted on exercise induced hypoalgesia, not much research has been done on athletes' conditioned pain modulation during experimental pain to see if this natural ability to decrease pain remains while they are not exercising. For the purpose of this study, we have defined an athlete as an individual taking part in varsity level sport or above, for example provincial teams. The effect of the number of training hours on CPM will be discussed later.

1.1 Pain in athletes

Having elucidated the fundamental aspects of this masters thesis, which is conditioned pain modulation, it is time to broaden the scope and delve into the discourse surrounding pain, with a particular focus on pain experienced by athletes. This population is not often targeted in experimental pain studies though their relationship to pain and their experience is said to vary from non-athletes. Before discussing specific aspects of pain and athletes, a more theoretical discussion about the physiology of pain and how it is measured will precede.

1.1.1 What is pain?

At some point in their lives, most people have felt an aching, shooting, throbbing or other type of pain. Sometimes it may have been debilitating and other times it may have been simply a nuisance. Many individuals may find themselves wondering why they experience such sensations and when the pain might cease. Nevertheless, its important to recognize that this is the body's method of signaling that there could be an underlying issue. The International Association for the study of Pain defines pain as, "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." (IASP) Pain is often associated with tissue deterioration or damage, however, the key aspect of this definition is that this damage is not necessary to feel pain. (IASP, [15]) This serves as a definition of pain, but there are various types of pain which we will elucidate below.

1.1.2 Types of pain

Pain sensation stems from a noxious, or painful stimulus, and nociception is, "the neural process of encoding [that] noxious stimul[us]".[44] Exposure to a noxious stimulus does not necessarily mean that pain will be sensed; the stimulus needs to be processes by the brain before it is perceived as pain. The body may have an autonomic response to that pain such as an elevated blood pressure, or a behavioural reaction as exhibited through the withdrawal reflex.[44] When associated with an injury, pain is like an alarm or a warning that something is happening in the body that may require attention. Though pain is good acutely to prevent further injury, it can become maladaptive and chronic.[44] The International Association for the study of Pain has defined the following three types of pain: nociceptive, neuropathic, and nociplastic.

- **Nociceptive pain**, "arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors."[44]
- **Neuropathic pain** is, "caused by a lesion or disease of the somatosensory nervous system." (IASP) The term neuropathic is not used based on symptoms or signs, but once imaging has shown a lesions or disease satisfying neurological diagnostic criteria.[44]
- **Nociplastic pain**, "arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain."[44]

The main difference between nociceptive and neuropathic pain is that while nociceptive pain occurs with a normal somatosensory nervous system, neuropathic pain is linked to an abnormal function of this system.[44] It is important to note that a patient can experience a mixed-pain state during which nociplastic pain arises during ongoing nociceptive pain.[44] Each type of pain will respond to different types of therapies, augmenting the importance of determining the type of pain an individual is experiencing. A certain amount of pain is important to allow tissues to heal following an injury, however maladaptive pain that remains without physiological cause becomes a hindrance to recovery.

1.1.3 Subjectivity of pain

Many individuals will experience pain at some point in their lives, but pain remains a subjective and complex subject. The International Association for the study of Pain states that pain may or may not be associated with actual tissue damage.[44] The presence of pain combined

with a lack of physiological deterioration suggests that other variables may impact one's pain.[15] Pain stems from a noxious stimulus that only becomes pain once it has reached the brain and is interpreted as such, making pain a unique experience for all.[44] The interpretation of a similar noxious stimulus in different individuals may therefore be affected by the events occurring in their life at that moment. Social and psychological factors such as depression, anxiety, and catastrophizing (a negative and magnified response to pain)[3] all influence a patient's pain experience by affecting factors such as their perceived pain intensity, and disability.[15] Pain is a personal experience; therefore, the same stimulus will yield completely different pain perceptions for all. This variability does not mean that some people's pain should be taken more seriously than others, simply that more investigation should be done to understand the underlying factors that may be magnifying certain individual's experiences.

1.1.4 Measuring pain

Pain is a subjective and personal experience, therefore self report is the best way to measure pain.[2] This subjectivity emphasizes the need for reliable and valid pain assessment tools to classify chronic pain conditions and monitor change in pain.[2] These assessment tools help track the change in pain over time and may help narrow down the cause of the pain.[2] Severity, quality, time, location, and distribution should be considered for clinical diagnosis.[2]

An important aspect of pain is its severity. The most used scale to assess pain intensity is the numeric rating scale (NRS), since it is easy to administer.[2] This scale should range from 0 (no pain at all) to 10 (worst pain imaginable). Another frequently used scale is the visual analogue scale (VAS) which is a printed scale from 0 to 10, much like the NRS on which patients circle their pain level.[2] A systematic review by Freeman et al., concluded that the NRS is easier to use and showed better compliance when compared to the visual analogue scale.[16]

The most common methods of eliciting pain are thermal stimuli, including heat, and cold, as well as mechanical stimuli consisting of tactile, pressure, and vibration stimuli.[2] Pain pressure threshold is the most frequently used mechanical stimulus when testing CPM. An algometer is pressed into a muscle until pressure becomes pain, the amount of force that is applied to the tissue is displayed.[17] The amount of pressure required to cause pain is called the pain pressure threshold.[17] Downes et al., conducted a study looking at the reliability of repeated PPT in participants without pain, and the reliability of PPT between examiners.[17] They concluded that pain pressure threshold is a reliable measure, and that reliability increases when all measurements are taken by one examiner.[17]

We have explained above that conditioned pain modulation (CPM) is the most common method to assess pain inhibition which is why we chose this protocol to study pain in athletes. CPM was used to measure athletes' change in sensitivity during experimentally induced pain by stimulating the body's natural pain reducing mechanism.

1.1.5 Pain in athletes

Athletes have a complex relationship with pain, though it is often assumed that they are good at handling and playing through their pain. This idea is reinforced by the saying, "no pain, no gain,"[3] a familiar phrase, especially in the context of sports where exposure to strain on the

body and pain is frequent.[4,18] Regardless of exposure to painful stimuli and injuries, athletes continue to play through their pain, tending not to find the pain as debilitating as non-athletic counterparts with similar injuries.[3] Athletes may be subject to nociceptive, nociplastic and neuropathic pain, and understanding the difference plays a key role in applying the right tools throughout their rehabilitation. Athletes and sedentary individuals are exposed to different painful stimuli, and it remains unclear if they experience pain in the same way. A more in depth understanding of the matter may be beneficial to health care professionals working with athletes.

1.1.6 Social and professional expectations of athletes

Social factors and ideologies surrounding sports play a big role in athletes' pain perception. Athletes are exposed to exertion, physical contact, delayed onset muscle soreness, and a wide variety of potential injuries due to their sport.[3] In 1999, a study looking at injury patterns in select high schools found that athletes at this level sustain on average 2 million injuries annually, which results in 500 000 doctors' visits and 30 000 hospitalizations.[19] The social and competitive environment of sports pushes athletes to play through their pain to succeed, gain their teammates respect, and maintain a reputation of toughness in front of them.[4] A much more recent study published in 2019 reviewing the risk-taking behaviour and sporting injury from an occupational safety and health perspective found similar results.[20] Still today, athletes involved in high performance sports are at high risk for injuries and expose themselves to risky behaviours by continuing to play through injuries instead of reporting them due to pressure from coaches, teammates, fans and parents.[20] Their frequent exposure to painful stimuli may lead to habituation, making athletes' pain experience less challenging compared to non-athletes.[18] For athletes, especially those at the professional level, their training environment can be considered their workplace. In a workplace, employers typically ensure the safety of their employees, but the competitive culture surrounding sports creates a conflict that prevents a safe working environment for elite athletes.[20] Instead, this culture encourages competition regardless of pain, quick return to play post-injury, and normalization of injuries starting at a young age.

1.1.7 Pain in athletes compared to non-athletes

Athletes generally feel less pain than their sedentary counterparts. Sullivan et al., looked at the difference in pain perception in varsity athletes (n=54) and a sedentary group (n=54), and the relationship of pain scores to the pain catastrophizing scale.[3] The athletes were part of varsity basketball or rugby, while the sedentary group consisted of participants that were physically active maximum once per week.[3] The Pain Catastrophizing scale (PCS) was filled out and their pain intensity was recorded during a painful task, the cold pressor test, which involved hand submersion in 2-4 degree Celsius water.[3] The athletes reported less pain and obtained a lower score on the PCS than sedentary individuals.[3] The total PCS score was significantly correlated with pain ratings, $r=0.43$, $p<0.01$ in sedentary and athlete samples, $r=0.3$, $p<0.05$. [3] Sullivan et al., are not only ones to compare pain in athletes versus non-athletes. A more recent study by Pettersen et al., comparing high-level and elite athletes to non-athletes found that elite and high-level athletes have an increased pain tolerance, higher heat pain thresholds, and lower reported pain intensity during experimental pain stimulation.[18] Similarly, Assa et al., compared different types of athletes to non-athletes and also concluded that pain ratings of athlete groups were significantly lower than those of non-athletes ($p<0.001$).[21] Previous studies looking at

experimental pain perception or tolerance have consistently found that high-level athletes are more tolerant to pain than non-athletes.[18] These results are interesting because they support the idea that athletes may have a different pain experience than non-athletes. Part of this may be their attitude towards pain, their exposure to pain, and their ability to cope with it.[3,4,18]

1.1.8 Type of sport and pain perception

Studies comparing pain perception of athletes versus non-athletes typically conclude that athletes have an increased pain threshold and tolerance, however there are some inconsistencies.[18,21]. The divergence may be caused by the type of sport.[18,21] Contact sports involve physical contact and have higher risks of acute musculoskeletal injuries versus endurance sports that rely on cardiovascular fitness and longer lasting physical activity.[18] Due to the different stimuli each type of athlete is exposed to in their respective sports, their pain threshold; the point at which a stimulus is considered painful, and their pain tolerance; how long a painful stimulus can be tolerated, vary.[18] Contact sports tend to lead to higher pain thresholds, while endurance sports lead to increased pain tolerance.[18] Pettersen et al., compared 17 soccer players to 15 endurance athletes (12 cross country runners and 3 long-distance runners). The authors concluded that the endurance athletes have a higher pain tolerance while the soccer players have a higher pain threshold.[18] Similarly, Assa et al., also looked at pain threshold, and tolerance in different types of athletes. The sample consisted of 19 endurance athletes (triathletes), 17 strength athletes (weightlifters and throwers), and 17 non-athlete controls.[21] Using a noxious heat stimulus and cold water immersion they concluded that strength athletes have a significantly ($p<0.05$) higher pain threshold than both endurance athletes and a non-athlete control. Comparatively, endurance athletes had a greater pain tolerance ($p<0.001$), while strength athletes showed similar results to the control group.[21] While there is some preliminary evidence to suggest that different sports may affect conditioned pain modulation in athletes, more studies are needed to determine if training hours or type of sport while controlling for psychological factors is what is contributing to the difference in conditioned pain modulation.

1.1.9 Factors affecting athletes' pain experience.

Pain experience in athletes can be affected by many factors. Exercise induced hypoalgesia, frequency and intensity of training, adaptation to pain due to exposure to intense physical training and injuries, and pain catastrophizing are examples of these factors.[21] We conducted a previous study looking at the association between catastrophizing, pain, and cardiovascular changes in athletes during a cold pressor test.[22] We found a correlation between athlete's pain catastrophizing and both pain intensity and change in heart rate during the cold pressor test ($p=0.02$ and $p=0.003$ respectively).[22] This suggests that these psychological factors are also present in athletes even if they might feel less pain than sedentary individuals. Injured athletes are often faced with the pressure of returning to play, therefore understanding the impact of catastrophizing on recovery is key. If health care practitioners are aware that certain players catastrophize their pain, steps need to be taken to address this, or it may delay their recovery.[3,23]

1.2.0 Conditioned pain modulation and athletes

Conditioned pain modulation is a, "pain inhibits pain" phenomenon that incorporates both psychological and physical factors.[9] In theory, humans should be capable of CPM, however various variables may impair this mechanism and lead to chronic pain. This has led us to question whether athletes who are exposed to pain and strain on the body, and who are encouraged to play through this pain may developed greater conditioned pain modulation.

1.2.1 Conditioned pain modulation of athletes compared to non-athletes

Athletes' conditioned pain modulation (CPM), or naturally occurring pain reducing mechanism, may be more efficient compared to non-athlete counterparts. Geisler et al., conducted a study to assess if 16 male endurance athletes compared to 17 male non-athletes have better CPM. Only males were included due to the possible effect of menstruation on pain processing.[24] Pain pressure threshold was used as a test stimulus, and a 10 degree Celsius cold pressor test as the conditioning stimulus.[24] Athletes rated their pain as less intense than nonathletes by an average of 20 visual analogue scale units, and showed higher CPM effects.[24] They also conducted exploratory analyses and found a correlation between the CPM effect and cardiorespiratory fitness, which they assessed through a submaximal ergometry test.[24] This suggests that acquiring greater aerobic capacity through intensive training may improve the ability of the endogenous system to inhibit pain.[24] Similarly, Flood et al., also conducted a study looking at conditioned pain modulation in 15 athletes and 15 non-athletes at rest using a sequential protocol. Pain pressure threshold was the test stimulus and a cold pressor test the conditioning stimulus. Athletes showed higher baseline pain pressure threshold ($p=0.03$), and lower average and peak pain ratings ($p<0.001$) than nonathletes.[25] Conditioned pain modulation was enhanced in athletes compared to nonathletes ($p<0.05$), since the conditioning stimulus was better able to inhibit the test stimulus.[25]

Vaegter et al., compared the efficiency of pain inhibitory systems in physically active and non-active participants. The physically inactive group completed less then 30 minutes a week of physical activity (median 0 minutes, range 0-30 minutes) while the active group completed greater than 60 minutes of moderate to high intensity physical activity (median 180 minutes, range of 60 to 420 minutes).[14] This is one of the few studies to compare both male (n=28) and female (n=28) participants. The 56 participant were divided into an active (n=30) and inactive (n=26) group.[14] The test stimulus was pain pressure threshold (PPT) and the conditioning stimulus was a cold pressor test.[14] Average baseline PPTs in inactive men (485.8 ± 237.0 kPa) were significantly higher ($p<0.02$) compared to inactive women (316.1 ± 95.9 kPa), however there was no significant difference between active men and women at baseline.[14] This suggests increased experimental pain sensitivity in inactive women compared to inactive men.[14] That said, the CPM response after the conditioning stimulus was maintained in females immediately after the cold pressor test but not males.[14] There may therefore be a difference in endogenous pain inhibitory systems between the two genders.[14] Contrary to other studies mentioned above, they did not find a significant difference between the CPM of active versus inactive subjects.[14] This was surprising even to them, as previous literature frequently shows the contrary, which led them to believe that their participants were not active enough, and that the level of activity is very important in this response.[14] When considering that the active group had a median of only 180 minutes of physical activity per week, compared to varsity athletes for example who train around 5 days a week for more than 60 minutes each session, this study does not truly reflect the population we observed. Though there may be some variation, overall, CPM seems to be more

efficient in individuals who frequently train or play sports, leading to better endogenous pain relief in this population.

Pain remains a subjective concept and the field is still lacking further information on pain and pain management specific to athletes. It is unclear if the pain experience of athletes is different than non-athletes and if pain management strategies such as medication have the same effect on them as non-athletes. A better understanding of how athletes perceive pain, and what may affect their experience might help clinicians better address the pain of their athletes.

1.3.0 Medication and athletes

When pain is experienced, the instinct is to seek medical help or do whatever is needed to get rid of that pain, especially when it becomes a barrier to basic everyday tasks and to activities that bring joy. Sports are an important part of athletes' lives and can frequently cause pain, however many athletes are willing to take medications beforehand to prevent that pain regardless of possible side effects. Overcoming pain and injuries is a central aspect of sports.[26] This impending pain pushes athletes to use pain analgesics before, during, and after competitions or practices as a prophylactic.[27]

1.3.1 Pain management

Protection, rest, ice, compression, elevation, oral Nonsteroidal anti-inflammatory drugs (NSAIDs) and oral or injected corticosteroids are some of the most common tools used for pain management.[27] When bodily tissues are damaged, this initiates an inflammatory cascade. [27] Phospholipids from cell membranes are broken down into arachidonic acid, a building block of inflammatory biomarkers, which in turn get broken down by the COX pathways. [27] NSAIDs function by inhibiting the cyclooxygenase (COX) pathway, which contains two types of COX enzymes; COX-1 and COX-2. The role of both these enzymes is to produce prostaglandins which promote inflammation, pain, and fever.[27] In addition, the COX-1 enzyme also protects intestinal and stomach lining and activates platelets.[27] NSAIDs reduce prostaglandin sensitivity to nociceptors, and reduce vascular permeability, inhibiting the COX pathways and therefore reducing pain and inflammation.[27] This suggests that NSAIDs require tissue damage, or an inflammatory cascade to show an analgesic effect since they work to prevent pain by inhibiting inflammation.

