The Effect of a 2-Week Ischemic Preconditioning Intervention on Anaerobic Performance in Non-Elite Male Soccer Players

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The candidate confirms that the work submitted is their own and that appropriate credit has been given where reference has been made to the work of others.

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Abstract

Introduction: Ischemic preconditioning (IPC), brief periods of ischemia immediately followed by reperfusion applied to a vascular bed, has emerged as a method to improve athletic performance across various types of exercise (aerobic and anaerobic). Although there has been a great deal of literature investigating IPC on exercise performance, there is a lack of focus on the effect of repeated episodes of IPC along with measuring anaerobic performance via repeated sprint ability (RSA). IPC has been reported to improve blood flow and enhance endothelial function, which could be mechanisms to explain enhanced RSA performance. The aim of this thesis was to: 1) determine if a 2-week repeated IPC intervention could enhance anaerobic performance in RSA in non-elite soccer players; 2) assess whether improvements in endothelial function is a mechanism explaining any performance enhancement. **Methods:** Using a randomised, single-blinded crossover design, 8 non-elite male academy soccer players completed two, 2-week intervention trials: six IPC episodes (4 x 5 mins at 220mmHg per episode), and six SHAM episodes (4 x 5 mins at 20mmHg per episode). Prior to and following each intervention trial, participants completed assessments of anaerobic performance (Running Anaerobic Sprint Test [RAST]), and femoral artery endothelial function (flow-mediated dilation [FMD]). **Results:** IPC significantly enhanced peak power output (PPO) in the RAST by 11.30% (p=0.010) and significantly increased femoral artery FMD by 1.72% (p=0.018). **Discussion**: A 2-week repeated IPC intervention can improve anaerobic performance by means of increased PPO during repeated sprints. The increase in endothelial function following the repeated IPC intervention suggests this may be a mechanism contributing to this enhancement of anaerobic performance. **Conclusion:** The present study supports the use of repeated IPC prior to matches and training sessions in order to enhance

anaerobic performance and encourages coaches to implement the cost-effective method into their teams' daily schedule.

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Abbreviations

IPC	**Ischemic Preconditioning**
RIPC	**Remote Ischemic Preconditioning**
IR-Injury	**Ischemic Reperfusion Injury**
PPO	**Peak Power Output**
MPO	**Mean Power Output**
BLA	**Blood Lactate**
FMD	**Flow-Mediated Dilation**
ROS	**Reactive Oxidative Species**
TET	**Total Exercise Time**
TW	**Total Work**
W_{MAX}	**Maximal Power Output**
WAnT	**Wingate Anaerobic Test**
RAST	**Running Anaerobic Sprint Test**
RSA	**Repeated Sprint Ability**
PCr	**Phosphocreatine**
ATP	**Adenosine Triphosphate**
ICC	**Interclass Correlation Coefficient**
CoV	**Coefficient of Variation**
PKC	**Protein Kinase C**
RIP	**IPC at Rest**

EIP	**IPC following Exercise**
RPE	**Rating of Perceived Exertion**
EMG	**Electromyogram**
sEMG	**Surface Electromyogram**
ECG	**Electrocardiogram**
SpO_2	**Oxygen Saturation**
PaO_2	**Arterial Pressure of Oxygen**
SJFT	**Special Judo Fitness Test**
RE	**Resistance Exercise**
MVC	**Maximal Voluntary Contraction**
NIRS	**Near Infrared Spectroscopy**
APD	**Action Potential Duration**
TTE	**Time To Exhaustion**
RTD	**Rate of Force Development**
MDF	**Mean Frequency of Power**
ICC	**Interclass Correlation Coefficient**

1.0 Literature Review

1.1 Introduction

In sport, as the competition gets stronger, the narrower the margins become for errors and success (Ntoumanis et al. 2014). In addition to this, athletes are always actively searching for ways their performance can be maximised to ensure they are consistently at their peak. An attractive method of searching for opportunities to enhance performance are by means of adopting certain ergogenic aids. An ergogenic aid is defined as a physical, mechanical, nutritional, psychological, or a pharmalogical item or treatment that has the potential to precisely improve performance by bettering the physiological variables in which are associated with performance (Bala and Bhalla 2022). An ergogenic aid can remove subjective restraints that may hinder the physiological capacity of the athlete (Bala and Bhalla 2022). A popular type of ergogenic aid athletes tend to utilise are nutritional ergogenic aids where the athlete consumes a substance knowing it contains a nutritional element that can enhance performance (Kerksick et al. 2018). However, when using a nutritional supplement, it is important to be aware of the risks associated with ingesting it. Therefore, athletes need to be extra cautious of the potential side effects when considering the use of certain nutritional supplements, in addition to consulting with a physician to determine if any concealed medical issues exist that may contradict the supplement's use (Gonzalez et al. 2022). Therefore, with some risk or restrictions associated with nutritional ergogenic aids, it is worthwhile exploring an ergogenic aid that does not demand the ingestion of a nutritional supplement.

Ischemic Preconditioning (IPC) consists of harmless periods of ischemia followed by periods of reperfusion to an organ or a limb to activate defensive mechanisms against ischemic-reperfusion

injury (IR injury). First used as a clinical method, IPC has recently (>12 years) been deemed as an ergogenic aid for athletes competing in various levels of sport (Caru et al. 2019). The mechanisms found for protecting IR-injury from a clinical standpoint were thought to elicit similar rewards in exercise performance. The mechanisms that IPC provides include protecting the skeletal muscle from IR-injury, enhancing oxidative capacity throughout the lengthened period of ischemia, improving blood-flow following ischemia, and enhancing muscle function following both ischemia and reperfusion (Lintz et al. 2013; Pang et al. 1995; Addison et al. 2003). Although these mechanisms have been supported in clinical research, there is still lack of research determining if the underlying mechanisms observed from the clinical benefits of IPC can be replicated in exercise performance. Consequently, the overarching aim of this thesis is to investigate the effects of IPC on exercise performance and to explore potential physiological mechanisms. Existing research exploring IPC and exercise performance and the potential physiological mechanisms will first be discussed in a review of the current literature.

1.2 Ischemia

Generally, a cause of hypoxia, or the lack of oxygen in cells and tissue can happen in various ways, and ischemia is one of them (Kaur, Foulds and Ling 2008). Ischo- refers to either “restraint” or “suppression”, and -emia refers to the blood. Therefore, ischemia is a type of suppression or a reduction of blood flow to a specific organ or tissue. Furthermore, the reduction in blood flow also decreases the amount of oxygen to the suppressed cells due to the lowered amount of blood flow in the blood vessels perfusing the tissue. This depleted amount of oxygen diminishes the capability for oxidative adenosine triphosphate (ATP) energy production, which can lead to cell

death (Cho et al. 1997). The term ischemia, in a clinical context with regards to the heart, is referred to as a period of reduced blood flow which in turn results in an insufficient amount of oxygen delivered to the myocardium (Kloner 2009; Wang, Baynosa and Zamboni 2011). Clinically, a familiar cause of ischemia is a buildup of fatty plaque inside systematic arteries, which is known as atherosclerosis (Pepine 2009). Atherosclerosis can affect most systematic arteries, but the coronary arteries are particularly susceptible (Frangos, Gahtan and Sumpio 1999), which ultimately limits the amount of blood flow perfusing cardiac muscle (Pepine 2009). Additionally, even if it is a minor or partial blockage of a coronary artery, ischemia can be present and, if a coronary artery becomes severely or completely blocked, ischemia can become serious enough to result in myocardial infarction (Eltzschig and Eckle 2011). Myocardial infarction, otherwise known as a heart attack, is a leading cause of death worldwide (Thygesen, Alpert and White 2007; Anderson and Morrow 2017). Although ischemia can occur at any time, cardiac tissue is especially vulnerable to ischemia during physical activity when the oxygen requirements for the heart are increased (Parker et al. 1994). Despite the risks of cell death associated with ischemia, applying significant occlusion to certain tissues causing ischemia followed by periods of reperfusion, otherwise known as ischemic preconditioning (IPC), has emerged as an approach to enhance cardioprotective effects.

1.3 Ischemic Preconditioning (IPC)

An intervention which consists of succinct periods of ischemia which is immediately followed by reperfusion is known as ischemic preconditioning (IPC) (Murry et al. 1986). Whilst ischemia causes an insufficient amount of blood supply to the organs and tissues, the following period of reperfusion, enables the restoration of perfusion and reoxygenation in the specific organ that is

being preconditioned (Hausenloy and Yellon 2012). IPC was first designed and utilised as a clinical method to protect canine myocardium from myocardial infarction (Murry et al. 1986). Murry et al. (1986) discovered in an animal model that four continuous periods of coronary occlusion consisting of 5 minutes per period had the ability to lower infarct size by as much as 75% when the myocardium was then subjected to a sustained bout of ischemia. Evidence of cardioprotective effects following IPC has since been shown in many follow-up studies (Pilcher et al. 2012). Furthermore, whilst originally the clinical benefits of IPC were only applicable to the myocardium, shortly after Murry et al. (1986) discovered the reduction of infarct size, it is now evident that IPC can protect other organs such as the brain, the small intestine, and post-ischemic skeletal muscle (Candilio, Malik and Hausenloy 2013).

IPC has also shown protective effects against (IR-injury) (Tapuria et al. 2008). IR-injury is referred to as a paradoxical exacerbation of cellular death following the restoration of blood flow to the tissues in which they were previously ischemic (Fitridge and Thompson 2011). Although the revival of blood flow is essential to be able to restore the ischemic tissues, reperfusion can be detrimental and can cause additional damage to the organ, which can further threaten the life of the organ (Fitridge and Thompson 2011). IR-injury can occur in many organs such as the heart, skeletal muscle, the brain, the kidney, the gut, and the lung (Fitridge and Thompson 2011). Despite IR-Injury occurring in a single organ, it can have a lasting effect on other organs, causing damage to the surrounding organs that are trying to tolerate IR-injury, resulting in multi-system organ failure (Fitridge and Thompson 2011). IR-injury however is not only derived by myocardial infarction but can be triggered by stroke and other conditions that are provoked by the lack of

blood supply by tissues and organs (Veighey and MacAllister 2012). Following the duration of ischemia, the period of restoration of blood flow which occurs drives the activation of macrophages in the vasculature and causes a creation of superoxide radicals, also referred to as reactive oxidative species (ROS), which is a main cause of oxidative stress (Tapuria et al. 2008). IPC has been found to reduce IR-injury (Peralta et al. 1996), which is partially due to the brief application of ischemia to the target organ followed by the periods of reperfusion, resulting in strength to the subsequent bouts of ischemia (Tapuria et al. 2008). Additionally, the ischemic strength is achieved by a regulation of endothelial function, blood flow, and decreased macrophage activation (Tapuria et al. 2008). In addition to this, IPC also decreases endothelial injury also leading to a reduced parenchymal injury (Tapuria et al. 2008). Although there are clinical benefits of IPC that lead to a reduced risk of IR-injury, there are significant disadvantages to the protocol. A main disadvantage of IPC that has limited its clinical application is regarding the direct stress towards the organ in which IPC causes, coupled with mechanical trauma to the vasculature structures (Tapuria et al. 2008).

In addition to the early findings of the benefits IPC has to offer clinically (Murry et al. 1986), it was also later discovered that IPC can protect tissues remote to the tissue exposed to the IPC treatment, which is often referred to as remote ischemic preconditioning (RIPC) (Przyklenk et al. 1993). RIPC has been established as a method to provoke endogenous protection methods by increasing ischemic tolerance to lower damage initiated by severe ischemia to non-ischemic organs and tissue (Lv et al. 2020). Furthermore, RIPC has also been found to alleviate reperfusion-

injury by restricting apoptosis correlated with ischemic stroke by the means of an endogenous mitochondrial pathway (Lv et al. 2020).

The mechanisms underlying the clinical benefits of IPC vary and remain uncertain (Chen et al. 2001). Across all human organs, the beneficial effects of IPC likely involve an activation of adenosine A_1 receptors (Ishida et al. 1997). The activation of A_1 receptors induces a decrease in the rate of metabolism, which enables the cells to manage noxious stimuli (Cunha 2005). Furthermore, A_1 receptors are believed to enhance the translocation and activation of specific isoforms of protein kinase C (PKC) which subsequently phosphorylate as unidentified cellular effector molecules (Ishida et al. 1997). Evidence supporting the activation of adenosine A_1 receptors is observed as, in a rabbit heart, the beneficial preconditioning effects were blocked by administrating nonselective adenosine receptor antagonists during the preconditioning and the prolonged ischemia periods (Walker and Yellon 1992; Lawson and Downey 1993). In addition to the A_1 receptors, in the heart, it has been established that ATP-sensitive potassium channels can represent important effectors of the preconditioning event (Pell et al. 1998), and display evidence that they may be linked to the A_1 receptors. In support of this link, a cardioprotective effect afforded by A_1 receptor stimulation was disregarded by ATP-sensitive potassium channel antagonists in animal models of infarction (Grover, Sleph and Dzwonczyk 1992). Pre-existing literature derived from animal studies have found that IPC can improve muscle blood flow by means of increases in ATP-sensitive potassium channels (Riksen, Smits and Rongen 2004). The increase in blood flow has enabled oxygen delivery to be enhanced and has also allowed for a greater amount of lactate to be removed (Kimura et al. 2007; Cooper and Brown 2008).

Overall, there is significant evidence regarding IPC's clinical role, including its positive influence on cardioprotection and on other organs. The benefits observed in a clinical setting have consequently led to IPC being considered as an ergogenic aid for exercise performance

1.4 IPC and Exercise Performance

Although IPC has been utilised as a clinical method to protect certain organs and delay cell injury (Tapuria et al. 2008), its reported mechanisms such as improving blood flow and endothelial function are also components that can lead to enhanced exercise performance (de Groot et al. 2010). In addition to the findings of IPC enhancing the vasculature, IPC has also improved muscle function and metabolism (Lawson and Downey 1993; Pang et al. 1995), which lead to further belief that these improvements can translate to benefits in exercise performance.

