THE EFFECTS OF REMOTE POST-EXERCISE ISCHEMIC CONDITIONING ON RECOVERY FROM STRENUOUS EXERCISE

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

BACKGROUND: Strategic limb occlusion applied after exercise (PEIC) may expedite recovery, not just in directly affected tissue, but over the entire body. **METHODS**: Twenty active college-age males took part in a single-blind randomized crossover design. Participants underwent intervention and SHAM treatments after strenuous exercise sessions. Peak Torque production and soreness measures were gathered directly before and 24-hours after two exercise sessions. **STATISTICAL ANALYSES**: A 2 x 2 repeated measures analysis of variance with sidak corrections (significance of $p<0.05$) was used to analyze peak torque and VAS scores. **RESULTS**: Significance was not observed between any associated pre- and post-peak torque test ($p > 0.05$). Post-treatment VAS scores were statistically higher than pre-treatment for all conditions except pre-and post-intervention in the direct leg ($P = 0.096$). **DISCUSSION**: The application of PEIC was not associated with any significant differences in peak torque production or soreness measures.

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DEDICATION

I would like to dedicate this research to my parents, who supported me throughout my entire education and gave me everything I have.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

IPC…..……..……...……Ischemic preconditioning.

PEIC……...……..Post-Exercise Ischemic Conditioning.

ATP……...…….Adenosine Triphosphate.

LAD……..Left Anterior Descending Artery.

SPT…….8-p-sulfophenyl theophylline (adenosine receptor blocker).

PD……..…….. PD 115,199 (adenosine receptor blocker).

PKC……...……Protein Kinase C.

K+ATP…….. ATP-sensitive Potassium [channels].

ES……Effect Size.

SD……..……Standard Deviation.

RIPC……...……Remote Ischemic Preconditioning.

BMI……...……Body Mass Index.

N……...……Newton.

ANOVA…….Analysis of Variance.

MIVC……Maximal Isometric Voluntary Contraction.

RPM……Rotations Per Minute.

PAR-Q+…….. Physical Activity Readiness Questionnaire.

IRB…….Institutional Review Board.

ROM…….…….Range of Motion.

PTP…….……Personal Tourniquet Pressure.

VAS……..Visual Analog Scale.

CHAPTER ONE: INTRODUCTION

An important and constantly evolving component of athletics is the use of ergogenic aids. In sport, an ergogenic aid can be defined as any technique or substance used for the purpose of enhancing performance (Thein, Thein, and Landry, 1995). Due to the naturally competitive nature and monetary interest surrounding athletics, there are a lot of investments surrounding performance enhancing techniques. These procedures may be used before competition to acutely improve performance or to expedite recovery.

Strenuous exercise is associated with exercise-induced muscle damage, which has been shown to impair muscle function and exacerbate soreness (Miyama and Nosaka, 2004). Timely and sufficient recovery from exercise is a concern for both athletes and coaches. The use of ergogenic aids which facilitate recovery have substantial value as they may allow athletes to return to training faster and be more prepared for a competition.

The market is currently well saturated with methods that claim to promote recovery, therefore substantial evidence is required before these aids are invested in for athletes. A few popular evidence-based post-exercise recovery strategies receiving attention include acupuncture, cold-water immersion, compression garments, red-light treatment, and massaging (Calleja et al, 2015). In addition to such methods, a procedure using an occlusion treatment based on Ischemic Preconditioning (IPC) has shown promise in expediting recovery.

Research on IPC began as a method used prior to a prolonged ischemic episode in the heart, whereby brief repeated periods of occlusion followed by reperfusion were used to minimize harmful impacts (Murry et al., 1986). Subsequently, as the mechanisms were better understood, they were also considered for improving athletic performance. Two systems that IPC manipulates to decrease injury of heart tissue are adenosine and adenosine triphosphate-sensitive

potassium channels. When reviewing their role in skeletal muscle, elevated activity levels of these two are known to increase vasodilation, and nutrient and oxygen delivery to muscle cells, while also aiding in the removal of catabolites (de Groot et al., 2010). Increased adenosine levels have similarly been found to increase nitric oxide production by endothelial cells, adding another potent vasodilator to increase blood flow (Li et al., 1995).

Based on a recent literature review, there have been 20 studies on IPC when applied before a performance test. Research has consisted of a variety of activities, including cycling, sprinting, long distance running, swimming, and resistance training. Of the 20 studies, only 9 have shown IPC to improve performance, 10 have shown IPC to result in no change compared to control, and one study has shown IPC to have a negative impact on performance (Horiuchi, 2017). Inconsistencies in results may be associated with numerous unknown variables which are still becoming better understood. One factor could be sex, such that men may receive more of a benefit from conditioning treatments than women due to naturally producing more testosterone, meaning any IPC study involving female participants may have skewed results (Paradis-Deschênes, Joanisse, and Billaut, 2017).

Two variables associated with IPC show promise in clinical literature but are scarcely focused on in research regarding athletics. The mechanisms IPC utilizes are able to remotely affect other areas of the body. Preconditioning is partly mediated by factors which are transported throughout the bloodstream after periods of ischemia and reperfusion (Przyklenk et al., 1993). Additionally, the beneficial effects of IPC have an initial protective window of roughly one to three hours; however, there is an additional "Late IPC" protective effect lasting about 48-72 hours after the occlusion treatment. The effects of late IPC are not as strong as the earlier counterpart, but still provide protective benefits due to the same mechanisms

(Loukogeorgakis et al., 2005). When an occlusion treatment is applied after exercise, these shared mechanisms have the potential to facilitate recovery, and have been termed Post-Exercise Ischemic Conditioning (PEIC). While much less research has been performed reviewing PEIC compared to IPC, the inconsistencies in research findings are not exclusive to IPC. A total of five studies have been published testing PEIC's ability to aid in the recovery process. Three studies support PEIC to be beneficial in certain aspects of recovery, while the other two show no benefit (Arriel et al, 2018; Beaven, Cook, Kilduff, Drawer, & Gill, 2012; Page, Swan, & Patterson, 2017; Northey et al., 2016; Williams et al., 2018). With such few studies on the topic, overlooked misinterpretations can become common and easily result in contradicting results. More research needs to be done regarding the effects of IPC and PEIC to better understand their limitations and benefits.

Specific Aims

Optimizing recovery from stressful exercise is a concern for athletes, trainers, and sports scientists. Ergogenic aids that facilitate recovery from practice or competition may allow athletes to make enhanced progress from training sessions and perform better when returning to competition. Additionally, there is potential for ischemic conditioning to enhance recovery in remote body parts. To the researcher's knowledge, no previous research has examined the remote effects of PEIC to improve recovery. Pressurized occlusion cuffs are becoming more affordable, transportable, and widely available. Since proper techniques should be adhered to for safety, it is important that the procedure is realistic for athletes and athletic trainers to follow.

Therefore, the purposes of this study were to examine the recovery effects of remote and direct PEIC on muscle strength, power, and rate of torque development 24-hours after a strenuous exercise session. We hypothesized both remote and direct PEIC treatment will result in

improved performance and lower levels of soreness in active young men. The results of this study provide insight into the future use of PEIC within athletic recovery programs.

CHAPTER TWO: LITERATURE REVIEW

Introduction

In 1986, researchers Reimer at al. observed a beneficial adaption in the vascular system while researching myocardial infarction in dogs. When a major coronary artery was blocked for 40-minutes, severe adenosine triphosphate (ATP) depletion occurred in the associated tissue causing irreversible cell death. However, when 40-minutes of restricted blood flow causing ischemia were split into four separate 10-minute periods with 5-minute breaks allowing reperfusion, no permanent cell death occurred. Additionally, Reimer et al. observed that ATP-depletion occurred at a slower rate in the later sets of ischemia. While unrefined, this observation demonstrated potential for how heart tissue might adapt to reduced blood flow.

This effect was examined in a study published by a few of the same researchers, which referred to it as ‘Ischemic Preconditioning' (Murry, Jennings, and Reimer, 1986). Dogs were used as subjects and were evenly divided into two groups. One group underwent ischemia of a major coronary artery, the circumflex, for five minutes followed by five minutes of reperfusion for four sets (total of 40-minutes), while the control group received no treatment. Furthermore, each group was divided in half once again, forming one treatment and one control group to undergo 40-minutes of ischemia and the other treatment and control to receive 180-minutes of ischemia. After the experimental protocol, the dogs' chest cavities were closed, and they were given four days to live to make any cell death more observable. Then the animals were euthanized, and their hearts removed to undergo postmortem analysis. The infarct sizes are reported as a percentage of the total area at risk of cell death plus or minus the standard error of the mean. Inspections concluded with the 40-minute control group accumulating $29.4 \pm 4.4\%$ cell death, while the treatment group only had $7.3 \pm 2.1\%$ ($p < 0.001$). Mean infarct size in the

180-minute control group was reported as 47.9 ± 6.6%, where the IPC group averaged 47.1 ± 4.8% infarct size. (Murry, Jennings, and Reimer, 1986). Thus, the results supported IPC's protective effect of delaying cell death caused by a relatively short amount of ischemia. However, increasing that time to 180-minutes proved to be too much, confirming that there is a limit to how long IPC can protect cells. If this phenomenon could be better understood, it could be manipulated to aid people at high risk of heart attacks or be utilized before entering surgery to prevent cell damage.

At the time of the study, the mechanisms behind the protective effects were unknown; however, the researchers presumed two general mechanisms to be involved based on their observations. First, the slowing of ATP depletion in the affected cells, and the second is limiting the accumulation of harmful byproducts of metabolism (Murry et al., 1986).

Beginning Research

With the introduction of IPC, researchers were optimistic and curious about its potential applications. Using similar experimental designs to Murry, Jennings, and Reimer (1986), IPC's protective effects were reported in pigs (Schott et al., 1990). Thirteen swine received a treatment protocol of 10 minutes of occlusion to the left anterior descending artery (LAD), followed by 30 minutes of reperfusion, for a total of two sets. Additionally, the control group of 12 pigs did not receive any IPC treatment. Immediately after the treatment protocol, both groups underwent 60-minutes of occlusion to the LAD followed by 90-minutes of reperfusion before the animals were put down and their hearts removed. Due to issues occurring during or after treatment, three treatment group pigs and six control group pigs were excluded from the study, resulting in data being reported from only 16 of the original 25 subjects. The area of dead tissue resulting from a lack of blood supply (infarct size) in the control group pigs was 48 ± 12.7% of the heart's risk

area, while the IPC group's infarct size was 10.4 ± 6.3% of the area at risk. Researchers were able to conclude that preconditioning the heart significantly reduced infarct size in swine hearts ($p < 0.005$). This study also showed two sets of 10-minutes of ischemia worked to induce a similar benefit as the four sets of five minutes used by Murry et al. Moreover, pig hearts are regarded as being remarkably similar to human hearts when compared to other species, further supporting the idea that IPC would also have a cardioprotective effect in humans (Schott et al., 1990).

IPC was first observed in live humans examining its ability to precondition the heart during coronary bypass grafting (Yellon, Alkhulaifi and Pugsely, 1993). Fourteen patients in need of coronary artery bypass surgery were randomly placed into two groups. After undergoing the cardiopulmonary bypass, the first group received three minutes of occlusion via artery cross-clamping followed by two minutes of reperfusion, and this was repeated two times. Following the IPC treatment, the subjects underwent 10-minutes of cross-clamping where no blood could flow through the artery while the linking was being concluded. Group two received the cardiopulmonary bypass and immediately followed with the cross-clamping without the IPC treatment. Myocardial tissue specimens were taken using a biopsy needle three times during the operation: during the cardiopulmonary bypass, before the cross-clamping (end of IPC for group one), and at the end of the cross-clamping. All samples were immediately frozen in liquid nitrogen and later analyzed for their ATP concentrations. Table 1 displays the data reported from the experiment. After the completion of the cross-clamp fibrillation, the ATP concentration was significantly higher in the IPC group compared to the control group ($p < 0.05$) (Yellon, Alkhulaifi and Pugsely, 1993). The researchers concluded that IPC was responsible for this protective effect and it could be used to prevent or reduce infarct size. This was the first study to

show the benefits of IPC treatment in humans under clinical conditions. The authors state more research needs to be done to find a practical way to achieve the protective effects for it to be more commonly used.

Table 1

ATP Results

	Before Preconditioning (biopsy A)	End of Preconditioning (biopsy A)	End of 1st cross-clamp fibrillation (biopsy C)
Group 1 (n =7 , IPC)	20.6 ± 1.3	10.5 ± (1.1)	12.0 ± 1.1
Group 2 (n = 7, control)	21.6 ± 1.5	19.8 ± 1.3	6.8 ± 0.2

Results are given as mean ± Standard Error of measurement in μmol/gram of dry weight.

IPC Mechanisms

The goal of early research was not only to confirm the existence of IPC's beneficial effects but also determine the mechanisms through which it occurs. Once the mechanisms are better understood, a stronger protective effect could be induced or perhaps done only using medication without the need for surgery.

Adenosine was hypothesized as a likely option since it was known to be released by ischemic myocytes and had been reported to contain cardioprotective properties (Liu et al., 1991). A study using rabbits utilized two forms of adenosine receptor blockers, 8-p-sulfophenyl theophylline (SPT) and PD 115,199 (PD) to determine the activity of adenosine during IPC. The experimental design was formed comparing treatment groups with: no treatment (control), IPC alone, SPT alone, PD alone, SPT + IPC, PD + IPC, and added intravenous adenosine. The preconditioning treatment consisted of 5 minutes of occlusion and 10 minutes of reperfusion. All groups underwent their assigned treatments, received 30-minutes of ischemia to a coronary

artery and three hours of reperfusion, and then the hearts were analyzed to determine infarct size. The average amount of cell death was 39% in the control group but 8% in the IPC group. Hearts that received either adenosine blocker (SPT or PD) accumulated infarct areas the same size as the control group despite receiving a preconditioning treatment. Also, the intracoronary infusion of adenosine did not substitute for IPC and resulted in an infarct size no different from the controls. Investigators concluded adenosine is released as a result of preconditioning, which aids in the protection of the cardiac cells. However, adenosine is not solely responsible for IPC's protective response; but rather, it is one piece of the proverbial puzzle of IPC. The researchers mention once the mechanisms are better understood; it could be possible to induce IPC in a semi-permanent state for people at a high risk to heart attacks as a method of preventing substantial amounts of cardiac cell death before arriving at a hospital for treatment (Liu et al., 1991).

Furthermore, Protein Kinase C (PKC) is responsible for a portion of IPC's beneficial effects. When adenosine is released, it binds to the corresponding protein receptor and stimulates the activation of messenger diacylglycerol, which is a known PKC activator. PKC is significant due to its ability to modify proteins (Ytrehus, Liu and Downey, 1994). To determine whether PKC was active during IPC, researchers used an experimental design with two parts. First, they examined whether blocking PKC would prevent the beneficial effects of IPC. Second, whether using a PKC injection would result in the same cardioprotective effects as IPC alone. Eight groups of rabbits were formed around receiving the treatment before 30-minutes of ischemia: a control group (no treatment)($n = 12$), only IPC group ($n = 5$), two groups used different PKC inhibitors and IPC treatment ($n = 6,8$), two groups used different PKC inhibitors without any IPC treatment ($n = 5,5$), and two groups went through exogenous activation through different PKC activators without IPC ($n = 8,8$). The preconditioning was performed with five minutes of

coronary branch occlusion followed by ten minutes of reperfusion. Infarction sizes were given as percentages of the total area at risk of cell death. Data gathered from the experimental protocol are presented in Table 2. Researchers concluded the inhibition of PKC prevents IPC's cardioprotective effects ($p < 0.05$) and applying a PKC drug mimics IPCs protective effects ($p < 0.05$). These findings support PKC activation as an essential mechanism through which IPC protects the myocardium. Additionally, it supports PKC being one of the primary contributors to IPC and potentially be the foundation of drugs engineered to imitate IPC protective effects (Ytrehus, Liu and Downey, 1994).

Table 2

Risk Zone and Infarct Size in Rabbits

	Risk Area (cm^3)	Infarction Size (cm^3)	% Infarction
Control	0.70 ± 0.05	0.19 ± 0.04	26.2 ± 3.5
IPC alone	0.86 ± 0.08	0.10 ± 0.02	11.8 ± 2.2
PKC activator 1	0.68 ± 0.08	0.08 ± 0.02	11.7 ± 3.3*
PKC activator 2	0.81 ± 0.06	0.04 ± 0.01	5.9 ± 1.2*
PKC Inhibitor 1 with IPC	0.61 ± 0.05	0.22 ± 0.01	36.2 ± 2.7
PKC Inhibitor 1 without IPC	0.65 ± 0.09	0.26 ± 0.03	40.5 ± 2.8
PKC Inhibitor 2 with IPC	0.73 ± 0.08	0.31 ± 0.04	40.9 ± 2.5
PKC Inhibitor 2 without IPC	0.76 ± 0.09	0.33 ± 0.07	42.0 ± 7.0

Values are mean ± standard error. * denotes statistical significance ($P < 0.05$ vs. control).

Finally, ATP-sensitive potassium (K+ATP) channels were hypothesized to be involved in IPC. The channels were first discovered in cardiac myocytes and are known to be involved in

the regulation metabolites and aerobic metabolism (Ashcroft and Ashcroft, 1990). There are two types of K+ATP channels, one located in the sarcolemma and one inside the mitochondria of the muscle cells. An IPC research review by Eisen (2004) contained a section describing the results of eight studies regarding the involvement of both channels describing the results of each study. The interventions consisted of pretreating a population with a K+ATP channel blocker or promoter to determine the activity of these channels in an IPC experimental protocol.