Further, oral corticosteroids prevent leukocytes (white blood cells) from attaching to blood vessels.[27] When inflammation is present, integrins, which are molecules on leukocytes, attach to adhesion molecules on the walls of capillaries, allowing the leukocytes to flatten and squeeze through the endothelial cells.[27] This is called diapedesis and allows inflammatory cells at injury sites to gather.[27] Oral corticosteroids prevent diapedesis and are therefore considered one of the most powerful anti-inflammatories.[27]

1.3.2 Prevalence of pain medication in athletes

Abuse of painkilling medication is very common among athletes, especially amid professionals.[26] Tricker et al., used a survey to observe student athletes' attitude toward painkilling drugs. In their sample, 60% of athletes believed that NSAIDs led to dizziness and

loss of balance.[26] Regardless of this, 58% regularly used painkilling medication throughout their season, 62% used them after difficult workouts and when their muscles were sore, and 62% believed that painkilling drugs were necessary for them to play at their best.[26] Evidently, many athletes rely on these drugs to play their sport, and more specifically to play well. These statistics are shocking, especially at such a young age and considering that professional athletes become even more dependent on NSAIDs[26]. Holmes et al., conducted a study on NSAID use in 211 college football players, 97.5% of whom had or were using NSAIDs.[28] Though the combined effect of training and NSAIDs tends to lead to greater gastrointestinal effects, 50% of players reported high NSAID use during their season, but only 14.6% during off-season.[28] In addition, Christopher et al., found that one in four females and one in five male athletes uses NSAIDs to treat or prevent pain[29].

Jelsema et al., conducted a survey in 2002 which was administered to the players of 30 NFL teams. This survey pertained to game day use of Ketorolac, a type of NSAID for short-relief of pain, which has become sports physicians' most used drug in athletes to help them return to play post injury.[27] 93.3% admitted to game day use of intramuscular ketorolac, with an average of 15 players in each team being injected hours before kickoff.[27] Considering that one injection can alleviate 50%-75% of pain for the athletes lasting 1-2 days,[27] the popularity of this drug among athletes who strive to be the best is easy to understand. These statistics are important and should be kept in mind by health care professionals working with athletes, especially considering that physicians only supervise 27% of NSAID use and that these medications have side effects.[28]

1.3.3 Routes of drug administration

There are different routes of drug administration, and Harle et al., looked at the prevalence of each in athletes. An oral mode of consumption is significantly more common than injectable, and more studies have been conducted on oral NSAIDs according to the authors' findings.[30] 13.5% of NFL athletes with hamstring injuries use injectable corticosteroids, and between 2.2% and 5.7% male athletes at FIFA futsal tournaments used injectable NSAIDs or corticosteroids between 2002 and 2021.[30] In addition, opioid use rates are below 1% in athletes.[30] It is intriguing that oral NSAIDs are most used, when they have greater side effects, which will be discussed later. When comparing topical and oral use of ibuprofen in injured athletes, the topical NSAID may lead to similar levels of pain and anti-inflammatory relief, however, bypasses the side-effects associated with oral intake.[31] Since athletes are frequently faced with acute injuries that become chronic, or overuse injuries, oral NSAIDs are often used to manage pain for an lengthy period of time.[31] This extended use can lead to gastrointestinal, renal and even cardiovascular damage.[31] If topical ibuprofen can decrease unwanted gastrointestinal side effects from orally administered ibuprofen, this is a route that should potentially be more heavily considered.

1.3.4 Efficacy of ibuprofen for reducing pain in athletes

Athletes are frequently experiencing pain and there is a high prevalence of medication use in this population, however only a handful of studies look at the efficacy of NSAIDs in injured athletes. Reynolds et al., looked at the effects of two NSAIDs (meclofenamate and diclofenac) and a placebo in combination with physiotherapy on the healing of acute muscle tears.[32] They found that although participants did improve from day 1-7, there was no difference in pain reduction and swelling as well as change in muscle strength and endurance in the groups

receiving physiotherapy alone or in combination with NSAIDs.[32] In addition, Dupont et al., looked at the efficacy of 2400 mg of ibuprofen per day and a placebo in the treatment of an acute ankle sprain during the first week of treatment.[33] They looked at subjective pain, objective pain via tenderness of the ligaments involved in the sprain, and edema.[33] Much like Reynolds et al., the authors of this study also concluded that although ibuprofen may help to reduce pain in the first few hours after an injury, its use during the first 7 days following an acute ankle sprain does not have much of an effect on recovery compared to functional treatments such as ice, elevation, crutches, and progressive joint mobilizations.[33] Similarly, Astrom et al., evaluated the effect of NSAIDs and a placebo on painful Achilles tendinopathy looking at pain, tenderness, swelling, ankle joint movement and muscle strength 3, 7, 14, and 28 days post injury.[34] There is no difference at any time point between the treatment and placebo group for all the variables.[34] They concluded that piroxicam (NSAID) does not play an important role in relieving symptoms in those with Achilles pain.[34]

These studies all suggest that physical therapy and rehabilitation exercises are the key to recovery and that NSAIDs do not actually play an important role in the healing process. The medications however continue to be frequently used by athletes regardless of potential complications and side effects.

1.3.5 Potential complications of pain analgesics

NSAIDs may cause a variety of gastrointestinal complications such as, mucosal ulceration, bleeding, and perforation. Van Wijck et al., looked at the effects of oral ibuprofen before exercise on gastrointestinal integrity and function in healthy individuals. Their sample included 9 healthy trained men and they compared the effect of 400mg of ibuprofen twice before cycling, cycling with no ibuprofen, 400mg ibuprofen twice at rest and rest without ibuprofen intake. Each participant was put through all of these conditions, with seven days between each test.[35] The authors found that even at rest, ibuprofen increases small intestinal injury ($p<0.003$), and when taken before exercise, it increases the permeability of the small intestine, stomach, and duodenum.[35] One hour of physical activity alone will also cause small intestine injury and affect gut barrier short-term.[35] These two findings led to their conclusion that although the small intestinal injury is reversible within 2 hours, the effects of NSAIDs combined with the physical activity that the athletes perform may increase their risks of GI complications.[35] This can affect their performance or their recovery, and long-term use of NSAIDs may further compromise the GI tract.[35] This is supported in a study by Holmes et al., looking at NSAID use in collegiate football players. Their findings suggest that NSAIDs taken for less than one week is unlikely to cause any complications in healthy people, however the stomach and duodenum may be affected by chronic use of 1 to 3 months.[28] Though these side-effects are known, individuals continue to use NSAIDs over a prolonged period, even athletes who may experience magnified side effects when combined with the irritation of the GI tract from physical activity.

Studying pain medication in athletes is important. Harle et al., conducted a review and looked at different studies focussed on pain tolerance in athletes and made the following bold statement, “Elite athletes, such as professional athletes competing internationally, likely experience pain and pain treatment differently than people undertaking general exercise.”[30] This is striking because if this population truly experiences pain and treatment differently, then maybe they should not be treated the same. Research is lacking on pain and pain management specific

to athletes that could help us truly understand the meaning of this statement, and potentially modify treatment plans to expedite recovery and return to play in this population.

1.4.0 The placebo effect

The placebo effect is very powerful and has been observed in many different contexts but is especially present regarding medication. Studies on the placebo effect as an analgesic in athletes are lacking and are focussed on ergogenic aids to improve performance but not on reducing pain, which is common in athletes.

1.4.1 Placebo

Athletes' response to placebo is of value, as certain aspects of it can be used within clinical treatments to enhance the results. The placebo effect was originally used as a control to help validate different types of therapies,[36] and is defined as a, "change in the body, or the body-mind unit, that occurs as a result of the symbolic significance which one attributes to an event or object in the healing environment."[36] This means that the psychosocial stimuli surrounding the administration of a placebo tells the patient that they should improve, which then leads to a positive response for some.[36] The psychological and social components of both pain and placebo make the latter especially effective in pain studies, more so than in any other conditions.[36] In order to measure the placebo effect, the difference in pain across an untreated and a placebo treated group is measured.[6,37]

1.4.2 Physiology of the placebo effect

Analgesic placebo functions by decreasing the activity in the pain processing regions of the brain and reducing nociception at the spinal cord.[37]. More specifically, reduction in brain activity following an analgesic placebo occurs in the dorsolateral prefrontal cortex, thalamus, insula, periaqueductal area, and anterior cingulate cortex.[6] When administering a placebo, instructions or verbal information, classical conditioning or the creation of association between different stimuli, and social learning will be provided to the recipient which will affect their expectancy of the treatment.[6] Next there will be a release of endogenous opioids and non-opioids which will alter the pain experience.[6] Not everyone responds to the placebo effect. While those that respond experience activation of endogenous opioids, non-responders experience deactivation of their dopaminergic system.[6] This suggests that the key to inducing a successful placebo effect lies in the context, information and environment created in part by the person administering the placebo.

1.4.3 Factors affecting the placebo effect

Many factors can impact the effectiveness of placebo. A person's perception of the intervention they are receiving is key to how effective it can be. Their experience involves sight, smell, and hearing of verbal cues or information.[6,37] The information they gather from the intervention using those senses is then integrated with their previous experiences and their

current expectations.[37] Klinger et al., also discuss the importance of expectancies in the placebo effect. The authors state that expectancies will trigger a cascade of endogenous opioids and nonopioids which then alter the pain experience.[6] In addition to this, patient-client relationship and the atmosphere is critical in generating significant placebo effects.[6] Social learning also plays a role since the placebo effect can be learned by observing other patient's treatment effect.[6] Not only is learning important, but verbal information about the benefits of the analgesic placebo make a big difference in its efficacy.[6] For example, emphasizing all the benefits of a medication, taking the time of explain how long the drug takes to start reducing pain, and describing realistic effects are all important strategies.[6] All of these factors are critical to consider and to maintain consistent when running a placebo trial. Failure to precisely administer a placebo is likely to skew the results.

1.4.4 Placebo and pain

The placebo effect can be powerful enough to reduce pain experience. Jones et al., compared 10 mg of morphine, 600 mg of ibuprofen and a placebo in 12 healthy volunteers using a cold pressor test. They then measured pain intensity before the medication, then at 30, 60, 90, 120 and 180 minutes post medication.[5] They found that morphine significantly reduced pain intensity compared to the placebo, however statistically, the results from the ibuprofen and the placebo trials were indistinguishable.[5] This means that the placebo was as effective as ibuprofen, a drug commonly used by athletes. Similarly, Klinger et al., looked at clinical use of placebo effects in patients with pain disorders by conducting a review. This led to the conclusion that analgesic placebos help patients with chronic, idiopathic, and neuropathic pain, as well as those with migraines and knee osteoarthritis.[6] Another study with 57 participants looked at the effect of 600mg ibuprofen, 600 mg ibuprofen and 1000 mg acetaminophen and a placebo on pain following root canal treatment.[38] When comparing these three treatments, they found a significant reduction in pain for all, though the combination medication group showed the best results.[38] The most interesting part of their findings is that there was no significant difference between the ibuprofen or placebo group.[38] The results of this study are important, because they show that ibuprofen is effective at decreasing pain, and that a placebo can be just as effective. The mentioned studies were not performed on athletes, and the effect of a placebo on this population remains unclear. Placebos cannot ethically be prescribed due to their deceptive nature, however if they have a similar pain reducing effect in athletes as they do in non-athletes, the principles surrounding the placebo effect, such as therapist-patient relationship, creating expectancy, and more can be applied to treatments to improve outcomes. This positivity surrounding the rehabilitation may even help decrease any catastrophizing and may allow athletes to continue playing while maintaining the confidence they acquire from the use of analgesics to prevent pain. Caution needs to be used however, because when patients find out that they were given placebos, they tend to loose trust in their physicians,[6] which can affect the efficacy of future treatment.

1.4.5 The type of outcome matters

The placebo effect is not always effective in all cases and may depend on the types of outcomes in the study. Hróbjartsson et al., conducted a systematic review of clinical trials where patients were assigned to either a placebo (pharmacologic, physical, or psychological) or no

treatment group. The authors made conclusions based on the type of outcomes, articulating that the placebo has no impact on binary outcomes, but has a beneficial impact on continuous outcomes.[39] They also noted that in the trials with continuous outcomes, though the placebo was beneficial, its effect decreased with increasing sample size,[39] suggesting a possible small impact of the placebo effect.[39] In contrast to this, Manoukian et al., conducted a review to compare topical versus oral ibuprofen and a placebo for pain reduction. They found similar anti-inflammatory and pain relief effects in both and compared the topical NSAID to a placebo. Studies that they looked at concluded that topical ibuprofen was superior to placebo in the treatment of joint and soft tissue injury.[31] Differing results in which some placebos decrease pain while others do not may be due to the psychosocial factors that influence the effect of an administered placebo. In addition, though the reason why is still unclear, some individuals seem to be responders, and some are non-responders, therefore certain studies may have randomly grouped more of one over the other.

1.4.6 Placebo and athletes

Placebos may play a role in sport performance. A systematic review by Hurst et al., looking at placebo effect on sports and motor performance in healthy athletes included 32 studies. The studies were grouped into two types of ergogenic aids: nutritional and mechanical. They found an overall small to moderate effect size, equal for both types of ergogenic aids.[40] The efficacy varied depending on the type of placebo and the protocol used to administer it.[40] When the participant is conditioned using a non-placebo before ingesting the placebo, larger effects are found ($n = 257$, $d = 0.82$) compared to studies simply including positive ($n = 985$, $d = 0.36 \pm 0.44$) or negative ($n = 265$, $d = 0.37$) expectations.[40] This reinforces the idea that the placebo effect is complex and relies on many factors. Though these findings are intriguing, future research is necessary to better understand the effect of pain analgesic placebo in athletes, and not only via ergogenic aids. One study by Geisler et al., compared the placebo effect in endurance athletes and non-athletes using conditioned pain modulation and a cold pressor test. They found a significant individual placebo effect in the overall sample showing a 20% reduction in pain for a placebo versus a control.[24] However, when they compared the placebo effect in the athletes versus nonathletes, they found that it only remained significant in the nonathletes (14.97, $p=0.006$) and not in the athletes (7.42, $p=0.111$).[24] Studies looking at the placebo effect in athletes are lacking and the few that have been done do not all come to the same conclusion. Further research is necessary to better understand its effect in an athletic population.

To conclude, the placebo effect can be beneficial for many individuals though athlete specific data is lacking. The administration of a placebo needs to be carefully thought out, as many variables such as our senses, the atmosphere, verbal cues, past experiences, and expectancies will all affect its efficacy. Though some studies find small to moderate effect of placebo, in the context of sports and injuries it is important to remember that even a small improvement can lead to a meaningful outcome, especially regarding performance and perceived quality of life.

1.5.0 Rationale and objectives

It has been suggested that athletes have a complex relationship with pain. In addition, there is evidence that athletes have a higher pain threshold and can tolerate more pain as well. Pain

killing medications, which are commonly used by athletes can have an inhibitory effect on pain, however there is limited data on their effect in athletes. Similarly, it remains unclear if athletes are responsive to the placebo effect, or if they may be more in tune with their pain and bodies, therefore do not respond as well. Conditioned pain modulation is a good measure of pain inhibition, therefore a great tool to measure the effects of ibuprofen and placebo on pain in athletes. **There were multiple objectives to this study. First, to compare the difference in pain between the ibuprofen, placebo, and control groups between visits 1 and 2, and second to look at the difference in pain between males and females. Third, we wanted to look at the difference in PPT between the ibuprofen, placebo, and control groups between visits 1 and 2, and fourth to compare PPT difference between males and females. Finally we wanted to see the difference in cardiovascular variables between the ibuprofen, placebo, and control groups during visits 1 and 2.**

1.6.0 Hypotheses

Our hypotheses are the following:

1. The athlete ibuprofen, placebo, and control groups will feel similar pain during the cold pressor test in visit 1, but the ibuprofen and placebo groups will feel less pain than the control group during the cold pressor test in visit 2 when they are given the appropriate treatment before the painful task.
2. All athletes will experience an increase in pain during the cold pressor test and a corresponding increase in pain pressure threshold after the cold pressor test demonstrating the amount of conditioned pain modulation during both visits.
3. The athletes in the ibuprofen group will experience a decreased change in PPT compared to the athletes in the control and placebo groups during the second visit.
4. The athlete ibuprofen and placebo groups will experience a decrease in blood pressure and heart rate change during the cold pressor test compared to the control group during the second visit.
5. Males and females will experience the same pain and change in PPT during both visits.

CHAPTER 2: METHODS

2.0 Study design:

This study was a semi-randomized control trial consisting of two visits. This study was approved by the University Human Research Ethics Committee of Concordia University (Certificate Number: 30015224) and all participants provided written informed consent.

