

2012-06-04

# Ischemic Preconditioning of the Legs Results in Small Improvements in Peak Exercise Capacity at Sea Level, but not Simulated High Altitude in Trained Male Cyclists.

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ISCHEMIC PRECONDITIONING OF THE LEGS RESULTS IN SMALL  
IMPROVEMENTS IN PEAK EXERCISE CAPACITY AT SEA LEVEL, BUT NOT  
SIMULATED HIGH ALTITUDE IN TRAINED MALE CYCLISTS

By

Elizabeth A. Hittinger

A DISSERTATION

Submitted to the Faculty  
of the University of Miami  
in partial fulfillment of the requirements for  
the degree of Doctor of Philosophy

Coral Gables, Florida

June 2012

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Ischemic Preconditioning of the Legs Result in Small Improvements in Peak Exercise Capacity at Sea Level, but Not Simulated High Altitude in Trained Male Cyclists

(June 2012)

Abstract of a dissertation at the University of Miami

Dissertation supervised by Professor Kevin Jacobs

No. of pages in text (28)

Ischemic preconditioning (IPC) may have profound local and systemic effects that improve blood flow and oxygen delivery to tissues, including skeletal muscle, and has the potential to improve intense aerobic exercise performance, especially that which results in arterial hypoxemia. **Purpose:** To determine the effects of IPC of the legs on peak exercise capacity ( $W_{\text{peak}}$ ), submaximal and peak cardiovascular hemodynamics, and arterial oxygen saturation ( $\text{SaO}_2$ ) in trained males at sea level (SL) and simulated high altitude (HA;  $F_{\text{I}}\text{O}_2 = 13.3\%$ ,  $\sim 3650$  m). **Methods:** Fifteen highly trained male cyclists and triathletes completed two  $W_{\text{peak}}$  tests (SL and HA) and four experimental exercise trials (10 min at 55% altitude specific  $W_{\text{peak}}$  increasing by 30 W every 2 min until exhaustion) with and without IPC. **Results:** HA resulted in significant arterial hypoxemia during exercise compared to SL ( $73 \pm 1$  vs.  $93 \pm 1\%$   $\text{SaO}_2$ ,  $p < 0.05$ ) that was associated with 21% lower  $W_{\text{peak}}$  values. IPC resulted in a  $1.9 \pm 0.8\%$  higher average  $W_{\text{peak}}$  value at SL compared to control ( $p = 0.032$ ). While IPC resulted in a  $4.7 \pm 2.3\%$  higher average  $W_{\text{peak}}$  value at HA compared to control, this difference failed to reach statistical significance ( $p = 0.084$ ). IPC did not significantly affect peak cardiovascular hemodynamics or  $\text{SaO}_2$  at SL or HA. **Conclusions:** IPC has little effect on systemic

oxygen delivery and future studies must examine its influence on local factors, including blood flow, oxygen delivery, and arteriovenous oxygen difference of the working limb.

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## Chapter 1: INTRODUCTION

Ischemic preconditioning (IPC) is a technique utilized to improve surgical outcomes when long periods of ischemia are experienced during procedures such as cardiac surgery or organ transplantation (Murry et al. 1986; Harkin et al. 2002; Kharbanda et al. 2002; Li et al. 2004; Moses et al. 2005; Cheung et al. 2006; Sadigh et al. 2009; Wenwu et al. 2010). Brief episodes of occlusion-derived ischemia applied either directly or indirectly before surgery appear to prevent or diminish many of the negative consequences of ischemia-reperfusion injury. While the precise mechanism is not yet clear, the possibility that IPC may have profound local and systemic effects that improve blood flow and oxygen delivery to tissues, such as skeletal muscle, may mean that it has the potential to improve intense aerobic exercise performance, but little is known of its efficacy to date.