All research supported the closing of sarcolemmal channels using a blocker prevented the cardioprotective effects of IPC. However, inconsistencies arise when researching the involvement of mitochondrial K+ATP channels. Four studies all treated rabbits or rats with diazoxide, a mitochondrial K+ATP opener, as a pretreatment before IPC. However, they disagreed on results; two found a decrease in infarct size (Garlid et al., 1997; Pain et al., 2000) while the other two found no differences in infarct size (Haruna et al., 1998; Hale Cloner et al., 2000). Then in dogs, both sarcolemmal and mitochondrial channels required a blocker in order to remove the cardioprotective effects of IPC (Sanada et al., 2001). The authors concluded while the activity of both channels is controversial, they do play a role in IPC, however more research needs to be done to determine their specific actions in IPC (Eisen, 2004).

IPC for Athletic Performance

The mechanisms that IPC uses to protect cardiac muscle may also be used to improve athletic performance. The beneficial effects of IPC have been observed in human skeletal muscle without exercise, even though the anatomy of cardiac muscle and skeletal muscle differ in their mitochondrial density and vascularization (Bøtker et al., 2010). All previously stated mechanisms also exist in skeletal muscle, supporting the claim IPC has for athletic applications. As previously mentioned, two systems that IPC manipulates to decrease cell injury rate in heart

tissue are adenosine and K+ATP channel sensitivity. When reviewing their role in skeletal muscle, elevated activity levels of these two structures are known to increase vasodilation and therefore increase nutrient and oxygen delivery to the muscle cells, while aiding in the transportation of catabolites away from the active muscle (de Groot et al., 2010). Increased adenosine levels have also been found to increase Nitric Oxide production by endothelial cells, adding another potent vasodilator to increase blood flow (Li et al., 1995). These systems play an active role during times of increased metabolic need, such as ischemia and exercise.

Different organizations and researchers began to focus on the application of IPC for athletic conditions. Part of the issue with understanding the mechanisms of IPC was also understanding the circumstances it may enhance athletic performance. The benefits were based on IPC's ability to promote slower ATP depletion for relatively short times when blood availability is reduced (Murry et al., 1986). Therefore, the exercise modality chosen should reflect these conditions. Exercise that is short and anaerobic are the best circumstances to test IPC's effects on skeletal muscle.

IPC for Cycling

The first test of IPC on human performance employed a maximal bike test. Fifteen healthy and well-trained individuals arrived at the testing site two times to perform a maximal test on a bike; one test was as a control, and the other was done after receiving an IPC treatment. Treatment was done using an occlusion cuff around the proximal portion of the thigh set to 220 mmHg, which was strong enough to cut off arterial blood flow. The cuff was inflated for five minutes of occlusion to one leg then five minutes of occlusion for the other for three sets (30 minutes total). Five minutes after the treatment was concluded, the participants began their incremental maximal test on a cycle ergometer. The control group received no occlusion before

performing their bike test. A total of seven things were tested for the tests: maximal heart rate, ventilation rate, lactate levels, Respiratory Quotient, blood pressure, oxygen consumption, and maximal power output. However, only two changed a statistically significant amount from the treatment to control group. Statistics were reported as the mean ± standard deviation for each variable. Average maximal oxygen consumption was reported as 56.8 ± 6.8 ml/kg/min in the control group and 58.4 ± 6.2 ml/kg/min in the treatment group. Mean maximal power output in the control group was recorded as 366 ± 62 Watts and improved to 372 ± 59 Watts in the treatment group. The results showed a 3% increase in oxygen consumption ($P = 0.003$) and a 1.6% increase in power output ($P = 0.05$) for the IPC treatment groups. These conclusions supported the hypothesis that IPC could improve performance (de Groot et al., 2010). Researchers described IPC's ability to prepare the muscles for vigorous activity as a unique and practical form of treatment which requires a minimal amount of portable equipment. The authors stated more research was needed to determine the most efficient IPC procedures for athletes of different sports; however, the potential performance improvement could make a significant difference in a competitive environment.

Cycle sprinting events were another test chosen by researchers to understand the applications of IPC. Short distance events require the athlete to move as fast as possible, which results in a limited amount of oxygen delivered to the primary muscles. Fourteen active males participated in the study and performed twelve, six-second sprints on a cycle ergometer on two separate days. One day was a part of a SHAM group receiving 20 mmHg of pressure, and the other in an IPC treatment group with 220 mmHg of pressure. Both groups received their given treatment for four sets of five minutes before beginning the repeated sprint protocol. Data were analyzed using a contemporary magnitude-based inference approach rather than P-values to

detect small changes in a small sample size. Only the first three sets showed statistical significance and were the only sets reported in the literature. The information regarding the cycle sprint sets can be found below in Table 3. When compared to the control, IPC treatment resulted in a 2-4% increase in mean and peak power during the first half of the sprint protocol (Patterson et al., 2015). This study demonstrated IPC's benefits may be time sensitive and should receive more research to understand what causes the limitation and what can be done to prolong it. These findings are similar to Murry, Jennings, and Reimer which found IPC to have a protective effect for 40-mintues of ischemia; however, pushing the time of ischemia to 180-minutes proved to be too much and the protection was lost (1986). The researchers suggest IPC may have a potential benefit earlier on in training, but the beneficial effects are limited to the earlier phase.

Table 3

Cycle Sprint Results

	Sprint 1	Sprint 2	Sprint 3
% increase in peak power output from placebo to IPC	2.4 ± 2.2	2.6 ± 2.7	3.7 ± 2.4
% likelihood IPC caused the increase in peak power	89% *likely*	87% *likely*	97% *very likely*
Peak power effect size	small	small	small
% increase in mean power output from placebo to IPC	2.8 ± 2.5	2.6 ± 2.5	3.4 ± 2.1
% likelihood IPC caused the increase in Mean power	91% *likely*	88% *likely*	98% *likely*
Mean power effect size	small	small	small

Mean ± standard deviation.

Ischemic preconditioning's effects during cycling have both been shown to improve performance and not induce any benefit at all. Studies by Patterson et al. and de Groot et al. both support IPC as a method of improving performance for cycling. However, two more cycling studies were published using similar sprint protocols on a cycle ergometer found no significant improvements in mean or peak power. Both studies used 14-17 active individuals, a random cross-over design, and IPC and control groups receiving 220 mmHg and 20-50 mmHg respectively for 3-4 sets of five minutes. The only significant difference between studies is approximately half of the participants in the two studies not supporting IPC are female (Lalonde and Curnier, 2015; Patterson et al., 2015), where the two supporting studies used 80% or 100% male participants (de Groot et al. 2010; Gibson et al., 2015). Due to these inconsistencies, supporting IPC's beneficial effects in athletics becomes more difficult.

The consensus of IPC for athletic purposes is roughly half in favor of benefits and half showing no improvement; however, Paixao et al. was the only to show a decrease in performance. Fifteen amateur cyclists participated in an IPC treatment protocol, same as the previous four cycling studies, before a Wingate cycling test of 30-second maximal sprints. The researchers measured performance through peak power and anaerobic power. Eleven of the 15 amateur cyclists had worse times on their cycling tests after receiving their IPC times compared to their control times. The researchers concluded IPC decreased peak power ($P < 0.01$) and total anaerobic power ($P < 0.01$) when compared to control (Paixao et al., 2014). As previously mentioned, this is the only study to show a decrease in performance caused by IPC. While it is feasible IPC is responsible, a number of other variables could be the culprit. There is no information on the gender of the participants mentioned in the study. Although this is the only

study resulting in a decrease in performance, and there are many studies in support of IPC's beneficial effects, it is difficult to determine whether IPC is genuinely beneficial for athletes.

Differences Between Sexes

Hormone levels may play an important role in how much of a benefit IPC provides. Testosterone is a steroid hormone that is primarily responsible for male sexual characteristics, and while both genders produce the hormone, on average males produce 15-20 times more (Brooks, Fahey and Baldwin, 1996). In rats, it has been shown in research that preconditioning required testosterone through the synthesis of heat shock protein 70. This protein is a mediator of delayed onset cardioprotection through an androgen receptor-mediated mechanism (Liu et al., 2006). Additionally, testosterone has been demonstrated to upregulate the a1-adrenoceptors after IPC, an additional mediator to promote a cardioprotective response (Tsang et al., 2008). Furthermore, since males have significantly more testosterone, IPC may benefit males more than females.

Research was needed to examine how IPC impacts performance differently between sexes. A 2017 study by Paradis-Deschenes, Joanisse, and Billaut did just that; examining eight men and nine women for muscle performance and vascular responses to IPC during resistance training. Participants started in either a SHAM or IPC group in a crossover design experiment, with the two treatments separated by three to seven days. The IPC treatment consisted of three sets of five-minute ischemia and reperfusion cycles at 200 mmHg pressure administered to the legs, and the SHAM group was administered 20 mmHg of pressure. Following the treatment, each participant performed five sets of five maximal voluntary knee contraction repetitions on an isokinetic dynamometer. Changes in deoxy-hemoglobin and total hemoglobin concentrations of the vastus lateralis were continuously supervised using near-infrared spectroscopy. Force was

measured using a force transducer connected to the end of the lever arm of the dynamometer. The performance data gathered from the experiment is described below in Table 4. Additionally, oxygen uptake was different between sexes in sets: 2 (males: 6.4% vs. females: −16.7%, ES 0.21), set 3 (males: 7.0% vs. females: −44.4%, ES 0.56), set 4 (males: 9.1% vs. females: −40.2%, ES 0.51), and set 5 (males: 10.2% vs. females: −40.4%, ES 0.52). During exercise, males demonstrated more statistically significant and beneficial reactions to the IPC treatment. The researchers were able to conclude IPC increased muscle force in males to a greater extent than females, increased oxygen extraction in males but decreased it in females and increased resting blood volume similarly in both sexes. More research should be done to confirm whether men benefit from IPC more than women, however this could help explain why there is so much variation in IPC research. Additionally, the issue lessens the general applicability of IPC for all athletics. Female athletics make up a large part of sports, and without women also receiving a benefit, IPC might be considered an unfair advantage (Paradis-Deschenes, Joanisse, and Billaut, 2017). These results challenge the accuracy of previous research, suggesting when men and women are tested together it negatively impacts the results.

Table 4

Performance Variables in IPC and SHAM between Males and Females

	Females			Males			Sex Difference
	SHAM	IPC	% difference, (ES) 90% CL	SHAM	IPC	% difference (ES) 90% CL	(ES) 90% CL
Peak force set one (N)	449.1 ± 37.2	481.3 ± 42.1	7.2%, ES 0.24*, -0.07;0.56	627.9 ± 45.1	685.3 ± 35.7	10.2%, ES 0.41*, 0.23;0.59	ES 0.10, -0.24;0.44
Peak force set two (N)	421.1 ± 32.8	446.3 ± 33.1	6.4%, ES 0.22*, 0.00;0.43	566.3 ± 31.3	648.9 ± 47.6	13.7%, ES 0.54*, 0.32;0.75	ES 0.24*, -0.03;0.50
Peak force set three (N)	402.5 ± 22.7	429.5 ± 28.3	6.3%, ES 0.22*, 0.05;0.38	558.8 ± 35.7	581.6 ± 41.7	3.8%, ES 0.16, -0.01;0.32	ES -0.09 -0.29;0.12
Peak force set four (N)	402.5 ± 24.7	422.0 ± 25.0	5.1%, ES -0.18, -0.06;0.41	526.3 ± 29.8	574.6 ± 43.2	8.4%, ES 0.34*, 0.06;0.54	ES 0.11, -0.20;0.42
Peak force set five (N)	401.8 ± 27.1	397.5 ± 24.5	-0.7%, ES -0.02, -0.17;0.12	506.9 ± 28.3	544.0 ± 39.1	6.7%, ES 0.27*, 0.01;0.54	ES 0.26*, 0.00;0.51
Force decrement (%)	10.4 ± 1.5	8.4 ± 1.4	-19.8%, ES -0.38*, -0.77;0.01	13.7 ± 2.7	15.2 ± 2.2	6.0%, ES 0.12*, -0.54;0.77	ES 0.45*, -0.16;1.07

Values are mean ± standard error. Asterisks (*) denote "clear" effect sizes

IPC for Swimming

Short distance swimmers were one group to receive attention since their arms undergo so much metabolic strain for during their sport. Improving oxygen consumption is especially sought after for swimming since it is one of the only sports requiring athletes to hold their breath. Using an occlusion protocol of 220 mmHg (10 mmHg for control) around the lower arm for four sets of five minutes, sixteen national level swimmers took part in a cross-over design to determine

whether IPC would improve maximal swimming times. The athletes received the day's given treatment, were given five minutes to rest, then began a standardized warm up before the maximal effort swims. Swimmers were allowed to swim their preferred lengths, 100 or 200-meters, using their preferred stroke styles. Average race times for all swim lengths were 66.98 ± 21.28 for the control and 66.28 ± 21.08 seconds for the IPC treatment group. While a 0.7-second difference may not seem significant, IPC resulted in an improvement of 22 International Swimming Federation points ($p = 0.01$). The researchers concluded that IPC treatment times were significantly faster ($P = 0.04$) than the control times, supporting the claim that IPC may result in improved exercise performance under some conditions (St Michel et al., 2011). This evidence supports the use of IPC to prepare swimmers before a maximal speed race to improve performance.

IPC and the Placebo Effect

The management of control groups in IPC research is the most prominent issue with minimizing the placebo effect. There is no standardized treatment that control groups universally receive. Commonly, researchers have either designed no treatment (de Groot et al., 2010) or light pressure from a blood flow restriction cuff ranging from 10-20 mmHg applied for the same duration as the treatment intervention (Patterson et al., 2015). Unlike taking a pill, participants can feel the difference in occlusion pressure when experiencing an IPC or control treatment. This feeling may result in participants determining on their own which treatment corresponds to which group, influencing the results of the study. Consequently, it was important for researchers to focus on whether the placebo effect impacts IPC protocols and how to reduce that effect as much as possible.

In a study regarding the effects of IPC on swimming, researchers used a similar design to a previously described swimming study by St Michel et al., but added another variable to better test the placebo effect. Participants (n = 15) participated in a cross-over design with two groups: IPC of 220 mmHg for four sets of 5 minutes, and a SHAM group receiving 20 mmHg occlusion for four sets of five minutes. Both IPC and SHAM also participated in a control group which experienced no occlusion at all. Participants were informed their occlusion treatment, IPC or SHAM, were being tested for potentially improving performance. The goal of this design was to make participants in the SHAM group believe they were receiving a genuine IPC protocol to determine the prevalence of the placebo effect. Each participant performed a 100-meter maximal effort swim as a part of either group. Eleven of the fifteen participants improved their race time after the IPC treatment, for a group average of 1.1-seconds compared to the control ($p = 0.036$). However, ten of the 15 participants improved their race time after the IPC treatment, for a group mean of 0.7-seconds ($p = 0.059$). IPC times were shown to be significantly faster than control group times, but IPC and SHAM were determined not to be significantly different ($p = 0.76$). This study was the first to reveal a possible bias affecting many studies on IPC. The researchers were able to conclude that IPC had a beneficial effect on performance, but the placebo effect was also responsible for some performance improvement (Marocolo et al., 2015).

Following the previous study, the same lead researcher performed two more studies which also illustrated how the placebo effect influences IPC's benefits. With the same IPC, SHAM, and control treatment cross-over design as the swimming study, thirteen male participants determined their 12-repetition maximum on the leg extension. Then participants received their given treatment and standardized warm-up, then did their previously determined 12-repetition maximum weight on the leg extension for as many repetitions as possible for three

sets with two minutes of rest between them. The study resulted in both IPC and SHAM increasing the number of repetitions in the first and second sets (IPC/SHAM 1st set p = 0.0036, 0.0016; 2nd set p = 0.011, 0.019; 3rd set p = 0.68, > 0.99), where the control treatment repetition count did not improve in any set (p > 0.99) (Marocolo et al, 2016). In another study, Marocolo et al. used the same design but supplemented IPC on the upper arms and only had participants perform one set of an elbow flexion exercise for maximal repetitions with their 12-repetition maximum weight. This research concluded with IPC and SHAM both enhancing resistance exercise performance by improving total repetition count (p = 0.033, 0.023) (Marocolo et al., 2016). Both of these studies supported the presence of the placebo effect and its ability to affect data gathered in research.

A study by Ferrerira et al. demonstrated the placebo effect may not have as large of an impact as previously thought (2016). The placebo effect had the potential to bring much of the previous research on IPC into question, but not all research regarding the subject supported the presence of the placebo effect. A study was designed observing swimmers, once again, but added more complexity to test the placebo effect even further. Twenty-three participants were randomly assigned to two groups, an IPC group or a SHAM group. The IPC participants underwent 220 mmHg of occlusion for five minutes, while the SHAM group received: 10 mmHg for two minutes, 220 mmHg for one minute, then ten mmHg for two minutes. Both groups also participated in a control treatment which was ten mmHg for five minutes. The control, SHAM, and IPC treatments were all repeated three times for a total of 30 minutes. Participants were told that both treatments, IPC and SHAM, would improve their swimming performance. Additionally, seven participants were randomly chosen to cross-over to the other group and receive all three possible treatments resulting in both the IPC and SHAM having 15 sets of

numbers. After given day's treatment, each participant performed six timed 50-meter sprints to be done every three minutes. Total race time for the control and IPC improved from 206.04 ± 4.56 to 203.64 ± 4.61 seconds ($p = 0.02$), respectively. Additionally, the total time for control and SHAM were 205.70 ± 4.40 to 205.53 ± 3.78($p = 0.90$), respectively. The study concluded with the treatment group's times being significantly faster than their control counterparts, where SHAM did not improve sprint times when compared to their control trials (Ferrerira et al., 2016). The results of this study disagree with what Marocolo et al. presented in their studies, which were in favor of the placebo effect skewing the results. These contrasting results confirm that determining the prevalence of the placebo effect requires more attention before any conclusions can be made.