2.1 Participants and recruitment

120 male and female athletes were recruited from Concordia University's Department of Recreation and Athletics. The recruitment process consisted of announcements at the different teams' practices, posters around campus, and word of mouth. The athletes were allocated to three groups; ibuprofen, placebo, or control until each group consisted of 40 athletes, 20 males and 20 females (see table 1 below). Athletes being recruited were asked if they typically used ibuprofen when they are in pain or sore after playing their sport. For ethical reasons, the ibuprofen group was made up of athletes who already took ibuprofen, and they were asked to bring their own regular strength ibuprofen and take one recommended dose (400mg every 4-6 hours). Once the ibuprofen group was complete, additional athletes who also said yes to taking ibuprofen were randomly allocated to the control or placebo group. Athletes who did not typically use ibuprofen were randomized into either a control, or placebo group.

Randomization process:

1. Participants were asked whether they take ibuprofen when they are injured.
2. For ethical reasons, those who said no were randomly allocated to the placebo or the athlete control group.
    a. Random allocation was conducted by using two envelopes with 40 papers in each, labelled either "P" (placebo) or "C" (control). We used two envelopes, one for males and one for females because we wanted to make sure each group consisted of 20 males and 20 females.
    b. The envelopes each contained 20 "P" and 20 "C" to ensure we reached our wanted sample of 40 participants per group.
    c. Without looking, we pulled a paper from the appropriate envelope (depending on the sex of the participant), and the participant was placed in the group written on the paper.
3. Participants who said yes were placed in the ibuprofen group until our sample of 40 athletes (20 females and 20 males) was filled. Once the ibuprofen group was complete, all other athletes who said yes to taking ibuprofen were randomly allocated to the placebo or athlete control group using the method explained in bullets 2, a-c above.

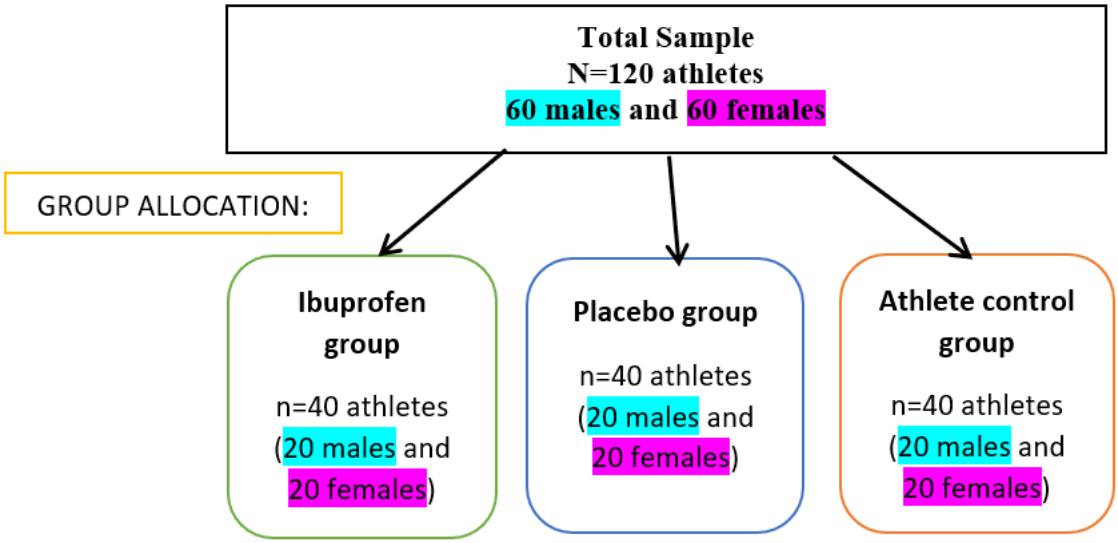

Figure 0 – Group allocations. 120 athletes were allocated to an ibuprofen, placebo, and athlete control group, each consisting of 50% males and 50% females.

2.1.1 Inclusion criteria

- Healthy varsity level athletes
- Male and female athletes
- Between or equal to the ages of 18-35

2.1.2 Exclusion criteria

- Smokers
- Taking medication that alters cardiovascular function.
- Reynaud's syndrome
- Elevated blood pressure (systolic BP over 140 mmHg and DBP over 90 mmHg)
- Current injury that is currently causing them any pain or preventing them from continuing to practice or play

2.2 Measures

2.2.1 Subjective pain rating

The Numeric Pain Rating Scale measured self-reported pain intensity on a scale of "0" (no pain at all), to "10" (the worst pain imaginable). The Numeric Pain Rating Scale is a reliable and valid tool used to measure pain.[41,42]

2.2.2 Pain pressure threshold

Pain pressure threshold was used to assess deep pressure pain sensitivity. Pressure was applied on a body part, and the recipient told the researcher as soon as the pressure became pain. This determined the pressure required over a given area for a non-painful stimulus to become painful. [9]

2.2.3 Cold pressor test

The cold pressor test (CPT) was used to induce pain, which was mentioned in the informed consent form. The CPT is a standard method of laboratory pain induction and can cause peak response within 90 to 120 seconds of stimulation.[43] A plastic cooler was filled with water to two thirds, and maintained at a temperature of 2°C,[41,42] with ice packs and crushed iced. The water temperature was recorded 6 times throughout the protocol, 3 times pre-CPT and 3 times during-CPT to control the water temperature. Pain during the CPT effectively mimics the effects of chronic conditions, has excellent reliability and validity, and has been used in studies to investigate many pain management techniques.[44] Although participants were encouraged to leave their hand in the cold water for the full 3 minutes, they are aware that they can choose to stop the test and remove their hand whenever they want as part of the ethics agreement.

2.2.4 Cardiovascular measures

In addition to pain scores, cardiovascular measures; heart rate and blood pressure, were recorded during the CPT. The heart rate and blood pressure were measured using ECG with the Edan iM50 Monitor. We used a 3-lead electrode placement with one lead below the right clavicle, one below at the left clavicle and the third at the hypogastrium, below the left 12th rib as shown in figure 1.

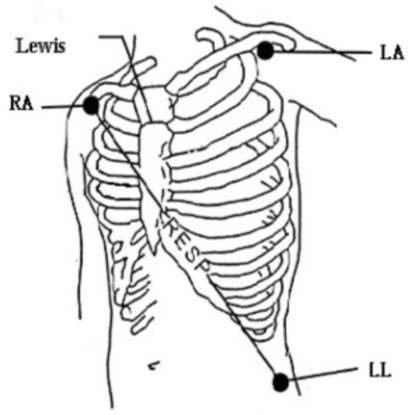

Figure 1 - 3-Lead electrode placement sites. Pad placement to measure heart rate via ECG using the Edan I M50 monitor.

During a painful task, such as the cold pressor test, heart rate and blood pressure increase. A previous study that we conducted showed that athletes' heart rate, and systolic and diastolic blood pressure increases during a painful task, such as the cold pressor test, [22] supporting findings from other similar studies in non-athletic populations. Other studies have shown that in addition to pain severity measures, a physiological change in heart rate and blood pressure occurs as a response to pain.[13,42] This increase has been shown to occur with different methods of

pain induction including the CPT, capsaicin and a heat thermode, [13,42] suggesting that the pain is causing the change in cardiovascular measures. This said, we cannot overlook the fact that the CPT is a sympathetic nervous system activator, which can also cause an increase of these variables, [13,42] thus we cannot be certain about what is driving this increase in HR and BP in our study. Change in cardiovascular measures of pain, such as heart rate and blood pressure may be good objective measures of pain in athletes in the future.

2.3 Protocol

The protocol included 2 visits, lasting 1 to 1.5 hours. Below is a description of how visit 1 and visit 2 were completed.

2.3.1 Visit 1

During visit 1, participants from every group came in and were told that instructions would be read to them from a script to ensure that the wording was the same for everyone. First a set of instructions was read explaining the study to the participants prior to going over the consent form. They were then given time read the consent form and ask any questions they may have had before signing it to provide informed consent. Next, they filled out an eligibility questionnaire to confirm that they fit the criteria required for the study. The questionnaire included a question asking if the participants were smokers, and since we did not define the frequency of smoking, they had to define it themselves, though all the participants reported that they were not smokers. The eligibility questionnaire was reviewed before continuing with the protocol.

If the participant was eligible, they then completed four questionnaires which were handed to them one at a time in the following order:

1. Demographic questionnaire
2. Athlete Fear Avoidance Questionnaire
3. Pain Catastrophizing Scale
4. State-Trait Anxiety Inventory Questionnaire

It is important to note that although all the athletes filled out the questionnaires, numbers 2-4 above were only analyzed by another graduate student whose thesis focussed on the psychological aspects of pain. Once the questionnaires were filled out, participants underwent a cold pressor test as a test stimulus and pain pressure threshold as a conditioning stimulus to measure conditioned pain modulation. Prior to beginning the test, the EDAN iM50 patient monitor was set up to measure blood pressure and heart rate throughout the protocol.

2.3.1.0 EDAN iM50 Patient Monitor setup

1. It was explained to participants that they would be hooked up to the monitor
2. Males were asked to remove their shirt, and females to be in their sports bras (mentioned in consent form)
3. An alcohol swab was used to clean electrode sites

1. Inferior lateral right clavicle
2. Inferior lateral left clavicle
3. Inferior to left rib 12 (hypogastrium)

4. The 3-Lead electrodes were placed on appropriate sites
5. The appropriately sized BP cuff was placed on the left arm

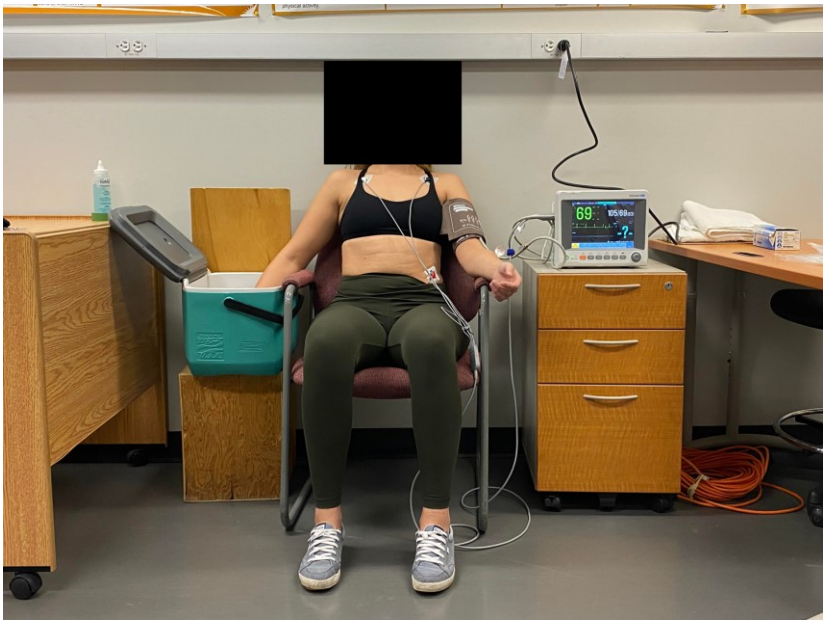

Figure 2 - Final set up with EDAN iM50 monitor. Showing the EDAN iM50 monitor, 3-lead electrode placement, blood pressure cuff on the left arm, and the cooler for the cold pressor test with the right hand submerged.

2.3.2 Cold pressor test and pain pressure threshold for conditioned pain modulation

Once the participants were hooked up the patient monitor, the cold pressor test was started. The cold pressor test was used to induce pain, which was mentioned in the informed consent form.

To set up the CPT, a plastic cooler was filled with water to two thirds, and was maintained at a temperature of 2°C-4°C[41,42], with ice packs attached by velcro on the walls of the cooler and crushed iced. The temperature was monitored using a mercury thermometer. The procedure involved a 10-minute baseline, a 2-minute anticipation period, a 3-minute cold pressor test, a 10-minute recovery period, and 2 pain pressure threshold measures taken before and immediately after the cold-water immersion. (See Figure below showing a timeline of the protocol).

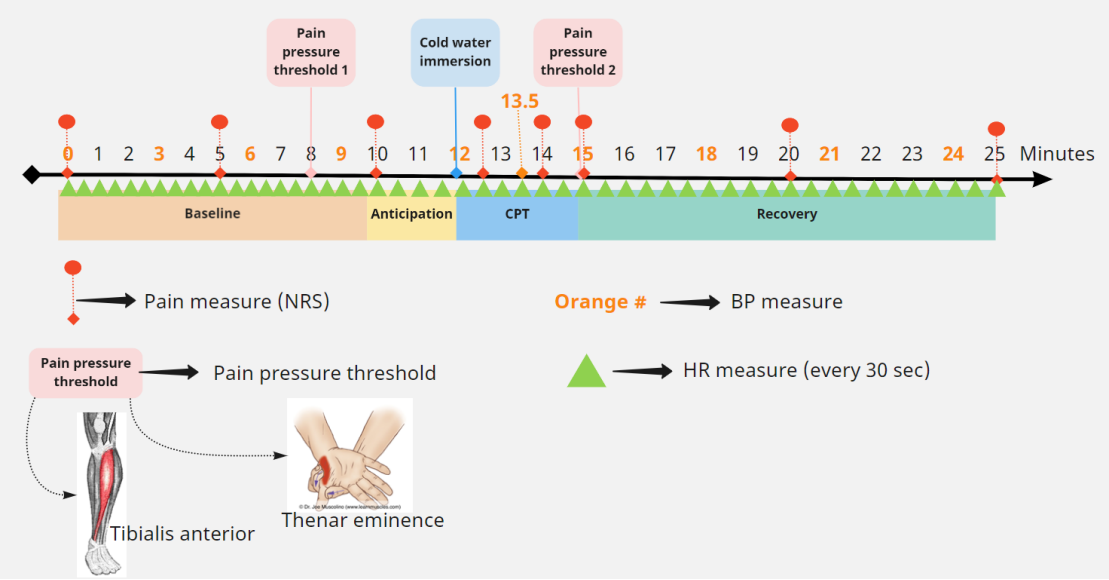

Figure 3 – Protocol timeline. Timeline shows the different sections of the protocol as well as the time points during which pain measures, blood pressure, heart rate, and pain pressure threshold were recorded. The anatomical landmarks for the PPT are also shown in the figure.

2.3.3 Testing protocol:

1. Participants were made aware that all the instructions would be read to them in order to keep the wording the same for everyone (see appendix for the script).
2. Participants were asked to stay seated upright with their feet flat since cardiovascular measures were taken throughout the 25-minute protocol.
3. At minute 0 the EDAN iM50 patient monitor was set up to begin recording blood pressure and heart rate.
4. Minutes 0 to 10 allowed us to obtain baseline measures of perceived pain intensity using a numerical rating scale of 0 to 10 (0, no pain at all and 10, the worst pain imaginable), blood pressure and heart rate.
5. At minute 8 during the baseline period, the first pain pressure threshold measures were recorded at both the tibialis anterior and the thenar eminence using a pressure algometer. Each location was tested twice in tandem to ensure accuracy. Right before the participant was instructed to say, “now” the moment the pressure became pain.
6. At minute 10 the cooler with the 2°C-4°C water was brought into the room and placed near the participant. When the cold water becomes visible to the participant, it can cause an anticipatory spike in blood pressure and heart rate, therefore during this anticipation period, no variables were recorded to allow the cardiovascular measures to return to baseline if a change had occurred.
7. Just before minute 12, participants were instructed to immerse their hand in the cold water up to 1 cm above their wrist. They were asked to keep their hand open and not to touch the ice packs that surround the cooler.
8. At minute 12 participants immersed their hand in the center of the cooler and were told to remove it at minute 15. Participants were encouraged to leave their hand in the

cold water for the full 3 minutes. Perceived pain intensity, blood pressure and heart rate were recorded during the submersion.

9. At minute 15 the second pain pressure threshold was recorded at both the tibialis anterior and the thenar eminence using a pressure algometer. Once again, each location was tested twice in tandem to ensure accuracy.
10. Minutes 15-25 consisted of a recovery period during which perceived pain intensity, blood pressure and heart rate continued to be recorded. This period allowed us to observe changes in the above-mentioned variables during CPT to post CPT, and to ensure that cardiovascular variables returned closer to baseline.

Visit 1 was identical for all participants regardless of group allocation.

2.3.4 Visit 2

During the second visit, the EDAN iM50 patient monitor set up was identical, and the exact same testing protocol was repeated. The difference between the two visits was that the questionnaires (Demographic questionnaire, Athlete Fear Avoidance Questionnaire, Pain Catastrophizing Scale, and State-Trait Anxiety Inventory Questionnaire) were not filled out again and that each group had a slightly different preparation leading up to the testing.

2.3.4.0 Control group

The participants in the control group showed up for visit 2. The questionnaires were not filled out again. During this visit they simply repeated the exact same testing protocol as visit 1 (see figure 3 above).