Regardless of the precise mechanism, the ability of IPC to reduce ischemia-reperfusion injury may mean that it can improve intense exercise performance that results in arterial hypoxemia and mimics ischemic injury (Jean-St-Michel et al. 2011). Indeed, two similar studies have found that IPC (3 cycles of 5 min of occlusion of both legs followed by 5 min of reperfusion) performed 5 min before exercise resulted in 2-4% higher maximal workloads in trained subjects at the end of a continuous progressive cycling test compared to control (de Groot et al. 2010; Crisafulli et al. 2011). These improvements in maximal workload corresponded to a 3% improvement in  $VO_{2max}$  in one study (de Groot et al. 2010). In the other study, the improvement in maximal workload did not correspond to a increase in  $VO_{2max}$ , but was accompanied by higher maximal ventilation and heart rate (HR) values (Crisafulli et al. 2011). Additionally, IPC did not affect



maximal stroke volume (SV) and cardiac output (Q) as assessed by impedance cardiography, but these variables were not assessed during submaximal exercise (Crisafulli et al. 2011).

IPC (4 cycles of 5 min of occlusion of one arm followed by 5 min of reperfusion) performed 40-45 min before a 100 or 200 m maximal swimming effort has also been shown to significantly improve swim time relative to personal best time (-1.1%) in elite swimmers (Jean-St-Michel et al. 2011). However, in the same study IPC did not affect submaximal exercise performance during a set of seven progressively faster 200 m intervals. Interestingly, dialysed blood samples taken from the swimmers after IPC and perfused into mouse hearts significantly reduced infarct size compared to the perfusion of blood samples taken before IPC. This finding strongly suggests that IPC may provide beneficial effects to maximal exercise performance through both local and systemic mechanisms. The authors speculated that arterial hypoxemia might limit maximal performance in elite swimmers more than other athletes due to the reduced breathing frequency demanded by their activity. In this way, this activity may mimic the conditions of ischemia-reperfusion stress increasing the possibility that IPC would have a beneficial effect. If attenuating the detrimental effect of arterial hypoxemia is a mechanism by which IPC may provide performance improvements in maximal swimming efforts, it seems reasonable to expect that IPC may be especially beneficial to activities performed under hypoxic conditions such as high altitude.

To date, only one published study has examined the effects of IPC prior to exercise performed under hypoxic conditions. IPC (4 cycles of 5 min of occlusion of one leg followed by 5 min of reperfusion) was performed 90 min before trained cyclists completed a time trial in the fastest time possible at sea level and simulated high altitude ( $F_{I}O_2 = 13\%$ ,  $\sim 3800$  m) (Foster et al. 2011). IPC resulted in a 2.6% improvement in time trial performance compared to a control condition under the same hypoxic conditions. However this difference did not reach statistical significance, likely due to the high degree of variability in time trial durations ( $526 \pm 184$  s vs.  $540 \pm 216$  s,  $p = 0.81$ ). The IPC did significantly attenuate the hypoxia-induced increase in pulmonary arterial systolic pressure (PASP) at rest by 72.8% compared to control, again demonstrating that IPC can have significant systemic effects. Significant increases in PASP with hypoxia are known to reduce arterial oxygen content and Q by hindering ventilation/perfusion matching and right ventricular afterload, respectively (Ghofrani et al. 2006). The lower PASP with IPC was associated with unchanged arterial oxygen saturation ( $Sa_{O_2}$ ) and a trend for higher Q values at rest under hypoxic conditions compared to control ( $4.6 \pm 0.7$  vs.  $4.2 \pm 0.7$  L/min,  $p = 0.09$ ). Unfortunately, these measures were not taken during exercise when arterial hypoxemia is most severe and IPC may have the greatest benefits. Additionally, the use of a maximal exercise task rather than the submaximal time trial could have maximized the degree of arterial hypoxemia.