Research that focuses explicitly on the placebo effect and IPC is indecisive, making it difficult to support either side. While convenient, it should be viewed with some skepticism that the same lead researcher, Marocolo, was a part of all the research supporting the placebo effect. While this does not automatically imply that the research should is not credible, it is worth noting. This unreliability could be in the form of how the participants were chosen, if the participants were somehow informed of the concept the studies, some bias on the university's part, or perhaps something even less notable. Until more research is done on the subject, researchers must continue to do their best to minimize the placebo effect. However, simply because a study could have an improved design in regard to the placebo effect does not necessarily mean the effect is responsible for any results not supporting IPC for performance.

IPC for Resistance Exercise

In a recent study by Tanaka et al. (2016), performance in single-joint resistance training was shown to improve as a result of ischemic preconditioning (IPC). Twelve male participants

(mean: ± standard deviation (SD); age: 22 ± 1 years, height: 172 ± 1 cm, weight: 63 ± 2 kg) underwent a cross-over design study, participating in both the control (no treatment) and IPC groups. Since the control group did not receive a lighter occlusion SHAM treatment, the study was more likely to experience the placebo effect as a limitation. Participants' maximal leg extension torque was tested before the experimental protocol using a BIODEX dynamometer system (BIODEX system 3; BIODEX Medical, Shirley, NY, USA). After receiving the IPC treatment, >300 mmHg of occlusion around the upper thighs for three sets of five minutes, participants performed an isometric unilateral knee-extension at 20% of their predetermined maximal torque until failure. In addition to timing until failure, electromyography activity and near-infrared spectroscopy-derived deoxygenation were recorded in the quadriceps vastus lateralis. The time until task failure was significantly higher in the IPC group than in control (mean ± SD; 233 ± 9 vs. 198 ± 9 seconds) ($p < 0.001$) although electromyography did not indicate differences between the groups. Therefore, the researchers concluded that IPC enhanced muscular endurance during isometric exercise. Interestingly, deoxygenation in the vastus lateralis was significantly faster during IPC than the control group ($p < 0.01$), indicating muscular oxygen extraction was increased without inducing an adverse effect on performance. The researchers inferred the beneficial effects of IPC might be due to enhanced mitochondrial metabolism in skeletal muscle, hence the increased rate of deoxygenation (Tanaka et al., 2016).

Vianna et al. found IPC to increase the number of repetitions completed per set and total volume of a resistance training workout (2018). Thirteen resistance-trained men (mean ± SD; age: 22.5 ± 4.2 years; mass: 76.4 ± 2.8 kg; height: 173.7 ± 9.2 cm) participated in the study. The experiment took place over five, nonconsecutive days. On the first and second day, participants tested and re-tested their one-repetition max in the: bench press, leg press, frontal pull, hack

machine, shoulder press, and smith-machine squat. From the third to the fifth visit, participants were randomly divided into IPC, SHAM, or control experimental conditions. IPC consisted of four cycles of five-minute occlusion at 220 mmHg and alternated with five minutes of reperfusion, SHAM received 20 mmHg of pressure and followed the same procedure as IPC, and control did not receive any occlusion cuff treatment.

Resistance exercises were performed in the same order each day and involved three sets at 80% one-repetition maximum until concentric failure. Repetition count was recorded at the end of every set. Total volume (weight x sets x repetitions) was significantly higher in the IPC group compared to control for the bench press, leg press, frontal pull, hack machine, and shoulder press ($p < 0.05$). There were also significant differences in total volume for the IPC and SHAM group in the bench press, leg press, and frontal pull ($p < 0.05$). Researchers concluded that the IPC treatment significantly increased the number of repetitions and total volume compared to SHAM and control treatments (Vianna et al. 2018). These results are in agreement with Tanaka et al. (2016) supporting the premise that IPC offers a non-invasive method to improve performance in resistance training. Vianna et al. also reported that IPC's benefits occurred in compound exercises, including ones where the primary muscle group responsible for the movement is not a part of the limb which was administered IPC, such as the frontal pull where the latissimus dorsi is the primary mover. While these findings may appear unusual, it is in agreement with swimming studies supporting IPC's beneficial effects (St Michel et al., 2011; Ferrerira et al., 2016). In swimming, the back and shoulder muscles are the primary movers; however, IPC treatment can only be administered to the arms. IPC can be used to increase the total number repetitions done in a resistance training session, including compound movements, aiding athletes by improving workouts and promoting increases in strength.

Remote IPC

Przyklenk et al. revealed IPC was able to protect myocytes in areas of the heart other than those subjected to the occlusion treatment (1993). Eighteen dogs were used in the study, reflecting the same species chosen for subjects as Murry et al. in the first study regarding IPC (1986). Each dog was put under anesthesia and underwent one hour of occlusion to the LAD and a subsequent four and a half hours of reperfusion. Prior to occlusion, the dogs were randomly placed in either a control group ($n = 10$) or an IPC treatment group ($n = 8$). The circumflex branch, rather than the LAD, received a preconditioning treatment of four repeated cycles for five minutes of occlusion followed by five minutes of reperfusion. Four and a half hours after reperfusion the dogs were put down, and the area at risk of necrosis and the area which accumulated necrosis were determined. In the control group, $16 \pm 5\%$ (mean ± SD) of the heart tissue at risk became infarcted, whereas the preconditioned group accumulated significantly less cell death at $6 \pm 2\%$ of the area at risk ($p < 0.05$). The researchers concluded that an IPC treatment to one area of a dog's heart produced a cardioprotective effect in another area, independent of the IPC treatment's location. These data imply that the mechanisms which produce the beneficial effects are not restricted to one area and may be transported throughout the heart's vascular system. If the remote effects of IPC can be initiated from areas other than the heart, IPC may have a less invasive clinical application than previously considered.

The first clinical study of remote IPC (RIPC) on humans found that occlusion treatment to the limbs was able to induce a protective effect in the heart (Cheung et al., 2006). To determine if IPC's remote effects could be observed in humans, investigators recruited people in need of heart surgery. Thirty-seven children, undergoing congenital heart defect repair, were selected as participants for the experimental procedure. Patients were randomized and placed in

the control group (mean ± SD, n = 20, 0.9 ± 0.9 years old, 6.9 ± 2.9 kg) or the RIPC group (n = 17, 2.2 ± 3.4 years old, 11.5 ± 10 kg). Although the age and mass of the participants appear to be different, the researchers stated there was no statistically significant differences (age: $p = 0.4$; mass: $p = 0.06$). Remote IPC was induced in the legs with four cycles of five minutes of ischemia, with the pressure determined by the child's blood pressure, followed by five minutes of reperfusion. Although there was little chance of a placebo effect, children in the control group were administered a SHAM treatment of having the cuff tightened around the leg without any inflation. Five to ten minutes after the completion of the IPC and SHAM protocol, the initiation of the heart surgery began.

All children underwent surgical repair using standard cardiopulmonary bypass techniques involving the temporary cessation of cardiac activity. The duration of the procedures was recorded in the event a surgery was too short and a participant needed to be excluded. Troponin I was used as the primary measure of myocardial injury in the study since it is the most common biomarker used for diagnosing myocardial cell death (Cheung et al., 2006). Levels of troponin I were taken pre-operation and at three hours, six hours, 12 hours, and 24 hours post-bypass. The difference between remote IPC and control troponin I levels, with all post-bypass measurements considered, met statistical significance ($p = 0.04$). The protocol of limb IPC protected children's myocardium from Ischemia-induced damage during heart surgery. In the clinical setting RIPC may allow doctors to reduce the amount of cell death occurring during heart surgery for patients of all ages without the need to localize treatment, making the process less intricate (Cheung et al., 2006).

For athletic purposes, RIPC has been observed in using a number of experimental protocols. The first study that can be considered as using RIPC is the previously discussed study

by St Michel et al. where swimmers were participants (2011). Blood flow restriction cuffs were placed around the swimmers' lower arms, and while the arms play a role in swimming movement, the shoulder, back, and leg musculature are the primary movers in in terms of swimming locomotion. There is still an argument to be made that while the arms are not the primary movers, IPC was still applied to body parts directly involved in the tested exercise. For this reason, more research was required about RIPC. (St Michel et al., 2011).

The first direct investigation into the capabilities of RIPC for athletic performance demonstrated its ability to delay fatigue development during handgrip exercise (Barbosa et al., 2014). Participants were physically active men (mean ± SD; age: 25 ± 4 years; BMI: 22.1 ± 2.7 kg/m^2, N = 13) who were non-smokers and not on any medication. The RIPC protocol consisted of occlusion cuffs placed proximally around both thighs and were simultaneously inflated to 200 mmHg for five minutes, then deflated for five minutes for three sets (15 minutes total per leg). Occlusion of the femoral arteries and subsequent limb ischemia was confirmed by imaging the popliteal artery via ultrasound. The control protocol comprised of the same methods as the RIPC, but the occlusion cuffs were only inflated to 10 mmHg, which did not cause any limb ischemia. Investigators who gave encouragement during the session were unaware of which procedure was being applied, and participants were unaware of the purpose of each procedure. After both treatments, participants performed rapid handgrip contractions in a rhythm of 60 contraction-relaxation cycles/min (controlled via metronome), in a supine position using their dominant hand holding a hand dynamometer. Target force was 45% of a previously determined maximal voluntary contraction, which was displayed on the ceiling in real time using a projector. Contractions were performed until task failure, which was determined when at least three consecutive contractions were lower than 40% maximal voluntary contraction. Time until task

failure was defined as the time from the onset of the first contraction to the end of the last valid contraction. Rate of force development during contraction and relaxation were calculated to assess the fatigue development throughout the protocol. Time to task failure was analyzed using a two-way repeated measure Analysis of Variance (ANOVA). While contraction and relaxation rates decreased throughout time points with both RIPC and control, rates were higher with RIPC ($P < 0.05$). Time to task failure increased after the RIPC treatment compared to control (RIPC: 198 ± 70 seconds, control: 179 ± 66 seconds, $P < 0.05$). The investigators were able to conclude RIPC delayed the development of fatigue during handgrip exercise, positively influencing the participants ability to perform exercise for longer periods of time (Barbosa et at., 2014). While the study is limited by a small sample size, it provides additional evidence to extend the applicability of RIPC.

A study mentioned earlier in this review by Lalonde and Curnier examined RIPC and found that it did not offer any significant benefits for anaerobic performance (2015). Seventeen healthy, regularly exercising participants (9 women, 8 men, mean ± SD: age: 28 ± 8 years) completed both an RIPC and SHAM intervention in a crossover design. Unlike most ischemic intervention approaches referenced in this literature review where the occlusionary pressure is at a constant 200-220 mmHg (de Groot et al, 2010), Lalonde and Curnier applied a pressure of 50 mmHg above systolic blood pressure to induce ischemia. Occlusion cuffs were placed on the right arm and inflated for four sets of five-minutes, with five-minutes of no pressure for reperfusion, at either the RIPC or SHAM (10 mmHg) pressure, depending on which protocol the participants were undergoing. Immediately after the RIPC protocol, participants began a standardized warm up, followed by an Alactic Anaerobic test on a cycle ergometer which consisted of six six-second sets at: 0.9, 1.0, 1.1, 1.2, 1.3, and 1.4 $Nm \times kg^{-1}$ of body weight.

Between each set, participants were allowed two minutes of active recovery followed by three minutes of passive rest. After the Alactic Anaerobic test, participants engaged in a Wingate protocol, which is a 30-second maximal sprint on a cycle ergometer against a resistance (0.8 Nm $\times$ kg^{-1} bodyweight for men and 0.77 Nm $\times$ kg^{-1} for women). Results of the Alactic Anaerobic and Wingate tests are displayed in Tables 5 and 6, respectively. Remote IPC was not associated with an increase in mean peak power, decreases in perceived effort, or alter any of the performance variables for the Alactic Anaerobic or Wingate tests (See Tables 5 and 6). Based on the results, the investigators concluded that RIPC demonstrated no potential benefit on performance (Lalonde and Curnier, 2015). While the study is well done overall, the significant number of female participants (nine of the seventeen) may have influenced the results. As demonstrated by Paradis-Deschenes, Joanisse, and Billaut, women do not get as significant of a benefit from IPC as men (2017). Therefore, grouping both sex's numbers together will skew the results towards no significance.

Table 5

Results for the Alactic Test

Variable	Mean RIPC	Mean SHAM	Mean of the Difference	SD of the Difference	Paired t-test (p)	Wilcoxon (p)
Borg Scale	7.24	7.85	-0.62	1.29	0.067	0.267
Mean Power ($W\times kg^{-1}$)	11.41	11.41	0.00	0.51	1.000	0.607
Mean Power (W)	740.35	740.35	0.00	33.15	1.000	0.629
Minimum power (W)	702.53	702.59	-0.06	62.64	0.997	0.629
Peak power ($W\times kg^{-1}$)	702.53	13.04	0.16	0.61	0.302	1.000
Peak Power (W)	13.19	846.59	9.06	41.24	0.379	0.804
Rate to fatigue ($W\times s^{-1}$)	855.65	61.72	6.86	32.19	0.393	1.000
Time to peak power (s)	3.59	3.52	0.07	0.45	0.524	0.549

W = watts, s = seconds, kg = kilograms, SD = standard deviation.

Table 6

Results for the Wingate Test

Variable	Mean RIPC	Mean SHAM	Mean of the Difference	SD of the Difference	Paired t-test (p)	Wilcoxon (p)
Borg Scale	9.15	10.00	-0.94	2.38	0.123	0.021
Mean Power ($W\times kg^{-1}$)	8.15	8.01	0.14	0.27	0.058	0.210
Mean Power (W)	529.47	520.35	9.12	20.07	0.079	0.143
Minimum power (W)	388.53	366.88	21.65	116.74	0.0456	1.00
Peak power ($W\times kg^{-1}$)	12.21	11.95	0.25	0.84	0.230	0.454
Peak Power (W)	794.35	776.71	17.65	55.51	0.208	0.629
Rate to fatigue ($W\times s^{-1}$)	15.68	15.59	0.09	5.28	0.946	0.804
Time to peak power (s)	3.60	3.49	0.11	0.71	0.546	1.000

W = watts, s = seconds, kg = kilograms, SD = standard deviation.

The pair of researchers, Richard and Billaut, have published two pieces of literature examining the effects of RIPC on speed skaters. Due to the low sitting position, isometric gliding, and high intramuscular forces required, speed skating fits the criteria to potentially receive a benefit from IPC treatment. Using near-infrared spectrometry, a low skating position has been associated with significant accentuated deoxygenation, even when compared to an upper-skating position (Rundell et al., 1997). Both studies utilized a randomized, single-blind, placebo controlled, crossover design with elite speed skaters. Nine skaters total (seven men and two women) were used as participants in the first study, while the second had seven male skaters. The limited number of high-level athletes available is the primary reason for the small sample size in these studies (Richard and Billaut, 2018; Richard and Billaut, 2018).

The RIPC treatment for the first study comprised of three alternating five-minute cycle of compression to both upper arms 30 mmHg above each participant's measured arterial systolic blood pressure (~150-155 mmHg), with 5 minutes of reperfusion between sets. The SHAM treatment followed the same protocol except the occlusionary pressure was limited to 10 mmHg. After a standardized warm-up, testing occurred 60-minutes after RIPC or SHAM and involved two on-ice 1000-meter race simulations. Under both conditions, participants were asked to complete the race in the fastest time possible. Remote IPC and SHAM differences were analyzed using Cohen's ES ± 90% confidence limits and magnitude-based inferences. Based on the data, RIPC had no clear effect on overall performance (0.03% mean differences; ES = 0.00; 90% CL, = -0.12 to 0.013). When the skaters were classified as sprinters or middle-distance athletes based on their preferred race distance (≤1000 meters or 1000-4000 meters), skating time was *possibly* improved by RIPC in middle-distance skaters at the 600m point (− 0.5%, ES = − 0.26; 90% CL, − 0.73 to 0.22) when compared to SHAM (Richard and Billaut, 2018).

In the second publication, a RIPC protocol utilizing180 mmHg of compression was applied to the upper arms (10 mmHg for SHAM) for three sets of five minutes, with five minutes of reperfusion. Both RIPC and SHAM interventions were applied ~48, ~24, and ~1.5 hours before testing to study the "chronic" effect of ischemic conditioning. The final compression occurred ~60-minutes before testing. Athletes were asked to perform their usual competition warm-up to promote a realistic context, which was followed by a 600-meter skate to be completed in the fasted time possible. Unlike the first study, the 1000-meter time-trial was avoided to prevent the athletes from experiencing high-level fatigue which may interfere with training. Remote IPC and SHAM differences were analyzed using Cohen's effect size (ES) ± 90% confidence limits. Similar to the previous study, RIPC had no clear effect on either overall performance (0.06% mean difference, ES 0.02; 90% confidence limits -0.09, 0.12). In addition to this, maximal HR remained unaffected by the intervention (189.83 ± 7.36 vs. 189.83 ± 9.09 beats/min: -0.03% mean difference, ES -0.01; -0.26, 0.25) (Richard and Billaut, 2018).