2.3.4.1 Ibuprofen group

The participants in the ibuprofen group were asked and reminded the day before their second visit to bring their own regular strength ibuprofen. The type of ibuprofen does not matter because whether it is a name brand or a generic brand, the ingredients are the same. When participants showed up to the lab, they did not have to fill out the questionnaires again. They were asked to take the recommended dosage (400mg) for ibuprofen and asked to sit down for 30 minutes until the medication took effect. Once the 30 minutes had passed, they simply repeated the exact same testing protocol as visit 1 (see figure 3 above).

2.3.4.2 Placebo group

The participants in the placebo group showed up for their second visit and were provided with a placebo analgesic medication; a lactose placebo pill. The questionnaires were not filled out again. They were asked to take the placebo analgesic and to sit down for 30 minutes until the medication takes effect. Once the 30 minutes passed, they repeated the exact same testing protocol as visit 1 (see figure 3 above). Before leaving the laboratory, all participants in the placebo group were given a deception form explaining that they had received a placebo (See appendix for deception form).

BASELINE – min 0-10	Anticipation – min 10-12	CPT – min 12-15	Recovery – min 15-25
HR – 20 measurements of HR	No values in this 2 min anticipation period are included in analysis.	**HR** – 6 measurements	**HR** -20 measurements
SBP – 4 measures		**SBP** – 2 measures	**SBP** – 4 measures
DBP -4 measures		**DBP** – 2 measures	**DBP** – 4 measures
Pain (NRS) – 3 measurements of pain		**Pain (NRS)** – 2 measurements of pain	**Pain (NRS)** – 3 measurements of pain

Table 2 – Breakdown of measurements during each segment of the CPT. This table shows the number of measurements taken during each time point. The measures in each section are averaged out to obtain average baseline, average CPT and average recovery HR, SBP, DBP, and Pain scores.

2.4 Statistical analysis

Pain scores, and cardiovascular values (heart rate and blood pressure), were averaged at 3 time points: baseline (min 0-10), CPT (min 12-15), and recovery (min 15-25). An analysis was conducted to compare values at these three time points.

All the data is presented as means ± standard deviation. Differences with $p<0.05$ were considered statistically significant. When Mauchly's test of sphericity was violated ($p<0.05$), Greenhouse-Geisser was chosen as an alternative univariate test. The section below will explain the statistical tests used for the different variables.

Participant demographics

- Group comparisons: An ANOVA was used to compare age, weight, and height between the ibuprofen, placebo, and control groups.
- Sex comparisons: Three t-tests were conducted to compare the age, height, and weight between males and females.
- Training hours between groups: An ANOVA was conducted to compare the training hours per week between the ibuprofen, placebo, and control groups.

Subjective pain outcomes

- One large repeated measures ANOVA was conducted to compare the three groups (ibuprofen, placebo, and control), the three time points (pre-, during-, and post-CPT), the two visits (day 1 and day 2) and the sex*time interaction.

Pain pressure threshold

- Pain pressure threshold was measured at the thenar eminence (upper extremity) and the tibialis anterior (lower extremity).

- One large repeated measures ANOVA was used to identify differences in upper extremity PPT among the three groups (ibuprofen, placebo, and control), the two time points (pre- and post-CPT), and the two visits (day 1 and day 2) using sex as a between subjects factor.
- An independent sample t-test was used to identify difference in conditioned pain modulation (change in PPT) between sexes for the upper extremity.
- Another repeated measures ANOVA was used to identify differences in lower extremity PPT among the three groups (ibuprofen, placebo, and control), the two time points (pre- and post-CPT), and the two visits (day 1 and day 2) using sex as a between subjects factor.
- An independent sample t-test was used to identify difference in conditioned pain modulation (change in PPT) between sexes for the lower extremity.

Cardiovascular measures

- To compare heart rate (HR), a large repeated measures ANOVA was conducted to compare the HR for the three groups (ibuprofen, placebo, and control), the three time points (pre-, during-, and post-CPT), and the two visits (day 1 and day 2). To compare HR in the two sexes, the sex*time interaction from this ANOVA was interpreted.
- The same procedure was repeated for systolic blood pressure and then diastolic blood pressure.

CHAPTER 3: RESULTS

3.0 Participant demographics

3.0.1 Study enrollment

A total of 126 athletes that play a sport at the varsity level, with some also part of the provincial or Canadian teams for their sport participated in the study. Of these individuals 6 were either unable to finish the 3-minute cold pressor test and withdrew their hand or were excluded.

As shown in Figure 4 below, 6 athletes; 3 females and 3 males were excluded after their first visit due to various reasons. Two of the females experienced a visceral response to the pain including pallor, sweating, nausea, and dizziness. They started to faint, so the testing was immediately stopped. They remained in the lab until they felt better, and their heart rates and blood pressures returned to normal. Since these two females experienced an adverse response to the painful stimuli, they were not asked to return for a second visit to prevent the reoccurrence of these symptoms. The third female stated that her subjective pain rating was 10 out of 10, and withdrew her hand, choosing to stop the testing. As was explained in the consent form, any participant had the right to stop testing whenever without any consequences. In contrast to this, two of the males experienced 0 on 10 pain during the cold pressor test. Conditioned pain

modulation requires a painful conditioning stimulus, in this case the immersion of the hand in cold water (CPT), which should lead to a decrease in perceived pain during the test stimulus (pain pressure threshold). If the conditioning stimulus is not painful, conditioned pain modulation cannot be observed, therefore these participants were excluded and did not come back for a second visit. The third male experienced 7/10 pain and withdrew his hand, stating that the pain was too intense.

Therefore, data from 120 participants completed the study and were analyzed (age= 22.7 ± 2.4 years, height = 172.1 ± 11.0 cm, mass = 77.1 ± 18.8 kg). 60 of these participants were males (age= 22.9 ± 2.2 years, height = 179.3 ± 9.6 cm, mass = 89.2 ± 18.2 kg), and 60 were females (age= 22.5 ± 2.5 years, height = 164.8 ± 6.7 cm, mass = 65.0 ± 9.2 lbs).

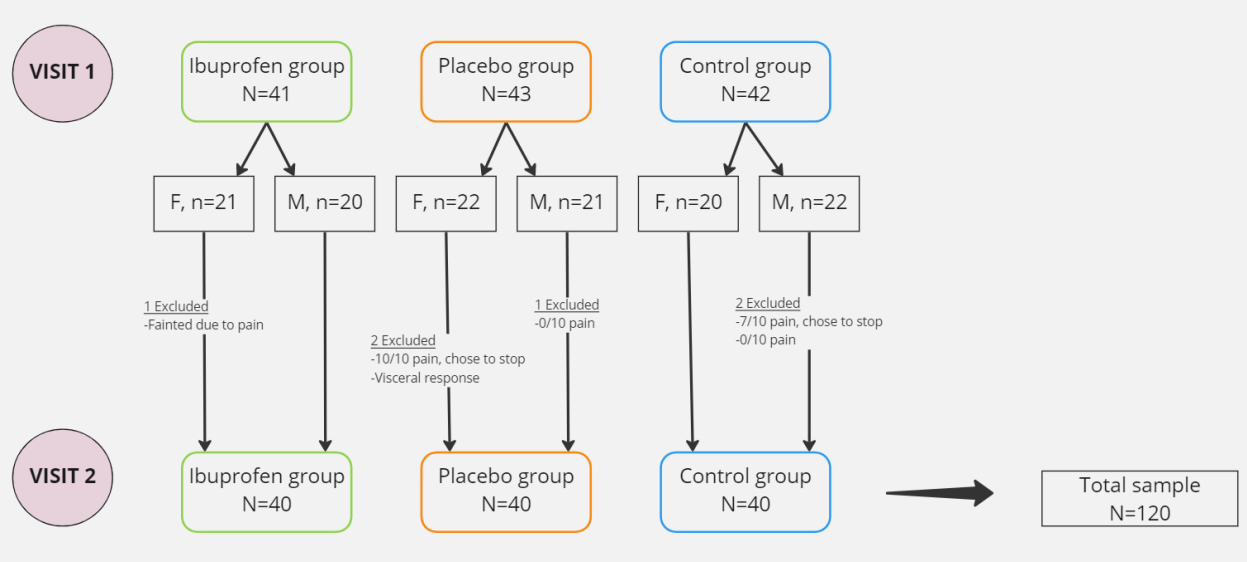

Figure 4 - Flow diagram of participant enrollment and group allocations of athletes. The goal was to obtain a sample size of 120 athletes, with 40 participants per group. As participants were excluded, recruitment was continued until the desired sample sized was achieved. Note that 6 participants were excluded.

3.0.2 Participant characteristics

Group	***Ibuprofen(n=40)***		***Placebo(n=40)***		***Control(n=40)***	
Sex	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Age	23.1±2.3	22.6±2.7	22.3±2.1	22.5±2.0	23.2±2.3	22.4±2.9
Height (cm)	178.5±11.1	165.4±6.6	177.9±13.1	164.9±9.0	179.2±11.7	169.6±6.4
Weight (kg)	89.3±15.7	66.5±9.9	85.2±17.5	65.4±9.8	89.4±18.3	63.5±8.0
Training hours/wk	12.8±5.9	11.3±2.7	14.0±3.6	14.9±4.8	13.2±4.5	13.7±4.0
Training sessions/wk	6.4±1.7	6.1±1.6	6.1±1.1	7.2±3.2	6.4±1.9	6.8±2.0
Rugby	6	4	2	7	3	7
Wrestling	1	0	0	4	3	1

Sport (# of athletes)	**Soccer**	2	6	6	3	1	5
	Synchronized figure skating	0	0	0	1	0	2
	Football	9	0	7	0	7	0
	Flag football	0	1	0	0	0	1
	Triathlon	0	1	0	0	3	0
	Boxing	0	0	0	0	0	1
	Basketball	1	4	4	5	3	1
	Hockey	0	4	0	0	0	2
	Baseball	1	0	1	0	0	0

Table 3 - Mean baseline demographic measures for all participants (n=120) that completed the study and were analyzed. The table shows demographic measures separated by group and sex allocation (mean ± SD), as well as the sports they performed.

The athlete sample was semi-randomly allocated into one of three groups: ibuprofen, placebo, or control. Table 3 shows the initial screening measures of demographics of all three groups. An ANOVA indicated no significant difference in age (p=0.641), weight (p=0.555), or height (p=0.134) for each treatment group within their own sex. This means that the demographics for all athletes were similar between the three treatment groups.

Independent sample t-tests were conducted to compare the difference in age, height, and weight between the two sexes. There was no significant difference in age between females (22.5 ± 2.5) and males (22.9 ± 2.2); t(118) = -0.847, p=0.398). Female athletes were significantly lighter (65.1 ± 9.2kg) than males (89.4 ± 18.3kg) (t(118)= -9.199, p=0.000), weighing an average 24.3 ± 2.6kg less. Similarly, females were significantly shorter (166.6 ± 7.5 cm) than males (179.2 ± 11.7 cm) by an average 12.6 ± 1.8 cm (t(118) = -6.999, p<0.001).

There was a statistically significant difference in training hours per week between the groups, determined by a one-way ANOVA (F=3.119, P=0.048). A Tukey post-hoc test showed that the training hours per week for the ibuprofen group were statistically significantly lower (12.1 ± 4.6) when compared to the placebo group (14.4 ± 4.2), with an average 2.3 hours less of training (p=0.037, 95% CI [-4.634, -0.116]). There was no statistically significant difference in training hours between the ibuprofen and control group (p=0.383) and the placebo and control group (p=0.964).

3.1 Subjective pain outcomes

3.1.0 Pain analysis for all athletes

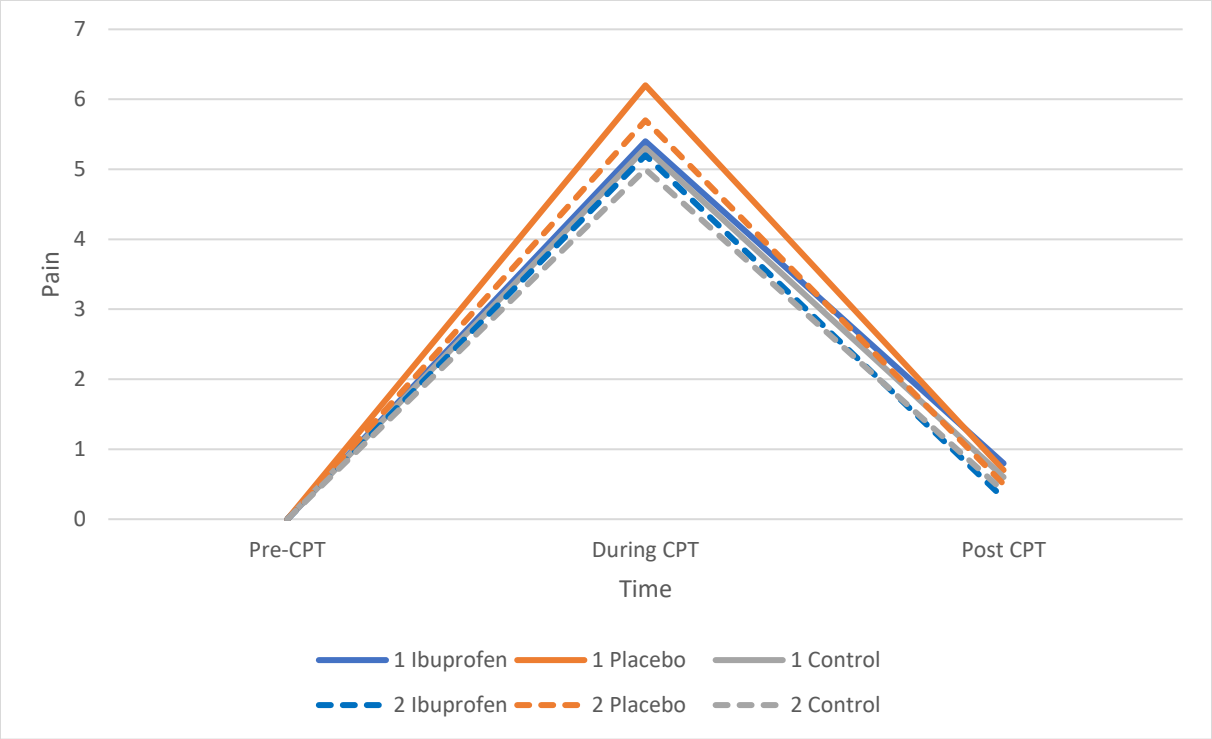

Figure 5 – Line graph showing average peak self reported pain values pre-, during-, and post-CPT of athletes in each treatment group, during visits 1 and 2. This is a visual depiction of the data in table 4.

	Visit 1			Visit 2		
Groups/Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**
Ibuprofen	0.0±0.0	5.4±1.9γ	0.8±1.2*	0.0±0.0	5.2±2.3γ	0.3±0.9*
Placebo	0.0±0.0	6.2±2.3γ	0.7±1.2*	0.0±0.0	5.7±2.2γ	0.5±0.8*
Control	0.0±0.0	5.3±1.8γ	0.6±0.8*	0.0±0.0	5.0±1.8γ	0.4±0.6*
Average Pain for all three groups	0.0 ± 0.0	5.5 ± 0.2γ	0.5 ± 0.1*	0.0 ± 0.0	5.3 ± 0.2γ	0.4 ± 0.1*

Table 4 - Average peak self-reported pain values pre-, during-, and post- CPT of athletes in each treatment group, during visits 1 and 2. For subjective pain ratings, a repeated measures ANOVA indicated a main effect of time, revealing a significant increase during-CPT followed by decrease post CPT. The γ represents the significant increase ($p<0.001$) in pain during-CPT for both visits. * Indicates a significant decrease ($p<0.001$) post-CPT.

All participants experienced an increase in pain from baseline to during the CPT, which can be seen by the γ in table 4, followed by a decrease in pain post-CPT shown by a * in table 4.

There were no differences in peak pain between all the athletes in the different groups, at the three time points, which can be confirmed with a repeated measures ANOVA ($F(2,76)=1.715$, $P=0.187$) and ($F(2,76)=1.388$, $p=0.256$) for visits 1 and 2 respectively.

No differences were found between the average peak pain scores of the three treatment groups, therefore an average of the peak pain scores of all the athletes at each time point, shown in the last row of table 4, was used to analyze the effect of time. A repeated measures ANOVA was used since the same variables were observed in the participants at three time points (pre-, during-, and post-CPT). Mauchly's test of sphericity was met when comparing the treatment groups ($p=0.0864$) but was violated when looking at time, visits*groups, and time*sex interaction ($p<0.001$ for all). Greenhouse-Geisser was chosen as an alternative univariate test if sphericity was violated. The repeated measures ANOVA indicated that the average peak subjective pain scores are significantly different across the three time points for visit 1 ($F(1.28,48.697) = 711.391$, $p<0.001$) and visit 2 ($F(1.234, 46.880) = 616.807$, $p<0.001$). A post hoc pairwise comparison using the Bonferroni correction showed a significant increase of 5.5 in average peak pain score from the pre-CPT to the CPT time point ($p<0.001$) and a significant decrease of 4.9 from the CPT to post-CPT time point ($p<0.001$). The post hoc pairwise comparison for visit 2 also using the Bonferroni correction showed a significant increase of 5.3 in average peak pain score from the pre-CPT to the CPT time point ($p = 0.000$) and a significant decrease of 4.9 from the CPT to post-CPT time point ($p<0.001$). The repeated measures ANOVA also indicated that there was no significant difference in average peak pain for each group during visit 1 compared to visit 2 ($F(1.956, 74.325) = 0.284$, $p=0.753$). This can be observed by comparing the visit 1 and 2 columns in table 4.