Previously our laboratory evaluated the effects of IPC (4 cycles of 5 min of occlusion of one arm followed by 5 min of reperfusion) 10-15 min before a maximal cycling test in male cyclists and triathletes at sea level and simulated high altitude ( $F_{I}O_2 = 12.8\%$ ,  $\sim 3900$

m). We found no significant differences between IPC and control in peak exercise capacity ( $W_{\text{peak}}$ ), maximal HR,  $\text{Sa}_{\text{O}_2}$ , RPE, or several ventilatory measures (FVC,  $\text{FEV}_1$ ,  $\text{FEV}_1/\text{FVC}$ ,  $\text{FEF}_{25-75\%}$ , or PEF) (unpublished observation). There were several limitations to the study including the small sample size ( $n = 9$ ) and the time of year (during the peak of triathlon season). The location of the IPC may have also been a limitation. The emerging trend in studies involving IPC and exercise is to perform IPC to the muscle groups that will be directly used during exercise (i.e. IPC of legs prior to cycling and the arm prior to swimming) (Groot et al. 2010; Crisafulli et al. 2011; Foster et al. 2011; Jean-St-Michel et al. 2011).

The purpose of this study was to determine the effects of IPC of the legs on  $W_{\text{peak}}$ , submaximal and peak cardiovascular hemodynamics (HR, SV, and Q), and  $\text{Sa}_{\text{O}_2}$  in trained males at sea level (SL) and simulated high altitude (HA;  $\text{F}_1\text{O}_2 = 13.3\%$ ,  $\sim 3650$  m). We hypothesized that IPC of the legs prior to a continuous progressive cycling test to volitional exhaustion would result in significantly greater  $W_{\text{peak}}$  values than control at SL and HA and significantly greater values for cardiovascular hemodynamics and  $\text{Sa}_{\text{O}_2}$  during steady state exercise and at  $W_{\text{peak}}$  compared to control at HA only. Additionally, we hypothesized that the effects of IPC on  $W_{\text{peak}}$  would be greater at HA than at SL.

## Chapter 2: METHODS

### *Subjects*

Twenty-eight highly trained men (cyclists and triathletes) between 18 and 39 years of age were recruited from the surrounding area. All potential subjects were screened using PAR-Q and health history questionnaires for health issues that could impact exercise performance or the safety of simulated high altitude and IPC procedures. Subjects were enrolled in the study only if they met the minimum criterion for peak oxygen consumption ( $VO_{2\text{peak}}$ ) of 50 ml/kg/min. This criterion placed all subjects above the 85<sup>th</sup> percentile for maximal aerobic power in their age range and gender according to ACSM guidelines. Subjects were excluded if they had lived at altitude (> 2100 m) for more than two years during their lifetime or spent more than two weeks at altitude over the last six months. Fifteen men met all of the qualifications and were enrolled in the study (Table 1). Subjects agreed not to travel to altitude during the investigation. The procedures and risks were thoroughly explained to the subjects, and their written, voluntary, informed consent was obtained.

### *General Experimental Design*

Following screening, subjects completed  $W_{\text{peak}}$  tests at SL and HA. Subjects then participated in four experimental exercise trials at SL and HA with and without IPC in randomized and counterbalanced fashion.

### *Screening*

During baseline screening, subjects completed PAR-Q and health history questionnaires, along with measurements of HR and blood pressure (Dinamap, GE Medical Systems Information Technology, Inc., Milwaukee, WI) at rest.  $VO_{2peak}$  was assessed at SL during baseline screening using a continuous progressive exercise test to volitional exhaustion on an electromagnetically braked cycle ergometer (Monark Ergometric 829e, Vansbro, Sweden). Subjects began cycling at 50, 100, and 150 W for 2 min each and the workload was then increased by 30 W every 2 min until exhaustion. To account for work performed in partially completed stages,  $W_{peak}$  was determined as previously described (Jeukendrup et al. 1996) using the following equation:

$$W_{peak} = W_{complete} + (t/120) \cdot 30$$

where  $W_{complete}$  is the power output of the last completed stage and  $t$  is the number of seconds completed in the final stage attempted. Expired respiratory gases were collected continuously and analyzed with an online open-circuit metabolic cart (Vmax Encore 29c, CareFusion, San Diego, CA).