The primary purpose of these investigations was to examine the potential ergogenic impact of preconditioning strategies on elite speed skaters. While select previously published research has shown benefits for athletes utilizing RIPC, the two studies described by Richard and Billaut both revealed no likely benefits supporting its use. While daunting, the small sample sizes and elite athletic levels of the participants make it more difficult to show significance from the data. The authors conclude by stating further studies are needed to better understand the impact of RIPC (Richard and Billaut, 2018). The inconsistent nature of much of the research revolving IPC in general supports the need for further research. Similar to how just recently it was discovered how an individual's testosterone levels have a significant impact on the benefits they

might receive from IPC, there may likely be other unknown variables skewing the research coming out now.

Post-Exercise Ischemic Conditioning

Traditionally, ischemic conditioning is performed prior to exercise to improve the muscle's ability to perform when it is not receiving adequate oxygen. This is a reflection of how IPC was first discovered and applied in the medical field; by using short, non-lethal periods of ischemia and reperfusion to adapt heart tissue for a subsequent prolonged, and potentially damaging, period of ischemia. While initially believed to be only a transient phenomenon, researchers also examined how long benefits might be seen from an IPC treatment.

Emulating the initial study by Murry, Jennings, and Reimer, the scientists Kuzuya et al. showed IPC's benefits to last longer than previously anticipated (1993). Adult dogs (N = 125) were divided into four groups, half of each group (n = 12-14) receiving an IPC (four sets of five-minute LAD occlusions, separated by five minutes of reperfusion) protocol or and the other half receiving no conditioning treatment at all. Following treatment, the LAD was occluded for 90-minutes then allowed five-hours of reperfusion. Infarct size was quantified for each participant via dual-staining method, and dogs were subsequently euthanized at the appropriate times of 0-, 3-, 12-, and 24-hours after the conclusion of the five-hours of reperfusion. The hearts were removed and divided, after incubation in a triphenyl tetrazolium chloride solution, the infarct area remained colorless. The percent of myocardium at risk that was infarcted was calculated and used to measure infarct size. The infarct size, as a percent of the anatomic area at risk, was significantly reduced ($p < 0.01$) in preconditioned dogs ($14 \pm 2.0\%$) compared with the control dogs (39 ± 3.7) when sustained ischemia immediately followed treatment. Similarly, infarct size was significantly smaller ($p < 0.05$) in the treated group ($18.8 \pm 3.4\%$) when compared to the

control group (35.1 ± 4.6%) for the dogs that underwent the prolonged ischemia 24-hours after IPC treatment. There was no statistically significant difference between treatment and control groups for the three-hour (31.2 ± 3.7% versus 37.5 ± 4.2%, respectively) and 12-hour (25.4 ± 4.8% versus 35.0 ± 5.3%, respectively) groups (Kuzuya et al., 1993).

The researchers concluded that IPC has a delayed effect shown 24-hours after and accompanying the same treatment that induces an immediate protective response (Kuzuya et al., 1993). The researchers don't specifically state any potential reasons as to why there were no benefits seen 3- or 12-hours after treatment; however, more research should be done on the subject since significance was found at the longest window of time between the IPC treatment and prolonged ischemia. If the delayed effects can be better understood and exploited, an IPC treatment would not necessarily need to be performed directly before a surgery or athletic event.

Testing delayed IPC's effects in humans revealed that it is similarly as effective as the early phase and can even be initiated remotely. Experimentally, an RIPC begins at the limbs to reduce infarct size in another area of the body. Loukogeorgakis et al. used an experimental protocol where an occlusion cuff was inflated 200 mmHg for three sets of five-minutes (allowing five-minutes of reperfusion) at 0-, 4-, 24-, and 48-hours before 20-minutes of ischemia for each participant (N = 16, 12 men, 4 women). The prolonged ischemia was induced on the opposite arm than the one that received the IPC treatment. Sessions were separated by at least 7 days. Endothelial functioning of the brachial artery was assessed by flow-mediated dilation (Loukogeorgakis et al. 2005). To determine neuronal involvement, an autonomic ganglion blocker (trimetaphan) was infused intravenously (1 to 6 mg/min) during the application of the RIPC treatment. Flow-mediated dilation was reduced by prolonged ischemia (8.7 ± 1.1% before ischemia, 4.9 ± 1.2% after ischemia; $p < 0.001$), but not when preceded by RIPC (8.0 ± 0.8%

after ischemia; p = not significant); RIPC did not provide any benefits after four-hours (4.9 ± 1.1%; $p < 0.001$), but protected at 24 (8.7 ± 1.1% after ischemia; p = not significant) and 48 h (8.8 ± 1.4% after ischemia; p = not significant). Trimetaphan attenuated early (8.3 ± 1.1% before ischemia, 4.2 ± 0.9% after ischemia; $p < 0.05$) and delayed (7.3 ± 1.0% before ischemia, 2.3 ± 0.6% after IR, $p < 0.001$) RIPC (Loukogeorgakis et al. 2005).

The data strongly suggests that RIPC in humans offers lasting protection, up to 48-hours, against endothelial ischemic injury. If applicable to other tissues, RIPC may be a simple way to reduce cell injury and provide protection both 24-48 hours before and immediately preceding an ischemic event.

Delayed IPC for Athletic Performance

Strenuous exercise, often incorporating eccentric muscle contractions, can easily lead to exercise induced muscle damage. This impairment is often expressed as structural damage within the muscle, including disruption to the sarcomeres and preventing efficient excitation contraction coupling (Byrne, Twist, and Eston, 2004). In addition to this, exercise induced muscle damage is associated with a reduced ability to produce muscle force, explosive muscle contractions, and muscle soreness (Howatson and Van Someren, 2008). Interestingly, the metabolic and contractile damage that occurs after exercise is similar to what is seen following prolonged ischemia. More specifically increased intracellular calcium concentrations and an increase in the manifestation of muscle proteins and cytokine markers in the blood (Wang, Baynosa, and Zamboni, 2011; Chan et al., 2004). Thus, PEIC may mitigate exercise induced muscle damage through increased blood flow by elevating adenosine, activating K+ATP channels, and reducing the inflammatory response (Liu et al., 1991; Ashcroft and Ashcroft, 1990; Konstantinov et al., 2004).

The first study published regarding PEIC's impact on recovery revealed there may be practical applications for its use in athletics. Fourteen healthy individuals (N=14, 10 males, 4 females) volunteered to participate in this study. After a familiarization session, participants performed a standardized warm-up followed by a set of three squat jumps with a 90-degree knee angle, then a set of three counter movement jumps, and concluded with a set of six leg press repetitions on a flywheel dynamometer with the intention of producing their maximal velocity.

All jumps were performed with a six kg barbell resting on the base of the neck, and an optical encoder was used to measure the characteristics of power production (maximum and mean eccentric and concentric peak power, velocity, acceleration as well as work, jump height, time to peak power, and time to peak velocity). The participants then performed three warm-up sprints before completing six maximal 40-meter sprints departing every 30 seconds. Immediately after completing the sprint protocol, participants took a supine position and were fitted with a unilateral occlusion cuff placed around the proximal portion of the leg. The cuff was inflated for two sets of three minutes at either an intervention pressure of 220 mmHg or a SHAM pressure of 15 mmHg, both allowing 3 minutes of reperfusion between sets of inflation. Within five minutes of the cuffs being removed, participants repeated the squat jump, counter movement jump, dynamometer leg press, and the 40-meter sprint protocol. In addition to this, the participants returned 24-hours later and repeated the warm-up and exercise protocol. One week later, the participants returned yet again and repeated the two days of testing while receiving the alternate occlusion treatment.

Magnitudes of the standardized effects were interpreted using thresholds of 0.2 (small), 0.6 (moderate), and 1.2 (large). To make inferences about the true (large sample) value of an effect, the uncertainty in the effect was expressed as 90% confidence limits (Beaven et al., 2012).

The PEIC treatment had a clear beneficial effect on the mean squat jump height immediately after the intervention (ES = 0.63) when compared to SHAM. The intervention produced delayed beneficial effects (24-hours post) in the countermovement jump test with concentric (ES = 0.36) and eccentric (ES = 0.26) velocity recovering more rapidly compared with the control. There were also small improvements on 10- and 40-m sprint times. In the squat jump test, there were delayed beneficial effects due to PEIC on eccentric power (ES = 1.38), acceleration (ES = 1.24), and an immediate positive effect on jump height (ES = 0.61). Additionally, total power produced in the dynamometer leg press test 24-hours post-exercise was also clearly enhanced as a result of the occlusion intervention (ES = 0.30), and the magnitude of this effect was greater in the male participants (ES = 0.68) (Beaven et al., 2012).

The researchers concluded by reporting that the PEIC treatment to both legs elicited substantial benefits on specific variables tested in this study both immediately following occlusionary treatment and 24-hours after. While this study took place prior to the publication by Paradis-Deschênes, Joanisse, and Billaut which examined the differences both sexes received from ischemic conditioning, the authors observed that the male participants appeared to elicit more robust improvements as a result of the ischemic intervention (2017). The primary limitation of this study was the small sample size, which becomes increasingly small if the female participants are not included in the data. While unable to completely support the use of ischemic conditioning for recovery, Beaven et al. set the standard for all future research regarding PEIC (2012).

As is commonly seen in any field of research, not all publications will support a given topic. Northey et al. evaluated the use of PEIC for recovery after an arduous resistance training session and found it to be an ineffective method for enhancing recovery (2016). Twelve strength-

trained male participants, partaking in resistance exercise at least three times a week for the past two years (mean three repetition maximum of 138.3 ± 29.1 kg for the back squat), volunteered to participate in the study. After a familiarization session, participants returned to the testing site a following day and underwent a standardized warm-up followed performance and perceptual measures. First, the perceived recovery status was assessed using Borg's CR10 (0 = very poorly recovered, 10 = very well recovered) from a half squat position. Participants were then seated and secured to an isokinetic dynamometer and the highest isokinetic peak torque was obtained from five voluntary maximal contractions at 30-degrees per second. Following the dynamometer, participants performed four static squat jumps starting from a squat position with the knees bent to 90-degrees before jumping to a maximum vertical height. After this, participants performed a set of four counter movement jumps by bending the knees to a self-selected half-squat position before rapidly jumping for a maximum vertical height. The fatigue protocol consisted of 10 sets of 10 repetitions on the back squat at 70% of their predicted one repetition maximum (based on three repetition maximum performed in the lab during the familiarization session). Squat repetitions began by standing straight with knees extended, the bar was lowered until the knees were to an angle of 90-degrees, then participants returned to a standing position before beginning the next repetition. Sets were performed with no more than three minutes rest between sets. Following exercise, the participants underwent the dynamometer, squat jump, counter movement jump, and perceptual measures once again. After the post-exercise outcome measures, participants underwent one of three recovery strategies, one of which was the use of sequential compression boots, which is of no significance for this particular literature review. The PEIC protocol consisted of an occlusion cuff being placed around the proximal portion of the legs and inflated to 220 mmHg for two sets of three minutes. All outcome measures tests were measured

once again at 1- and 24-hours post exercise. The control protocol consisted of no occlusion cuff being placed around the legs and the participants rested for that period. The participants then returned seven days later and underwent the alternative intervention (Northey et al., 2016).

Parametric data are presented as mean ± SD, and statistical significance was set at $p < 0.05$. A two factor repeated measures analysis of variance was used to determine changes in performance outcomes (condition [PEIC, compression (irrelevant), and control] and time [pre, post, 1-hour post, and 24-hours post]) and to identify week-to-week differences in the total lifting volume during the fatiguing resistance exercise and between the different recovery conditions. Concentric peak isokinetic torque at 30 degrees per second decreased significantly over time ($p < 0.001$). Peak torque was significantly higher at 24 hours compared with post ($p = 0.003$), but there were no significant differences in peak torque between conditions ($p = 0.561$). Mean vertical jump height for the squat jump ($p < 0.001$) and counter movement jump ($p < 0.001$) significantly decreased over time, but there were no significant differences in mean jump height between conditions ($p = 0.843$, $p = 0.879$, respectively). Perceived recovery status decreased significantly ($p < 0.001$) over time for all recovery conditions; however, there were no significant differences between conditions at any time (pre [$p = 0.690$], post [$p = 0.886$], 1 hour [$p =0.406$], and 24 hours [$p = 0.401$]) (Northey et al., 2016).

The results of this study were that PEIC (and sequential compression for that matter) did not offer any statistically significant benefit to improving recovery after a difficult resistance training session over a passive control. No advantage was seen either by muscular performance test or by perceptual measures, despite participants stating they preferred the unique recovery methods. The PEIC protocol used in this study is the same as the one used in the publication by Beaven et al., although the ladder study found PEIC to provide a benefit to improving recovery.

While this procedure worked for Beaven et al., a more common set and duration method is three sets of five minutes, which *may* be more appropriate to provide enough ischemic stimulus. Additionally, while the study does exclusively use participants with a history of resistance training, their sample size is rather small and their results might differ if they had used effect size to compensate that limitation (Northey et al., 2016).

The recovery benefits of PEIC can be tested as long as 72-hours after a stressful exercise session. Sixteen healthy males volunteered to participate in a study and were split into two groups, one received a PEIC protocol and the other a SHAM protocol, there was no cross-over approach used in this investigation. Participants attended a familiarization session then returned seven days later to begin the four-day testing procedure. The first day began with performance tests, which were comprised of a standardized warm-up followed by a maximal isometric voluntary contraction (MIVC) and counter movement jumps. Peak knee extension torque was evaluated on the dominant leg via a digital strain gauge, participants were seated with their knees flexed at 90-degrees and were instructed to extend as forcefully as possible for three seconds and was performed three times. Participants then performed a counter movement jump with hands on their hips and dropped to a self-selected level (roughly a 90-degree knee angle) before jumping to a maximal vertical height, performing this jump three times. Plasma creatine kinase was determined from fingertip capillary blood samples. To induce muscle damage, drop jumps were repeated from a 0.6-meter high box for five sets of 20-repetitions separated by two minutes rest between sets. Once the drop jumps were completed, participants took a supine position and occlusion cuffs were placed around the proximal portion of their thighs. The cuffs were then inflated to 220 mmHg (PEIC) or 20 mmHg (SHAM) for three sets of five minutes, allowing five minutes of reperfusion between sets. Participants then repeated the warm-up and performance

tests immediately, 24-, 48-, and 72-hours after the intervention (Page, Swan, and Patterson, 2017).

Maximal isometric voluntary contraction was not different between groups at baseline (611 ± 51vs 629 ± 136 N, for PEIC and SHAM respectively). Rather, MIVC showed a significant group ($P < 0.05$) and interaction effect ($P < 0.05$). Post-hoc analysis specified that the decrease in MIVC was significantly reduced ($P < 0.05$) in the PEIC group compared to the SHAM group at 24- (90.4 ± 10.7 vs 81.5 ± 6.7%), 48- (96.2 ± 6.1 vs 84.5 ± 7.1%) and 72-hours (101.1 ± 4.2 vs 89.7 ± 7.5%) post exercise protocol. The counter movement jump was not different between groups at baseline (34.0 ± 4.4 vs 38.9 ± 8.1 cm). There was a significant effect for counter movement jumps ($P < 0.05$) with time as peak loss occurred 24-hours post exercise (84.3 ± 4.3 and 80.0 ± 6.5% of baseline values for PEIC and SHAM respectively). There was no significant interaction ($P = 0.098$) or group effect observed ($P = 0.069$). There was a significant time effect for creatine kinase ($P < 0.05$); however, there was no significant effect differing from group observed ($P = 0.78$). A significant interaction between time and treatment for creatine kinase ($P < 0.05$) was observed, with post-hoc analysis revealing creatine kinase to be lower in the PEIC group at 24- (335 ± 87 vs 636 ± 300 IU) and 48-hours (244 ± 70 vs 393 ± 248 IU) after the exercise protocol when compared to the SHAM group. Delayed onset muscle soreness demonstrated a significant interaction between time and treatment ($P < 0.05$) and group effect ($P < 0.05$). Post-hoc analysis indicated that the difference in DOMS was significantly lower ($P < 0.05$) in the PEIC compared to the SHAM group at 24-, 48-, and 72-hours post drop-jumps (Page, Swan, and Patterson, 2017).

The authors state that the findings support the hypothesis that PEIC can shorten the recovery process following a stressful exercise session. This is reinforced by the study data

where participants returned to their starting strength levels 24-hours faster than the SHAM condition. The enhanced recovery may be due to decreased inflammation, this response was demonstrated in the study by more rapidly reduced levels of creatine kinase and perceived soreness. Although the study had 16 total participants, they were not subjected to both treatment protocols, which is a favorable study design. Cross-over designs provide a certain degree of reliability, as all participants are unique and having data regarding both protocols on them make more accurate data. However, this was most likely in the study design since the participants have to come to the testing site four days in a row and asking participants to do that even one more time would require more compensation and much more time from both the researchers and participants alike. Overall, the data presented supports previous work that PEIC may be an effective method of enhancing recovery following arduous exercise (Page, Swan, and Patterson, 2017).