It can be concluded that the results of the ANOVA indicate a significant time effect for average peak pain scores meaning that all the athletes experienced and increase in pain during the CPT followed by a decrease in pain post CPT, however, pain did not change for any group during the second visit meaning that the ibuprofen and placebo did not reduce the pain.

3.1.1 Pain analysis for males versus females

	Visit 1			Visit 2		
Sex/Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**
Females	0.0±0.0	5.7±1.7 γ	0.9±1.3*	0.0±0.0	5.4±0.3 γ	0.4±0.1*
Males	0.0±0.0	5.6±2.4 γ	0.5±0.9*	0.0±0.0	5.2±0.3 γ	0.3±0.1*

Table 5 Average peak self-reported pain values pre-, during-, and post- CPT of all males and all female athletes that completed the study at each time point, and at both visits. These values represent the average peak pain of all the females in the three groups (n=60) and the males in the three groups (n=60). For subjective pain ratings, a repeated measures ANOVA indicated a main effect of time, revealing a significant increase during-CPT followed by decrease post CPT. The γ represents the significant increase ($p<0.001$) in pain during-CPT for both visits. * Indicates a significant decrease ($p<0.001$) post-CPT.

Since there were no differences in pain between the ibuprofen, placebo, and control group, differences between male and female athletes' average peak pain were examined by grouping each sex together regardless of group allocation. These values are shown in table 5. Although all athletes show a significant increase in pain during the CPT (see highlighted columns in table 4) and a significant decrease in peak pain post-CPT (see * in table 4), males and females experienced similar pain scores throughout the procedure. There was no significant time*sex interaction (p=0.441 and p=0.779 for visits 1 and 2 respectively). This can be observed by comparing the females and males rows of table 4 suggest that there was no difference between the pain experience of male and female athletes during the cold pressor test.

3.2 Pain pressure threshold

3.2.0 Upper extremity PPT: Thenar eminence

3.2.0.1 UE PPT for all athletes

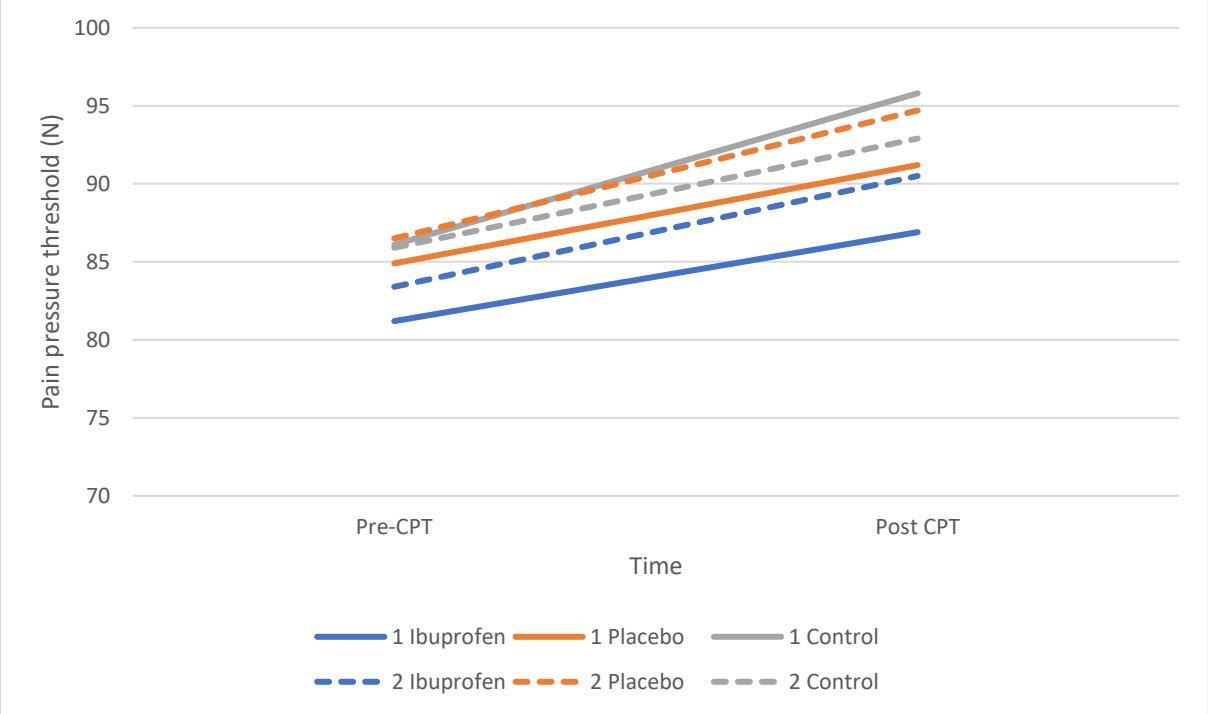

Figure 6 – Line graph showing thenar eminence (upper extremity) average PPT values for all athletes that completed the study separated by groups, during visits 1 and 2, at each time point (pre-CPT and post-CPT) (n=120). This is a visual depiction of the data in table 6.

Visit	Time	Ibuprofen Group	Placebo Group	Control Group	Average	
Visit 1	Pre-CPT	81.2 ± 30.1N	84.9 ± 29.0N	86.1 ± 35.6N	84.1 ± 31.5N	**
	Post-CPT	86.9 ± 32.6 N	91.2 ± 34.7N	95.8 ± 36.6N	91.3 ± 34.6N	
Visit 2	Pre-CPT	83.4 ± 33.9 N	86.5 ± 31.8N	85.9 ± 34.5N	85.2 ± 33.1N	**
	Post-CPT	90.5 ± 29.7 N	94.7 ± 35.6N	92.9 ± 32.5N	92.7 ± 32.4N	

Table 6. Thenar eminence (upper extremity) average PPT values for all athletes that completed the study separated by groups, during visits 1 and 2, at each time point (pre-CPT and post-CPT) (n=120). Average UE PPT is displayed in the last column of the table and represents the average PPT value of all the groups together at each visit and time point. A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in PPT post-CPT. The ** show a significant increase ($p<0.001$) in PPT for all groups from pre- to post-CPT time points for both visits.

All participants experienced an increase in pain pressure threshold (PPT) on the thenar eminence from pre- to post-CPT which can be observed in table 6 above. This change in PPT signifies that the conditioned pain modulation model has worked for all athletes using the CPT as a conditioning stimulus and the PPT as a test stimulus.

There is no difference in average upper extremity (UE) PPT measures between the different groups ($F(2,76)=0.327$, $p=0.722$) and between the two visits ($F(1,38)=0.547$, $p=0.464$). This can be seen in table 6 above, which shows average UE PPT values for all the athletes in each group

A repeated measures ANOVA determined that the average UE PPT scores are significantly different across the two time points ($F(1,38) = 81.076$, $p<0.001$). A post hoc pairwise comparison using the Bonferroni correction showed a significant increase of 7.4 ± 0.8 N in average UE PPT score from time 1 to time 2 ($p<0.001$). This can be observed by looking at rows 2 and 3 of table 6 for visit one and rows 4 and 5 for visit 2. Overall, there was no difference between the different treatments during visit one or visit two. There was however a significant time main effect during both visits showing that everyone experiences and increase in UE PPT post-CPT.

3.2.0.2 Sex differences in UE PPT

	Visit 1			Visit 2			Average UE PPT for each sex	
Sex/Time	**Pre-CPT**	**Post-CPT**	**CPM**	**Pre-CPT**	**Post-CPT**	**CPM**		
Females	70.2 ± 3.6 N	74.7 ± 3.9 N γ	4.5 ± 11.6 N	70.2 ± 3.8 N	78.2 ± 3.5 N γ	8.0 ±10.7 N	73.3 ± 3.4 N	€
Males	98.0 ± 3.6 N	107.9 ± 3.9 N γ	9.9 ± 15.1 N	100.2 ± 3.8 N	107.2 ± 3.5 N γ	7.0 ± 16.4 N	103.3 ±3.4 N	

Table 7. Average upper extremity PPT pre-, and post- CPT of all male and all female athletes that completed the study at each time point, and at both visits. (n=120) These values represent the average UE PPT of all the females in the three groups combined (n=60) and the males in the three groups combined (n=60). A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in UE PPT post-CPT. The γ represents a significant increase ($p<0.001$) in PPT from pre- to post-CPT time points. € indicates a significant difference in UE PPT between males and females at all time points and both visits ($p<0.001$). CPM refers to the change in PPT pre- and post-CPT.

While observing sex as a between subjects effect in the repeated measures ANOVA, a significant difference in UE PPT scores between males and females was shown ($F(1, 38) = 38.837$, $p<0.001$). A post hoc pairwise comparison using the Bonferroni correction showed a significant difference of 30.0 ± 4.8 N between the average UE PPT of the two sexes, which can be seen in the last column (average) of table 7 above ($p<0.001$).

In addition to observing the average PPT scores, it is important to notice the change in PPT between the two time points for each sex which indicates the conditioned pain modulation value and is displayed in table 7 under CPM. An independent sample t-test was conducted to observe the change in PPT between the sexes at each visit. The independent sample t-test found a statistically significant difference of 5.4 N between the average UE PPT difference of females and males (which can be seen in column 4 of table7) during visit 1 (($t(118) = -2.191$, $p= 0.030$), 95% CI: -10.28, -0.52). No significant difference was found during visit 2 for the UE PPT difference between females, whom experienced a change 1.0 N greater than males (($t(118)= 0.393$, $p=0.012$), 95% CI: -4.00, 6.00). Overall, females have consistently lower pain pressure threshold values at the thenar eminence, but males and females have similar CPM values.

3.2.1 Lower extremity PPT: Tibialis anterior

3.2.1.1 LE PPT for all athletes

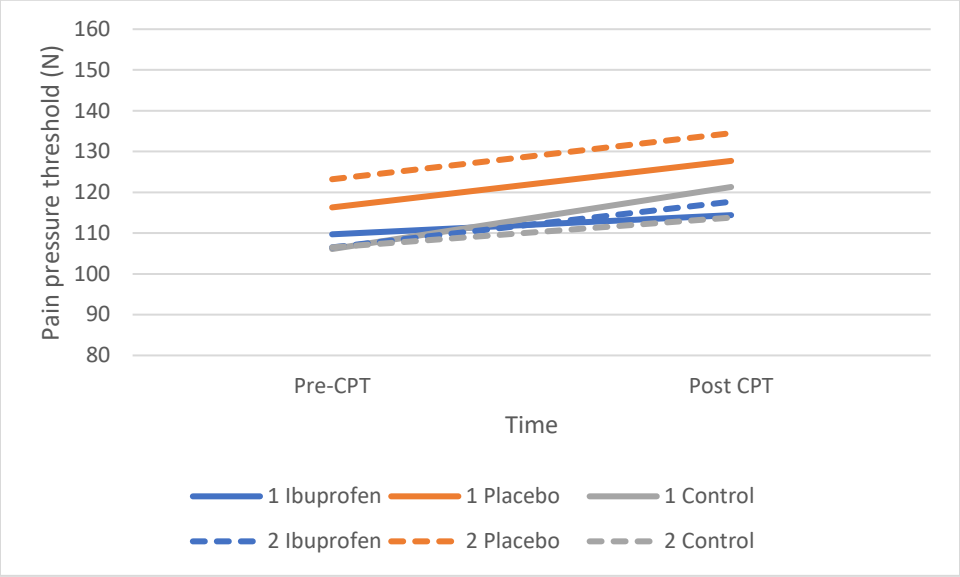

Figure 7 – Line graph showing tibialis anterior (lower extremity) average PPT values for all athletes that completed the study separated by groups, during visits 1 and 2, at each time point (pre-CPT and post-CPT) (n=120). This is a visual depiction of the data in table 8.

Visit	Time	Ibuprofen Group	Placebo Group	Control Group	Average	
Visit 1	Pre-CPT	109.7 ± 40.3N	116.3 ± 42.6N	106.1 ± 43.8N	110.7 ± 3.4N	
	Post-CPT	114.4 ± 47.6N	127.7 ± 45.9N	121.3 ± 43.7N	121.1 ± 3.8N	**
Visit 2	Pre-CPT	106.5 ± 41.0N	123.2 ± 50.9N	106.5 ± 42.0N	112.1 ± 3.0N	
	Post-CPT	117.7 ± 47.5N	134.5 ± 53.4N	113.8 ± 42.6N	122.0 ± 3.7N	**

Table 8. Tibialis anterior (lower extremity) average PPT values for all athletes that completed the study separated by groups, during visits 1 and 2, at each time point (pre-CPT and post-CPT) (n=120). Average UE PPT is displayed in the last column of the table and represents the average PPT value of all the groups together at each visit and time point. A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in PPT post-CPT. The ** show a significant increase ($p<0.001$) in PPT for all groups from pre- to post-CPT time points for both visits.

All participants experienced an increase in pain pressure threshold (PPT) on the tibialis anterior from pre- to post-CPT which can be observed in table 8 above. This change in PPT signifies that the conditioned pain modulation model has worked for all athletes at the tibialis anterior using the CPT as a conditioning stimulus and the PPT as a test stimulus.

There is no difference in average lower extremity (LE) PPT measures between the different groups and between the two visits. This was indicated by a repeated measures ANOVA ($F(2,76)=1.493$, $p=0.231$) and ($F(1,38)=0.231$, $p=0.634$) for groups and visits respectively and the results can be seen in table 8.

The repeated measures ANOVA indicated that the average LE PPT scores are significantly different across the two time points ($F(1,38) = 55.611$, $p<0.001$). A post hoc pairwise comparison using the Bonferroni correction showed a significant increase of 10.2 ± 1.4 N in average LE PPT score from time 1 to time 2 ($p< 0.001$). This increase was observed during both visits and can be seen by comparing the pre- and post-CPT rows for each visit in table 8. Overall, there was no difference between the different treatments on visit one or visit two. However, it can be concluded that the results of the ANOVA indicate a significant main time effect for average lower extremity pain pressure threshold measures.

3.2.1.1 Sex differences in LE PPT

	Visit 1			Visit 2			Average LE PPT for each sex
Sex/Time	**Pre-CPT**	**Post-CPT**	**CPM**	**Pre-CPT**	**Post-CPT**	**CPM**	
Females	94.3 ± 4.8N	104.5 ± 5.4N γ	10.2 ± 17.6	93.9 ± 4.2	103.9 ± 5.2N γ	10.0 ± 13.8	99.1 ± 4.5 €
Males	127.1 ± 4.8N	137.8 ± 5.4N γ	10.7 ± 24.6	130.2 ± 4.2	140.1 ± 5.2N γ	9.8 ± 19.1	133.8 ± 4.5 €

Table 9. Average lower extremity PPT pre-, and post- CPT of all male and all female athletes that completed the study at each time point, and at both visits. (n=120) These values represent the average LE PPT of all the females in the three groups combined (n=60) and the males in the three groups combined (n=60). A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in UE PPT post-CPT. The γ represents a significant increase ($p<0.001$) in PPT from pre- to post-CPT time points. € indicates a significant difference in LE PPT between males and females at all time points and both visits ($p<0.001$). CPM refers to the change in PPT pre- and post-CPT.

While observing sex as a between subjects effect in the repeated measures ANOVA, a significant difference in LE PPT scores between males and females was shown ($F(1, 38) = 29.413$, $p<0.001$). A post hoc pairwise comparison using the Bonferroni correction showed that the average female LE PPT was 34.7 ± 6.4 N lower than males ($p<0.001$). This can be seen in the last column of table 9.

In addition to observing the average PPT scores, it is important to notice the change in PPT between the two time points for each sex which indicates the conditioned pain modulation

value and is displayed in table 9 under the CPM columns. An independent sample t-test was conducted to observe the change in PPT between the sexes at each visit and found no statistically significant difference between the average LE PPT difference of females and males during visit 1 ((t(118) = -0.128, p= 0.898), 95% CI: -8.24, 7.24) and visit 2 ((t(118)= 0.063, p=0.950), 95% CI: -5.84, 6.22).

3.3 Cardiovascular measures

To analyze cardiovascular measures, repeated measures ANOVAs were used since the same variables were observed in the participants at more than two time points (pre-, during-, and post-CPT). When Mauchly's test of sphericity was violated ($p<0.05$), Greenhouse-Geisser was chosen as an alternative univariate test.