IPC has been investigated acutely and chronically to explore its impact on various aspects of exercise performance, including exercise tasks that involve aerobic and anaerobic capacity, and tasks that comprise of strength and resistance exercise (Caru et al. 2019). In addition to assessing exercise performance following application of IPC, there has also been research investigating the effects of IPC on recovery methods following exercise. Although recovery is not a direct form of measuring performance, enhanced recovery needs to be considered because it is an essential requirement for optimal performance (de Nardi et al. 2011; Soultanakis, Nafpaktiitou and Mandaloufa 2015). Moreover, besides measuring exercise performance following application of IPC in numerous exercise types and intensities, other attributes of research have investigated

specific areas related to IPC such as pressure cuff location, the dose, the possibility of responders and non-responders (Incognito, Burr and Millar 2016; Caru et al. 2019). These aspects are critical to future and on-going research with regards to IPC and exercise performance because they analyse if there are certain thresholds that need to be reached for IPC in order to benefit performance (Ghosh, Standen and Galinanes 2000; Incognito, Burr and Millar 2016). Furthermore, researching the mechanisms and implementing thorough physiological testing of participants is vital because it has potential to identify responders and non-responders to IPC (Incognito, Burr and Millar 2016). Having the ability to realise if certain training populations respond to the application of IPC in a more advantageous way than others is valuable because it increases the impact and usefulness of IPC within certain populations. These topics will be explored in greater detail in the following sections.

1.4.1 IPC and Aerobic Exercise Performance

The first peer-reviewed study to test IPC on athletic performance in healthy individuals found that maximal oxygen uptake and time to exhaustion significantly improved during cycling performance by 3% and 1.6%, respectively, following IPC administration (de Groot et al. 2010). Since de Groot and colleagues' findings, there have been over 20 peer-reviewed studies that have investigated the impact IPC has on aerobic exercise, with over 10 of them finding statistical significance (p<0.05) in support of IPC enhancing aerobic exercise performance (Cocking et al. 2018a). A wide range of aerobic exercise intensities have been assessed in these studies and range from, but are not limited to, aerobic moderate domain (<lactate threshold), aerobic heavy domain (> lactate threshold < critical power/velocity), and aerobic severe domain exercise (>

critical power/velocity) (Cocking et al. 2018a). Cycling, running, and swimming are the main types of exercise that have been examined following application of IPC and have displayed significant enhancements in sub-maximal aerobic performance. Additionally, the participants taking part in the IPC and exercise trials are male and female individuals that come from healthy, to recreational, to competitive, to moderately trained and well-trained backgrounds (Cocking et al. 2018a). This demonstrates that IPC has the potential to enhance aerobic exercise performance across various levels of competitive and training statuses and strengthens the rationale for investigating IPC in not just one population, but to continue to explore its ergogenic potential within varied populations.

Shortly after the enhancements in endurance performance were discovered by de Groot et al. (2010), it was later replicated by the work of Crisafulli et al. (2011). It was identified that total exercise time (TET), total work (TW) and maximal power output (W_{MAX}) all significantly improved following the application of IPC, however, it did not improve $VO_{2\ MAX}$ amongst the participants (Crisafulli et al. 2011), which contradicted the findings by de Groot et al. (2010). Differences in the IPC protocol adopted may explain this discrepancy. Crisafulli et al. (2011) used an IPC protocol of 3 sets of 5 mins ischemia, with each bout of ischemia followed by 5 mins of reperfusion, due to this protocol having success in the previous study by de Groot et al. (2010). Additionally, the cuff pressure protocol chosen was to add 50 mmHg to the participant's systolic blood pressure (SBP), as opposed to the standard 220 mmHg used by de Groot et al. (2010). Furthermore, Crisafulli et al. (2011) analysed two different methods of IPC; IPC at rest (RIP), and IPC following exercise (EIP). In these conditions, RIP was administered prior to the incremental maximal task,

whereas EIP was conducted after performing a 5-minute exercise at a constant workload that corresponded to 70% of participant's anaerobic threshold (Crisafulli et al. 2011). Nonetheless, the authors found no difference in the capacity to enhance performance between the types of IPC. A potential explanation for the lack of contrast between the two types of IPC was because of the RIP condition was adequate enough to reach the threshold for metabolite accumulation and launch the metabolic overflow that leads to IPC, which appears to proceed independently from total metabolite blood concentration (Crisafulli et al. 2011). Although enhancements in TW, TET, and W_{MAX} were noticeable following both conditions of IPC, the incremental maximal task was informed by participant's time to exhaustion, which is does not have the best within subject reliability in comparison to time trials (Jeukendrup et al. 1996). The work of Crisafulli et al. (2011) highlights the improvements following IPC in comparison to a reference test, however, it lacks the addition of a SHAM treatment group (intervention aimed to mimic as closely to the actual treatment procedure) and lacks the explanation for the cuff pressure for both IPC conditions.

Whilst aiming to look at the effects of IPC on maximal load constant cycling in recreationally active cyclists, Cruz et al. (2015) found an 8.0% improvement in performance and 2.9% increase in peak VO_2. In addition to these findings, it was also identified that the participant's rating of perceived exertion (RPE) was significantly lower (p=0.01) throughout the maximal load constant cycling test following the 4 x 5 cycles of IPC (Cruz et al. 2015). The lower assessment of RPE following the IPC condition suggests that the participants were less exhausted or underwent a delay in exhaustion throughout the exercise task. Furthermore, whilst recording an EMG measurement from the right vastus lateralis, the results revealed a progressive increase of

myoelectrical activity in the muscle (Cruz et al. 2015). A combination of the lower score of RPE throughout and following exercise and an increase of the myoelectrical activity in the vastus lateralis suggests that a reduced sensitivity of body to fatigue levels and rises in central motor output potentially contribute to the benefits of IPC on endurance performance (Cruz et al. 2015).

Further evidence supporting IPC and enhanced aerobic exercise performance was evidenced by the work of Bailey et al. (2012) who discovered that the athlete's blood lactate accumulation following submaximal aerobic exercise was significantly less (p<0.05). Lower blood lactate accumulation levels have been historically associated with athletes with faster endurance time trial performances at a submaximal intensity over different levels of athletes including elite and well-trained (Lucia et al. 2004; Lorenzo et al. 2011). This indicates that since IPC provided an enhancement in submaximal aerobic capacity and was associated with reduced blood lactate accumulation levels then it is possible that IPC can be responsible for the lowered blood lactate accumulation levels.

Previous research has also investigated the effect of IPC during endurance performed at various levels of altitude (Paradis-Deschênes, Joanisse and Billaut 2018). At a moderate altitude (2400m above sea level), it was discovered that IPC improved time trial performance amongst male endurance cyclists (Paradis-Deschênes, Joanisse and Billaut 2018). Part of the rationale for testing if IPC had an ergogenic effect at a moderate altitude was due to previous literature citing IPC's benefits when exercise initiates hypoxemia alike a static breath-hold or underwater swimming (Jean-St-Michel et al. 2011). Similar to hypoxemia, training at a moderate altitude allows athletes

to encounter hypoxia where they experience a severe lack of oxygen (Paradis-Deschênes, Joanisse and Billaut 2018). When training at a moderate altitude, athletes can experience a negative impact on their endurance performance due to the obstruction of O_2 diffusion, whether that is at the level of the alveoli or the microvasculature (Chapman, Laymon and Levine 2013). Implementing IPC was thought to be able to enhance the oxidative response to exercise training at hypoxia and mitigate the decline in SpO_2 (oxygen saturation) which is usually observed at moderate altitude (Paradis-Deschênes, Joanisse and Billaut 2018). Additionally, the mechanisms for IPC enhancing the oxidative response and leading to better performance are products of initiating the acceleration of muscle deoxygenation dynamics (Kido et al. 2015) and increasing the peripheral O_2 extraction (Paradis-Deschênes, Joanisse and Billaut 2016). The data and reasoning behind the mechanisms of IPC at moderate altitude further demonstrate that implementing IPC prior to endurance exercise can offer an ergogenic effect.

Although, enhancements have been plentiful following application of IPC prior to endurance exercise performance (Caru et al. 2019), the different modes of endurance exercise explored may explain in part why improvements in performance are not always observed (Montoye et al. 2020). For example, IPC provided no benefit to running time trial performance in recreational athletes (Montoye et al. 2020) or well-trained runners (Tocco et al. 2015; Slysz and Burr 2019). The mechanics between running and cycling are very different from each other. Cycling is largely dependent on the muscles of the quadriceps, as opposed to running, where its dependencies lie on leg muscles, core, and arm muscles (Millet, Vleck and Bentley 2009). As a result, due to optimal running performance requiring a greater ratio of musculature between different muscle groups,

and cycling predominantly demanding effort from the quadriceps, the lack of significant benefit from IPC on endurance running performance may be a product of mode of exercise being studied.

As has been discussed, a range of literature has found performance enhancing effects from IPC on aerobic exercise performance. Research has sought to extend this work to assess if these improvements in performance are observed at other exercise intensities, such as anaerobic exercise performance.

1.4.2 IPC and Anaerobic Exercise Performance

Whilst previous studies have investigated the potential for enhancement of IPC on aerobic performance, however, very few studies have analysed the benefits of IPC on anaerobic performance, and within these studies, conflicting results have been observed (Horiuchi 2017).

Enhanced performance following IPC has been observed in sprint swimming. Remote IPC (RIPC) improved maximal swim time for 100m male and female National Level swimmers (Jean-St-Michel et al. 2011). During swimming, the adopted breathing cycle results in breath holding, which can lead to significant decreases in arterial pressure of oxygen (PaO_2), resulting in exercise-induced arterial hypoxemia and decreased blood pH (Jean-St-Michel et al. 2011). The exercise-induced arterial hypoxemia could potentially be a key contributor of the development of fatigue in the respiratory, skeletal and cardiac muscles which are responsible for weakened performance in maximal swimming performance (Noakes 2000; Jean-St-Michel et al. 2011). RIPC was able to

render the tissues more resistant to the detrimental metabolic effects of high-intensity exercise, similar to tissue responses to clinical ischemia (Jean-St-Michel et al. 2011).

Research exploring shorter anaerobic efforts has also observed performance enhancements. For example, in three 50m swimming sprint trials, IPC positioned bilaterally to the thigh and unilaterally to the arms significantly improved performance 2- and 8-hours following administration (Lisbôa et al. 2017). Alternatively, in a study investigating IPC in healthy athletes, no significant improvements in alactic anaerobic performance (6 seconds of effort) and Wingate test performance were observed (Lalonde and Curnier 2015). Differences between the IPC methodologies adopted may explain these contradictory findings. Lalonde and Curnier (2015) investigated RIPC on the participant's non-exercising arms using a cuff inflation pressure of 50 mmHg above systolic blood pressure, whereas Lisbôa et al. (2017) analysed local IPC using a 220-mmHg cuff inflation protocol. In addition, the timing of IPC prior to exercise differed. Lisbôa et al. (2017) assessed 50m swimming performance at 1h, 2h, and 8h after IPC, while Lalonde and Curnier (2015) only tested anaerobic performance once immediately following the RIPC intervention. Additionally, the only time where performance was not enhanced in the 50m swimming trial was 1h following local IPC (Lisbôa et al. 2017), which can be deemed similar to Lalonde and Curnier (2015) as they measured Wingate Test performance at a similar time period following the RIPC intervention and found no significant enhancement. The time dependency of IPC application supports meta-analytical data which observed that for anaerobic performance, the longer the time between the application of IPC and the exercise test, the greater the

performance benefit (Salvador et al. 2016). The influence of the timing of IPC on exercise performance is discussed in more detail in Section 1.6.2.

In addition to the timing of application, the frequency of IPC may also influence performance outcomes. Studies adopted one application of IPC and assessed performance in multiple bouts of the 30-second Wingate test and repeated sprint test ability, yet no significant performance enhancement was observed (Lalonde and Curnier 2015; Gibson et al. 2013, 2015; Gürses, Akgül and Baydil 2017; Thompson et al. 2018; Baydil 2020). Therefore, as opposed to just administering IPC on the day or prior to measuring anaerobic performance, it may be necessary to administer repeated sessions of IPC in multiple days leading up to a measurement of anaerobic performance. In support, 7 days of IPC significantly increased peak power output, average power output, and fatigue index amongst recreationally active cyclists (Lindsay et al. 2018). The influence of repeated IPC application and exercise performance is discussed in more detail in Section 1.6.3.

Overall, IPC has the potential to enhance anaerobic performance. In support, a recent meta-analysis observed a small beneficial effect (effect size 0.23) on anaerobic performance following application of IPC (Salvador et al. 2016). However, compared to aerobic exercise, less research has explored this exercise intensity, therefore future research is needed considering the protocol of IPC used and different types of anaerobic exercise performance.

1.4.3 IPC and Sport-Specific Performance

Acknowledging if IPC can improve sport-specific performance is important because it enhances the practicality of utilising the potential ergogenic aid. However, there have been very few studies that have explored IPC's effect on sport-specific exercise performance tasks. Recently, it was found that acute IPC significantly improved judo athlete's performance in the Special Judo Fitness Test (SJFT) in comparison to a SHAM condition (Ribeiro et al. 2019). In addition to analysing judo performance, research has also investigated its effect on rowing performance. The repeated application of IPC at two separate times in the same day improved 1000m rowing time trial performance, suggesting that IPC can be utilised in rowing tournament formats where there may be gaps in between events (Halley et al. 2020). Employing IPC in a tournament format where more than one event/race take place highlights its potential real-world applicability. It was also investigated if 2000m rowing performance could be improved by IPC, however, performance was not enhanced (Turnes et al. 2018). This could be due to the IPC methodology utilised, as 3 cycles of IPC were administered lasting for 5- and 10-min periods, therefore only allowing for very short periods of ischemia-reperfusion to take place per cycle, which may not have been sufficient to be effective (Turnes et al. 2018). Moreover, IPC has been explored as a method to enhance speed skating performance (2x 1000m time trial), but no improvement on self-paced performance was observed (Richard and Billaut 2018). However, IPC was found to attenuate tissue saturation index, and could perhaps be linked to a greater amount O_2 extraction (Caru et al. 2019; Richard and Billaut 2018).

Being able to administer IPC in applied sporting environments, such as prior to an exercise task is important because it increases IPC's practicality, and the likelihood of its translation to being adopted by coaches as a method in their training schedules. It is also important that IPC research considers ecologically valid measures of performance for a range of sports to further increase it applicability. More research is therefore necessary to understand IPC's role in enhancing performance in other forms of sports and exercise tasks.