### *HA $W_{peak}$*

$W_{peak}$  at HA was determined at least 72 h after the SL  $VO_{2peak}$  test. Subjects breathed hypoxic gas (13.3%  $F_{iO_2}$  or ~3650 m) for 45 min prior to and throughout the HA  $W_{peak}$  test. Hypoxic generators (HYP-123, Hypoxico, New York, NY) along with high altitude adapters were used to provide the normobaric hypoxic condition of this test and the

subsequent HA experimental exercise trials. Hypoxic gas was delivered to the subject through a facemask that was sealed over the subject's nose and mouth at a rate that exceeded the subject's ventilation. The oxygen composition of the hypoxic gas was monitored before and after each trial with a portable oxygen monitor (Handi O<sub>2</sub>, Maxtec, Salt Lake City, UT). The HA  $W_{\text{peak}}$  test used the same protocol as the SL  $VO_{2\text{peak}}$  test, except that respiratory gas measurements were not taken due to the high rate of hypoxic gas delivery through the facemask preventing accurate measurements of  $V_E$ ,  $F_{EO_2}$ , and  $F_{ECO_2}$ .

#### *Experimental Exercise Trials*

Subjects performed four experimental exercise trials at SL and HA with and without IPC before exercise in randomized and counterbalanced fashion with at least 72 h between trials. Each trial consisted of baseline measurements, IPC (if that condition), 45 min of rest, and 10 min of steady-state exercise at 55% of altitude-specific  $W_{\text{peak}}$  followed immediately by a continuous progressive exercise test to volitional exhaustion on an electromagnetically braked cycle ergometer.

Subjects recorded their diet for 24 h prior to the first experimental exercise trial and they were asked to maintain the same dietary pattern for the 24 h preceding each of the other exercise trials. Subjects were asked to refrain from consuming caffeine the day of the trial and to arrive fully hydrated. Subjects were also asked to refrain from moderate to high intensity exercise and alcohol for at least 24 h prior to the tests. As described

previously, subjects rested while breathing hypoxic gas (13.3% F<sub>I</sub>O<sub>2</sub> or ~3650 m) for 45 min prior to and throughout exercise during the HA trials.

HR, SV, and Q were measured continuously throughout the experimental exercise trials with a noninvasive impedance cardiography device (PhysioFlow PF05 L1, Manitec Biomedical, Macharen, France) as previously described (Hsu et al. 2006). The PhysioFlow device emits a low-amperage (3.6 mA), high frequency (75 KHz), alternating electrical signal between two sets of electrodes. One set was placed on the supraclavicular fossa on the left side of the neck; the other set on the middle of the back at the level of the xiphoid process. SV was calculated from the measurement of changes in transthoracic electrical impedance during the cardiac cycle while simultaneous measurements of ECG activity (V1 and V6) allowed for the HR measurement and, therefore, the calculation of Q. When compared to the direct Fick method at rest and during submaximal and maximal incremental exercise, the PhysioFlow device has been shown to be very reliable ( $r = 0.95$ , mean difference for Q of 0.009 L/min) with clinically acceptable accuracy ( $r = 0.85 - 0.94$ , mean difference for Q of 0.07 - 0.58 L/min) (Charloux et al. 2000; Richard et al. 2001). The coefficient of variations for SV and Q from the PhysioFlow across repeated cycle ergometer  $\text{VO}_{2\text{peak}}$  tests in healthy, trained men was reported to be 3.6 and 3.4%, respectively (Hsu et al. 2006).  $\text{Sa}_{\text{O}_2}$  was measured continuously using a portable dual wavelength pulse oximeter placed over the index finger of the left hand (PulseOx 300i, Konica Minolta Sensing, Inc., Osaka, Japan). The pulse oximeter has an operating range of 70-100%  $\text{Sa}_{\text{O}_2}$  and an accuracy of  $\pm 2\%$  as stated by the manufacturer.