When considering a more sport specific and realistic application of PEIC, investigators have tested its ability to improve recovery for rugby players. Since short-term post-match fatigue impairs subsequent athletic performance, recovery strategies are an essential element in the schedules for all types of athletes. To more directly understand PEIC's ability to help athletes in their conditions, Williams et al. utilizes Academy rugby union players to test their hypothesis (2018). Twenty-four male athletes (who were currently participating in preseason training, 1-2 training sessions per day, 4-5 days a week) participated in the study. After a standardized warm-up, each participant was tested for salivary testosterone and cortisol, blood sampling for blood lactate and creatine kinase, completed a muscle soreness questionnaire, and performed a counter movement jump on a force platform. The vertical component of the ground reaction force and participants' body weight were used to calculate displacement of the center of gravity and

instantaneous velocity. After baseline tests, each participant performed six timed maximal 50-meter timed sprints (separated by five minutes rest) to induce muscle damage. After sprinting, occlusion cuffs were placed around the proximal portions of both legs and inflated to either an individually calculated pressure for PEIC (171 – 266 mmHg), or a SHAM pressure of 15 mmHg, for two sets of three minutes and three minutes of reperfusion. Two and 24-hours after occlusionary treatment the same tests that occurred at baseline were repeated. Saliva was sampled once again after a 30-min resistance exercise session performed 24 h after sprinting. Participants then returned at least a week later to perform the same tests but undergoing the other occlusionary protocol (Williams et al., 2018).

Although sprinting influenced creatine kinase ($p < 0.001$, $+457.1 \pm 327.3$ μL^{-1}, at 24 h), lactate ($p < 0.001$, 6.8 ± 2.3 mmol L^{-1}, post), testosterone ($p < 0.001$, $-55.9 \pm \_63.2$ pg mL^{-1}, at 2 h) and cortisol ($p < 0.001$, -0.3 ± 0.3 $\mu g\ dL^{-1}$, at 2 h) concentrations, countermovement jump power output ($p < 0.001$, -409.6 ± 310.1 W; -5.4 ± 3.4 cm, post), perceived recovery ($p < 0.001$, -3.0 ± 2.3, post), and muscle soreness ($p < 0.001$; 1.5 ± 1.1, at 24-hours), PEIC treatment had no effect (all $p > 0.05$) on recovery. In response to subsequent exercise performed 24 h after vascular occlusion, testosterone increased pre- to post-exercise (PEIC: $p = 0.031$, 21.6 ± 44.9 pg mL^{-1}; Control: $p = 0.178$, 10.6 ± 36.6 pg mL^{-1}) however the change in testosterone was not significantly different ($p = 0.109$) between conditions (Williams et al., 2018).

Vascular occlusion did not facilitate recovery following arduous exercise for rugby players. Neither phycological or neuromuscular recovery markers measured 2- or 24-hours after exercise supported any sort of benefit from the PEIC treatment. Total ($p = 0.238$) and average ($p = 0.674$) sprint times were constant between conditions with comparable physiological responses being observed. Because of this, the researchers concluded by stating the PEIC protocol used in

this study did not have any influence on recovery, but since there were no negative effects more research should be done on athletes around their training to test its practical application (Williams et al., 2018).

With regards to cycling, declines in exercise performance have been shown to be avoided 24-hours after PEIC treatment. Researchers Arriel et al lead a randomized, single blind study, 28 male amateur cyclists participated. The first session comprised of anthropometric measures along with the familiarization of procedures (cycle ergometer set up, perceived scale training, etc.), 72-hours later the participants were put through a familiarization incremental test to allocate the groups. Another 48-hours after that, the baseline incremental was carried out. The outcome measures were: creatine kinase, muscle soreness and perceived recovery status, heart rate, perceived exertion, and power output. After a standardized warm-up, the cyclists pedaled at a constant pace of 80-90 rotations per minute (RPM) starting at 40 W, which was increased by 20 W/minute until voluntary exhaustion or they were unable to maintain a pace of at least 80 rpm for 10 seconds or more. Five minutes after completing the bike test, the participants received one of four treatments: two sets of five minutes with five minutes of reperfusion between sets (PEIC or SHAM, 2 x 5) or five sets of two minutes of occlusion with 2 minutes of reperfusion between sets (PEIC or SHAM, 5 x 2). The PEIC (50 mmHg above systolic blood pressure) and SHAM (20 mmHg) treatments were applied unilaterally on alternating thighs. At 24-hours after intervention, the outcome measures were taken once again and a second maximal incremental cycling tests was performed (Arriel et al., 2018).

In all groups, the creatine kinase levels were increased compared with the baseline ($p < 0.05$) after the 24-hour bike test. Both PEIC groups maintained their performance (2 x 5: $p = 0.819$; 5 x 2: $p = 0.790$) even though they both reported feeling more tired at 24-hours post

intervention ($p < 0.05$). The SHAM groups exhibited decreased performance at 24-hours post intervention compared to baseline (2 x 5: $p = 0.015$; 5 x 2: $p = 0.045$). A decrease in maximal heart rate was only exhibited in the SHAM 2 x 5 group ($p = 0.015$). There were no other significant differences in the heart rate, perceived exertion, or power output 24-hours after baseline values for any of the interventions ($p > 0.05$) (Arriel et al., 2018).

According to the researchers, no previous study has evaluated the effect of different PEIC protocols. The results found in this publication suggest that different variations of protocols can have the same resulting benefits for recovery. This may be useful if an athlete is sensitive to five-minute sets of occlusion and may better handle two minute sets. The data presented from this study supports the use of a PEIC treatment as a practicable method of enhancing recovery after a strenuous exercise, potentially due to delayed IPC, which may help with training or competitions on consecutive days (Arriel et al., 2018).

Conclusion

Ischemic conditioning still needs to be determined whether or not it can be applied for athletic purposes. While there is a decent amount of literature on the topic, the findings are inconsistent, especially with PEIC, between it being beneficial or having no effect. Before a decision can be made and PEIC can be supported for real world application, the body of literature surrounding the topic needs to expand. To the knowledge of this researcher, there is no published research investigating the remote effects of PEIC on recovery from strenuous exercise, but based on the aforementioned research there is a strong chance it may yield a beneficial impact.

CHAPTER THREE: METHODS

This experimental study measured participants' muscular soreness and ability to produce maximal torque directly prior and 24-hours after two stressful plyometric jumping exercise sessions. Participants received a compression treatment after each exercise session, one intervention and one SHAM. Additionally, the intervention treatment consisted of one leg receiving a high pressure and the other SHAM. The purpose of this study was to identify if direct or remote PEIC had any recovery effects regarding objective measures of soreness and peak torque production.

Research Question

1. What impact does a remote and direct PEIC treatment have on recovery?
    a. Will it allow participants to perform better 24-hours after difficult exercise when compared to SHAM?
    b. Will objective measures of soreness be lower 24-hours after difficult exercise compared to SHAM?
2. Was ischemia induced in the intended treatment so that PEIC is properly tested?

Participants

Inclusion

A sample of 20 active and healthy males aged 18-30 years were recruited for participation. The sample size was chosen based on other similar studies and accounted for participant attrition (Horiuchi, 2017). Activity criteria stated that participants must be recreationally active men who have participated in resistance exercise at least two times a week for the last two months. Before being accepted into the study, participants were informed of the research procedures that would be used and briefed on the responsibilities of testing. Participants

had the opportunity to ask any questions or concerns, and were presented a written informed consent to voluntarily sign.

Exclusion

The participants' Physical Activity Readiness Questionnaire (PAR-Q+) was reviewed to determine if they were generally healthy enough for the required exercise. If a participant answered 'yes' to any of the questions on the PAR-Q+ were excluded from the study pending review of their answer. Those with, or at risk for, hypertension or hypotension were excluded. The National Institute of Health and American Heart association have identified being "at risk for hypertension" as any blood pressure ≥140 mmHg for systolic and ≥80 mmHg for diastolic; and hypotension as any blood pressure <90 for systolic and <60 for diastolic. Blood pressure was measured in each participant by a trained member of the lab team after five minutes of rest. Immediately following, the participants were asked to stand for two minutes so their blood pressure could be retested for an orthostatic blood pressure test. If their systolic blood pressure dropped by at least 20 mmHg or diastolic dropped by at least 10 mmHg, those participants were excluded. Since the study incorporates blood flow restriction techniques, participants reviewed a Deep Vein Thrombosis risk assessment form with their answers reviewed to ensure they were not at high risk. Individuals with a history of leg, neck, and lower back injuries that may be aggravated by jumping were not included in the study. Additional exclusions included: a history of rhabdomyolysis, sickle cell anemia, a calculated BMI greater than or equal to 35 kg/m^2, and current recreational/prescription use of drugs where their combined use with BFR is untested. The study was considered no more than minimal risk for participants; however, participants may have experienced moderate muscular fatigue during exercise and the potential for delayed onset muscle soreness following the plyometrics exercise for 24-72 hours. Participants will be

compensated up to $80 for their time upon the completion of the study. Institutional Review Board (IRB) approval was earned prior to testing by North Dakota State University (#HE19244).

Instrumentation

Muscular Testing

The Biodex Isokinetic Dynamometer was used to measure peak torque production in the knee flexors and extensors (Biodex Medical Systems Inc., New York, United States). Unique dynamometer seat settings were recorded for every participant for the first use and kept the same for each session. The range of motion (ROM) was set with an away limit of 20-degrees and toward limit of 95-degrees relative to the individual's knee angle. The tests performed on the Biodex included: maximal isometric flexion/extension contractions at 75-degrees of ROM for three seconds (two warm-up repetitions, 3 testing repetitions), maximal isokinetic contractions at speeds controlled by the Biodex (flexion/extension in degrees per second: 60/60, 120/120, 180/180, 240/240, 300/300), and a maximal eccentric extension resistance (three warm up repetitions, two testing repetitions).

PEIC Treatment

The occlusion treatment was carried out with the Delfi Portable Tourniquet System (Delfi Medical Innovations, Vancouver, Canada). The device has a function which determines an individual's unique Personal Tourniquet Pressure (PTP) where arterial blood flow is completely restricted. This pressure was used for the PEIC treatment.

Blood Oxygen Content

MOXY sensors were applied to the vastus lateralis to monitor oxygen saturation levels during occlusion treatments to ensure ischemia had occurred (Fortiori Design LLC, Minnesota, United States). The MOXY sensor has been used in numerous studies that support the reliability

and validity of the device, especially during rest or low-moderate intensity activity (Crum et al., 2017; McManus, Collision, and Cooper, 2018; Feldmann, Schmitz, and Erlacher, 2019).

Perceived Muscle Soreness

A visual analog scale (VAS) was used to assess perceived muscle soreness. This scale is a widely accepted and repeatable method of measuring pain perception (Rosier, Iadarola, & Coghill, 2002). The VAS is a 10-cm horizontal line marked 0-10, with 0 being no pain and 10 being the worst pain imaginable. Participants were instructed to mark a vertical line on the VAS that corresponds to their perceived level of soreness when performing a standardized standing quadricep stretch (Jakeman et. al, 2010).

Testing Protocol

Participants were asked to visit the testing site on five separate occasions. The first meeting being a familiarization session, wherein participants were informed of the details of the study and signed the written and informed consent. Next was completing the PAR-Q+, deep vein thrombosis, and screening question forms. Blood pressure was measured twice by a trained individual after participants were resting in a seated position for five minutes to ensure they were within the inclusion criteria. Immediately following the seated test, participants stood for two minutes before blood pressure was tested once again, and if blood pressure dropped by more than 20 mmHg systolic and 10 mmHg diastolic. To measure participant height and body mass a Stadiometer (Seca 213, Chino, CA) and an Eye level scale (Detecto, Webb City, MO) were used.

Participants warmed up for five minutes on a cycle ergometer at a self-determined moderate intensity, then were secured to the Biodex isokinetic dynamometer performed full testing protocol with one leg. The purpose of this Biodex session was to allow the participants to have experience with testing before data were recorded. Once off the Biodex, participants took a

laying position and had Delfi occlusion cuffs placed around the proximal portions of their thighs. One leg at a time, the Delfi units inflated to determine each participant's PTP.

There were two pairs of testing days, one pair organized around an intervention treatment and one built around a SHAM. Starting one day prior to both the control and treatment phases, and continuing until the end of each experimental phase, participants were asked to refrain from alcohol, vigorous exercise, and maintain their normal nutrition, hydration, and sleep routine. A self-reported two-day food and sleep log for the was used to promote compliance and consistency. At the beginning of each first day, the participants completed the VAS before the standard cycle ergometer warm-up, then were seated and secured to the Biodex isokinetic dynamometer and perform three distinct tests with one leg, then the Biodex was adjusted to perform the same three tests on the alternate leg. Following the test, participants were removed from the Biodex and performed 10 sets of 10 drop-jumps from a 0.6-meter box, similar to Page et al.'s (2017) and Talaski's (2016) study design, to induce significant stress to the leg musculature. Rest time between sets was kept at one to two minutes.

In the control phase, immediately after completing the box jumps, the participants had an occlusion cuffs placed around the proximal portion each legs, had a MOXY sensor secured to the designated vastus lateralis, and receive 20 mmHg of pressure (SHAM) for three sets of five minutes per leg, for a total of 30-minutes. The participants returned at the same time the following day (± 2-hours), measure their soreness for both legs using the VAS, warm up on the cycle ergometer, and perform the Biodex test once again. In the treatment phase, immediately after completing the box jumps, participants once again had occlusion cuffs placed around the proximal portion of the legs, have the MOXY sensor secured to the leg receiving a high pressure, and were administered 220 mmHg of pressure (treatment) to one leg and 20 mmHg of pressure

(SHAM) to the other leg for three sets of five minutes per leg. The leg that received the treatment was randomly selected. Then the participants will return at the same time to following day (± 2 hours), measure their soreness for both legs using the VAS, warm up on the cycle ergometer, and perform the same test on the Biodex.

Statistical Analysis

The study was of experimental design. All analyses were performed using SPSS (IBM, Armonk, NY). Of the 20 participants recruited, only 19 completed all peak torque tests. If all tests were not completed, the participants were excluded from peak torque data. All 20 participants data were used for VAS and MOXY analyses. There were four conditions of treatment (Remote, 220 mmHg and SHAM (remote leg), SHAM (direct leg)) and two conditions of time (baseline and 24-hours post exercise). Therefore, the analyses used for peak torque and VAS were a 2 x 2 repeated measures analysis of variance with sidak corrections for multiple comparisons. A paired t-test was used to compare oxygen saturation between intervention and SHAM treatments. Statistical significance was set at alpha ≤ 0.05 level of confidence.

CHAPTER FOUR: RESEARCH ARTICLE

Abstract

BACKGROUND: Optimizing athletes' recovery from stressful exercise is a concern for athletes, trainers, and sports scientists alike. Strategic limb occlusion applied after exercise may have the potential to expedite recovery, not only in the directly affected tissue, but all over the body via circulating factors. **PURPOSE:** The purpose of this study was to determine whether a PEIC treatment applied to one leg after arduous exercise facilitates performance recovery in both legs. **METHODS:** Twenty active and healthy college age males took part in a single-blind randomized crossover design. Participants underwent two exercise sessions, separated by at least one week, that were immediately preceded and followed 24-hours after by muscular tests. Immediately after each exercise session, occlusion cuffs were applied unilaterally (3 x 5-min per leg) with a pressure of either 20 mmHg (SHAM) or at their personal tourniquet pressure (intervention). The intervention treatment consisted of one leg receiving the personal tourniquet pressure and the other SHAM. Muscle soreness was evaluated using Visual Analog Scales (VAS) before each muscular test. **STATISTICAL ANALYSES:** A 2 x 2 repeated measures analysis of variance with sidak corrections for multiple comparisons (significance of $p<0.05$) was used to analyze peak torque and VAS scores across the different tests and conditions. **RESULTS:** Across all muscular tests, significance was not observed between any associated pre- and post-test ($p > 0.05$). Post-treatment VAS scores were statistically higher than pre-treatment for all conditions except pre-and post-intervention in the direct leg ($P = 0.096$), while it was near significance. **DISCUSSION:** The application of PEIC was not associated with any significant differences in peak torque production or objective measures of soreness.

Introduction

An important and ever-evolving factor related to performance is the athlete's ability to recover from training and competition. With the intention of improving performance, numerous post-exercise recovery strategies have been tested to mitigate performance declines and muscle soreness for subsequent training and competition (Reilly and Ekblom, 2005). When applied before exercise; short, non-damaging, periods of limb ischemia followed by reperfusion (IPC) have shown benefits regarding maximizing sports performance (Horiuchi, 2017).

Originally, ischemia and reperfusion treatments were administered to cardiac tissue to produce a protective effect during prolonged ischemia (Eisen et al., 2004). The mechanisms though which IPC protects the heart were later considered for improving athletic performance. Three systems that IPC manipulates to decrease necrosis of heart tissue are adenosine, K+ATP channels, and nitric oxide. When reviewing their role in skeletal muscle, elevated activity levels of these are known to increase vasodilation and increase nutrient and oxygen delivery to muscle cells, while aiding in the removal of catabolites (De Groot, Thijssen, Sanchez, Ellenkamp, & Hopman, 2010). Nitric oxide reacts with reactive oxygen species and limits tissue injury (Raat and Gladwin, 2009). Likewise, research supports that the effects of ischemic conditioning to occur in two phases, an early and late phase. The early portion lasting between 3-4 hours after the ischemic intervention, and the late phase lasting up to 48-72 hours (Loukogeorgakis et al., 2005). A total of five studies have been published testing PEIC's ability to aid in the recovery process. Three studies support PEIC to be beneficial in certain aspects of recovery, while the other two show no benefit (Arriel et al, 2018; Beaven, Cook, Kilduff, Drawer, & Gill, 2012; Page, Swan, and Patterson, 2017; Northey et al., 2016; Williams et al., 2018).

Additionally, ischemic conditioning produces in circulating factors, providing benefits to tissues not directly undergoing ischemia (Przyklenk et al., 1993; Loukogeorgakis et al., 2005). Regarding physical activity, there have only been five studies examining IPC's remote effects. Of the five, two presented data supporting RIPC's beneficial effects while the other three did not (Jean St Michel et al., 2011; Barbosa et al., 2015; Lalonde and Curnier, 2015; Richard and Billaut, 2018; Richard and Billaut 2018).