3.3.0 Heart rate

3.3.0.1 Average heart rate of all participants

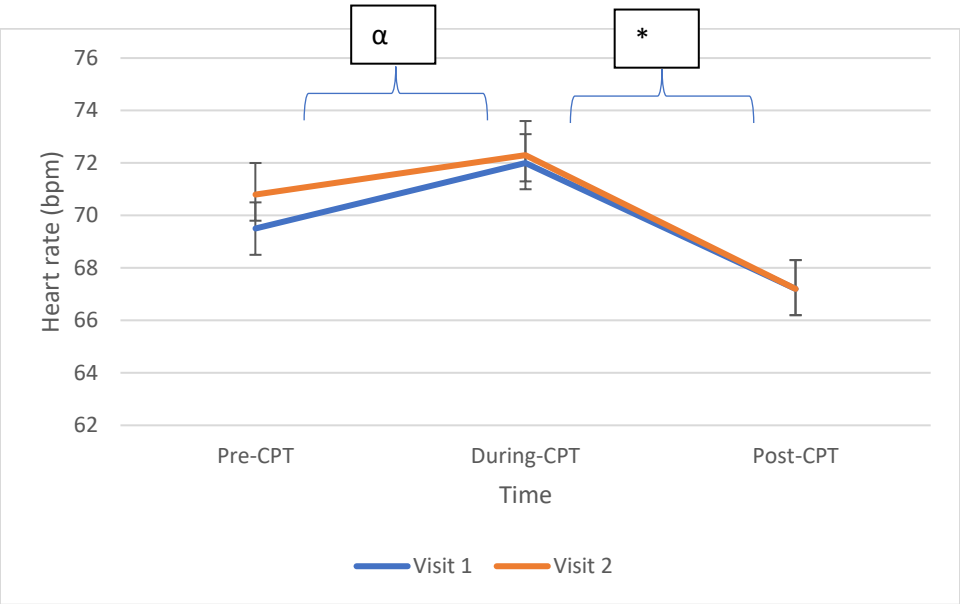

Figure 8 - Average heart rate for all participants (n=120) that completed the study pre-, during- and post-CPT, during visit 1 and visit 2. The bars indicate standard deviation. A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in heart rate during the CPT followed by a significant decrease post CPT. α represents a significant increase in heart rate during-CPT ($p<0.001$) and * represents a significant decrease in HR post-CPT.

Group	Ibuprofen			Placebo			Control		
Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**
Visit 1	70.1±10.1 bpm	72.7±10.0 bpm γ	66.1±9.3 bpm *	69.5±9.1 bpm	71.4±9.9 bpm γ	65.8±9.6 bpm *	68.3±9.6 bpm	71.7±10.6 bpm γ	65.6±9.0 bpm *
Visit 2	70.7±9.4 bpm	70.9±9.5 bpmγ	66.2±9.3 bpm *	69.6±9.2 bpm	72.6±10.2 bpm γ	66.7±8.8 bpm *	72.1±12.3 bpm	73.3±13.2 bpm γ	68.7±11.2 bpm *

Table 10 - Average heart rate (bpm) values of all participants (n=120), in each group, during visits 1 and 2, at the three time points: pre-, during-, and post-CPT. For heart rate, a repeated measures ANOVA indicated a main effect of time, revealing a significant increase during-CPT followed by decrease post CPT. The γ represents the significant increase ($p<0.001$) in pain during-CPT for both visits. * Indicates a significant decrease ($p<0.001$) post-CPT.

All participants experienced an increase in heart rate (HR) during the cold pressor test, followed by a decrease afterward. A repeated measures ANOVA determined that there was no main effect of groups ($F(1.703,64.703) = 0.112$, $p=0.864$) nor visits ($F(1.000, 38.000) = 2.427$, $p=0.128$), meaning that there was no difference between average heart rate between the ibuprofen, placebo, and control groups, at the 2 visits, which can be seen in table 10 above.

The same repeated measures ANOVA indicated a main effect of time ($F(1.521, 57.789) = 88.278$, $p<0.001$). A post hoc pairwise comparison using the Bonferroni correction showed a significant increase of 2.5 in average heart rate from the pre-CPT to the CPT time point ($p< 0.001$) and a significant decrease of 6.2 from the CPT to post-CPT time point ($p<0.001$) for visit 1. This can be seen on the blue visit 1 line in figure 5. The post hoc pairwise comparison for visit 2 also using the Bonferroni correction showed a significant increase in average heart rate of 1.5 from the pre-CPT to the CPT time point ($p< 0.001$) and a significant decrease of 5.1 from the CPT to post-CPT time point ($p<0.001$). This can be seen on the orange visit 2 line in figure 5 above. It can be concluded that the results of the ANOVA indicate a significant time effect for average heart meaning that heart rate increases during the CPT and decreases post-CPT for all participants at the two visits.

3.3.0.2 Average heart rate in males versus females

	Visit 1			Visit 2		
Sex/Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**
Female	70.1±1.4 bpm	73.0±1.5 bpm γ	66.5±1.2 bpm *	70.8±1.7 bpm	71.9±1.8 bpm γ	67.4±1.5 bpm *
Male	68.9±1.4 bpm	71.0±1.5 bpm γ	65.1±1.2 bpm*	70.7±1.7 bpm	72.6±1.8 bpm γ	66.9±1.5 bpm *

Table 11 - Average heart rate pre-, during-, and post- CPT of all male and all female athletes that completed the study at each time point, and at both visits. (n=120) These values represent the average HR of all the females in the three groups combined (n=60) and the males in the three groups combined (n=60). A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in HR post-CPT. The γ represents a significant increase ($p<0.001$) in PPT from pre- to post-CPT time points. * indicates a significant decrease in SBP post-CPT.

In addition, there was no time x sex interaction ($F(1.521, 57.789) = 3.297$, $p=0.838$) suggesting similar heart rates for males and females over time which can be seen by comparing the male and female rows in table 11. Overall, male and female athletes had similar heart rates throughout the testing.

3.3.1 Systolic blood pressure

3.3.1.1 Average systolic blood pressure of all participants

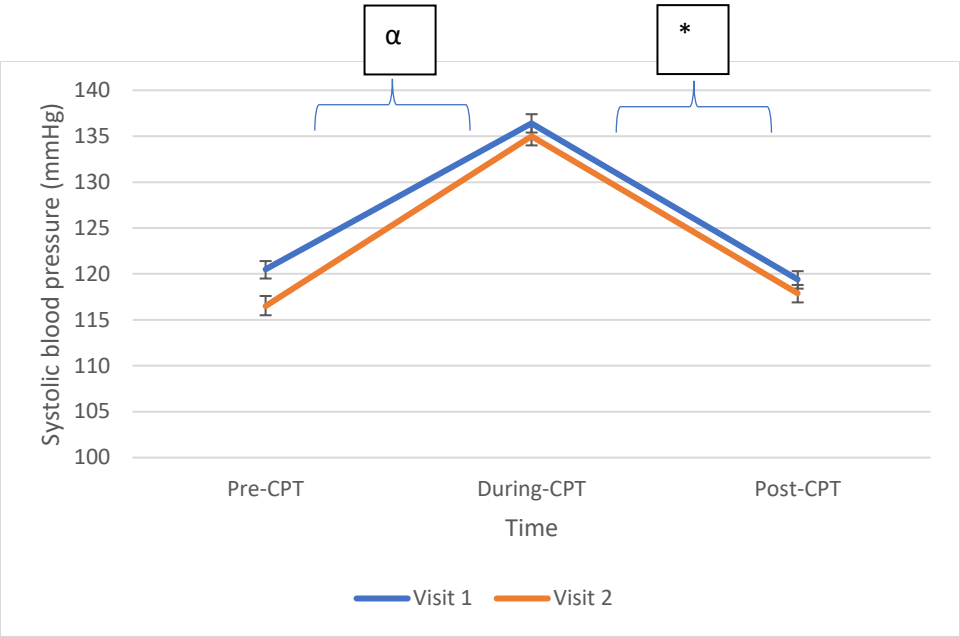

Figure 9 – Average systolic blood pressure for all participants (n=120) that completed the study pre-, during- and post-CPT, during visit 1 and visit 2. The bars indicate standard deviation. A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in SBP during the CPT followed by a significant decrease post CPT. α represents a significant increase in SBP during-CPT ($p<0.001$) and * represents a significant decrease in SBP post-CPT.

Group	Ibuprofen			Placebo			Control		
Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**
Visit 1	121.7±14.0 mmHg	137.9±14.1 mmHg γ	120.1±14.9 mmHg *	118.2±13.1 mmHg	133.8±13.8 mmHg γ	117.6±13.5 mmHg*	121.6±14.0 mmHg	137.5±13.7 mmHg γ	120.5±12.9 mmHg*
Visit 2	116.1±12.0 mmHg	136.0±13.5 mmHg γ	117.7±12.4 mmHg*	115.1±14.9 mmHg	132.1±14.9 mmHg γ	116.8±13.7 mmHg*	118.4±12.4 mmHg	137.0±13.8 mmHg γ	119.2±11.0 mmHg*

Table 12 – Average Systolic blood pressure values of all participants (n=120), in each group, during visits 1 and 2, at the three time points: pre-, during-, and post-CPT. For SBP, a repeated measures ANOVA indicated a main effect of time, revealing a significant increase during-CPT followed by decrease post CPT. The γ represents a significant increase ($p<0.001$) in pain during-CPT for both visits. * Indicates a significant decrease ($p<0.001$) post-CPT.

All participants experienced an increase in systolic blood pressure (SBP) during the cold pressor test, followed by a decrease afterward. A repeated measures ANOVA determined that there was no main effect of groups ($F(2, 76) = 1.286$ $p=0.282$), meaning that there was no difference between average systolic SPB between the 3 groups which can be observed in table 12. The same repeated measures ANOVA indicated a main effect of visits ($F(1.000, 38.000) = 9.676$, $p=0.004$). A post hoc pairwise comparison using the Bonferroni correction showed a significant decrease in average SBP of 2.3 mmHg from visit 1 to visit 2 (125.4 ± 0.8 to 123.2 ± 1.0 mmHg, $p = 0.004$).

In addition, the repeated measures ANOVA also showed a main time effect ($F(1.524, 57.917) = 361.879$, $p=0.000$). The post hoc pairwise comparison showed a significant increase in SBP from pre-CPT to during CPT ($p<0.001$) and a significant decrease post-CPT ($p<0.001$) for both visits which can be seen in figure 6. This means that for both visits, all participants showed an increase in SBP during the CPT followed by a decrease post-CPT.

3.3.1.2 Average systolic blood pressure in males versus females

	Visit 1			Visit 2			
Sex/Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**	
Female	112.0±1.2 mmHg	129.3±1.4 mmHg γ	111.7±1.2 mmHg *	110.0±1.6 mmHg	129.7±1.8 mmHg γ	111.6±1.3 mmHg*	€
Male	129.0±1.2 mmHg	143.5±1.4 mmHg γ	127.1±1.2 mmHg*	123.1±1.6 mmHg	140.4±1.8 mmHg γ	124.1±1.3 mmHg*	

Table 13 - Average systolic blood pressure pre-, during- and post- CPT of all male and all female athletes that completed the study at each time point, and at both visits. (n=120)
These values represent the average SBP of all the females in the three groups combined (n=60) and the males in the three groups combined (n=60). A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in HR post-CPT. The γ represents a significant increase ($p<0.001$) in PPT from pre- to post-CPT time points. * Indicates a significant decrease in SBP post-CPT. € indicates a significant difference ($p<0.001$) in SBP between males and females.

Although no sex*time interaction was demonstrated ($F(1.524, 57.917)= 1.627$, $p=0.203$), when looking at sex as a between subjects factor there was a significant difference in systolic blood pressure between males and females ($F(1, 38) = 68.803$, $p<0.001$) with an average female SBP 13.8 mmHg lower than males, $p<0.001$ (117.4±1.2 and 131.2±1.2 mmHg respectively). Female SBP increased by 17.3 mmHg during CPT and then decreased by 17.6 mmHg post-CPT during visit 1 and increased by 19.7, then decreased by 18.1 during visit 2 (see table 13 for female SBP values). Male average SBP increased by 14.5 mmHg during CPT and then decreased by 16.4 mmHg post-CPT during visit 1 and increased by 17.3, then decreased by 16.3 during visit 2. These results suggest that although the change in systolic blood pressure of each sex between the time points is similar, females have significantly lower systolic blood pressure at all time points.

3.3.2 Diastolic blood pressure

3.3.2.0 Average diastolic blood pressure of all participants

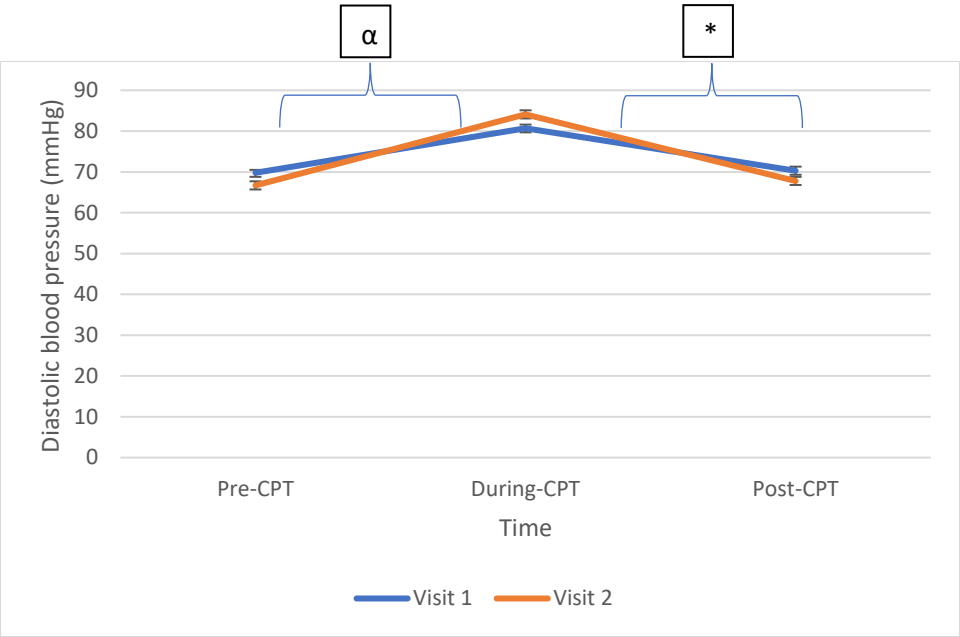

Figure 10 – Average diastolic blood pressure for all participants (n=120) that completed the study pre-, during- and post-CPT, during visit 1 and visit 2. The bars indicate standard deviation. A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in DBP during the CPT followed by a significant decrease post CPT. α represents a significant increase in DBP during-CPT ($p<0.001$) and * represents a significant decrease in DBP post-CPT.

Group	Ibuprofen			Placebo			Control		
Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**
Visit 1	71.0±10.4 mmHg	83.1±10.7 mmHg γ	70.7±12.5 mmHg*	68.9±7.8 mmHg	79.5±8.3 mmHg γ	70.1±10.9 mmHg*	69.5±7.5 mmHg	79.7±9.1 mmHg γ	70.0±9.5 mmHg*
Visit 2	67.1±8.7 mmHg	85.8±10.6 mmHg γ	68.3±8.9 mmHg*	64.7±7.4 mmHg	82.6±9.7 mmHg γ	67.3±7.5 mmHg*	68.2±9.4 mmHg	83.8±11.1 mmHg γ	67.9±6.7 mmHg*

Table 14 – Average diastolic blood pressure values of all participants (n=120), in each group, during visits 1 and 2, at the three time points: pre-, during-, and post-CPT. For DBP, a repeated measures ANOVA indicated a main effect of time, revealing a significant increase during-CPT followed by decrease post CPT. The γ shows the significant increase ($p<0.001$) in pain during-CPT for both visits. * Indicates a significant decrease ($p<0.001$) post-CPT.

All participants experienced an increase in diastolic blood pressure (DBP) during the cold pressor test, followed by a decrease afterward. A repeated measures ANOVA determined that there was no main effect of groups ($F(2, 76) = 0.863$, $p=0.426$) or visits ($F(1.000, 38.000) = 2.293$, $p=0.138$), meaning that there was no difference between average diastolic blood pressure (DBP) between the 3 groups and at the two visits.

The same repeated measures ANOVA also showed a main time effect ($F(2, 76) = 414.937$, $p<0.001$). The post hoc pairwise comparison showed a significant increase in DBP from pre-CPT to during CPT ($p<0.001$) and a significant decrease post-CPT ($p<0.001$) for both visits. During visit 1, DBP increased by 10.9 mmHg followed by a decrease of 10.4 mmHg. A similar trend can be seen in DBP during visit 2 which increased by 17.4 mmHg then decreased by 16.3 mmHg post CPT. The change in diastolic blood pressure can be seen in table 14. This means that for both visits, all participants showed an increase in diastolic blood pressure during the CPT followed by a decrease post-CPT.