1.4.4 IPC and Resistance Exercise Performance

The effect of IPC on resistance exercise (RE) performance has received minimal research attention compared to other aspects of performance (i.e., anaerobic and aerobic performance). RE is an appreciated tool for athletes looking to optimise performance, increase muscle mass and strength, and limit the risk of injury (Kraemer, Duncan and Volek 1998). Based on the theories surrounding the potential enhancements IPC provides in ATP production by glycolytic and phosphogenic pathways, it is appropriate to assume that IPC may be able to enhance RE performance due to its dependence on these energy pathways (Marocolo et al. 2016a). Recently, it was found that in comparison to a control condition, 5-days of repeated IPC using of high and low inflation pressures significantly enhanced the number of repetitions and total workload completed (de Souza et al. 2019). Total workload was defined as the participants completing exercise tasks that were equal to maximal voluntary isometric contraction (MVIC) which involved the subjects performing knee extension with hip (100 degrees) and knee (90 degrees) fixed angles (de Souza et al. 2019). An additional mechanism thought to be responsible for the enhancement of RE performance is the possibility of ATP-sparing causing an enhancement in muscle efficiency or bettering the efficiency in excitation-contraction coupling (Pang et al. 1995; Bailey et al. 2012).

Additionally, improvements in muscle performance have been highlighted in both isometric RE (Barbosa et al. 2015; Tanaka et al. 2016; Libonati et al. 1998) and dynamic RE (Paradis-Deschênes, Joanisse and Billaut 2016; Pang et al. 1995; Marocolo et al. 2016a, 2016b).

In addition to increased number of repetitions as a measure of performance, other physiological enhancements such as increased force production, and hemodynamic variables such as greater muscle blood perfusion and increased oxygen consumption following knee extensions have led to greater repeated force capacity as a measure of strengthened performance (Paradis-Deschênes, Joanisse and Billaut 2016). Furthermore, in a recent study analysing performance during an RE training session following acute IPC, both total work and number of repetitions were enhanced (da Silva Novaes et al. 2020). Due to this study analysing RE performance in a training session, the exercises lasted much longer, and they were also focused on multijointed exercises, meaning performance relied more strongly on aerobic capacity (da Silva Novaes et al. 2020). The findings therefore indicate that the improvements in RE exercise performance may have been due to greater blood perfusion at rest and during muscle contraction, which allowed for higher removal of oxygen from circulation (da Silva Novaes et al. 2020). Moreover, in addition to these mechanisms, it has also been theorised that IPC may improve mitochondrial metabolism and is able to reduce neurological inhibition (Andreas et al. 2011; Crisafulli et al. 2011). Inhibition of afferent fibers such as type III and type IV, which are mechanoreceptors and metaboreceptors, caused by endogenous opioids released following IPC can possibly be responsible for improved muscular performance (da Silva Novaes et al. 2020), since reductions in metabolic sensory muscle afferent feedback may restrict the development of muscular fatigue (Crisafulli et al. 2011).

These initial studies exploring IPC and RE show potential for its use as an ergogenic aid. Further research is warranted to investigate this in more detail.

1.5 Potential Mechanisms Underlying IPC Performance Benefits

As mentioned, the mechanisms for IPC influencing performance are unknown and depending on the research methodology adopted, it is not always easy to determine the mechanisms that influence performance improvements mediated by IPC. For example, performance improvements following IPC could perhaps be placebo driven or caused by external factors (Marocolo, Billaut and da Mota 2018). Nonetheless, there are still physiologically driven mechanisms that have been identified as potential influencers of performance increments by IPC that are supported by the results from physiological measurements.

1.5.1 Metabolic Factors

A possible reason for the performance benefits following IPC are the changes in aerobic metabolism during exercise. The finding from Bailey et al. (2012) who discovered an improvement in blood lactate accumulation following cycling time trial performance hints that performance improvements from IPC could be recognised by a metabolic component. Despite a finding that shows improved blood lactate accumulation following a moderate-domain aerobic exercise intensity, it is otherwise difficult to identify improvements and metabolic changes in various other exercise intensities. When the exercise intensity is greater than the lactate threshold, literature has suggested that blood lactate levels are no longer influenced by IPC

(Sabino-Carvalho et al. 2017; Seeger et al. 2017). Also, blood lactate levels show very little effect on an athlete's anaerobic capacity in comparison to submaximal intensities. This questions if blood lactate accumulation can only be improved by IPC if exercise is performed at a certain submaximal intensity.

1.5.2 Vascular Factors

In addition to a metabolic component, blood flow regulation has been investigated as a possible explanation for enhancements in performance following IPC (Cocking et al. 2019). Blood flow regulation allows for the delivery of oxygen to tissues, removal of carbon dioxide and hydrogen ions from the tissues, and the distribution of nutrients including glucose, amino acids, and fatty acids. With regards to exercise, blood flow regulation is vital. When exercising, blood flow regulation allows the distribution of blood to exercising muscles (i.e., legs when running), and permits blood flow to be reduced in other non-exercising organs (Limberg et al. 2010). When there is a requirement for intense exercise, there is a metabolic need for oxygen in the skeletal muscle to increase over the resting value. Therefore, in order to accommodate this oxygen demand, blood flow to the contracting muscle must increase. The blood flow in the exercising muscles also induces vasodilation which supports greater amount of blood flow to enter the exercising muscle (Segal 2005). In addition, vasodilation also allows for an increase in nutrient delivery, which contributes to greater energy production within the muscles, and it improves the removal of lactic acid, a key contributor of muscle fatigue.

In recent literature investigating the effect of IPC on athletic performance, many studies have found that following IPC results in an increase of arterial vasodilation when exercising compared to a control or SHAM condition (Paradis-Deschênes, Joanisse and Billaut 2016; Horiuchi, Endo and Thijssen 2015; Grau et al. 2022). The regulation of blood flow is aimed to lower the work required for the heart, whilst also accounting for the necessary amount of oxygen supply for the exercising muscle (Gliemann et al. 2019). Previous studies have used near infrared spectroscopy (NIRS) as an index of muscle perfusion capacity to determine if tissue oxygenation is increased following exercise (Cocking et al. 2017). Previously, a study recorded muscle perfusion using NIRS on leg muscles after IPC was administered prior to repeated maximal voluntary knee extensions and identified that perfusion increased both at rest and during exercise, which led to a 12% enhancement in performance (Paradis-Deschênes, Joanisse and Billaut 2016). Also, Horiuchi, Endo and Thijssen (2015) implemented IPC prior to a hand-grip exercise at 10% maximal voluntary contraction (MVC), followed by sympathetic activation by means of a cold-presser test and observed that, in comparison to a control condition, there was a significant increase (4.2%) in oxygenated hemoglobin and myoglobin. This suggests that IPC can alter sympathetic vasoconstriction throughout rest and during moderate intensified exercise, which highlights a potential mechanism in enhancing skeletal muscle function. Additionally, it also suggests that IPC may enhance performance by the means of local oxygen extraction where there is unaltered blood volume following IPC (Horiuchi, Endo and Thijssen 2015). However, there are still limitations associated with NIRS, one being the presence of marked changes in skin blood flow that occur during exercise, which can decrease the accuracy of measurements obtained using NIRS (Cocking et al. 2018a). Further research should be conducted to determine the vascular

mechanisms which are responsible for the enhancement in performance following IPC using additional or alternative measurement techniques.

1.5.3 Cardiovascular Function

IPC has also been discovered to alter an athlete's cardiovascular function. Recent literature has investigated the effect of IPC on cardiac function and have recorded no changes in cardiac biomarkers as a marker of damage or function response post exercise (Cocking et al. 2017). However, Caru et al. (2016) has found evidence of modified electrical activity (QT-shortening) during exercise. The authors implemented unilateral RIPC on each participant's arm and found that following moderate and high-intensity exercise, QT intervals (via use of ECG readings) decreased significantly in comparison to a control condition (Caru et al. 2016). The QT interval is the contraction of the ventricle which lasts from the beginning of the Q wave to the end of the T wave, where it is normally about 35 seconds (Hall and Hall 2020). Although, the QT interval for a given heart rate will still differ, throughout exercise, the QT interval shortens because of exercise-induced autonomic responses (Lecocq, Lacocq and Jaillon 1989). Throughout exercise, the increase in heart rate induces the shortening of QT intervals, which also mirrors a shortening of action potential duration (APD), which in turn is achieved by IPC stimulating the activation of PKC (Speechly-Dick, Mocanu and Yellon 1994). PKC was identified as a contributor in the mechanism of IPC because it can transduce the protective signal evoked by the triggering of IPC (Ytrehus et al. 1994). Furthermore, when high intensity exercise is performed, it is commonly associated to instantaneous vascular injury, which then leads to reductions in vascular function. Athletes that take part in chronic exercise training have the vascularity of their trained muscles increase in

order to entertain their need for greater blood flow (Hall and Hall 2020). The lesser ability of vascular function could have contradictory impacts on the effectiveness to maintain intense performance, which ultimately weakens the capacity for blood to be delivered the exercising muscles (Cocking et al. 2018a).

IPC has the capability to preserve the vasculature against catastrophic stimuli such as endothelial IR-injury (Kharbanda et al. 2001; van den Munckhof et al. 2013; Seeger et al. 2017). In addition to IPC, regular exercise can also protect against vascular injury in younger individuals due to its preconditioning properties. Furthermore, the work of Bailey et al. (2012) identified that RIPC can prevent a reduction in brachial artery endothelial function (assessed via flow-mediated dilation [FMD]) following strenuous exercise. Bailey et al. (2012) identified an approximate 1.4% decrease in brachial artery endothelial function following strenuous exercise. Therefore, using IPC on the lower limbs prior to strenuous exercise can be vital to performance and health as it prevents an exercise-induced decrease of FMD (Bailey et al. 2012). Additionally, explanations for the decreases in FMD could be possibly due to greater sustained increases in shear during the exercise that can result in damaged nitric oxide biosynthesis due to the deficiency of L-arginine (Dawson et al. 2008). The finding that IPC in the legs can prevent a decrease in brachial artery endothelial function suggests that these effects are systemic as opposed to localised.

1.5.4 IPC and Perception of Effort

Research has identified that IPC has the potential to attenuate RPE. The efforts of ter Beek et al. (2020) found that IPC lowered RPE at 210 W and 245 W, respectively. Additionally, this reduction

in RPE was coupled with an 8.0% improvement in an incremental cycling test, where at the end of the fourth and final minute of the exercise task, RPE was 0.8 units lower in the IPC condition. Furthermore, following the completion of the Wingate test, measures of RPE were 9/10 for the RIPC group, in comparison to 10/10 for the control group (Lalonde and Curnier 2015). Group III and group IV afferent neurons are activated by various forms of exercise which induce metabolites such as lactate, ATP, K^+, adenosine, inflammatory cytokines and protons (Bangsbo et al. 1993, 2001; Adreani, Hill and Kaufman 1997; Hellsten et al. 1998). The feedback from group III and group IV muscle afferents increases with the onset of exercise, and can affect the key determinants of exercise performance, which include the activation of central and peripheral fatigue (Sidhu et al. 2014; Amann et al. 2015). The metabolic sensitivity of the muscle afferents could be decreased by applying IPC according to the efforts of Incognito et al. (2017). When there is greater sensitivity of the group III and group IV muscle afferents, this can lead to reduced fatigue to the central nervous system (Crisafulli et al. 2011; Cruz et al. 2017). Therefore, the feedback from the thinly myelinated group III and IV muscle afferents can be used to explain the previous examinations of reductions in RPE during exercise. However, in a study specifically analysing the central and peripheral fatiguing mechanisms associated with a maximal effort isokinetic limb exercise, IPC was unable to influence measures of neural activity or peripheral fatigue measurements (Halley, Marshall and Siegler 2019). The findings of Halley, Marshall and Siegler (2019) suggests that the previous evidence of increased sEMG (surface electromyography) in recent literature (Cruz et al. 2015, 2016) may not be associated with neural drive and may be a product of a lack of control for contraction velocity, which may explain the lack of significant findings in their own study. The increase in sEMG activity suggests an increase

in skeletal muscle activation, which then alludes to IPC facilitating greater muscle activity by means of a disruption to the central feedback loop (Cruz et al. 2017). However, due to no changes found in sEMG by Halley, Marshall and Siegler (2019), more research should investigate the role of sEMG and central and peripheral fatigue following IPC.

Although some studies have noticed reductions in perceived exertion in exercise following by means of an IPC condition, other studies have found no differences in RPE between IPC and SHAM/control trials following exercise (Behrens et al. 2020; da Silva Novaes et al. 2020). If IPC can lower the RPE of an exercise task, it could mean that participants experience less fatigue and impairment in exercise performance, which could otherwise lead to an inability to produce a greater force or power output (Hampson et al. 2001). Additional research is required exploring the RPE of exercise tasks following IPC application and to determine the mechanisms explaining the reduction of effort that has been observed.

1.6 IPC and Protocol Methodology

The most advantageous and optimal protocol for carrying out IPC is unknown (Incognito, Burr and Millar 2016; O'Brien and Jacobs 2021). However, IPC is traditionally and has historically been used in 4 sets of 5 minutes of ischemia followed by reperfusion after each set, known as the *classic* dose (Cocking et al. 2019), although, other protocols have been tested. Recently, Cocking et al. (2018b) administered multiple conditions that included a) IPC dose of the *classic* 4 x 5 minutes, b) SHAM, and c) an additional IPC dose that contained 8 sets of 5 minutes. The authors

found that the increased number of sets (8 x 5 mins) did not significantly provide any positive enhancement on time trial performance and concluded that extra sets of IPC do not lead to better performance. Furthermore, a bilateral dose of IPC, but not a unilateral dose of IPC, may be more effective in enhancing endurance performance (Cocking et al. 2018b). Similar observations have occurred for anaerobic performance as a bilateral dose of IPC improved sprint cycling performance, whereas this enhancement was unnoticeable using IPC unilaterally (Kraus et al. 2014).