With such few studies on RIPC and PEIC, overlooked misinterpretations can become common and can easily result in a lack of evidence supporting IPC. Specifically, men may receive more of a benefit from ischemic conditioning than women due to natural testosterone production. In rats, preconditioning required testosterone for the synthesis of heat shock protein 70, which is a protein mediator of delayed onset cardio protection through an androgen receptor-mediated mechanism (J. Liu, Tsang, and Tak, 2006). Additionally, testosterone has been demonstrated to upregulate the a1-adrenoceptors, an additional mediator which promotes a cardioprotective response (Tsang, Wu, Liu, and Wong, 2008). When men and women's performance were compared after an IPC treatment, researchers were concluded that IPC: increased muscle force in males to a greater extent than females, increased oxygen extraction in males but decreased it in females, and increased resting blood volume similarly in both sexes. Based on these data, any study that employs a significant number of female participants may have skewed results (Paradis-Deschênes, Joanisse, and Billaut, 2017).

To the researchers' knowledge, there has not been any research examining the potential effects of remote PEIC. The purpose of this study was to determine whether a PEIC treatment applied to one leg after arduous exercise facilitates performance recovery in both legs.

Methods

Participants

Participants experienced both control and intervention sessions in a within subjects, cross-over design. All procedures and instruments used during this study were approved by the North Dakota State University Institutional Review Board (#HE19244). Twenty healthy male participants with resistance training experience (21.8 ± 2.80 years, 181.35 ± 6.93 cm, 81.93 ± 13.70 kg) volunteered and gave written informed consent to participate in the study. Any participant with, or at risk of, hypertension or hypotension, deep vein thrombosis, or classified as obese (BMI ≥ 35 kg/m^2) were excluded.

Table 7

Descriptive Statistics

N	20
Age (years)	21.8 ± 2.80
Height (cm)	181.35 ± 6.93
Weight (kg)	81.93 ± 13.70
BMI (kg/m^2)	24.79 ± 3.02
Thigh Circumference (cm)	
Right Leg:	59.65 ± 4.72
Left Leg:	59.78 ± 4.76
Personal Tourniquet Pressure (mmHg)	
Right Leg:	197.95 ± 20.17
Left Leg:	199.2 ± 20.76

Note: Data are mean ± standard deviation. cm = centimeters, kg = kilograms, m = meters.

Instrumentation

Blood pressure was taken using a manual sphygmomanometer cuff and stethoscope. The Biodex Isokinetic Dynamometer was used to measure peak torque production in the knee flexors

and extensors (Biodex Medical Systems Inc., New York, United States). The occlusion treatment was carried out with the Delfi Portable Tourniquet System (Delfi Medical Innovations, Vancouver, Canada). The device has a function which determines an individual's unique Personal Tourniquet Pressure (PTP) where arterial blood flow is completely restricted. This pressure was used for the PEIC treatment. MOXY sensors were applied to the vastus lateralis to monitor oxygen saturation levels during occlusion treatments to ensure ischemia had occurred (Fortiori Design LLC, Minnesota, United States). A visual analog scale (VAS) was used to assess perceived muscle soreness. This scale is a widely accepted and repeatable method of measuring pain perception (Rosier, Iadarola, & Coghill, 2002).

Procedures

Participants were asked to visit the testing site on five separate occasions. The first meeting being a familiarization session, wherein participants performed the standardized warm-up (five minutes on a cycle ergometer at a self-determined moderate intensity) then were secured to the Biodex isokinetic dynamometer performed the full testing protocol with one leg. The purpose of this Biodex session was to allow the participants to have experience with testing before data were recorded. Unique dynamometer seat settings were recorded for every participant during the first use and kept the same for each session. The range of motion (ROM) was set with an away limit of 20-degrees and toward limit of 95-degrees relative to the individual's knee angle. The tests performed on the Biodex included: maximal isometric flexion/extension contractions at 75-degrees of ROM for three seconds (two warm-up repetitions, 3 testing repetitions), maximal isokinetic contractions at speeds controlled by the Biodex (flexion/extension in degrees per second: 60/60, 120/120, 180/180, 240/240, 300/300), and a maximal eccentric extension resistance (three warm up repetitions, two testing repetitions)

Once off the Biodex, participants took a laying position and had Delfi occlusion cuffs placed around the proximal portions of their thighs. One leg at a time, the Delfi units inflated to determine each participant's PTP.

There were two pairs of testing days, one pair organized around an intervention treatment and one built around a SHAM. Starting one day prior to both the control and treatment phases, and continuing until the end of each experimental phase, participants were asked to refrain from alcohol, vigorous exercise, and maintain their normal nutrition, hydration, and sleep routine. A self-reported two-day food and sleep log for the was used to promote compliance and consistency. At the beginning of each first day, the participants completed the VAS before the standard cycle ergometer warm-up, then were seated and secured to the Biodex isokinetic dynamometer and perform three distinct tests with one leg, then the Biodex was adjusted to perform the same three tests on the alternate leg. Following the test, participants were removed from the Biodex and performed 10 sets of 10 drop-jumps from a 0.6 m box, similar to Page et al.'s (2017) and Talaski's (2016) study design, to induce significant stress to the leg musculature. Rest time between sets was kept at one to two minutes.

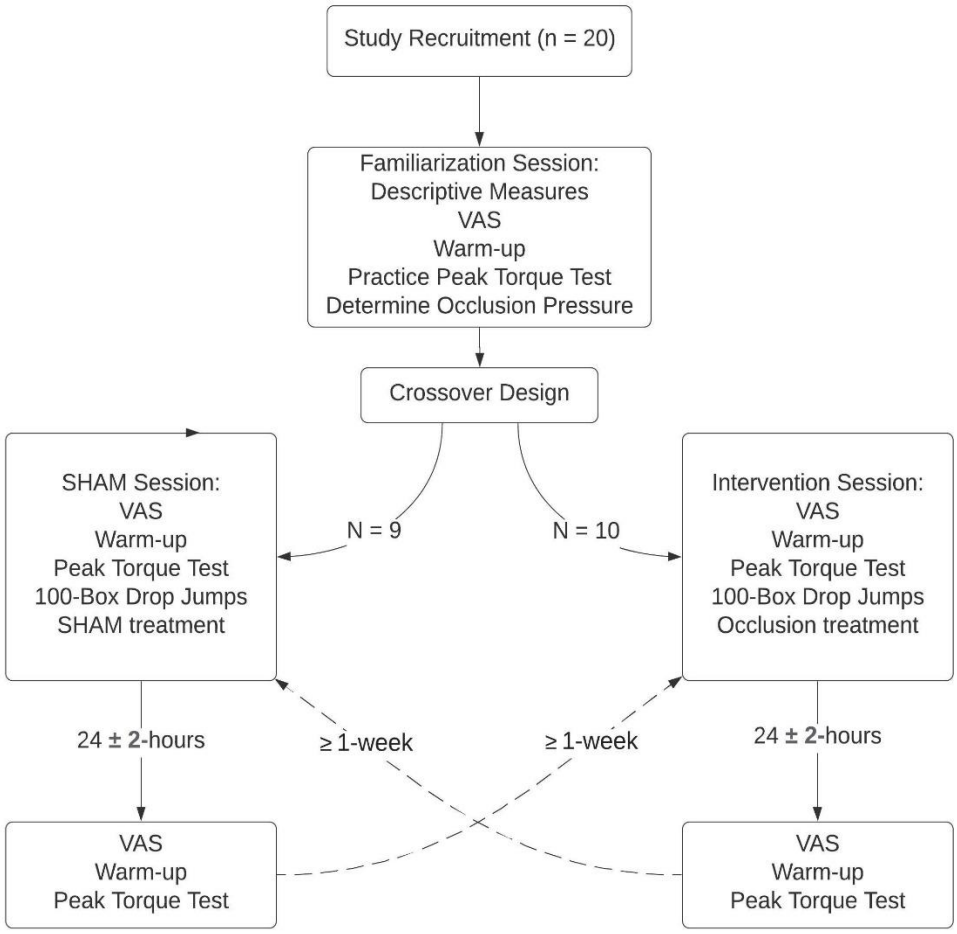

Figure 1. Experimental design.
VAS = visual analog scale. One participant was unable to complete all peak torque tests.

In the control phase, immediately after completing the box jumps, the participants had an occlusion cuffs placed around the proximal portion each legs, had a MOXY sensor secured to the designated vastus lateralis, and receive 20 mmHg of pressure (SHAM) for three sets of five minutes per leg, for a total of 30-minutes. The participants returned at the same time the following day (± 2 hours), measure their soreness for both legs using the VAS, warm up on the cycle ergometer, and perform the Biodex test once again. In the treatment phase, immediately after completing the box jumps, participants once again had occlusion cuffs placed around the proximal portion of the legs, have the MOXY sensor secured to the leg receiving a high pressure,

and were administered 220 mmHg of pressure (treatment) to one leg and 20 mmHg of pressure (SHAM) to the other leg for three sets of five minutes per leg. The leg that received the treatment was randomly selected. Then the participants will return at the same time to following day (± 2 hours), measure their soreness for both legs using the VAS, warm up on the cycle ergometer, and perform the same test on the Biodex.

Statistical Analysis

All analyses were performed using SPSS (IBM, Armonk, NY). Of the 20 participants recruited, only 19 completed all peak torque tests. If all tests were not completed, the participants were excluded from peak torque data. All 20 participants data were used for VAS and MOXY analyses. There were four conditions of treatment (Remote, 220 mmHg and SHAM (remote leg), SHAM (direct leg)) and two conditions of time (baseline and 24-hours post exercise). Therefore, the analyses used for peak torque and VAS were a 2 x 2 repeated measures analysis of variance with sidak corrections for multiple comparisons. A paired t-test was used to compare oxygen saturation between intervention and SHAM treatments. Statistical significance was set at alpha ≤ 0.05 level of confidence.

Results

Mean oxygen saturation was significantly lower during the intervention treatment when compared to SHAM (72.8 ± 8.66% vs. 3.05 ± 5.51%, $P < 0.001$) (Figure 2). Post-treatment VAS scores were statistically higher than pre-treatment for all conditions except pre-and post-intervention in the direct leg ($P < 0.05$) (Figure 3). Across all muscular tests, significance was not observed between any associated pre- and post-test. In the 300-degrees/second isokinetic knee flexion assessment, there was a significant increase in peak torque production observed between pre-SHAM and post-intervention tests (85.98 ± 28.95 Nm vs. 96.47 ± 36.55 Nm, p =

0.028). Post-intervention peak torque for the same 300-degrees/second tests tended to be significantly higher than pre-intervention (90.06 ± 34.96 Nm vs. 96.47 ± 36.55 Nm, p = 0.057) for the direct leg (Figure 5).

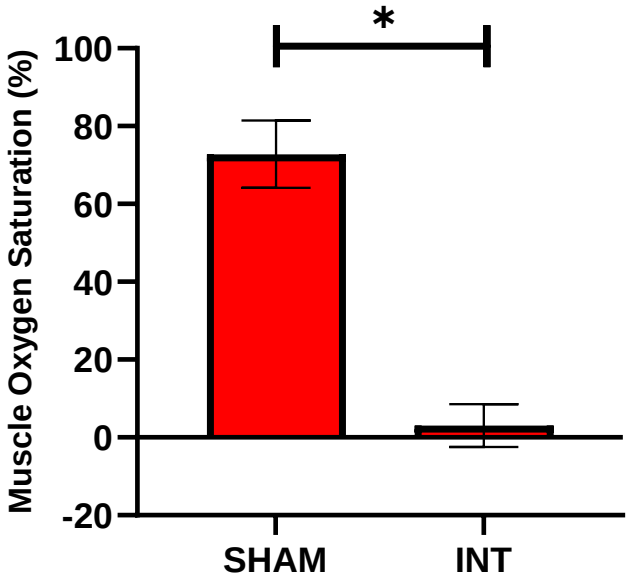

Figure 2. MOXY data.
Note: * denotes p < 0.001. INT = Intervention, n = 20.

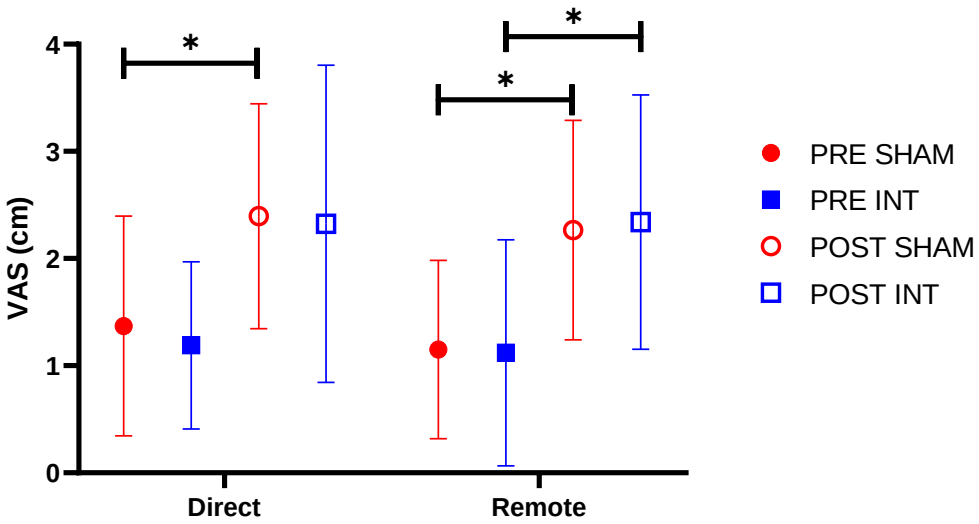

Figure 3. VAS data.
Note: * denotes p < 0.05.

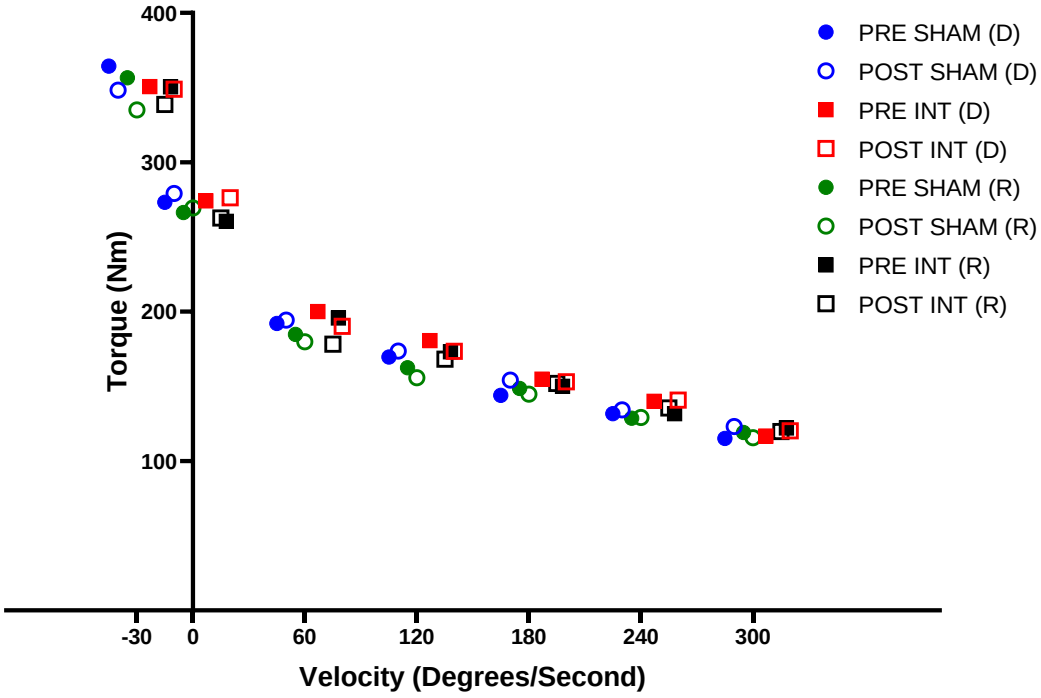

Figure 4. Knee extension tests.
Note: N = 19, Nm = newton meters, (D) = direct leg, (R) = remote leg. Seven tests were performed, x-values are staggers within tests so that they may be observed more clearly.