3.3.2.1 Average diastolic blood pressure in males versus females

	Visit 1			Visit 2			
Sex/Time	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**	
Female	67.3±1.0 mmHg	78.0±1.2 mmHg γ	69.3±1.4 mmHg*	65.7±1.1 mmHg	82.1±1.4 mmHg γ	66.6±1.0 mmHg*	€
Male	72.3±1.0 mmHg	83.4±1.2 mmHg γ	71.2±1.4 mmHg*	67.7±1.1 mmHg	86.1±1.4 mmHg γ	69.1±1.0 mmHg*	

Table 15 - Average diastolic blood pressure pre-, during- and post- CPT of all male and all female athletes that completed the study at each time point, and at both visits. (n=120) These values represent the average DBP of all the females in the three groups combined (n=60) and the males in the three groups combined (n=60). A repeated measures ANOVA indicated a main effect of time, revealing a significant increase in HR post-CPT. The γ show a significant

increase ($p<0.001$) in PPT from pre- to post-CPT time points. * Indicates a significant decrease in SBP post-CPT. € indicates a significant difference ($p<0.001$) in SBP between males and females.

Although no sex*time interaction was demonstrated ($F(2,76)= 2.579$, $p=0.082$), when looking at sex as a between subjects factor there is a significant difference in diastolic blood pressure between males and females ($F(1, 38) = 5.890$, $p=0.020$). Female DBP increased by 10.7 mmHg during CPT and then decreased by 8.7 mmHg post-CPT for visit one and increased by 16.4 mmHg, then decreased by 15.5 mmHg during visit 2. Male average DBP increased by 11.1 mmHg during CPT then decreased by 12.2mmHg post-CPT during visit one and increased by 18.4 mmHg followed by a decrease of 17 mmHg during the second visit. The male and females DBP are shown in table 15 above. These results mean that although the change in diastolic blood pressure of each sex between the time points is similar, females have significantly lower diastolic blood pressure at all time points.

CHAPTER 4: DISCUSSION

The aim of this study was to compare the effect of ibuprofen and a placebo on conditioned pain modulation in athletes, assessed through changes in pain intensity, pain pressure threshold (PPT), heart rate, and systolic and diastolic blood pressure during a cold pressor test (CPT). Initially, we expected that the athletes who received ibuprofen or received the placebo would experience reduced pain during the CPT. However, contrary to our hypothesis, both the ibuprofen and placebo groups experienced almost the identical amount of pain during the CPT. As stated in the literature review, measuring conditioned pain modulation involves applying a noxious stimulus and then measuring the change in PPT. Since the pain did not change in the ibuprofen and placebo group, it was not surprising to see that the PPT did not changes as well between visit 1 and visit 2 in both the ibuprofen and placebo group. This lack of change in PPT can be attributed to the constant noxious stimulus since conditioned pain modulation relies on this stimulus.

Furthermore, all cardiovascular measures (BP and HR) increased during the CPT and decreased after the test, but there were no significant differences between the ibuprofen and placebo group. These findings also align with what was stated earlier about the PPT. Since the noxious stimuli and pain did not change between visits, neither did the heart rate or blood pressure. Despite the lack of pain reduction between visit 1 and visit 2 in the ibuprofen and placebo groups, our model of using CPT to measure conditioned pain modulation was successful. Our data indicated an increase in PPT from pre- to post-CPT for all participants. However, there were also some interesting male female differences which we will address after discussing the lack of pain difference in the ibuprofen and placebo groups.

Lack of effect of Ibuprofen on pain during cold pressor test

Despite its analgesic properties, Ibuprofen did not have an analgesic effect during the cold pressor test, and its physiological mechanism may help to explain why. Ibuprofen acts on inflammation to reduce pain. [27,28,45] Inflammatory pain is a natural response to tissue damage or infection, activated by the immune system to protect and promote healing.[46] Inflammation discourages movement to allow for recovery. In contrast to this, experimental pain, like the CPT, is not linked to inflammation and occurs without tissue damage. Instead, the CPT activates Ab and c-fibers as well as nociceptors in cutaneous veins, which the brain interprets as pain.[47] The analgesic effect of ibuprofen arises from blocking COX enzymes, which then inhibits prostaglandin synthesis.[27,28,45] Prostaglandins are often found in inflamed tissue as they are important in the mediation of inflammation and do not directly cause pain but rather sensitize pain receptors. [27,28,45] Inhibiting prostaglandins therefore reduces inflammation and then pain.[27]

Since CPT-induced pain is not inflammation-driven, ibuprofen's mechanism may not directly address the underlying cause of pain in this context, which could explain its lack of efficacy in this study. Jones et al., conducted a study comparing the efficacy of 10mg of morphine, 600mg of ibuprofen and a placebo at reducing pain during a cold pressor test.[5] Though non-opiate analgesics have been shown to reduce pain, they have not been shown to do so consistently during experimental pain (pain induced in a controlled environment with a standardized task).[5] The authors found that although morphine was able to significantly reduce pain, ibuprofen and a placebo did not have a significant effect.[5]

The cold pressor test is a stress-inducing test that activates the sympathetic nervous system, leading to changes in cardiovascular activity,[11,12,22] therefore the neural drive from the cold water might overpower the analgesic effect of ibuprofen. Klement and Arndt observed that when using cold water as a noxious stimulus, a cutaneous analgesic did not decrease pain while an intravenous nerve block did, which led to the observation that nociceptors of cutaneous veins mediate cold pain.[48] It is possible that the mechanism of action of ibuprofen does not affect nociceptors in cutaneous veins and therefore was limited in its ability to decrease cold pain. The cold pressor test's sympathetic activation causes vasoconstriction and increases in blood pressure,[11,48] and this change in cardiovascular measures may be more heavily regulated than pain during the test. This may also contribute to the limited effect of the ibuprofen on cold pain during the CPT.

Lack of effect of placebo on reducing pain during cold pressor test

The placebo effect is well-known for its effectiveness, and its application is crucial[36,40] to its efficacy and may offer an explanation for the lack of a placebo effect in our study. Believing that pain might disappear can lead to pain reduction. This is the placebo effect.[49] It is a misconception that placebo is equivalent to no treatment, as a placebo can lead to pain reduction.[37,49] Wall writes about a study conducted at the Eastman Dental Hospital in London following wisdom tooth extraction which causes pain, swelling and decreased jaw mobility.[49] Since ultrasound decreases inflammation, it was used by Doctors in a double-blind test with the machine being turned on for half the patients and turned off for the second half. [49] Interestingly, both groups (those receiving ultrasound and those that did not) improved equally, suggesting that improvements might be attributed to factors other than ultrasound. Patients were subsequently taught to self-administer the same massage technique used by the doctors with the ultrasound head but improvement was seen.[49] This highlights the importance of expectation and trust in treatment effectiveness for the placebo. In our study, data collection was conducted by master's students rather than Doctors in impressive white coats, therefore it is possible that the athletes did not experience the necessary expectation and trust they may have had in a doctor for our placebo to be effective. This is important because it has been suggested that creating expectation with a placebo causes a cascade of endogenous opioids and non opioids which alter pain experience.[6] The U.S. National Institutes of Health in Bethesda, Maryland conducted a double-blind study on 30 individuals who sought emergency care due to intense headaches.[49] One third of the patients received a ketorolac injection, one third received a narcotic injection of meperidine, and the last third received a saline solution. [49] Both ketorolac and meperidine have been shown to be more effective than a placebo on relaxed patient during a pain test, however in this case, while these patients experienced pain so intense that it brought them to the emergency, the placebo was as effective as the drugs.[49] These patients in pain had a strong expectation of what the medication could do for them, contributing in the placebo's success in reducing their pain. In contrast, the athletes in our study arrived relaxed and pain free. When we explained to them that the medication (the placebo) would decrease their pain during the cold water immersion, they were already pain-free, and this may have diminished the impact of our words and the creation of expectations. In addition, Wall writes about the impact of the pill itself, a factor that is taken advantage of by pharmaceutical companies, where a colored pill, especially red which has been shown to be associated with power, has a stronger effect than a white round tablet. [49] To summarize, the placebo effect relied on proper application and the creation of

expectations. Factors such as the person administering the treatment, the patient's expectations, and even the appearance of the placebo can influence its effectiveness in pain reduction. Understanding these nuances can help optimize the use of placebos in clinical setting and research studies.

Various methods that can be used to enhance a placebo response, presenting intriguing possibilities for future research. A study at La Trobe University in Australia was conducted to observe the creation of a placebo response using a painful stimulus to one arm in healthy individuals. [49] Initially, participants experienced the painful stimulus, followed by the application of a regular face cream, presented to them as a potent analgesic to their.[49] Without telling the participants, the researchers reduced the intensity of the shock, while informing the participants that they would reapply the same stimulus as the first time. Due to their belief in experiencing a significant reduction in pain due to the cream, when the original stimulus was repeated once more, participants felt that it was weak and not very painful. [49] Researchers Montgomery and Kirsh later replicated this study and had the same result, however they added another group which was told that the intensity of the shock was lowered, and they never experienced a placebo response[49] indicating the importance of participants genuinely believing in pain relief to experience the effect. For future research, it may be interesting to conduct a cold pressor test without any medication at 2° Celsius, then repeat the test with the placebo but at a higher and less painful temperature without disclosing this to the athletes. This approach could potentially trigger a learned placebo response. If the test was then repeated once more with the placebo but at 2 deg Celsius, maybe the athletes might anticipate less pain due to their previous experience, leading to an actual reduction in pain perception. To conclude, the findings from our study show the complexity of the placebo effect and the challenges of inducing it in an experimental setting. The CPT, and its intense visceral response may explain why students, who are not medical Doctors in impressive white coats, and who are explaining the placebo's analgesic potential to athletes that are not in pain during the explanation, did not create enough expectation to see the placebo effect during a painful stimulus. Wall mentions a quote by President Thomas Jefferson stating that "One of the most successful physicians [he has] ever known […] used more bread pills, drops of coloured water and powders of hickory ash than all other medicines put together."[49] This quote about successful use of placebo-like treatments shows that the efficacy of the placebo effect has been historically recognized. However, considering that neither the placebo nor the ibuprofen was successful in reducing the pain it is possible that the noxious stimulus caused by the experimental pain was too strong or affected different neural pathways than those that are normally affected by an analgesic or a placebo.

Male – Female difference: who experienced more pain?

Despite the absence of pain changes in the treatment groups and no change in CPM between visits, intriguing sex difference were observed. Both male and female athletes exhibited a similar pattern of increased pain during-CPT followed by a decrease in pain post-CPT, which comparable perceived pain scores. However, there was a notable distinction in PPT values, as females consistently had lower PPT values compared to males. Despite this difference in PPT values, the change in PPT otherwise known as CPM, along with pain scores, remained similar for both sexes.

During the cold pressor test, all athletes experienced an increase in pain, and a corresponding increase in pain pressure threshold after the cold pressor test demonstrating conditioned pain modulation. There were no significant differences in UE or LE PPT between the groups which makes sense considering that pain did not change in the treatment groups. The independent sample t-test that was conducted to observe the change in PPT between the sexes at each visit and found a statistically significant difference of 5.4 N between the average UE PPT difference of females and males during visit 1. Although there appears to be some difference between these two values, a difference of 5.4N between the two sexes is not very big and the standard deviation is large, therefore this is not actually clinically significant which is why we say there was no difference in UE PPT between sexes. Since pain was not reduced during the CPT, consequently PPT also did not change. There is some evidence to suggest that an increase in noxious stimuli can result in an increase in hypoalgesia,[8,49] so a larger change in pain response could have led to a more pronounced effect on PPT. Interestingly, when pain was induced with the cold pressor test, both male and female athletes reported similar perceived pain scores. However, PPT scores in females were consistently lower than males for both upper and lower extremity. In addition to this, the conditioned pain modulation values, or the difference in PPT was similar between the sexes. Pain pressure threshold is a measure of the pressure required over a given area to become painful, in other words the lowest intensity a stimulus is applied before it becomes painful.[9,17] For example, with the algometer, pressure was applied until the first sensation of pain. It has been used as an objective measure to quantify pain.[9,17] Epidemiological studies have shown that females tend to report pain more frequently and earlier than males,[7] suggesting a lower pain threshold in females. This may explain why PPT values are consistently lower in females, who report the first sensation of pain more quickly than males. In contrast to this, the numeric pain rating scale is subjective in nature which can influence pain ratings. Participants are asked to rate their pain during the CPT from "0", no pain at all to "10", the worst pain imaginable. Since self reported pain is subjective, people tend to relate, "worst pain imaginable" to the worst pain they've experienced because that is all they know and therefore their point of reference. All participants in our study were varsity athletes who experienced similar training hours and strain on their bodies as well as similar injuries due to their sports and may have related their, "worst pain imaginable" to similar experiences. This may explain why the subjective pain ratings are similar between male and female athletes in this study. The role of sex in conditioned pain modulation remains unclear, with studies yielding inconsistent findings, some showing no difference, and others suggesting better CPM in males.[7,8] Studies looking at pain difference between sexes tend to look at a regular healthy population and not athletes. The lifestyle and pain experience of male and female athletes is a lot more similar than male and female non-athletes. A study showed that the different occupations and hobbies of each sex might affect their pain experience.[49] For example, women tend to handle heat more, therefore have a higher heat pain threshold, compared to males who might work on care engines more frequently and therefore might tolerate electric shocks more easily.[49] In the case of varsity athletes, their main occupation and hobby tends to be their sport which may be why our results did not show a difference in self-reported pain.

CPM is a measure the efficacy of descending pain pathways, or the brain's ability to initiate endogenous analgesia.[9] Since the CPM values for the upper and lower extremity were similar for both sexes in our study, this implies that males and females' possess comparable analgesic capabilities. Although females' PPT scores were consistently lower than males, the similarity in pain scores and CPM between the sexes suggests that we cannot conclude that

females experience more pain than males. Overall, our study revealed interesting differences in PPT between male and female athletes but demonstrated similar perceived pain and analgesic capabilities. Further investigation to understand pain experience in each sex is necessary to make conclusions about which sex feels more pain.

HR and blood pressure results from cold pressor test

During the cold pressor test, all cardiovascular measures exhibited an increase and then a subsequent decrease post-CPT. The expectation was that the athlete ibuprofen and placebo groups would experience a decrease in blood pressure and heart rate change during the cold pressor test compared to the athlete control group. The hypothesis assumed that reduced pain perception in the treatment groups would lead to fewer cardiovascular changes. However, since the pain remained unchanged, it is understandable that there was no difference in cardiovascular measures between the groups. This aligns with findings from previous studies indicating that blood pressure and heart rate should increase during the CPT due to sympathetic nervous system activation. [13,22,42] As mentioned in the results, the repeated measures ANOVA indicated a main effect of visits with the post hoc pairwise comparison showing a significant decrease in average SBP of 2.3 mHg from visit 1 to visit 2. Although this may be statistically significant, a change in systolic blood pressure of 2.3 mmHg between visits is not clinically relevant especially when you consider the standard deviations shown in table 12, and the large size of the sample, and may be slightly lower because participants knew what to expect during the second visit.

Our results also demonstrated that average systolic blood pressure is higher in males than females, while diastolic blood pressure was slightly higher in males. Heart rate, on the other hand was similar in both sexes. Etherton et al. conducted a similar study observing pain and cardiovascular variables during a cold pressor test and their results demonstrated that males had an overall higher systolic and diastolic blood pressure but that females had a higher heart rate.[42] In general, females tend to have a slightly more elevated HR than males. [42] It is possible that our study included female athletes, who might have had heart rates more similar to males due to their cardiovascular training. Sex differences in cardiovascular measures remain uncertain, as another study by Miller et al., found no difference in male and female heart rate during a cold pressor test, much like our findings.[50] The authors of the study conducted a cold pressor test on young males and females and continuously measured femoral artery diameter to calculate femoral blood flow, vascular resistance and conductance.[50] They found that young women had a significantly greater femoral blood flow and conductance in response to the CPT than males and therefore experience paradoxical vasodilation during the stress test. [50] This vasodilation may explain why females had consistently lower blood pressure than males. Overall, our study demonstrated expected changes in cardiovascular measures during the cold pressor test, with no significant differences between the treatment groups. Further investigations are warranted to better understand these sex differences and their implications in pain perception and cardiovascular health.

Limitations

Our experiment was conducted in a controlled setting. Unfortunately, this limits the generalizability of the results beyond this experimental setting. Patrick Wall, a neuroscientist known as one of the world's leading experts on pain calls this, "artificial pain outside of normal

experience."[49] While competing, athletes are constantly faced with the risk of prolonged injury and pain, as well as the pressure to perform well, and the worry of letting down their teammates. During the CPT, the athletes know that they could stop the testing, and therefore the pain whenever they choose to. There is nothing unpredictable about the testing, and they are aware that the cold water will not lead to prolonged pain. This experiment therefore observed pure pain sensation without external factors involved in sports and affecting pain such as fear, adrenaline, or psychological factors, limiting the results to this context and potentially affecting perceived pain of the athletes. Induced experimental pain is not the same as clinically experienced pain, and therefore more studies are needed on the effect of medication on clinical pain in athletes.