Clinically, it has been discovered that the protective effects of RIPC against brachial artery endothelial IR-injury have been identified to be comparable when the pressure cuffs were applied to the lower limbs and arms whilst being completed three times (Loukogeorgakis et al. 2007). Additionally, a clinical study found that only a single 4-minute occlusion period may be plentiful enough to influence a threshold for ischemic provocation, disregarding the number of preconditioning cycles (Ghosh, Standen and Galinanes 2000). However, recent literature has determined that supplementary cycles (4 x 5 mins) of IPC enhances performance from aerobic to anaerobic capacity (Cocking et al. 2019). Although, there has been little to no research regarding whether shorter sets and a briefer duration of IPC has the same or a greater benefit as the traditional longer sets of IPC. Knowing if a shorter duration of IPC can be administered to athletes on a repeated basis, or only prior to athletic competition is important because it may become a more practical and potential ergogenic aid. For example, da Silva Telles et al. (2020) found that unilateral, 4 x 5 mins of IPC enhanced the number of repetitions in bench press and leg press in comparison to a specific warm-up. However, the authors highlighted that the practicality of these

observations remains low. More research should be conducted to determine if reduced lengths of IPC will continue to have the same performance enhancing impact. If the execution of IPC takes less of the athlete's time, it may be more feasible for athletes to use this method. Lastly, there has been no research relating optimal occlusion pressure to use. Most research uses an arbitrary 220 mmHg occlusion pressure; however, some studies have adopted a dose in which the cycle is 30-50 mmHg greater than the participant's resting systolic blood pressure (Lalonde and Curnier 2015; Crisafulli et al. 2011; Caru et al. 2016). It has been shown that occluding 30-50 mmHg above the participant's resting systolic blood pressure can consistently and reliably occlude arterial blood flow in the lower limb (Sharma et al. 2014).

Part of the rationale for researching the optimal dosage of IPC to athletes is because it has been suggested there are responders and non-responders of IPC, meaning that some individuals react to IPC interventions, and some do not (Caru et al. 2019). Being a responder or non-responder to any kind of therapy or treatment is common due to the internal and external factors including the environment where the treatment is conducted, the genetic variation of the individual, and what their medical profile may consist of (Bouchard and Rankinen 2001). There is a great amount of fluctuation of the endothelial, hemostatic, and inflammatory responses to IPC as a method to strengthen performance, and gene expression has been cited as a possible reason to explain this variation (Incognito, Burr and Millar 2016; Caru et al. 2019).

In any potential ergogenic aid, there also lies strong possibility for a placebo/nocebo effect. In a recent review, Incognito, Burr and Millar (2016) note that within the studies including a placebo

group, only 24% found performance enhancements. It is common for reputable IPC peer-reviewed articles to include a SHAM-Control group as one of the conditions in a study (Incognito, Burr and Millar 2016; Caru et al. 2019). This condition is essentially applying pressure cuffs to the athlete at a substantially lower pressure (for example: 20 mmHg compared to 220 mmHg for the actual IPC treatment). However, Jean-St-Michel et al. (2011) compared IPC to a SHAM condition (low cuff inflation on the athlete's arm) on elite swimmers' performance and observed that their SHAM condition enhanced performance compared to IPC. This indicates that, in some circumstances, IPC may be placebo driven as opposed to acting an ergogenic aid. Therefore, it remains unclear whether IPC can consistently improve performance amongst athletes.

1.6.1 Remote or Local IPC

There is also speculation regarding the most effective and applicable location for IPC to be applied to the athlete's tissues. Local IPC is where the pressure cuffs are applied to the athlete's exercising limb whereas RIPC is where the cuffs are located on the non-exercising limbs of the body (Incognito, Burr and Millar 2016). In a recent review, only 18 of 81 studies of IPC on exercise performance analysed RIPC (O'Brien and Jacobs 2021). Additionally, only a select few of these studies analysing RIPC on exercise performance found significant enhancements on performance measures. It was discovered that a five-day, low-reflow intervention of RIPC increased peak power when measuring cycling anaerobic performance (Grau et al. 2022). Furthermore, the authors noted that the enhancement in peak power derived from RIPC could be a product of the shear stress during the reperfusion phases inducing the performance enhancing effects (Grau et al. 2022). Shear stress is the frictional force on the vessel lumen as blood flows along the luminal

area (Yuan 2019) which functions as a stimulus to enact a signalling cascade that leads to nitric oxide (NO) production and artery dilation (Corretti et al. 2002). Moreover, in a study investigating RIPC in aerobic performance, RIPC increased accumulated oxygen deficit combined with improving time-to-exhaustion (TTE) by 22% in comparison to SHAM (Paull and van Guilder 2019). Also, when investigating lower-body anaerobic performance, bilateral RIPC in the arms significantly enhanced 30-second Wingate Test performance which was recognised by improvements in mean and peak power output (Kraus et al. 2014). In addition to the exercise performance enhancements, clinically, unilateral RIPC has prevented ischemia-reperfusion (IR) inducing endothelial dysfunction in the opposite limb, whilst IR in one arm formed vasodilatory affects in the brachial artery in the opposite arm (Enko et al. 2011; Cheng et al. 2021). The performance enhancements made possible by RIPC may be due to modulating the production of vasoactive substances which include NO and oxygen free radicals, which lower the overproduction of reactive oxygen species (ROS), which in turn provides protection against longer periods of ischemia reperfusion (Hausenloy and Yellon 2016; Ferdinandy and Schulz 2003; Grau et al. 2022). Despite the many significant clinical and exercise performance enhancements, in some studies, RIPC has shown no significant improvements in exercise performance (Caru et al. 2016; Cocking et al. 2017; Banks et al. 2016; Zinner, Born and Sperlich 2017). Although, there is evidence that the central humoral, neural, and the systemic ischemic protection combine as assets that lead to potential the benefits of IPC (Paradis-Deschênes, Joanisse and Billaut 2016). This proposes that there may not be an optimal location for IPC, however, there are clear differences between local and remote IPC. Local IPC has been shown to be responsible for muscle deoxygenation responses, whereas this mechanism has not been observed for RIPC (Paradis-

Deschênes, Joanisse and Billaut 2016). Furthermore, in a systematic review, Salvador et al. (2016) reported that the placement of the pressure cuffs provided no extra benefit or detriment towards performance. Also, in a study directly comparing the performances between local IPC and RIPC, Cocking et al. (2018b) found no differences in cycling time trial performances between the two types of IPC. Additionally, no differences were observed in D1 collegiate basketball player's anaerobic capacity between local IPC and RIPC (Cheng et al. 2021). From the underlying literature, it may be suitable to believe that local IPC and RIPC share very similar benefits in performance. Although, they may have different mechanisms of enhancing performance, despite the different locations of application on the athlete's tissue, both methods of (R)IPC have still shown ergogenic properties. Further research is needed to explore differences in performance between local IPC and RIPC in more depth (O'Brien and Jacobs 2021).

1.6.2 Timing of IPC

IPC has been found to be more effective during certain time periods. There are two windows of protection that IPC exerts, an early window of protection and a late window of protection (Hausenloy and Yellon 2009). The first window of protection can last for up to three hours, whereas the late window of protection, otherwise known as the secondary window of protection (SWOP) commences 24 hours following the occlusion and can last up to 72 hours (Hausenloy and Yellon 2009). Administering performance tests following application of IPC should look to be in either of these windows of protection solely because it is reported that this is where IPC treatment is most effective, even if the windows of protection were discovered throughout clinical research, rather than specifically exercise performance (Cocking et al. 2019). Previous

research recommends for a greater amount of time in between the IPC intervention and exercise performance (Salvador et al. 2016). The greater amount of time between the IPC intervention and the subsequent exercise task has shown greater effect sizes with regards to both anaerobic exercise and sprint and power performance (r=0.58, 90% CI-0.28-0.92; r=0.78, 90% CI-0.12-0.98) (Salvador et al. 2016). Therefore, the literature suggests that a minimum time of 45 minutes is required following application of IPC prior to examining exercise performance (Salvador et al. 2016). The necessity for a greater interval between the IPC intervention and the exercise task is needed so metabolite concentrations which IPC administration lowers, can return to an appropriate level (Pang et al. 1995). Specifically, the metabolites in ATP muscle content, PCr, and adenosine nucleotides are all lowered following the IPC intervention (Pang et al. 1995; Sharma et al. 2014). Whilst the metabolites are at a lower concentration level, they can lead to deterioration in performance, especially in anaerobic exercise due to its dependence on the metabolic state (Bogdanis et al. 1996). In addition to the lowering of the metabolites following IPC, it also recognised that there is a minimum time needed for the IPC activators to reach the non-preconditioned tissues (Alkhulaifi, Pugsley and Yellon, 1993). Taking the above factors into account, it is recommended that a minimal time of 45 minutes is utilised between the IPC intervention and the exercise task (Salvador et al. 2016).

Overall, although IPC can enhance performance, considering the interval time between the intervention period and the exercise task is vital to ensure IPC can display its ergogenic aid properties. Future research should look to continue to implement a significant window of time in between IPC and the exercise task.

1.6.3 Repeated IPC

In comparison to a single dose of IPC on healthy subjects, there is very little research exploring administering repeated bouts of IPC, that is IPC applied across several days. Although there is limited research on the method of repeated IPC, it does appear that by using this method a greater dose of IPC can be administered to overcome issues related to a single bout of IPC regarding ensuring the required metabolic threshold to produce a performance enhancing effect is reached (Patterson et al. 2021). Additionally, it is also speculated that the repeated utilisation of IPC across a series of days will enhance changes in skeletal muscle, such as increased skeletal muscle oxidative capacity and microvascular blood flow, in turn enhancing exercise performance (Patterson, Burr and Warmington 2021). Consequently, whilst there have been beneficial effects of a single dose of IPC on athletic performance (Crisafulli et al. 2011; Ferreira et al. 2016), recent literature suggests that future studies should analyse multiple IPC sessions over extended periods of time (Lindsay et al. 2017). The repeated sessions of IPC have been endorsed to ensure a certain metabolic threshold is met to induce the beneficial effects of IPC (Crisafulli et al. 2011; de Groot et al. 2010; Jean-St-Michel et al. 2011).

In contrast to administering IPC via a single dose and utilising the first window of protection or the SWOP, repeated IPC allow for a new cardioprotective window to be induced, which has effects on vasculature and ischemia, like the early and late phases of protection (Jones et al. 2014, 2015). Additionally, episodes of repeated IPC can also lead to a potential overlap of both the early and late phase of protection, which could possibly lead to greater effects with regards to exercise

performance (Niespodziński et al. 2021). Furthermore, whilst comparing single dose and repeated exposure to IPC, Depre et al. (2010) identified differences in gene expressions via microarray gene expression analysis. The efforts of Depre et al. (2010) found that in response to coronary blood flow, the key adaptation of gene expression is largely influenced by the repeated aspect of ischemia, as opposed to just being affected by the ischemic stimulus.

In clinical studies, repeated IPC has improved brachial artery endothelial function (Jones et al. 2014, 2015; Luca et al. 2013), blood pressure (Jones et al. 2014), and skeletal muscle oxidative function (Jeffries et al. 2019). Recently, application of IPC over 8 weeks, with participants receiving three episodes of IPC per week, improved endothelial function in just two weeks (Jones et al. 2015). The purpose of trialling IPC over 8 weeks as opposed to acute exposure was to combine the early and late phase of protection to identify potential vascular adaptation, and given the great length of the late phase of protection, less frequent visits over a greater amount of time is arguably more practical (Thijssen et al. 2016). Repeated sessions of IPC have also shown greater increases in vasodilation and sympathetic activation, which can lead to greater oxygen delivery within skeletal muscle tissue, a product of enhanced contractile function (Kimura et al. 2007; Lindsay et al. 2018; Thijssen et al. 2016). Furthermore, the process of repeated IPC can potentially be responsible for the athlete's cell's ability to modulate physiological stress response and more expertly improve performance through oxidative stress-dependent mechanisms (Tu et al. 2015). Consequently, repeated IPC may represent a potential performance-enhancing strategy for exercise performance. Indeed, previous research has discovered that 5 days of bilateral IPC improved oxygen saturation at high altitude (4342m) (Foster et al. 2014). In addition,

7 days of repeated IPC improved O_2 efficiency and microvascular O_2 distribution (Chopra et al. 2022). Finally, improvements in neuromuscular performance via rate of force development (RTD) and median frequency of power (MDF) have been found in a MVC task following 10 days of repeated RIPC (Niespodziński et al. 2021).

Although performance enhancements have been recognised following use of repeated IPC, greater rationale for the number of repeated IPC episodes administered should be researched. Additionally, further research is necessary to investigate the effects of repeated IPC on different forms of aerobic and anaerobic exercise to determine repeated IPC's full performance-enhancing potential.

1.7 Sex and Age Effect on IPC

Currently, there has been very little research conducted surrounding the influence of age and sex on IPC and exercise performance. In fact, in a systematic review, Caru et al. (2019) noted that out of 52 studies on exercise performance included in the review, and 873 healthy participants, only 16.4% of participants were female. Recently, it was noted that potential patterns of responders and non-responders to IPC existed, specifically with female populations obtaining a significantly reduced effect than male populations (Beaven et al. 2012; Gibson et al. 2013). However, more recent research investigating the effect of IPC between male and female team sport athletes observed no difference in responses to IPC between sexes, apart from blood lactate (Gibson et al. 2015). Regarding blood lactate, it was found that the female team sport athletes attained significantly lower blood lactate measures post-exercise, potentially suggesting that this was due

to improved blood flow by means of vasodilation (Gibson et al. 2015). Although, this shows there is a contradiction within the literature regarding sex differences and the effects of IPC on exercise performance, it has been widely researched and found in clinical studies that sex and age are dependent factors that influence the benefits of IPC (Heinen et al. 2018). For example, in a clinical study investigating if IPC would improve post-ischemic functional recovery in female mice hearts, it was established that post-ischemic functional recovery was not improved for 10-week-old female mice, however, it significantly improved recovery in 18-week-old female mice (Turcato et al. 2006). It may therefore be important to consider participant characteristics when exploring IPC and exercise performance, due to previous clinical literature citing that the cytoprotective effects are expected to be less in aged, female, and diabetic participants, an indication of perhaps responders and non-responders to IPC (Wever et al. 2015).