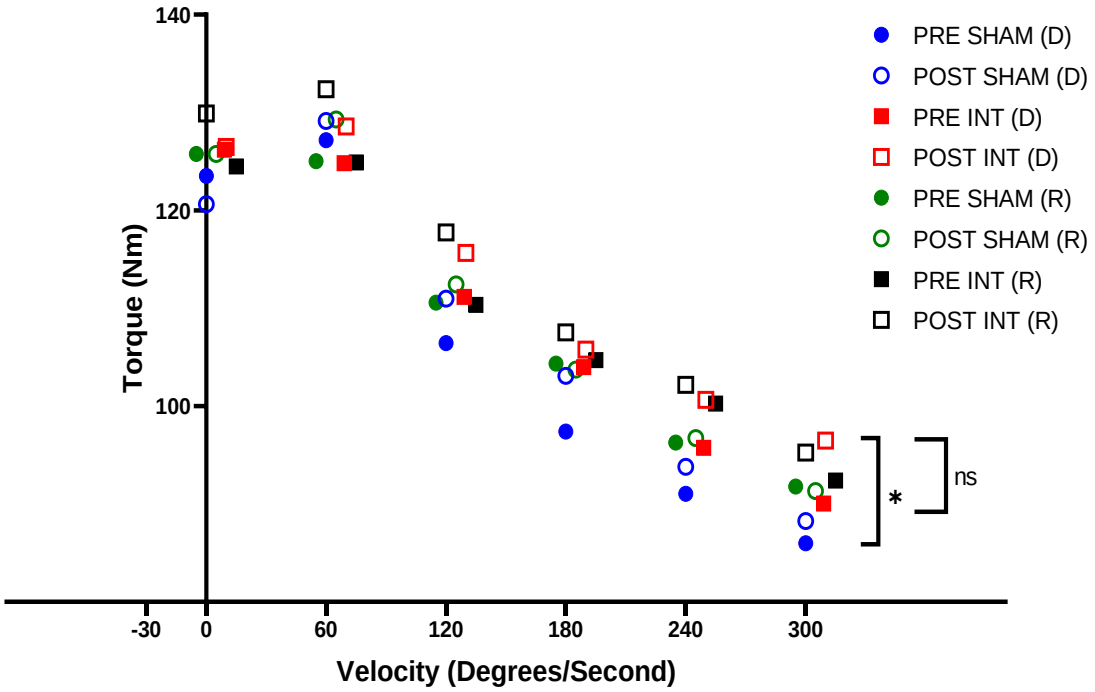

Figure 5. Knee flexion tests.
Note: * denotes p<0.05, ns = near significance, N = 19. Nm = newton meters, (D) = direct leg, (R) = remote leg. Six tests were performed, x-values are staggers within tests so that they may be observed more clearly.

Table 8

Peak Torque, Knee Extension

	Direct Leg Mean Peak Torque (Nm)				Remote Leg Mean Peak Torque (Nm)			
	Pre-SHAM	Pre-Interv.	Post-SHAM	Post-Interv.	Pre-SHAM	Pre-Interv.	Post-SHAM	Post-Interv.
-30 d/s (eccentric)	364.4 ± 114.8	350.7 ± 134.4	348.2 ± 117.0	349.0 ± 128.8	356.6 ± 110.3	350.0 ± 141.2	335.0 ± 109.1	338.7 ± 141.1
0 d/s (isometric)	273.2 ± 75.8	274.2 ± 99.5	279.0 ± 103.0	276.2 ± 100.6	266.3 ± 92.6	260.5 ± 102.9	269.5 ± 97.2	262.6 ± 96.7
60 d/s	192.1 ± 56.2	200.1 ± 67.9	194.3 ± 60.8	190.2 ± 59.0	184.8 ± 51.6	195 ± 65.1	179.9 ± 60.9	178.2 ± 67.5
120 d/s	169.6 ± 53.1	180.7 ± 52.2	173.7 ± 51.8	173.5 ± 51.0	162.5 ± 50.7	173.1 ± 70.2	155.8 ± 50.2	168.2 ± 64.3
180 d/s	144.0 ± 47.1	154.8 ± 50.1	154.2 ± 39.3	153.1 ± 45.6	148.6 ± 44.9	150.0 ± 58.4	144.8 ± 42.3	152.0 ± 57.5
240 d/s	131.7 ± 37.0	139.9 ± 42.2	134.3 ± 41.3	140.7 ± 40.2	128.7 ± 43.9	131.7 ± 54.4	129.2 ± 37.1	135.6 ± 45.2
300 d/s	115.2 ± 38.0	116.7 ± 43.6	123.2 ± 37.2	120.3 ± 39.8	119.2 ± 36.8	122.1 ± 55.8	115.6 ± 35.1	119.7 ± 44.4

Note: Data are mean ± standard deviation. N = 19, d/s = degrees/second, Nm = newton meters.

Table 9

Peak Torque, Knee Flexion

	Direct Leg Mean Peak Torque (Nm)				Remote Leg Mean Peak Torque (Nm)			
	Pre-SHAM	Pre-Interv.	Post-SHAM	Post-Interv.	Pre-SHAM	Pre-Interv.	Post-SHAM	Post-Interv.
0 d/s (isometric)	123.5 ± 46.4	126.2 ± 45.4	120.6 ± 47.8	126.5 ± 42.9	125.8 ± 45.9	124.5 ± 44.0	125.8 ± 46.6	129.9 ± 44.9
60 d/s	127.2 ± 44.5	124.8 ± 44.8	129.1 ± 50.1	128.6 ± 48.8	125.0 ± 39.8	124.9 ± 46.5	129.3 ± 46.6	132.4 ± 49.8
120 d/s	106.4 ± 41.0	111.2 ± 40.8	111.0 ± 39.9	115.7 ± 42.4	110.6 ± 38.8	110.3 ± 41.0	112.4 ± 38.7	117.7 ± 38.0
180 d/s	97.4 ± 39.2	104.0 ± 39.1	103.1 ± 40.9	105.8 ± 42.7	104.4 ± 37.1	104.7 ± 40.4	103.7 ± 39.6	107.5 ± 35.2
240 d/s	91.0 ± 33.9	95.7 ± 36.2	93.8 ± 39.3	100.6 ± 38.5	96.3 ± 36.4	100.2 ± 40.6	96.7 ± 38.2	102.2 ± 34.7
300 d/s	86.0 ± 29.0	90.1 ± 35.0	88.3 ± 33.2	96.5 ± 36.6	91.8 ± 29.9	92.4 ± 36.4	91.3 ± 34.4	95.2 ± 34.9

Note: Data are mean ± standard deviation. N = 19, d/s = degrees/second, Nm = newton meters.

Discussion

The purpose of this study was to examine the recovery effects of remote and direct PEIC on peak force 24-hours after a strenuous exercise session. Additionally, the study investigated the relationship between PEIC and perceived soreness. The major findings of this study were remote and direct PEIC did not have a clear effect regarding performance or objective measures of soreness.

Oxygen Saturation

The application of BFR cuffs restricted venous blood flow to the desired muscles, resulting in ischemia. Previous research on IPC and PEIC have either used a standard pressure of 220 mmHg or a certain amount of pressure above the individual's systolic blood pressure

(Horiuchi, 2017). This study utilized a function of the Delfi software, where the device determined the appropriate pressure to restrict blood flow. To ensure that ischemia was achieved and thoroughly test PEIC, MOXY sensors were placed on the vastus lateralis during compression treatments. The lowest percent oxygen saturation recorded during the final set of ischemia was significantly lower during the intervention treatment when compared to SHAM (3.05 ± 5.51 vs 72.8 ± 8.66%, $P < 0.001$).

Muscle Soreness

Post-exercise ischemic conditioning did not result in reduced muscle soreness when compared to a SHAM intervention. While VAS scores pre- and post-intervention for the direct leg were the only pair of variables not to be significantly different, it did approach significance (p=0.096). This does warrant some discussion; however, the researchers cannot confidently conclude direct PEIC decreases soreness. The legs did not perform significantly differently even though the directly treated leg tended to feel less sore. The sensation of muscular soreness may also be more affected by the placebo effect than performance-based tests.

Previous research has found PEIC not to improve measures of soreness, even when performance is improved when compared to SHAM (Northey et al., 2016; Williams et al., 2018; Arriel et al., 2018). Only one study, which also used a VAS to measure muscle soreness and was the only study to show significantly lower soreness resulting from PEIC compared to SHAM (Page, Swan, and Patterson et al., 2017).

Muscular Performance

The application of PEIC was not associated with any significant improvements in peak torque production. In all tests performed, remote and direct PEIC did not improve performance when compared to SHAM. Previous research on the topic, all looking at similar outcome

measures, tend to be inconclusive. Using similar protocols to the one used in this study, participants maintained performance in counter-movement jumps, squat jumps, maximal incremental cycling tests, and peak isometric torque as a result of a PEIC treatment when compared to a SHAM (Beaven et al., 2012; Page, Swan, & Patterson, 2017; Arriel et al., 2018). However, other studies have shown no performance benefits regarding counter-movement jumps, squat jumps, and concentric peak torque because of PEIC (Northey et al., 2016; Williams et al., 2018). While peak torque was not improved as a result of PEIC, performance did not decline. Being such a controversial topic, with conflicting evidence on the same tests, it is difficult to ascertain if PEIC provides a benefit to athletes.

Limitations

The primary limitation of this study, as with all studies regarding PEIC, is the lack of a true control treatment. While researchers may incorporate a SHAM or low-pressure treatment, participants can clearly feel the difference between treatments. When using FDA approved devices, deception is not allowed to be a part of the research protocol. Therefore, written in the informed consent and when participants in this study asked why the pressures were different, the answer was "We are simply testing if one pressure improves performance more than the other." For the knowledgeable population, this may not have been enough to reduce the placebo effect, which may be why VAS scores tended to show a benefit from PEIC. If the study were to be repeated then perhaps adding another pair of testing days where occlusion cuffs are not used, as a true control treatment, would be worth considering.

Conclusion

The findings from this research do not support the use of remote or direct PEIC for improving performance. There was a small benefit regarding muscular soreness in the leg that

directly received the conditioning treatment. When reviewing the MOXY data, it is reasonable to conclude that ischemia was produced and PEIC was correctly tested. These findings do not necessarily go against previous findings, studies have employed similar procedures and outcome measures but do not find the same results (Beaven et al., 2012; Northey et al., 2016). With such variance in the literature it is difficult to determine how future research should attempt to understand ischemic conditioning. Similar to how Paradis-Deschênes, Joanisse, and Billaut found that men receive more of a benefit from ischemic conditioning, there may be other variables diminishing the benefits observed (2017). This study attempted to measure performance using very precise single join tests, whereas whole body movements like squat jumps, might be more open to inconsistencies. While diminished performance was not prevented by PEIC, the intervention did not worsen performance more than SHAM. Further research studies will be needed to officially ascertain if PEIC is a sensible method of improving recovery.

REFERENCES

AHA/ACSM Joint Position Statement: Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities. (1998). Medicine & Science in Sports & Exercise, 30(6), 1009-1018. Retrieved February 8th, 2015, from http://journals.lww.com/acsm-msse/Fulltext/1998/06000/AHA_ACSM_Joint_Position_Statement__Recommendations.34.aspx

Arriel, R. A., de Souza, H. L. R., da Mota, G. R., & Marocolo, M. (2018). Declines in exercise performance are prevented 24 hours after post-exercise ischemic conditioning in amateur cyclists. *PloS one*, *13*(11), e0207053.

Ashcroft, S. J., & Ashcroft, F. M. (1990). Properties and functions of ATP-sensitive K-channels. *Cellular signalling*, *2*(3), 197-214.

Beaven, C. M., Cook, C. J., Kilduff, L., Drawer, S., & Gill, N. (2012). Intermittent lower-limb occlusion enhances recovery after strenuous exercise. *Applied Physiology, Nutrition, and Metabolism*, *37*(6), 1132-1139.

Bøtker, H. E., Kharbanda, R., Schmidt, M. R., Bøttcher, M., Kaltoft, A. K., Terkelsen, C. J., . . . Trautner, S. (2010). Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *The Lancet*, *375*(9716), 727-734.

Brooks, G. A., Fahey, T. D., & White, T. P. (1996). *Exercise physiology: Human bioenergetics and its applications*: Mayfield publishing company.

Byrne, C., Twist, C., & Eston, R. (2004). Neuromuscular function after exercise-induced muscle damage. *Sports medicine*, *34*(1), 49-69.

Calleja-González, J., Terrados, N., Mielgo-Ayuso, J., Delextrat, A., Jukic, I., Vaquera, A., ... & Ostojic, S. M. (2016). Evidence-based post-exercise recovery strategies in basketball. *The Physician and sports medicine*, *44*(1), 74-78.

Chan, R. K., Austen Jr, W. G., Ibrahim, S., Ding, G. Y., Verna, N., Hechtman, H. B., & Moore Jr, F. D. (2004). Reperfusion injury to skeletal muscle affects primarily type II muscle fibers1. *Journal of Surgical Research*, *122*(1), 54-60.

Cheung, M. M., Kharbanda, R. K., Konstantinov, I. E., Shimizu, M., Frndova, H., Li, J., . . . Van Arsdell, G. S. (2006). Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *Journal of the American College of Cardiology*, *47*(11), 2277-2282.

Crum, E. M., O'Connor, W. J., Van Loo, L., Valckx, M., & Stannard, S. R. (2017). Validity and reliability of the Moxy oxygen monitor during incremental cycling exercise. *European journal of sport science, 17*(8), 1037-1043.

de Groot, P. C., Thijssen, D. H, Sanchez, M., Ellenkamp, R., & Hopman, M. T. (2010). Ischemic preconditioning improves maximal performance in humans. *Eur J Appl Physiol, 108*(1), 141-146. doi:10.1007/s00421-009-1195-2

Eisen, A., Fisman, E. Z., Rubenfire, M., Freimark, D., McKechnie, R., Tenenbaum, A., . . . Adler, Y. (2004). Ischemic preconditioning: nearly two decades of research. A comprehensive review. *Atherosclerosis, 172*(2), 201-210.

Feldmann, A., Schmitz, R. W., & Erlacher, D. (2019). Near-infrared spectroscopy-derived muscle oxygen saturation on a 0% to 100% scale: reliability and validity of the Moxy Monitor. *Journal of biomedical optics, 24*(11), 115001.

Ferreira, T. N., Sabino-Carvalho, J. L., Lopes, T. R., Ribeiro, I. C., Succi, J. E., Da Silva, A. C., & Silva, B. M. (2016). Ischemic preconditioning and repeated sprint swimming: a placebo and nocebo study. *Medicine & Science in Sports & Exercise, 48*(10), 1967-1975.

Garlid, K. D., Paucek, P., Yarov-Yarovoy, V., Murray, H. N., Darbenzio, R. B., D'Alonzo, A. J., . . . Grover, G. J. (1997). Cardioprotective effect of diazoxide and its interaction with mitochondrial ATP-sensitive K+ channels: possible mechanism of cardioprotection. *Circulation research, 81*(6), 1072-1082.

Gibson, N., Mahony, B., Tracey, C., Fawkner, S., & Murray, A. (2015). Effect of ischemic preconditioning on repeated sprint ability in team sport athletes. *Journal of sports sciences, 33*(11), 1182-1188.

Hale, S. L., & Kloner, R. A. (2000). Effect of combined KATP channel activation and Na+/H+ exchange inhibition on infarct size in rabbits. *American Journal of Physiology-Heart and Circulatory Physiology, 279*(6), H2673-H2677.

Haruna, T., Horie, M., Kouchi, I., Nawada, R., Tsuchiya, K., Akao, M., . . . Sasayama, S. (1998). Coordinate interaction between ATP-sensitive K+ channel and Na+, K+-ATPase modulates ischemic preconditioning. *Circulation, 98*(25), 2905-2910.

Horiuchi, M. (2017). Ischemic preconditioning: potential impact on exercise performance and underlying mechanisms. *The Journal of Physical Fitness and Sports Medicine, 6*(1), 15-23.

Howatson, G., & Van Someren, K. A. (2008). The prevention and treatment of exercise-induced muscle damage. *Sports medicine, 38*(6), 483-503.

Iknonomidis, J., Tumiati, L., Weisel, R., Mickle, D., & Li, R. (1994). Preconditioning human ventricular cardiomyocytes with brief periods of simulated ischemia. *Cardiovasc Res, 28*, 1285-1291.

Jakeman, J., Byrne, C., & Eston, R. (2010). Lower limb compression garment improves recovery from exercise-induced muscle damage in young, active females. *Eur J Appl Physiol*, 109(6), 1137-1144.

Jean-St-Michel, E., Manlhiot, C., Li, J., Tropak, M., Michelsen, M. M., Schmidt, M. R., . . . Redington, A. N. (2011). Remote preconditioning improves maximal performance in highly trained athletes. *Medicine & Science in Sports & Exercise, 43*(7), 1280-1286.

Konstantinov, I. E., Arab, S., Kharbanda, R. K., Li, J., Cheung, M. M., Cherepanov, V., ... & Redington, A. N. (2004). The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. *Physiological genomics, 19*(1), 143-150.

Kuzuya, T., Hoshida, S., Yamashita, N., Fuji, H., Oe, H., Hori, M., ... & Tada, M. (1993). Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. *Circulation research, 72*(6), 1293-1299.

Lalonde, F., & Curnier, D. Y. (2015). Can anaerobic performance be improved by remote ischemic preconditioning? *The Journal of Strength & Conditioning Research, 29*(1), 80-85.

Li, G. C., Vasquez, J. A., Gallagher, K. P., & Lucchesi, B. R. (1990). Myocardial protection with preconditioning. *Circulation, 82*(2), 609-619.

Li, J.-m., Fenton, R. A., Cutler, B. S., & Dobson Jr, J. G. (1995). Adenosine enhances nitric oxide production by vascular endothelial cells. *American Journal of Physiology-Cell Physiology, 269*(2), C519-C523.

Liu, G. S., Thornton, J., Van Winkle, D. M., Stanley, A. W., Olsson, R. A., & Downey, J. M. (1991). Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. *Circulation, 84*(1), 350-356.

Liu, J., Tsang, S., & Wong, T. M. (2006). Testosterone is required for delayed cardioprotection and enhanced heat shock protein 70 expression induced by preconditioning. *Endocrinology, 147*(10), 4569-4577.

Liu, Y., & Downey, J. M. (1992). Ischemic preconditioning protects against infarction in rat heart. *American Journal of Physiology-Heart and Circulatory Physiology, 263*(4), H1107-H1112.

Loukogeorgakis, S. P., Panagiotidou, A. T., Broadhead, M. W., Donald, A., Deanfield, J. E., & MacAllister, R. J. (2005). Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans: role of the

autonomic nervous system. *Journal of the American College of Cardiology*, *46*(3), 450-456.