Studies have suggested that the menstrual cycle may affect pain perception in females, however we were not able to control for the stage of the menstrual cycles. First, 11 girls said that they never get their period and second, 53% of the girls were on birth control which can eliminate menstruation which would make identifying where the participant is in their cycle impossible. So more studies are needed that includes blood measurements of the female cycle on pain.

Conclusion

This study aimed to compare the effect of ibuprofen and a placebo on conditioned pain modulation in athletes during a cold pressor test. Contrary to the initial hypothesis, neither ibuprofen nor the placebo effectively reduced pain during the CPT for male and female athletes. The lack of change of the PPT can be attributed to the constant noxious stimulus, which is essential for CPM. Although cardiovascular measures (BP and HR) increased during-CPT and decreased post-CPT, there were no significant differences between the groups, consistent with the unaltered pain scores. Interesting sex differences were observed, with females exhibiting consistently lower PPT values compared to males. However, the overall change in PPT (CPM) and perceived pain scores remained similar for both sexes, suggesting comparable analgesic capabilities. The placebo effect was not shown in this study, possibly due to the absence of adequate expectation and trust from the participants. Future research exploring methods to enhance the placebo response and understand its complexities could be warranted. Moreover, the mechanism of ibuprofen's action may explain its lack of efficacy during the CPT, as it primarily targets inflammation, which is not a factor in experimental pain. This highlights the importance of considering the intensity and nature of the noxious stimulus in experimental pain research.

APPENDIX

Conditioned Pain Modulation Script

Visit 1:

Introduction

To ensure the wording is the same for all participants, we will be reading all the instructions to you aloud.

Humans have a natural occurring pain reducing mechanism which can be measured experimentally using a protocol called conditioned pain modulation. Athletes are commonly thought to experience pain differently than non-athletes possibly because they are frequently exposed to pain through training and competition. Our lab is interested in any factors that can affect conditioned pain modulation in athletes so that we can better understand pain experienced by athletes to improve treatments in the future.

For this study, you will be asked to visit our lab two times to assess conditioned pain modulation.
At the first visit, you fill out a series of questionnaires that will assess psychological factors that can influence pain. It is very important that you fill out the psychological questionnaires honestly. These questionnaires are kept confidential, and no one will see them. This includes your coaches or any athletic staff.

Then we will measure point tenderness using a pressure measuring device. After, you will complete a cold pressor test which involves submerging your hand in a cold-water bath. Right after this, we will re-test the point tenderness. The point tenderness and cold pressor tests will be the only measures repeated in the next visit.

Now I am going to give you the consent form. This contains an in-depth description about the study. If you have any questions while you are reading the document, please do not hesitate to ask. If you choose to consent to participate in the study, we will ask you to sign the document.

PAUSE – GIVE PARTICIPANTS CONSENT FORM

Now that the consent form is signed, we can begin the study with a general health screening document. Answer the questions as best as you can and let us know if you have any questions or need clarifications on a question.

PAUSE – ADMINISTER DEMOGRAPHIC QUESTIONNAIRE

Thank you for completing the eligibility questionnaire. While we go over this document, you will complete the Athlete Fear Avoidance Questionnaire, the State-Trait Anxiety Inventory, and

the Pain Catastrophizing Questionnaire. These questionnaires will be coded so no-one will be able to identify your results.

Carefully read the instructions for each questionnaire and pay attention to the scales, as they are unique to each document. If you have any questions, do not hesitate to ask.

HANDOUT QUESTIONNAIRES ONE AT A TIME

Protocol

To make sure these tests are always performed in the same manner, the instructions will be read to you aloud. If you have not understood the instructions, please feel free to immediately ask for clarification. We cannot discuss the nature of these tests during this current session and the next, but we are happy to share your results with you at the end of the study.

The testing procedure takes 25 minutes. During this time, we will regularly measure your heart rate and blood pressure. Please note that the blood pressure cuff with inflate multiple times throughout the study. We will also ask you to rate any pain in your left and right arm on a scale of 0 to 10 multiple times, with 0 being no pain and 10 being the worst pain imaginable.

PPT (READ AT **MINUTE 7**)

We are going to test your pressure pain above the muscle. We will press this pressure measuring device against the muscles on your hand and on your shin two times each. Please say 'now' as soon as the sensation of pressure changes towards pain. This is not a test of tolerance, but rather your first sensation of discomfort. This will be done once now and repeated later in the procedure after the CPT. Before we begin, please rate any pain in your left hand and shin on a scale of 0 to 10, with 0 being no pain and 10 being the worst pain imaginable.

MEASURE PPT AT MINUTE 8

BRING WATER AT 10 AND EXPLAIN CPT AT 10.5 MINUTES

CPT

We will soon begin the CPT. Please do not put your hand in the water until I tell you. For this test, we will ask you to submerge your right hand in the water, up to the wrist. Please keep your hand open and avoid touching the walls of the container. You will rate your pain 3 times during the test, using the same scale of 0 to 10, with 0 being no pain and 10 being the worst pain imaginable. Most people can tolerate this test without any problems, but if you wish to stop, you can take your hand out. After the cold pressor test is complete, we will repeat the pressure test. Please leave your left arm in the same position.

Visit 2

Analgesic Medication:

As discussed, you have brought in your own ibuprofen for the study. You will now take the ibuprofen as instructed on the bottle with the goal that it will decrease your pain during today's test. You will sit for 30 min before starting the procedure for the medication to have effect and the same procedure as your first session will be repeated.

Placebo Analgesic:

Today you will be given a pain analgesic medication. This is a new medication that looks and tastes different than what you may be used too. You will now take the pain analgesic with the goal that it will decrease your pain during today's test. You will sit for 30 min before starting the procedure for the medication to have effect and the same procedure as your first session will be repeated.

DECEPTION FORM

Thank you for participating in this study. Your contribution is important to our research, and we are looking forward to the results. Since athletes are often exposed to stimuli that may be painful, it has been reported that many have an increased capacity to endure discomfort. This has led researchers to believe that athlete's pain experience is different than that of non-athletes, and studies are lacking to better understand this difference.

At this point we want to inform you that you received a placebo medication prior to your second lab visit. This means that the medication you took had no direct physiological pain-relieving properties. This was important to do for our study because understanding how these variables impact athletes can improve rehabilitative and sports performance programming and is not limited to other non-athletic populations. This research will also improve Athletic Therapists' education on pain and pain medication, in which this study can contribute to the needed literature.

If you feel concerned or uncomfortable about the fact that you were intentionally deceived, you have the right to withdraw your data from the sample. Remember that your results are anonymized and that all results are published as anonymized group data. Please note that you will have *2 days after the last visit* to withdraw your data from the study. There are no penalties associated with withdrawing your data from the study, this includes the compensatory stipend you have received as part of completing this study.

As stated earlier, your responses to all of the questionnaires will be absolutely confidential. In return, we want you to honor our confidentiality -- please do not tell anyone about the details of this study. If the other participants know about the study before they participate, their data will be biased and thus cannot be included.

If you have any further questions regarding the study, please contact us at:
Ilana Patlan and Matylda Lentini - painstudy.concordia@gmail.com
Principle Investigator: Geoffrey Dover – (514)-848-2424 ext. 3304 or geoffrey.dover@concordia.ca

By signing this document, you are consenting researchers to use your data in this research project. You have the right to withdraw your data in the event you feel coerced.

Print name: _____
Signature: _____
Date: _____

	Group	Ibuprofen			Placebo			Control		
	Time	Pre-CPT	During-CPT	Post-CPT	Pre-CPT	During-CPT	Post-CPT	Pre-CPT	During-CPT	Post-CPT
Males	**Visit 1**	0.0±0.0	5.1±2.1	0.7±1.0	0.0±0.0	6.1±2.8	0.6±1.0	0.0±0.0	5.6±2.1	0.3±0.5
	Visit 2	0.0±0.0	5.0±2.5	0.3±0.4	0.0±0.0	5.8±2.9	0.4±0.8	0.0±0.0	4.9±2.0	0.4±0.6
Females	**Visit 1**	0.0±0.0	5.7±1.7	1.0±1.4	0.0±0.0	6.4±1.7	0.9±1.4	0.0±0.0	5.1±1.5	0.9±1.0
	Visit 2	0.0±0.0	5.4±2.0	0.4±1.1	0.0±0.0	5.7±1.3	0.5±0.8	0.0±0.0	5.1±1.6	0.5±0.6
Average	**Visit 1**	0.0±0.0	5.4±1.9	0.8±1.2	0.0±0.0	6.2±2.3	0.7±1.2	0.0±0.0	5.3±1.8	0.6±0.8
	Visit 2	0.0±0.0	5.2±2.3	0.3±0.9	0.0±0.0	5.7±2.2	0.5±0.8	0.0±0.0	5.0±1.8	0.4±0.6

Table 1. Peak self-reported pain of males, females, and average for all participants, in each group, during visits 1 and 2, at the three time points: pre-, during-, and post-CPT.

Visit	Time	Ibuprofen Group	Placebo Group	Control Group
Visit 1 Males	**Pre-CPT**	91.0 ± 28.9	97.6 ± 27.5	105.3 ± 37.4
	Post-CPT	98.6 ± 36.1	107.0 ± 33.2	118.1 ± 36.2
	Change in PPT	7.6 ± 17.0	9.3 ± 14.5	12.9 ± 14.1
Visit 2 Males	**Pre-CPT**	96.6 ± 39.9	101.2 ± 32.5	102.9 ± 36.6
	Post-CPT	102.8 ± 32.0	110.8 ± 38.6	108.1 ± 32.6
	Change in PPT	6.2 ± 15.3	9.6 ± 18.9	5.3 ± 15.1
Visit 1 Females	**Pre-CPT**	71.4 ± 28.7	72.2 ± 24.9	67.0 ± 20.9
	Post-CPT	75.2 ± 24.2	75.5 ± 29.1	73.6 ± 19.9

	Change in PPT	3.8 ± 15.5	3.3 ± 10.1	12.9 ± 14.1
Visit 2 Females	**Pre-CPT**	70.2 ± 20.0	71.8 ± 23.6	68.7 ± 22.1
	Post-CPT	78.2 ± 21.7	78.7 ± 23.8	77.7 ± 24.8
	Change in PPT	8.0 ± 14.0	6.9 ± 8.6	9.0 ± 9.1

Table 2. Upper extremity (thenar eminence) pain pressure thresholds and change in PPT of males and females in each group, during visits 1 and 2, at the two time points: pre-, and post-CPT.

Visit	**Time**	**Ibuprofen Group**	**Placebo Group**	**Control Group**
Visit 1 Males	**Pre-CPT**	121.2 ± 44.2	132.5 ± 48.2	127.7 ± 50.2
	Post-CPT	126.8 ± 54.6	143.4 ± 47.3	143.2 ± 47.3
	Change in PPT	5.6 ± 20.4	10.9 ± 31.0	15.6 ± 21.3
Visit 2 Males	**Pre-CPT**	120.0 ± 47.2	146.3 ± 56.7	124.3 ± 46.1
	Post-CPT	134.0 ± 53.6	156.3 ± 59.4	129.9 ± 47.7
	Change in PPT	13.8 ± 17.8	10.1 ± 21.4	5.6 ± 17.9
Visit 1 Females	**Pre-CPT**	98.2 ± 33.1	100.2 ± 29.1	84.6 ± 21.1
	Post-CPT	102.1 ± 36.7	112.0 ± 34.2	99.4 ± 25.9
	Change in PPT	4.1 ± 14.3	11.9 ± 22.1	14.8 ± 14.3
Visit 2 Females	**Pre-CPT**	92.8 ± 28.7	100.2 ± 31.4	88.7 ± 28.6
	Post-CPT	101.4 ± 34.8	112.7 ± 36.4	97.6 ± 30.0
	Change in PPT	8.5 ± 14.8	12.5 ± 14.5	9.0 ± 12.5

Table 3. Lower extremity (tibialis anterior) pain pressure thresholds and change in PPT of males and females in each group, during visits 1 and 2, at the two time points: pre-, and post-CPT.

Group		**Ibuprofen**			**Placebo**			**Control**		
Time		**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**	**Pre-CPT**	**During-CPT**	**Post-CPT**
Males	**Visit 1**	130.1±11.4	145.3±9.8	127.9±13.6	126.5±11.2	141.2±11.5	124.6±11.6	130.5±13.0	143.9±13.3	128.9±12.5
	Visit 2	124.2±9.8	143.2±9.8	125.4±9.0	120.9±17.1	137.2±13.2	122.1±13.9	124.1±13.5	140.8±15.3	124.9±11.2
Females	**Visit 1**	113.2±11.0	130.6±14.0	112.3±11.9	109.9±8.9	126.4±12.0	110.7±11.8	112.7±8.1	131.0±11.0	112.1±6.2
	Visit 2	108.1±7.8	128.7±12.9	109.9±10.4	109.3±9.6	127.1±15.1	111.6±11.5	112.7±7.9	133.2±11.2	113.4±7.2
Average	**Visit 1**	121.7±14.0	137.9±14.1	120.1±14.9	118.2±13.1	133.8±13.8	117.6±13.5	121.6±14.0	137.5±13.7	120.5±12.9
	Visit 2	116.1±12.0	136.0±13.5	117.7±12.4	115.1±14.9	132.1±14.9	116.8±13.7	118.4±12.4	137.0±13.8	119.2±11.0

Table 4. Average systolic blood pressure (mmHg) values of male and female participants, and average heart rate for all participants, in each group, during visits 1 and 2, at the three time points: pre-, during-, and post-CPT.

Group		Ibuprofen			Placebo			Control		
Time		Pre-CPT	During-CPT	Post-CPT	Pre-CPT	During-CPT	Post-CPT	Pre-CPT	During-CPT	Post-CPT
Males	Visit 1	68.2±10.5	69.3±9.4	64.3±10.1	69.2±10.9	72.5±9.7	65.9±10.5	69.3±11.7	71.1±12.1	65.1±9.3
	Visit 2	68.8±10.2	68.9±10.0	64.3±10.3	70.2±10.3	74.3±10.5	67.5±9.4	73.2±11.1	74.7±15.0	68.9±11.1
Females	Visit 1	72.0±9.5	76.1±9.6	67.8±8.3	69.8±7.4	70.2±10.3	65.7±8.9	68.5±9.5	72.6±9.1	66.1±8.9
	Visit 2	72.5±8.3	73.0±8.8	68.0±8.1	68.9±8.2	70.8±9.8	65.9±8.2	71.0±13.6	71.9±11.4	68.5±11.7
Average	Visit 1	70.1±10.1	72.7±10.0	66.1±9.3	69.5±9.1	71.4±9.9	65.8±9.6	68.3±9.6	71.7±10.6	65.6±9.0
	Visit 2	70.7±9.4	70.9±9.5	66.2±9.3	69.6±9.2	72.6±10.2	66.7±8.8	72.1±12.3	73.3±13.2	68.7±11.2

Table 5. Average heart rate (bpm) values of male and female participants, and average heart rate for all participants, in each group, during visits 1 and 2, at the three time points: pre-, during-, and post-CPT.

Group		Ibuprofen			Placebo			Control		
Time		Pre-CPT	During-CPT	Post-CPT	Pre-CPT	During-CPT	Post-CPT	Pre-CPT	During-CPT	Post-CPT
Males	Visit 1	73.2±11.4	86.0±11.4	71.7±12.7	71.5±7.2	82.2±6.8	70.8±7.3	72.3±7.9	82.1±9.5	71.3±8.1
	Visit 2	67.0±10.3	88.7±9.9	69.7±10.1	66.3±7.8	85.0±7.7	69.9±6.8	67.8±5.9	84.6±12.5	67.6±6.3
Females	Visit 1	68.8±8.9	80.1±9.3	69.8±12.5	66.3±7.7	76.8±9.0	69.4±13.7	66.8±6.1	77.3±8.3	68.8±10.9
	Visit 2	65.3±6.7	82.9±10.8	66.9±7.7	63.1±6.8	80.3±11.0	64.7±7.4	68.7±12.1	83.1±9.7	68.2±7.2
Average	Visit 1	71.0±10.4	83.1±10.7	70.7±12.5	68.9±7.8	79.5±8.3	70.1±10.9	69.5±7.5	79.7±9.1	70.0±9.5
	Visit 2	67.1±8.7	85.8±10.6	68.3±8.9	64.7±7.4	82.6±9.7	67.3±7.5	68.2±9.4	83.8±11.1	67.9±6.7

Table 6. Average diastolic blood pressure (mmHg) values of male and female participants, and average heart rate for all participants, in each group, during visits 1 and 2, at the three time points: pre-, during-, and post-CPT.

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