1.8 Future Research on IPC

In addition to the lack of research surrounding repeated sessions of IPC on exercise performance, there are also further aspects of IPC that have yet to be thoroughly investigated. Although previous research has regarded IPC as an ergogenic aid for some whilst also providing no athletic benefit for others, more exploration is required to identify the participant phenotype for an IPC responder (Incognito, Burr and Millar 2016). However, it is unclear if a participant phenotype to IPC even exists. This is due to research identifying the lack of valid control groups, decreased statistical power, the potential presence of a placebo effect, and the incapacity to SHAM-control treatments (Marocolo et al. 2015). Therefore, in addition to administering research that ensures that treatment is SHAM-controlled, and a placebo effect is limited, more analysis on a potential

participant phenotype is required to classify whether responders and non-responders to IPC exist. Moreover, to increase the practicality of IPC to athletes that participate in different sports, additional research is required to investigate whether shorter periods of IPC have the same performance benefits as the *classic* 4 x 5 method (da Silva Telles et al. 2020). The 4 sets of 5 minutes of IPC with each set followed by 5 minutes of reperfusion is a protocol which lasts for about 40 minutes, where for some sports, implementing that cycle may not be feasible. However, the work of Halley et al. (2020) discovered that implementing the 4 x 5 dose of IPC prior to a 1,000m rowing time trial and doing the exact same prior to a second 1,000m time trial the same day enhances rowing time trial performance. This is important to note because it shows that IPC can be used in sports where there are gaps between events (for example: rowing, athletics, sports that require tournaments/meets). Although, in this study Halley et al. (2020) were still able to use the classic IPC protocol, this may not be feasible due to time restrictions in other sports. Therefore, it is important to identify if shorter protocols carry the same or similar benefits for that matter.

1.9 Summary

This literature review highlights how IPC has developed from a clinical tool to a potential ergogenic aid for exercise performance. To date, research has explored the use of IPC to enhance aerobic, anaerobic, and resistance exercise performance and possible mechanisms for potential performance enhancements have been considered. However, most research has considered aerobic performance. Furthermore, whilst improvements in these exercise domains have been observed, this is not a universal finding. Alongside this, the optimal IPC protocol methodology

has also been considered. There is evidence to suggest that administering repeated IPC prior to exercise may enhance performance to a greater extent than a single dose. Research also indicates that the time between the dose of IPC and the exercise task is important to consider accounting for the different windows of protection that IPC can provide. Whilst some studies have demonstrated enhanced performance using repeated IPC, more research is needed across different types of exercise performance tasks. The next chapter of this thesis will present a primary research study that aims to address some of the knowledge-gaps in the field of IPC and exercise performance.

2.0 The Effect of a 2-Week Ischemic Preconditioning Intervention on Anaerobic Performance in Non-Elite Male Soccer Players

2.1 Introduction

Repeated Sprint Ability (RSA) describes the ability to produce high-intensity, short duration efforts, followed by short (≤60 seconds) recovery periods (Bishop, Girard and Mendes-Villaneuva 2011). RSA has been deemed as method for characterising anaerobic performance (Bishop, Girard and Mendes-Villaneuva 2011), with the rise in blood lactate accumulation following RSA tests indicating use of the glycolytic energy pathway (Gliemann et al. 2019). RSA is an important fitness component for team sports, such as soccer (Girard, Mendes-Villaneuva and Bishop 2011). Indeed, enhanced RSA performance has been regarded as a critical determinant of success in soccer (Impellizzeri et al. 2008; Rampinini et al. 2009) and RSA scores can segregate elite from non-elite players (Impellizzeri et al. 2008). Within a soccer match, male elite soccer players will sprint on average 17.2 times (Schimpchen et al. 2016). Furthermore, previous research has shown within a 19-match window, an elite soccer player will complete an average of 35 repeated sprints (minimum of three consecutive sprints with a recovery duration of <30s separating efforts), which corresponds to an average of one repeated bout of sprinting per every 463 minutes of playing time (Schimpchen et al. 2016). The requirement for a high quantity of sprints to be produced in a soccer match highlights the importance of RSA for enhanced player performance. In addition to this, it has been recognised that outfield soccer players are expected to produce and reproduce maximal or close to maximal effort sprints lasting for 1-7 seconds followed by very short recovery times (Girard, Mendez-Villanueva and Bishop 2011; Bishop et al. 2001; Carling, le Gall and Dupont 2012). Moreover, straight-line sprinting has been established as a very frequent action for outfield soccer players to contribute to goal scoring and goal assisting settings (Faude, Koch and Meyer 2012). Given the importance of sprinting with

shortened recovery times on a male soccer player's performance, methods that may enhance this component of fitness are needed. From the research already conducted so far, a possible intervention strategy may be to administer IPC.

IPC can enhance many aspects of sports performance (as outlined in Section 1.4). However, in comparison to aerobic performance, there is less empirical research investigating the effects of IPC on anaerobic performance (Caru et al. 2019). In a recent review, Caru et al. (2019) highlights that out of 25 studies, a total of 8 studies analysing anaerobic performance in some capacity found a performance enhancement (Cruz et al. 2016; Ferreira et al. 2016; Griffin et al. 2018; Kraus et al. 2014; Lalonde and Curnier, 2015; Lindsay et al. 2017; Lisboa et al. 2017; Patterson et al. 2015). However, only three of these studies assessed repeated sprint performance, and two of those studies were investigating performance via swimming (Ferreira et al. 2016; Lisboa et al. 2017). Recently, Cheng et al. (2021) utilised acute IPC with team sports athletes and discovered enhanced anaerobic sprint performance in Division I collegiate basketball players. However, other research using acute IPC intervention and team-sport athletes, including soccer players, has observed no improvements in sprint performance (Gibson et al. 2013). Consequently, whilst previous literature demonstrates improved anaerobic performance following IPC, more research is necessary to investigate the effects in team sports such as soccer.

The application of IPC, in terms of single or repeated dose, may also influence its effectiveness. Although there has been an abundance of research demonstrating significant performance improvements following a single dose of IPC, as discussed, this is still not a universal finding (Caru

et al. 2019). The lack of performance improvements following only a single dose of IPC could be a result of low sample size, the potential of non-responders, and failure to meet the metabolic threshold required to induce beneficial effects of IPC (Cocking et al. 2018). Therefore, to ensure a metabolic threshold allowing for physiological enhancements in measurements is met, a loading period of IPC prior to a measurement of performance may be necessary. As mentioned in Section 1.6.3, there is minimal research assessing repeated IPC and exercise performance, however, it has been shown to be a useful ergogenic aid in the few studies that have adopted this treatment method (Lindsay et al. 2017; Foster et al. 2014; Jeffries et al. 2019). Furthermore, repeated IPC can lead to significantly greater performance enhancement compared to studies only implementing a single dose of IPC prior to exercise (de Groot et al. 2010). For example, a single dose of IPC improved aerobic performance by 3% and peak power output by 1.6% (de Groot et al. 2010), whilst 7 days of repeated IPC improved aerobic performance by 9.5% and anaerobic performance by 11% (Lindsay et al. 2017). In addition to this, existing research has shown a 7-day repeated IPC intervention can enhance muscle efficiency throughout cycling by 3.1% and enhance time-to-exhaustion performance by 9% (Jeffries et al. 2019). Despite this, time-to-exhaustion is not the most valid measure of performance due to its poor within-subject reliability in comparison to time trial (Jeukendrup et al. 1996). Additionally, often a 30s Wingate test has been used to assess anaerobic performance, which is less ecologically valid for soccer performance due to the test's inability to be specific to running-based sports (Coppin et al. 2012). Furthermore, recent literature has also analysed a short-term repeated IPC intervention prior to measuring 600m speed skating performance but found no significant improvement following the intervention (Richard and Billaut 2019). However, the authors only applied three IPC sessions

(48h-, 24h-, and 1.5h) prior to measuring performance (Richard and Billaut, 2019), meaning the required metabolic threshold may not have been achieved to allow the intervention to act as an ergogenic aid. Within the existing literature, it is coherent that more research is required to determine an acceptable repeated IPC dose and to involve the assessment of anaerobic capacity which is specific to physiological demands of soccer players.

The mechanisms that may explain the performance-enhancing role of IPC for anaerobic performance are also unclear. Most research analysing repeated IPC has been completed in clinical studies in which improvements have been discovered in endothelial function and microcirculation (Jones et al. 2014, 2015; Luca et al. 2013). IPC may therefore have the capacity to strengthen skeletal muscle blood flow by retaining endothelial function and microvascular function (Kharbanda et al. 2002; Bailey et al. 2012; Loukogeorgakis et al. 2005). The first study to investigate repeated IPC and arterial endothelial function reported that endothelial function was enhanced by means of increases in nitric oxide (Kimura et al. 2007) and nitric oxide is responsible for regulating vasodilation, blood flow and mitochondrial respiration (Besco et al. 2012). As stated in Section 1.5.2, when blood flow to the exercising muscles is improved, it allows vasodilation to be induced which permits greater blood flow to infiltrate into the exercising muscle. It is therefore possible that repeated IPC may enhance anaerobic exercise performance through increased endothelial function and skeletal blood flow during exercise, however this mechanism has not been explored.

Overall, there is a current lack of literature investigating the effect of repeated IPC on exercise performance, especially anaerobic performance, such as RSA. Given the importance of RSA on soccer performance, there is a need to explore this as a possible intervention, and its underlying physiological mechanisms. Therefore, this study aimed to explore if a 2-week repeated IPC intervention could enhance anaerobic performance in RSA in sub-elite soccer players. Additionally, this study assessed whether improvements in endothelial function was a mechanism explaining any performance enhancement. It was hypothesised that the repeated IPC intervention would enhance anaerobic performance, via increases in peak and mean power output, and improve endothelial function.

2.2 Methods

2.2.1 Participants

Eight, male, full-time soccer academy student-athletes from York St John University and i2i International Soccer Academy were recruited. Sample size was informed by existing research exploring the effect of IPC on exercise performance which recruited between 6 and 8 healthy, trained participants (Foster et al. 2011; Garcia et al. 2017; Birkelund et al. 2015; Kjeld et al. 2014). Inclusion and exclusion criteria were stated clearly in the participant information sheet that was given to all participants who expressed an interest in completing the study. Each participant recruited was an outfield player (no goalkeepers) and was aged between 18 and 24 years. Participants were screened prior to testing using the Physical Activity Readiness Questionnaire (Warburton et al. 2018) and participants regularly taking medication or diagnosed with a chronic disease were excluded (Lalonde and Curnier 2015). Additionally, any participant with a resting blood pressure that exceeded 140/100 mmHg (systolic/diastolic) (Gibson et al. 2015) or who was recently injured (>2 weeks) was not eligible to take part.

2.2.2 Ethical Approval

Participants were informed of the procedures and requirements for each study in writing and then written informed consent was obtained prior to inclusion. All study procedures were approved by the York St John School of Science, Technology and Health Ethics Committee (RECELP00006) and adhered to the Declaration of Helsinki.

2.2.3 Experimental Design

A randomised, sham-controlled and single-blinded crossover trial design was conducted. Each intervention trial lasted 2-weeks. The participants were randomly allocated to the order they completed trials by the principal researcher using computer-generated random numbers. Prior to beginning the 2-week intervention trial, participants were required to attend the laboratory to obtain anthropometric measurements and baseline measurements of anaerobic performance and endothelial function. Following the baseline measurements, participants were separated into one of the two trial intervention groups: IPC or SHAM-controlled. Throughout the intervention, participants visited the laboratory on six separate occasions within a 2-week time period to receive IPC or SHAM-controlled treatment. A 2-week intervention period was chosen as previous research has shown in healthy, young males, endothelial function increases following six episodes of IPC over a 2-week period (Jones et al. 2015). Additionally, the less frequent number of IPC treatments compared to daily IPC treatments is informed by the timing of the late phase of protection against endothelial ischemia-reperfusion injury that IPC can provide (Jones et al. 2014; Loukogeorgakis et al. 2005). At the end of the two weeks, anaerobic performance and endothelial function measurements were repeated. There was a minimum 7-day washout period before the crossover of the IPC and SHAM-controlled trial intervention groups (Cocking et al. 2017). All laboratory testing and treatment sessions took place at York St John University's Physiology Laboratory and Sports Hall, respectively.

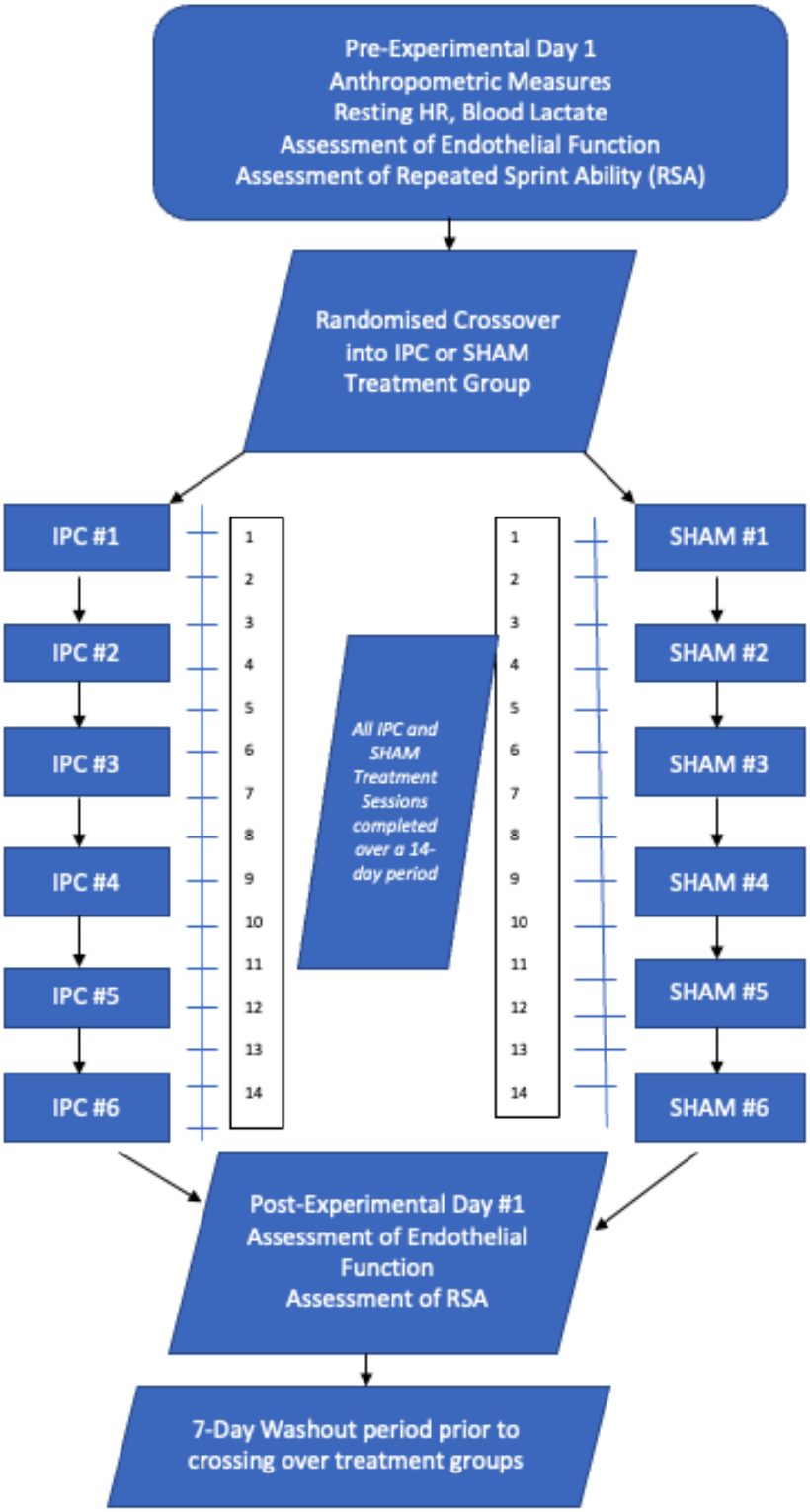

Figure 1: Schematic of Experimental Study Design.