Marocolo, M., Da Mota, G., Pelegrini, V., & Appell Coriolano, H. (2015). Are the beneficial effects of ischemic preconditioning on performance partly a placebo effect. *Int J Sports Med, 36*(10), 822-825.

Marocolo, M., Marocolo, I., Da Mota, G., Simao, R., Maior, A., & Coriolano, H.-J. A. (2016). Beneficial effects of ischemic preconditioning in resistance exercise fade over time. *International journal of sports medicine, 37*(10), 819-824.

Marocolo, M., Willardson, J. M., Marocolo, I. C., da Mota, G. R., Simão, R., & Maior, A. S. (2016). Ischemic preconditioning and placebo intervention improves resistance exercise performance. *The Journal of Strength & Conditioning Research, 30*(5), 1462-1469.

McManus, C. J., Collison, J., & Cooper, C. E. (2018). Performance comparison of the MOXY and PortaMon near-infrared spectroscopy muscle oximeters at rest and during exercise. *Journal of biomedical optics*, *23*(1), 015007.

Miyama, M., & Nosaka, K. (2004). Muscle damage and soreness following repeated bouts of consecutive drop jumps. *Adv Exerc Sports Physiol*, *10*(3), 63-69.

Murry, C. E., Jennings, R. B., & Reimer, K. A. (1986a). Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation, 74*(5), 1124-1136.

Northey, J. M., Rattray, B., Argus, C. K., Etxebarria, N., & Driller, M. W. (2016). Vascular occlusion and sequential compression for recovery after resistance exercise. *The Journal of Strength & Conditioning Research*, *30*(2), 533-539.

Page, W., Swan, R., & Patterson, S. D. (2017). The effect of intermittent lower limb occlusion on recovery following exercise-induced muscle damage: A randomized controlled trial. *Journal of science and medicine in sport*, *20*(8), 729-733.

Pain, T., Yang, X.-M., Critz, S. D., Yue, Y., Nakano, A., Liu, G. S., . . . Downey, J. M. (2000). Opening of mitochondrial KATP channels triggers the preconditioned state by generating free radicals. *Circulation research, 87*(6), 460-466.

Paixao, R., da Mota, G. R., & Marocolo, M. (2014). Acute effect of Ischemic Preconditioning is Detrimental to anaerobic performance in cyclists. *Int J Sports Med, 35*, 912-915.

Paradis-Deschênes, P., Joanisse, D. R., & Billaut, F. (2017). Sex-specific impact of ischemic preconditioning on tissue oxygenation and maximal concentric force. *Frontiers in physiology, 7*, 674.

Patterson, S. D., Bezodis, N. E., Glaister, M., & Pattison, J. R. (2015). The effect of ischemic preconditioning on repeated sprint cycling performance. *Med Sci Sports Exerc, 47*(8), 1652-1658.

Przyklenk, K., Bauer, B., Ovize, M., Kloner, R. A., & Whittaker, P. (1993). Regional ischemic preconditioning protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation, 87*(3), 893-899.

Raat, N. J. H., Shiva, S., & Gladwin, M. T. (2009). Effects of nitrite on modulating ROS generation following ischemia and reperfusion. *Advanced drug delivery reviews, 61*(4), 339-350.

Reilly, T., & Ekblom, B. (2005). The use of recovery methods post-exercise. *Journal of sports sciences, 23*(6), 619-627.

Reimer, K. A., Murry, C. E., Yamasawa, I., Hill, M. L., & Jennings, R. B. (1986). Four brief periods of myocardial ischemia cause no cumulative ATP loss or necrosis. *American Journal of Physiology-Heart and Circulatory Physiology, 251*(6), H1306-H1315.

Richard, P., & Billaut, F. (2018). Time-trial performance in elite speed skaters after remote ischemic preconditioning. *International journal of sports physiology and performance, 13*(10), 1308-1316.

Richard, P., & Billaut, F. (2018). Combining Chronic Ischemic Preconditioning and Inspiratory Muscle Warm-Up to Enhance On-Ice Time-Trial Performance in Elite Speed Skaters. *Frontiers in physiology, 9*.

Rosier, E., Iadarola, M., & Coghill, R. (2002). Reproducibility of pain measurement and pain perception. *Pain*, 98(1), 205-216

Rundell, K. W., Nioka, S., and Chance, B. (1997). Hemoglobin/myoglobin desaturation during speed skating. Med. Sci. Sports Exerc. 29, 248–258. doi: 10.1097/00005768-199702000-00014

Sanada, S., Kitakaze, M., Asanuma, H., Harada, K., Ogita, H., Node, K., . . . Shinozaki, Y. (2001). Role of mitochondrial and sarcolemmal KATP channels in ischemic preconditioning of the canine heart. *American Journal of Physiology-Heart and Circulatory Physiology, 280*(1), H256-H263.

Schott, R. J., Rohmann, S., Braun, E. R., & Schaper, W. (1990). Ischemic preconditioning reduces infarct size in swine myocardium. *Circulation research, 66*(4), 1133-1142.

Talaski, J. L. (2016). Use of Compression Garments for Recovery From Plyometric Exercise (Doctoral dissertation, North Dakota State University).

Tanaka, D., Suga, T., Tanaka, T., Kido, K., Honjo, T., Fujita, S., . . . Isaka, T. (2016). Ischemic preconditioning enhances muscle endurance during sustained isometric exercise. *International journal of sports medicine*, *37*(08), 614-618.

Thein, L. A., Thein, J. M., & Landry, G. L. (1995). Ergogenic aids. *Physical therapy*, *75*(5), 426-439.

Tsang, S., Wu, S., Liu, J., & Wong, T. (2008). Testosterone protects rat hearts against ischaemic insults by enhancing the effects of α1-adrenoceptor stimulation. *British journal of pharmacology*, *153*(4), 693-709.

Vianna, J., Telles, L., Araújo, G., Chaves, E., Reis, V., & Novaes, J. (2018) Effect of Ischemic Preconditioning in a resistance training session on muscle performance and rating perceived effort. Poster session presented at the International NSCA Conference, Madrid, Spain.

Wang, W. Z., Baynosa, R. C., & Zamboni, W. A. (2011). Therapeutic interventions against reperfusion injury in skeletal muscle. *Journal of Surgical Research*, *171*(1), 175-182.

Williams, N., Russell, M., Cook, C. J., & Kilduff, L. P. (2018). The effect of lower limb occlusion on recovery following sprint exercise in academy rugby players. *Journal of science and medicine in sport*, *21*(10), 1095-1099.

Yellon, D., Alkhulaifi, A., & Pugsley, W. (1993). Preconditioning the human myocardium. *The Lancet*, *342*(8866), 276-277.

Ytrehus, K., Liu, Y., & Downey, J. M. (1994). Preconditioning protects ischemic rabbit heart by protein kinase C activation. *American Journal of Physiology-Heart and Circulatory Physiology*, *266*(3), H1145-H1152.

APPENDIX A. IRB APPROVAL LETTER

NDSU NORTH DAKOTA STATE UNIVERSITY

June 25, 2019

Dr. Kyle Hackney
Department of Health, Nutrition and Exercise Sciences

IRB Approval of Protocol #HE19244, "The Effect of Remote Post-Exercise Ischemic Conditioning on Recovery from Strenuous Exercise"
Co-investigator(s) and research team: Thomas Lillquist

Approval expires: 6/13/2020 Continuing Review Report Due: 5/1/2020

Research site(s): NDSU Funding agency: n/a
Review Type: Full Board, meeting date – 6/14/2019
Risk Level: A minor increase over minimal risk
IRB approval is based on original submission, with revised: protocol, recruitment flyer, consent, and screening questionnaires (received 6/21/2019). Please utilize the stamped consent which accompanies this letter.

Additional approval is required:
o prior to implementation of any proposed changes to the protocol (Protocol Amendment Request Form).
o for continuation of the project beyond the approval period (Continuing Review/Completion Report Form). A reminder is typically sent two months prior to the expiration date; timely submission of the report is your responsibility. To avoid a lapse in approval, suspension of recruitment, and/or data collection, a report must be received, and the protocol reviewed and approved prior to the expiration date.

A report is required for:
o any research-related injuries, adverse events, or other unanticipated problems involving risks to participants or others within 72 hours of known occurrence (Report of Unanticipated Problem or Serious Adverse Event Form).
o any significant new findings that may affect risks to participants.
o closure of the project (Continuing Review/Completion Report Form).

Research records are subject to random or directed audits at any time to verify compliance with IRB regulations and NDSU policies.

Thank you for cooperating with NDSU IRB procedures, and best wishes for a successful study.

Sincerely,
Kristy Shirley
Kristy Shirley, CIP
Research Compliance Administrator

For more information regarding IRB Office submissions and guidelines, please consult www.ndsu.edu/irb. This Institution has an approved FederalWide Assurance with the Department of Health and Human Services: FWA00002439.

INSTITUTIONAL REVIEW BOARD
NDSU Dept 4000 | PO Box 6050 | Fargo ND 58108-6050 | 701.231.8995 | Fax 701.231.8098 | ndsu.edu/irb
Shipping address: Research 1, 1735 NDSU Research Park Drive, Fargo ND 58102

APPENDIX B. INFORMED CONSENT FORM

Health, Nutrition, and Exercise Sciences
1301 Centennial Blvd
Fargo, ND 58108-6050
(701)231-8011

The Effects of Remote Post-Exercise Ischemic Conditioning on Recovery from Strenuous Exercise

This study is being conducted by: Thomas Lillquist, B.A.S., and Masters Student & Kyle Hackney, PhD, and assistant professor in HNES, at North Dakota State University.

Key Information about this study:

This consent form is designed to inform you about the study you are being asked to participate in. Here you will find a brief summary about the study; however, you can find more detailed information later on in the form.

We are Looking for 20 participants for this research study. Participants must be men who are currently engaging in moderate to vigorous physical activity at least two times per week. Upon the completion of the study participants will receive $80.

You will be performing a strength test followed by strenuous plyometric exercise with the intent of making you slightly sore. After the exercise you will receive a blood flow restriction (occlusion) treatment, then return the following day to determine if the treatment improved your recovery by rating your soreness and taking the strength test once again. There will be two pairs of exercise and testing days, at least a week apart, to test two different occlusion treatments and determine if one is better.

Why am I being asked to take part in this study?

We are looking for 20 participants for this research study. You are being asked to participate in this study because you:

- Are male and between the ages of 18 and 30 years.
- Are healthy and have experience with resistance exercise (≥2 times a week for last 2 months).

You should not participate in this study if you:

- Have a history of leg/neck/lower back injuries that may be aggravated by jumping.
- Previous cardiovascular disease or related vascular disorders.
- Have a blood pressure greater than 140/80 mmHg.
- Do not want to get sore from exercise.
- Have a BMI above 35 kg/m^2.

What will I be asked to do?

I. **Group Instruction Session**

You will be asked to complete a group session with other potential participants and learn about the study, and if you are still interested to fill out the necessary forms to see if you are still eligible. Several screening forms are used to determine if you are overall healthy enough to participate in the study. Those who are able to be in the study will then set up appointment to begin testing.

II. **Exercise/Testing Session(s)**

The first time you return we will measure your height using a height stand and weight using a digital scale. There are two exercise sessions and two testing sessions that make up this study. Testing sessions will take place roughly 24-hours after the exercise session, making them a pair of research days. There must be at least a week between both pairs of testing days. During the exercise sessions you will be performing the strenuous exercise. They will begin with a warm up on a stationary bike followed by sitting on and being fitted to a research device called the Biodex. Then you will perform a short test for both legs by performing three knee extension and flexion repetitions as quickly as possible. After that test, you will perform 10 sets of 10 box-drop jumps from a 0.6-meter box (getting up on the box however you like then jumping down with knees bent and both feet landing at the same time). After this exercise, you will be given a place to lie or sit down and an occlusion cuff will be placed around your thigh. It will be inflated to a certain pressure in an effort to enhance recovery. Each leg will receive three sets of five minutes of inflation and five minutes of recovery, lasting a total of 30 minutes.

When you arrive to the site for the testing sessions you will use a ranking scale to rank the soreness you feel in each your legs. Then you will warm-up on the cycle ergometer and perform the same strength test on the Biodex that you did the day before. After the strength test is complete you are done participating in the study for at least a week, if not completely done.

Starting the day before exercise sessions until the completion of the testing session we ask that you do not participate in any moderate or vigorous exercise, as it may have an effect on your performance. We also ask that you make sure to get enough sleep, food, and water to perform properly. One the testing session is complete, may exercise as soon as you would like.

Where is the study going to take place, and how long will it take?

The group instruction session will take place in room 14, 5 or 16 at the Bentson Bunker Fieldhouse, and will last between 45-minutes and one hour. If you are able and agree to be a part of the study, all exercise and testing sessions will take place room 15, 15, or 16 at the Bentson Bunker Fieldhouse. Exercise session length may depend on how quickly a person can perform the box-drop jumps but should get within 90-minutes. Testing sessions do not include the occlusion treatment or box-drop jumps and will be completed in approximately 30 minutes.

What are the risks and discomforts?

- Physical discomfort due to delayed onset muscle soreness (DOMS) from the box-drop jumps is expected.
- General injury to muscles, joints, ligaments, and bones is also possible.
- Skin irritation from the occlusion cuff is possible, but you will be wearing a garment under the cuff to reduce this (low risk of issue).

- Loss of health information from questionnaires (low risk of issue).
    - All health assessments will be completed with only one study team present in rooms with closed doors and windows, we will keep health information confidential and locked in an office. We will also shred all personal health information once the study is completed.

What are the expected benefits of this research?

Individual Benefits: You may ask for a summary of your own data, showing you whether or not you received a benefit from the treatment.

Societal Benefits: This treatment has had mixed results in other studies regarding if it works. Through this research we will add another publication to either support or not support its development.

Do I have to take part in this study?

Your participation in this research is your choice. If you decide to participate in the study, you may change your mind and stop participating at any time without penalty or loss of benefits to which you are already entitled.

What are the alternatives to being in this study?

Instead of being in this research, you may choose not to participate.

Who will have access to my information?

We will keep private all research records that identify you. Your information will be combined with information from other people taking part in the study. When we write about the study, we will write about the combined information that we have gathered. We may publish the results of the study; however, we will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under password protection. IF you withdraw before the research is over, your information will be retaining in the research record and we will not collect additional information about them.

How will my information be used?

Your information will be used to determine if the occlusion treatment resulted in any benefit to your rating of soreness or ability to complete the strength test the day after strenuous exercise.

Can my participation in the study end early?

If you fail to participate in all scheduled sessions or choose not to continue in the study, you will be removed from the study.

Will I receive any compensation for participating in the study?

After completing each pair, testing sessions the participant will earn $40, for a total of $80 compensation for this study. The earned amount will be mailed to you at the end of the study.

What happens if I am injured because of the study?

If you are injured during the course of this study, you should contact the Kyle J. Hackney, PhD at 701.231.6706 or. Treatment for mild discomfort will be available including general first aid. However, more serious emergency treatment will need to be provided by licensed medical professional. Payment for this treatment must be provided by you and your third party payer (such as health insurance). This does not mean that you are releasing or waiving any legal right you might have against the researcher or NDSU as a results of you participation in this research.

What if I have questions?

Before you decide whether you'd like to participate in this study, please ask any questions that come to mind now. Later, if you have questions about the study, you can contact Thomas Lillquist at (651)226-0657 or thomas.lillquist@ndsu.edu, or Kyle Hackney at 701-231-6706 or kyle.hackney@ndsu.edu.

What are my rights as a research participant?

You have rights as a research participant. All research with human participants is reviewed by a committee called the *Institutional Review Board (IRB)* which works to protect your rights and welfare. If you have questions about your rights, an unresolved question, a concern or complaint about this research you may contact the IRB office at 701.231.8995, toll-free at 855-800-6717 or via email (ndsu.irb@ndsu.edu).

Documentation of Informed Consent:

You are freely making a decision whether to be in this research study. Signing this form means that

1. you have read and understood this consent form
2. you have had your questions answered, and
3. you have decided to be in the study.

You will be given a copy of this consent form to keep.

Your signature	Date
Your printed name	Date
Signature of researcher explaining study	Date
Printed name of researcher explaining study	

APPENDIX C. RECRUITMENT EMAIL

We are currently recruiting participants for our study, "The Effects of Remote Post-Exercise Ischemic Conditioning on Recovery from Strenuous Exercise" and seek healthy men. Participants should be non-smokers and participate in resistance exercise at least two days per week.

Participants will receive $80 as compensation after completing the required testing.

We are conducting research to find out if blood flow restriction techniques can enhance recovery from a difficult exercise session.

- Seeking healthy men aged 18-30 years.
- You will be asked to fill out health screening forms and have your height and weight measured.
- Over four meetings, you will participate in four muscle tests, two short exercise sessions, and two blood flow restriction sessions.
- The study will take a total of 5 hours, most of which the participants are seated or laying down.

Eligible men must not have any health issues (such as cardiovascular disease, uncontrolled hypertension, significant orthopedic conditions, history of leg or back injuries worsened by plyometric exercise, or sickle cell anemia); eligible men are able to participate in moderate to vigorous physical activity.

This research is conducted under the direction of Dr. Kyle Hackney in the Department of Health, Nutrition and Exercise Sciences, along with colleagues. This study has been approved by the NDSU Institutional Review Board (HE19244).

Please email Thomas Lillquist at thomas.lillquist@ndsu.edu if interested in participating or regarding any questions about the study.