2.2.4 Laboratory Testing Visits

Prior to each laboratory testing visit, participants were asked to complete an overnight fast and to refrain from caffeine and the consumption of alcohol, and to avoid strenuous physical activity for 24 hours (Incognito, Burr and Millar 2016). Additionally, each participant was asked to go to sleep and wake up at a similar time before each trial in order to standardise sleep. To standardise dietary intake, participants recorded the food they ate the day before each visit in a food diary and were asked to keep this the same for subsequent laboratory visits. At the start of Visit 1, participants' height, weight, and resting blood pressure were recorded. Following this, participants rested supine for 20 minutes before endothelial function was assessed via non-invasive vascular ultrasound. Participants then completed the Running-based Anaerobic Sprint Test (RAST) to achieve a baseline measurement of anaerobic performance. After completion of the 2-week intervention, all baseline measurements were repeated.

2.2.5 Treatment Visits

For each treatment visit, participants were required to attend the laboratory for approximately 40 minutes to receive either SHAM-controlled treatment (blood pressure cuffs inflated to 20 mmHg) or IPC treatment (blood pressure cuffs inflated to 220 mmHg). Although, it can be difficult to effectively SHAM-control treatment in human subjects, previous literature recommends that research studies should acknowledge the participants' understanding of the IPC, whilst potentially utilising deception (Incognito, Burr and Millar 2016). Therefore, participants were also not made aware which condition was expected to be performance enhancing. Bilateral occlusion was performed simultaneously on the right and left thighs. Participants lay in the supine position

for all treatments and blood pressure cuffs (20.5-28 cm, M1753A, Phillips, The Netherlands) were positioned on the proximal portion of the thighs. Cuffs were inflated for 5-minutes at the required pressure, using an automatic rapid cuff inflator (Vascular Assessment Pressure Cuff Controller, Moor Instruments, Devon, UK). Four sets of 5-minutes of inflation (4 x 5 mins) were completed. Following each set of 5 minutes, the cuffs were deflated for 5-minutes, before administering another set to allow reperfusion to take place. After the four sets of SHAM/IPC treatment were finished, that concluded one day of treatment. This occlusion/reperfusion protocol has been used in previous studies assessing repeated IPC and sports performance (Cheng et al. 2021; Incognito, Burr and Millar 2016). Three treatments per week were administered for two weeks (Jones et al. 2015). Participants were supervised for each treatment. See Figure 2 for treatment visit model.

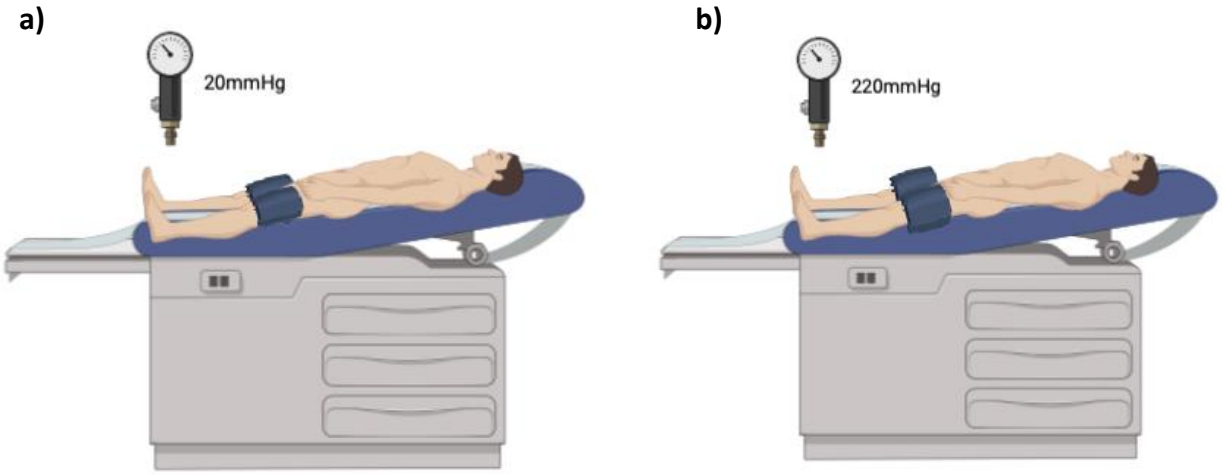

Figure 2: A model of a a) SHAM (4 x 5 mins at 20 mmHg), or b) ischemic preconditioning (IPC; 4 x 5 mins at 220 mmHg) treatment session.

During the 2-week treatment period, participants were able to complete their habitual exercise and dietary patterns. Participants were asked to report their training load using a training diary. Participants reported the number of hours they trained each day and rated the intensity of each training session on a 0-10 scale. Training load was then calculated by multiplying the hours of training and the intensity of training. This method based on rating of perceived exertion (RPE) is known as the session-RPE approach and was established by Foster et al. (2001) to quantify high-intensity exercise training. Additionally, in a recent study, the session-RPE method was further strengthened by its validity and reliability (session-RPE and repeated bouts, r=0.88) of a subjective measure of exercise training intensity (Herman et al. 2006).

2.2.6 Measurements

2.2.6.1 Demographics

Participants' age, typical training load and years of soccer academy playing experience were recorded. Typical training load was assessed subjectively via the previously described session-RPE method. Session-RPE is related to other objective measures of exercise intensity load suggesting it can be viewed as an acceptable method of recording a participant's training load (Haddad et al. 2017).

2.2.6.2 Sleep

The day prior to each laboratory testing visit, participants' sleep was monitored since sleep has been identified as a crucial factor for optimal athletic performance (Bird 2013). Obtaining the sleep pattern of participants therefore enabled the researcher to account for any differences in performance following both assessments of the RAST that may be explained by changes in sleep.

Sleep was assessed via actigraphy, an approach widely used to objectively assess sleep based on movement patterns (Cellini et al. 2013). Compared to the gold standard measure of assessing sleep, polysomnography (PSG), actigraph devices have obtained various agreement rates of sleep and wake epochs ranging from 85-95% (Sadeh 2008). Participants were required to wear an accelerometer (ActiGraph GT3X, Pensacola, Florida) on their non-dominant wrist. Wrist actigraphy achieves a more valid measure of sleep compared to hip actigraphy, in addition to a moderate ability to recognise periods of wake during the time in bed (Slater et al. 2015). In addition, participants completed the Consensus Sleep Diary (Carney et al. 2012) as recommended in conjunction with actigraphy to prevent periods of non-wear time being incorrectly classed as sleep (Sadeh and Acebo, 2002). Participants answered questions relating to bedtime, wake up time, and number of awakenings, which were used to confirm the metrics collected from the accelerometer. Data from the accelerometer were downloaded in 60-s epochs and analysed utilising ActiLife Software (Version 6.13.4) and using the Sadeh algorithm which is validated in a young (10 to 25 years) population (Sadeh et al. 1994). Each night of sleep was analysed for the sleep parameters: time in and out of bed, total sleep time, sleep efficiency, and sleep fragmentation index (Cellini et al. 2013).

2.2.6.3 Anthropometrics

Stature and body mass were recorded on Visit 1. Participants were required to stand as still as possible underneath a stadiometer (SECA, Hamburg, Germany) to obtain a measure of stature, recorded to the nearest 0.1 cm. In minimal clothing and without shoes, body mass was measured

to the nearest 0.1 kg using an electronic scale (Tanita BC-543 Body Composition Monitor, Amsterdam, Netherlands). Body mass index (BMI) was subsequently calculated (mass/stature^2).

2.2.6.4 Resting Heart Rate and Blood Pressure

Resting heart rate and systolic and diastolic blood pressure were assessed using an oscillometric cuff at the left brachial artery (Carescape V100, Dinamap, GE Healthcare, UK). Measurements were obtained after participants had completed the 20-minute supine rest.

2.2.6.5 Femoral Artery Endothelial Function

Peripheral femoral artery endothelial function was assessed using the standardised flow-mediated dilation (FMD) technique, according to published guidelines (Thijssen et al. 2011). Participants laid in a supine position while the test was conducted and was instructed to remain as still as possible during the test. A rapid inflation and deflation pneumatic cuff were positioned on the left thigh, just above the patella. To record an image of the left femoral artery, a 10MHz multi-frequency linear array probe connected to a high-resolution ultrasound machine (T3000; Terason Burlington, MA) was used (Figure 3). Images were captured above the occlusion cuff and distal from the artery bifurcation. In order to obtain the arterial diameters, the ultrasound parameters were adjusted to enhance the B-mode image of the lumen-arterial wall interface. Once a suitable image was detected, the probe was held in this position. Additionally, blood flow was assessed via Doppler ultrasound using the same machine with an insonation angle of 60 degrees. Following a 1-minute baseline, the cuff was inflated to 220 mmHg for 5 minutes to induce local ischemia. After cuff deflation, ultrasound recordings continued for a further 3

minutes. The same procedures were used for each endothelial function assessment. Figure 4 provides an outline of the three phases (baseline, ischemia and vasodilation) of the FMD protocol and the typical arterial diameter response.

2.2.6.6 Femoral Artery Endothelial Function Data Analysis

Data were analysed using Cardiovascular Suite (Version 2.8.1 Software, Quipu, Italy), an automated edge-detection and wall-tracking software. The software tracks the blood vessel walls and blood velocity trace via pixel density and frequency distribution algorithms. The software enables an optimal region of interest (ROI) to be selected from the initial frame of the B-mode and Doppler waveform. For diameter analysis, the ROI was selected based on B-mode image quality and the clear distinction between the artery walls and lumen, whilst for blood velocity analysis, a second ROI was selected to encompass the Doppler waveform. Each frame was analysed, enabling synchronised arterial diameter, blood velocity, blood flow (arterial cross-sectional area x blood velocity), and shear rate (SR) data to be acquired. SR (4 x [blood velocity/arterial diameter]) was used as an estimation of shear stress due to the inability to measure blood viscosity.

For the FMD assessment, within the software, each phase of the FMD protocol (baseline, ischemia, cuff deflation) was selected by the researcher. Baseline arterial diameter and blood flow were determined as the mean of the data acquired 1 min prior to cuff inflation. Following cuff deflation, peak arterial diameter was automatically calculated and FMD (%) was calculated as the percentage change in arterial diameter from baseline diameter ([peak arterial diameter-

baseline arterial diameter]/baseline arterial diameter) x 100 %). SR area under the curve (AUC) was automatically calculated from post cuff deflation until the point of peak arterial diameter.

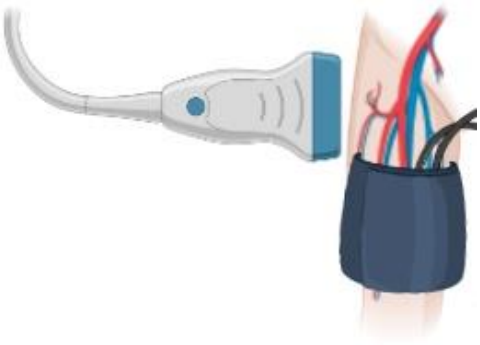

Figure 3: A model of the FMD (Flow-Mediated Dilation) protocol on the left femoral artery with the cuff placed just above the patella (inflated to 220 mmHg for 5 mins) to image the femoral artery during cuff inflation and deflation.

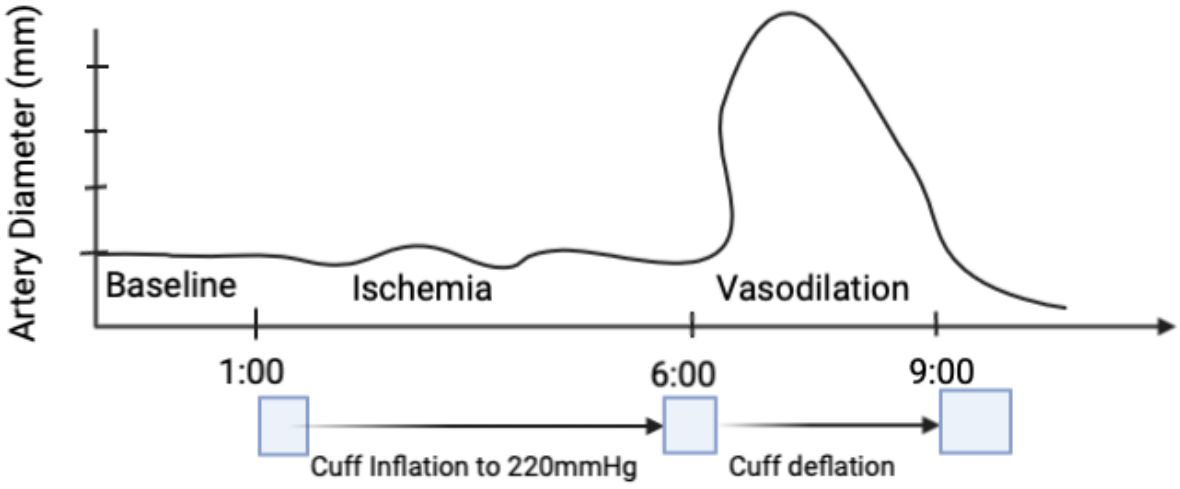

Figure 4: A model of the three different phases of (Baseline, Ischemia and Vasodilation) throughout the duration of the flow-mediated dilation (FMD) assessment and the typical arterial diameter response.

2.2.6.7 Running-Based Anaerobic Sprint Test (RAST)

To determine repeated sprint ability and anaerobic performance, participants completed the Running-based Anaerobic Sprint Test (RAST; Zagatto, Beck and Gobatto, 2009). The RAST, specifically, is a test that has been adopted by coaches and trainers in soccer populations due to the sport's requirements of a continuous high number of repeated sprints (Keir, Riault and Serresse, 2013). Additionally, repeated sprint ability has been recognised as an important physical fitness component for soccer players (Helgerud et al. 2001; Impellizzeri, Rampinini and Marcora 2005; Spencer et al. 2005). The RAST was developed by Wolverhampton University (United Kingdom) and is adapted from the original Wingate Anaerobic Sprint Test (WAnT) to assess anaerobic power (Zagatto, Beck and Gobatto, 2009). The RAST was completed indoors in the University's Sports Barn. Indoor testing was adopted to remove the influence of differential outdoor conditions (e.g., wind, temperature) influencing sprint performance, whereas the conditions in an indoor environment controlled for such variations.

Each participant was required to complete six, maximal effort 35m sprints. Each sprint was separated by 10 seconds of rest before completing the next 35m sprint. The time to complete each sprint was measured by photocell timing gates placed 1.0 m above ground level at the start and end of the 35m distance (Witty System, Microgate, Italy). See Figure 5 for the RAST testing field set-up. Peak power was then calculated for each sprint, calculated as: (body mass x distance^2)/time^3. Peak power was defined as the greatest power obtained from one of the six sprints, while average peak power was calculated by obtaining the mean peak power value from each of the six sprints. Fatigue index was calculated as: (maximal power - minimum power)/total

time to complete all six sprints. The RAST has shown strong criterion validity for measuring peak power and average power ($r=0.70$, $p<0.001$; $r=0.60$, $p<0.01$, respectively) (Burgess et al. 2016). Additionally, the RAST has shown strong reliability scores for measuring peak power output and average power output (ICC=0.72; ICC=0.88) (Burgess et al. 2016). During the RAST, heart rate was monitored using a telemetry system with a wireless chest strap (Polar V800, Polar H10 Heart Rate Sensor, Helsinki, Finland). Maximal heart rate at the end of the final sprint was recorded.

Prior to completing the RAST, participants completed the Fédération Internationale de Football Association (FIFA) 11+ warm-up protocol, a warm-up created by FIFA's Medical and Research Centre (F-MARC) as a complete warm-up programme to prevent injuries in amateur soccer players (Bizzini and Dvorak 2015). The warm-up contains a series of dynamic stretches that are specific for soccer players to compete prior to physical exertion to help reduce injuries (Liu et al. 2021).

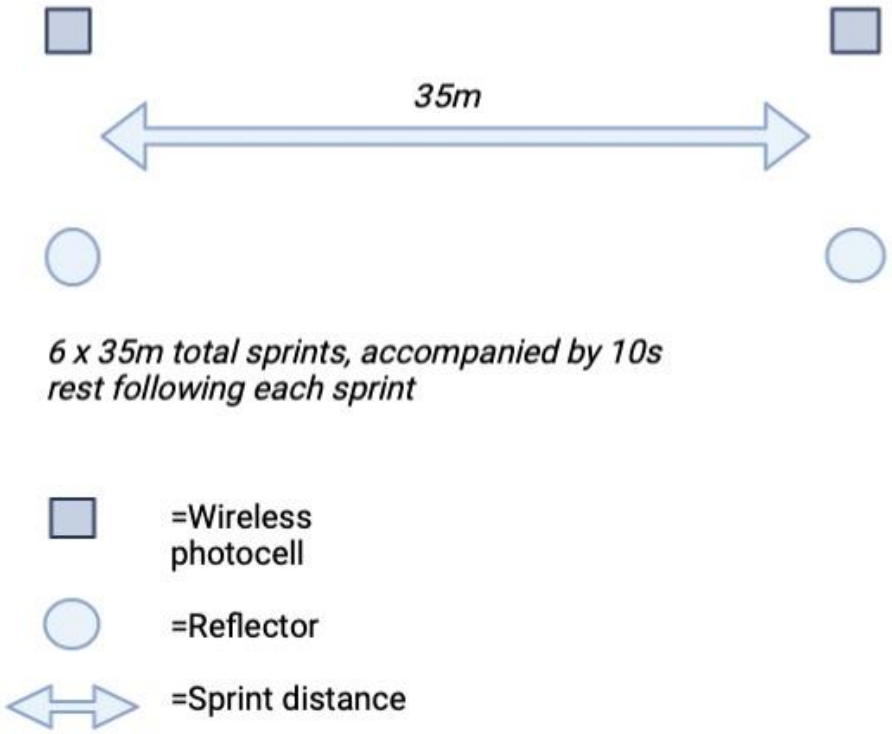

Figure 5: A Model of the RAST (Running-Based Anaerobic Sprint Test) testing set-up (6 x 35m sprints followed by 10s of rest) with electronic timing gates at each end.

2.2.6.8 Blood Lactate

Blood lactate was drawn at rest and immediately following the completion of the RAST via finger-prick sampling from the participant's non-dominant hand. Following each finger prick, blood lactate was assessed using a portable lactate analyser (Lactate Pro 2 Analyser, Kyoto, Japan), with the sample collected using a lactate test strip obtained at a 90-degree angle from the blood sample. The Lactate Pro 2 analyser has shown strong reliability (CoV=3.3%; ICC=0.99) and showed acceptable levels of construct validity (ICC=0.87) in comparison to the YSI Sport 1500, a laboratory-based blood lactate analyser (Crotty et al. 2021).

2.2.6.9 Heart Rate

Heart rate (V800 GPS Sports Watch and H10 Heart Rate Sensor, Polar, Helsinki, Finland) was recorded at rest and following the culmination of the RAST. The heart rate sensor was attached to a chest strap and placed just beneath the participant's sternum, ensuring skin contact. The Polar H10 Heart Rate Sensor can recognise electrical activity throughout each beat and transfer real time data to the Polar V800 GPS Sports Watch (Mohapatra, Preejith, and Sivaprakasam 2017).

2.2.7 Statistical Analyses

Data were analysed using SPSS Statistics (Version 17, IBM SPSS Inc., Chicago, IL, USA), with significance accepted if $p<0.05$. Data were assessed for normality using the Shapiro-Wilk normality test. Data obtained from the RAST (peak power, average power output, fatigue index), blood lactate, heart rate, blood pressure, FMD variables, sleep variables and training load were

analysed using two-way repeated measures ANOVAs. Post-hoc analyses were completed via paired samples t-test with LSD adjustment. Data are presented as mean ± standard deviation (SD), from which, effect sizes (partial eta squared, η^2) were calculated. These were considered as: small (η^2=0.01), medium (η^2=0.06), and large (η^2=0.14) (Cohen, 1988).

2.3 Results

2.3.1 Descriptive Statistics

Eight non-elite male academy soccer players completed the study and were included in analyses. Full descriptive characteristics are shown in Table 1. Participants completed all 12 treatment sessions (6 IPC and 6 SHAM) for each intervention trial.

Table 1: Descriptive characteristics (n=8)

	Mean±SD
Age (years)	20.8±1.0
Body Mass (kg)	78.3±14.3
Height (cm)	177.8±5.6
Body Mass Index ($kg \cdot m^{-2}$)	24.6±3.4
Academy Playing Experience (years)	3.0±0.9
Typical Training Load (units/week)	630±0

2.3.2 Physiological Measurements at Rest

No significant main effects were observed for heart rate, systolic blood pressure, and diastolic blood pressure at rest (p>0.05; Table 2). A significant main effect for time was observed for resting blood lactate (p=0.035, η^2=0.533) with POST (1.23±0.05) higher than PRE (1.14±0.06). No significant condition or interaction effects were observed for resting blood lactate (p>0.05; Table 2).

Table 2: Resting physiological measurements taken before (PRE) and after (POST) the completion of the ischemic preconditioning (IPC) and SHAM-controlled (SHAM) trials (Mean±SD).

	IPC		**SHAM**		***p-value and partial eta squared***		
	PRE	**POST**	**PRE**	**POST**	***Time***	***Condition***	***Interaction***
Heart Rate (bpm)	61±11	64±13	57±6	65±14	*p=0.072,* η^2*=0.339*	*p=0.528,* η^2*=0.053*	*p=0.468,* η^2*=0.608*
Systolic Blood Pressure (mmHg)	120.6±9.9	124.5±9.9	117.8±7.5	122.0±9.7	*p=0.347,* η^2*=0.160*	*p=0.506,* η^2*=0.087*	*p=0.921,* η^2*=0.0001*
Diastolic Blood Pressure (mmHg)	71.4±2.6	68.1±5.8	66.5±3.3	67.9±18.9	*p=0.814,* η^2*=0.023*	*p=0.460,* η^2*=0.155*	*p=0.522,* η^2*=0.425*
Blood Lactate (mmol/L)	1.32±0.27	1.58±0.31*	1.16±0.13	1.44±0.40*	*p=0.035,* η^2*=0.533*	*p=0.392,* η^2*=0.141*	*p=0.950,* η^2*=0.002*

* Significant main effect for time (*p*=0.035) with POST higher than PRE

2.3.3 Running-Based Anaerobic Sprint Test Performance

Mean power, peak power, maximal heart rate, blood lactate, and fatigue index data for each RAST performance are presented in Table 3. A significant interaction effect was observed for peak power output, with post hoc analyses revealing at POST the IPC trial had a higher peak power output compared to the SHAM trial (p=0.010, η^2=0.639). Additionally, a significant interaction effect was observed for fatigue index, with post hoc analyses showing at POST the IPC trial had a higher fatigue index compared to the SHAM trial (p=0.013, η^2=0.608). There was also a significant main effect for condition for mean power output (p=0.024, η^2=0.540), with the IPC trial (525.3±58.3) higher than the SHAM trial (469.9±52.5). There were no other significant main effects for RAST performance measures (p>0.05).

Table 3: Running-Based Anaerobic Sprint Test performance before (PRE) and after (POST) the completion of the ischemic preconditioning (IPC) and SHAM-controlled (SHAM) trials (Mean±SD).

	IPC		**SHAM**		***p-value and partial eta squared***		
	PRE	**POST**	**PRE**	**POST**	***Time***	***Condition***	***Interaction***
Peak Power Output (W)	632.8±199.1	708.6±217.6*	640.5±166.2	572.3±174.2	*p=0.851, η^2=0.005*	*p=0.102, η^2=0.337*	*p=0.010, η^2=0.639*
Mean Power Output (W)	498.2±170.5[#]	552.4±167.2[#]	486.2±148.6	453.6±161.0	*p=0.627, η^2=0.035*	*p=0.024, η^2=0.540*	*p=0.058, η^2=0.421*
Maximal Heart Rate (bpm)	183±9	182±10	179±7	180±11	*p=0.966, η^2=0.001*	*p=0.263, η^2=0.175*	*p=0.647, η^2=0.032*
Blood Lactate (mmol/L)	9.50±3.90	9.41±2.35	8.49±2.79	7.78±2.81	*p=0.535, η^2=0.057*	*p=0.118, η^2=0.312*	*p=0.720, η^2=0.020*
Fatigue Index (W/sec)	5.53±2.49	6.95±2.80[+]	6.46±2.25	5.08±1.96	*p=0.960, η^2=0.001*	*p=0.551, η^2=0.053*	*p=0.013, η^2=0.608*

* Significant main effect for interaction (p=0.010) with IPC POST higher than SHAM POST

[+] Significant main effect for interaction (p=0.013) with IPC POST higher than SHAM POST

[#] Significant main effect for condition (p=0.024) with IPC higher than SHAM

2.3.4 Femoral Artery Flow-Mediated Dilation

The results showed a significant interaction effect for relative FMD (p=0.018, η^2=0.577), with post hoc analyses revealing at POST the IPC trial had a higher FMD compared to the SHAM trial (Table 4). There were no significant main effects for any other FMD measurements (p>0.05; Table 4).

2.3.5 Sleep

Sleep parameters for the night before each laboratory testing visit are shown in Table 5. There was a significant main effect for condition for minutes in bed (p=0.001, η^2=0.847), with the IPC trial (545±118 minutes) higher than the SHAM trial (464±73 minutes). There were no other significant main effects for measures of sleep (p>0.05).

2.3.6 Training Load

There were no significant main effects observed for session-RPE assessed prior to each laboratory testing visit (p>0.05; Table 6).

Table 4: Femoral artery flow-mediated dilation (FMD) before (PRE) and after (POST) the completion of the ischemic preconditioning (IPC) and SHAM-controlled (SHAM) trials (Mean±SD).

	IPC		**SHAM**		***p-value and partial eta squared***		
	PRE	**POST**	**PRE**	**POST**	***Time***	***Condition***	***Interaction***
Relative FMD (%)	4.68±2.04	6.40±2.14*	6.67±3.18	4.96±2.65	*p=0.992,* η^2*=0.001*	*p=0.815,* η^2*=0.008*	*p=0.018,* η^2*=0.577*
Absolute FMD (mm)	6.69±0.69	6.69±0.74	6.55±0.91	6.71±0.38	*p=0.660,* η^2*=0.029*	*p=0.606,* η^2*=0.040*	*p=0.640,* η^2*=0.033*
FMD Baseline Diameter (mm)	6.39±0.72	6.29±0.69	6.15±0.89	6.48±0.40	*p=0.462,* η^2*=0.080*	*p=0.825,* η^2*=0.007*	*p=0.141,* η^2*=0.282*
Shear Rate AUC (s^{-1} x 10^3)	4.4±6.4	8.5±6.0	10.6±2.9	10.1±7.1	*p=0.351,* η^2*=0.125*	*p=0.346,* η^2*=0.127*	*p=0.347,* η^2*=0.127*

* Significant main effect for interaction (*p*=0.017) with IPC POST higher than SHAM POST
Shear Rate AUC- Shear Rate Area Under the Curve

Table 5: Measures of sleep before (PRE) and after (POST) the completion of the ischemic preconditioning (IPC) and SHAM-controlled (SHAM) trials (Mean±SD).

	IPC		**SHAM**		***p-value and partial eta squared***		
	PRE	**POST**	**PRE**	**POST**	***Time***	***Condition***	***Interaction***
SF Index	32.5±17.9	33.6±13.0	45.1±15.3	41.1±13.0	*p=0.757,* η^2*=0.015*	*p=0.158,* η^2*=0.263*	*p=0.636,* η^2*=0.034*
Sleep Efficiency (%)	76.8±10.4	81.5±10.6	72.8±11.0	71.2±8.6	*p=0.601,* η^2*=0.041*	*p=0.125,* η^2*=0.303*	*p=0.264,* η^2*=0.174*
Total Minutes in Bed (mins)	609±106*	644±61*	447±64	482±81	*p=0.409,* η^2*=0.001*	*p=0.001,* η^2*=0.847*	*p=0.982,* η^2*=0.099*
Sleep Duration (mins)	447±82	456±52	347±85	395±100	*p=0.197,* η^2*=0.136*	*p=0.064,* η^2*=0.407*	*p=0.329,* η^2*=0.225*

*Significant main effect for condition (*p*=0.001) with IPC higher than SHAM
SF Index- Sleep Fragmentation Index

Table 6: Training load assessed using session-RPE before (PRE) and after (POST) the completion of the ischemic preconditioning (IPC) and SHAM-controlled (SHAM) trials (Mean±SD).

	IPC		**SHAM**		***p-value and partial eta squared***		
	PRE	**POST**	**PRE**	**POST**	***Time***	***Condition***	***Interaction***
Session-RPE	5.38±3.38	3.63±4.00	4.50±3.78	4.00±3.38	*p=0.161,* η^2*=0.260*	*p=0.351,* η^2*=0.125*	*p=0.460,* η^2*=0.080*

Session-RPE- Session-Rating of Perceived Exertion

2.4 Discussion

The aim of the present study was to determine if a 2-week repeated IPC intervention would enhance anaerobic performance in RSA in non-elite, male academy soccer players. Results demonstrate that the repeated IPC intervention enhanced peak power output during the RAST but had no effect on mean power output. In addition to the primary aim, it was explored if improvements in endothelial function could be a possible mechanism to explain improvements in anaerobic performance. The present study discovered that endothelial function significantly increased following the repeated IPC intervention, suggesting that enhanced endothelial function may improve peak power. The present study demonstrates IPC can improve anaerobic performance in non-elite, male academy soccer players.

This study's central finding was that repeated administration of IPC over 2-weeks enhanced anaerobic performance by increasing peak power output during repeated sprints. This supports existing research whereby bilateral IPC increased peak power in the first three out of a total of twelve, 6-s cycling sprints (Patterson et al. 2015). However, previous research investigating IPC prior to anaerobic exercise has provided conflicting results (Horiuchi 2017; Patterson et al. 2015) and this study's finding contrasts other literature using IPC to enhance anaerobic performance by means of RSA. In well-trained male and female team sport athletes, no improvement was observed in RSA assessed via sprint cycling performance (5 x 6 maximal effort sprints) following a single dose of IPC (Gibson et al. 2015). However, this study only administered IPC unilaterally, in comparison to the present study where IPC was conducted bilaterally. Importantly, it has been suggested that IPC applied bilaterally to the limbs improves exercise performance to a greater

extent compared to IPC applied unilaterally (Cocking et al. 2019). In another study, Cocking et al. (2021) investigated whether a single dose of bilateral IPC would enhance repeated cycling sprint performance (10 x 6s sprints with 24s of recovery), however no performance enhancements were observed. Furthermore, whilst less research has assessed the influence of IPC on running-based sprint performance, in such studies they have utilised only a single dose of IPC and observed no performance enhancement (Gibson et al. 2013; Griffin et al. 2018). The lack of performance enhancement following a single dose of IPC suggests a repeated method of IPC, as adopted in the present study, is required to surpass a threshold where IPC can be effective (Salvador et al. 2016). Collectively, the use of bilateral and repeated IPC in this study may therefore have provided a more optimal dose of IPC to enhance running RSA. However, comparisons to literature are challenging as studies have adopted various methods to assess RSA ranging from 5x6s, 10x6s, 12x6s, to 6x30s sprint efforts, and have mainly assessed cycling performance (Gibson et al. 2015; Patterson et al. 2015; Cheng et al. 2021; Cocking et al. 2021). Consequently, more research is needed to verify IPC's role in enhancing running-based anaerobic performance.

In the present study, peak power output was significantly enhanced by 11.3% using repeated IPC over 2-weeks in comparison to the SHAM condition. Sprints that are performed within field-based team sports generally obtain sizeable amounts of energy via anaerobic glycolysis and phosphocreatine (PCr) (Spencer et al. 2005). In addition to this, the peak power output derived from the RAST has been shown to significantly correlate with the phosphagen pathway contribution ($r=0.65$, $p<0.05$) (Milioni et al. 2017). It is therefore plausible that the improvement in peak power output observed in the present study can be attributed, in part, to an

enhancement in phosphagen pathway energy production. In support of this, it has also been noted that IPC increases PCr production (Andreas et al. 2011), a molecule in the phosphagen pathway. Additionally, in a clinical setting, IPC application in an animal model maintained ATP content in the heart muscle following IR-Injury via an increased concentration of PCr (Lukes et al. 2005). Furthermore, previous reviews have deemed IPC possible to promote PCr resynthesis (Incognito, Burr and Millar 2016; Salvador et al. 2016). Overall, repeated IPC may have increased PCr content, leading to an improvement in peak power output, and is a mechanism that should be further explored.

The observed improvement in endothelial function following repeated IPC may also explain the increase in peak power output. It has been suggested that IPC may increase blood flow to skeletal muscle which improves the conservation of power by the strengthening of microvascular pressure and enhancing metabolite washout (Libonati et al. 2001; Wang, Baynosa and Zamboni 2011). Additionally, IPC potentially improves skeletal muscle blood flow by inducing conduit artery vasodilation which enhances functional sympatholysis (the blunting of sympathetically mediated vasoconstriction during exercise) and conserves endothelial and microvascular function during shear stress (Cocking et al. 2018a). Previous research has also discovered enhancements in skeletal muscle oxidative capacity and microvascular blood flow following a repeated IPC intervention, which may be responsible for greater improvements in peak power output (Jeffries et al. 2019). Moreover, in short duration cycling performance, an increased activation of skeletal muscle was observed alongside a significant improvement in mean power output (Cruz et al. 2016). It is therefore possible that the increase in endothelial function in the

present study allowed for greater skeletal muscle blood flow which contributed towards the improvement in peak power output. Further research is required to decipher if this is a mechanism responsible for the observed improvement in peak power output.

The present study revealed no improvement in mean power output following repeated IPC. Previously, research has associated mean power output in an all-out 30s anaerobic capacity test with energy produced from the glycolytic pathway (r=0.58; p=0.03) (Zagatto et al. 2017). However, with regards to the RAST, mean power output has been shown to correlate significantly with the phosphagen energy pathway (r=0.65; p<0.05) suggesting mean power output is perhaps not influenced by the glycolytic energy production pathway (Milioni et al. 2017). In addition to this, the present study revealed IPC had no significant influence on blood lactate concentration following the RAST, suggesting that IPC had no influence on blood lactate accumulation. Previous research analysing the effect of acute IPC prior to 50m sprint swimming trials, which predominantly utilises the glycolytic energy system (Capelli, Pendergast and Termin 1998), observed faster swimming sprint times which was also associated with greater blood lactate accumulation, indicating greater glycolytic contribution to enhance performance (Lisbôa et al. 2017). However, in the RAST, sprint performance by means of peak power and mean power output are not correlated to the glycolytic energy pathway (r=0.28; p>0.05) (r=0.23; p>0.05) (Milioni et al. 2017). In the present study, IPC may not have had a significant effect on blood lactate accumulation due to minimal contribution of glycolytic energy pathway in the RAST. However, it is unclear why mean power output was not significantly enhanced due to its

association with the phosphagen pathway. Further research is required to understand IPC's influence on mean power output and its relation to the phosphagen pathway.

To the author's knowledge, the present study is the first explore the effects of repeated IPC on non-elite academy soccer players' anaerobic performance. A 2-week IPC protocol consisting of 6 sessions (4 x 5 mins) was administered as previous literature demonstrated the sufficiency of a 2-week period to improve endothelial function (Jones et al. 2015). The present study corroborates this finding by also observing enhanced endothelial function utilising a 2-week IPC protocol. After a single dose of IPC is completed, the cardioprotective effects are present for 1-2h following the dose, and although they reduce, remain present for 3-4 days, therefore, endothelial function can be improved utilising both the first and second windows of protection (Loukogeorgakis et al. 2007). The observed improvement in endothelial function in the present study may therefore be the product of the timing of late phase of protection, which activates the synthesis of certain cardioprotective proteins including an upregulation of the NO-pathway and cyclooxygenase-2 (Jones et al. 2015; Xuan et al. 2001). Previous research has analysed the effect of repeated IPC on exercise performance, ranging from 7 to 10 days to 8 weeks of exposure prior to measuring exercise performance (Jeffries et al. 2019; Slysz and Burr 2019; Niespodziński et al. 2021). Additionally, the present study further supports previous findings that have utilised repeated IPC and have demonstrated improvements in performance (Foster et al. 2014; Lindsay et al. 2017; Jeffries et al. 2019) As mentioned in Section 1.6.3, whilst a single dose of IPC has been found to enhance exercise performance (Crisafulli et al. 2011; Ferreira et al. 2016b), the application of repeated IPC utilises the late window of protection (Loukogeorgakis et al. 2007)

and may ensure a certain metabolic threshold is met to induce the beneficial effects of IPC (Crisafulli et al. 2011; de Groot et al. 2010; Jean-St-Michel et al. 2011). Although, following the repeated IPC intervention peak power output significantly improved and provided an ergogenic effect, the most advantageous dose of repeated IPC to obtain a performance enhancement is still unclear (Lindsay et al. 2017). Further research is recommended to determine the optimal repeated IPC dosage that elicits the greatest performance enhancing effects for anaerobic performance.

In the present study, parameters of sleep were assessed the night prior to each experimental trial since greater sleep at night prior to athletic performance has led to improvements in performance (Mah et al. 2011). Importantly, no significant differences were observed in sleep duration, sleep efficiency or sleep fragmentation between the IPC or SHAM conditions. As such, acute differences in sleep cannot be attributed to the enhanced peak power output that was observed. In addition to sleep, the present study also assessed session-RPE prior to each of the experimental trials to control for influences of training load on performance outcomes. It was discovered that there was no difference between session-RPE between either condition, indicating each trial was completed with participants enduring a similar previous training load. Collectively, measuring sleep and session-RPE strengthened this study by controlling for external factors that could influence performance and supports recommendations for greater pre-study restrictions and control measures in IPC and exercise performance research (Incognito, Burr and Millar 2016).

2.4.1 Limitations

The present study had limitations that should be acknowledged. Firstly, it was not possible to design the study to be double-blinded, therefore, the participants knew whether they were receiving the high- or low-cuff inflation treatment condition. However, the participants were not informed which treatment condition researchers predicted would enhance performance in order to reduce any placebo effect. Secondly, the study only analysed the effect of IPC on anaerobic performance in non-elite male academy soccer players, consequently, results are not generalisable to other populations, such as females or other sports. The present study was therefore unable to explore sex-based differences which has importance since differences between males and females have been suggested in terms of their response to IPC (Paradis-Deschênes, Joanisse and Billaut 2017). Thirdly, during the intervention periods, participants were still training with their soccer academy, which may have allowed their fitness levels to vary throughout the intervention period. However, the content of the training sessions within the academy during this time had a greater emphasis on match preparation and tactics, as opposed to fitness development. Additionally, the testing took place mid-season, in contrast to completing it in pre-season or the off-season, where there is a greater focus on the progression of fitness levels. Lastly, a limitation of the present study was the sample size, which was small, and future research should aim to expand these findings in a larger sample size.

2.4.2 Future Directions

Future research should continue to analyse the effect of repeated IPC on athletic performance. Specifically, future research should explore the effects of extended repeated IPC sessions on anaerobic performance. This will determine if longer intervention periods are associated with

greater enhancements in performance. The mechanisms explaining IPC's performance enhancing effect should also be further explored. Future research should aim to analyse if repeated IPC alters muscle PCr content by including additional assessment techniques which could include, but are not limited to, muscle biopsies, blood samples, and magnetic resonance imaging of PCr. In addition to this, although literature has investigated repeated IPC protocols administered over a period of several days to several weeks (Jones et al. 2015; Foster et al. 2014; Lindsay et al. 2017), there has been minimal literature assessing the effects of multiple IPC sessions per day on exercise performance (Lindsay et al. 2017). Applying multiple IPC sessions over a day could be more feasible and time efficient for participants/athletes, and it would identify whether a strategy like this contributes to greater magnitude of performance enhancements. Lastly, future research should aim to analyse the effects of repeated IPC on performance in female athletes due to the considerably less research conducted on female participants (Caru et al. 2019). This is because as discussed in Section 1.6, this will enable researchers to detect if there are any differences in IPC response and exercise performance in male or female participants.

2.4.3 Practical Applications

The results from this study have potential practical implications for soccer academy athletes, coaches, and physical performance coaches. Coaches and physical performance coaches could look to implement IPC in the days leading up to training and matches and it could be used for the athletes as a loading period. The repeated aspect of IPC adds to the practicality of the intervention as it allows IPC to be conducted on days where matches are not taking place, or it could be implemented in the days leading up to matches. In addition, although IPC may provide

an improvement in performance, it also carries no risk of fatigue or high exertion associated with physical training methods. Also, the opportunity to implement IPC on a non-matchday is essential to the planning for coaches as it would not affect the coach's preparation as much if IPC had to take place on a matchday to get the maximum performance benefit. IPC can also be viewed as a cost-effective method to enhance performance, increasing its accessibility to non-elite players and coaches who may have fewer financial resources.

2.5 Conclusion

This study demonstrates that a 2-week IPC intervention can enhance peak power output in non-elite male academy soccer players. Moreover, endothelial function was also significantly improved following the repeated IPC intervention, providing a potential mechanistic explanation for the observed enhancement in performance. These findings present IPC as a potential intervention strategy for coaches and physical performance coaches to carry out prior to matches and training in order to enhance anaerobic performance. Future research should look to analyse the effect of repeated IPC in a more diverse sample and utilising a larger sample size to confirm these initial findings.

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