During the IPC trials, blood pressure cuffs were fitted around both thighs and inflated to 10-20 mm Hg above systolic blood pressure and left at this pressure to occlude blood flow for four 5-min cycles, allowing 5 min of reperfusion of blood between occlusions. Absence of a pulse during the occlusion phase was confirmed by palpitation of the posterior tibial and dorsalis pedis pulses.

The exercise task commenced approximately 45 min after the end of the IPC cycles. The workload on the ergometer was progressively ramped in the first minute until the subject reached 55% of the altitude-specific  $W_{\text{peak}}$ . Subjects remained at this steady state workload for 10 min and the workload was then increased by 30 W every 2 min until volitional exhaustion. HR, SV, and Q were recorded continuously and averaged every 30 s by the PhysioFlow. RPE was recorded between minutes 8-10, and at the end of every 2-min stage of the progressive portion of the exercise test. Subjects were asked to rest the left hand on top of the handlebar as much as possible to prevent occlusion and faulty  $\text{SaO}_2$  measurements.  $W_{\text{peak}}$  was determined as previously described.

### *Statistics*

Data are represented as means  $\pm$  SE. The normal distribution of the data was examined with Shapiro-Wilks tests. The significance of within- and between-condition differences was assessed by ANOVA with repeated measures followed by post hoc analyses using the Least Significant Difference test. Significance was set *a priori* at  $\alpha < 0.05$



## Chapter 3: RESULTS

### *Cardiovascular hemodynamics, Sa<sub>O2</sub>, and RPE during rest and steady-state exercise*

In the transition from rest to steady state exercise at both SL and HA, there were significant increases in HR (110%), SV (35%), and Q (181%) ( $p < 0.05$ ; Fig. 1-3). HR and Q also significantly increased slightly during steady state exercise between minutes 4-6 and 8-10 at SL and HA, while SV only significantly increased between these time points at SL. At rest, HR, SV, and Q were not different between SL and HA. HR and SV were not different during steady state exercise between SL and HA. Q was significantly higher at HA than SL at minutes 4-6 ( $14.4 \pm 0.8$  vs.  $12.5 \pm 0.7$  L/min,  $p = 0.034$ ), but not at minutes 8-10. IPC did not significantly affect HR, SV or Q at rest or during steady state exercise at either SL or HA.

Sa<sub>O2</sub> significantly decreased from rest to steady state exercise at SL and HA ( $p < 0.05$ ; Fig. 4). Compared to SL, Sa<sub>O2</sub> was significantly lower at HA both at rest and during steady state exercise in both control and IPC conditions ( $p < 0.05$ ). Compared to control, IPC resulted in significantly higher Sa<sub>O2</sub> values at rest and during steady state exercise at SL only ( $p < 0.05$ ). IPC did not significantly affect Sa<sub>O2</sub> at HA.

RPE was significantly higher during exercise at HA than SL ( $11.1 \pm 0.6$  vs.  $9.7 \pm 0.4$ ,  $p = 0.011$ ), but was unaffected by IPC at SL or HA.

*W<sub>peak</sub>, and cardiovascular hemodynamics, Sa<sub>O2</sub>, and RPE at W<sub>peak</sub>*

The  $W_{\text{peak}}$  values obtained during the experimental exercise trials at SL and HA without IPC (Fig. 5) were not different than those obtained during screening at SL ( $326 \pm 7$  vs.  $331 \pm 10$  W) and HA ( $271 \pm 8$  vs.  $261 \pm 10$  W).  $W_{\text{peak}}$  was 20-21% lower at HA than SL in both control and IPC conditions ( $p = 0.0001$ ). IPC resulted in a  $1.9 \pm 0.8\%$  higher average  $W_{\text{peak}}$  value (range -1 to 8%) at SL compared to control ( $p = 0.032$ ) (Fig. 5). While IPC resulted in a  $4.7 \pm 2.3\%$  higher average  $W_{\text{peak}}$  value (range -6 to 23%) at HA compared to control, this difference failed to reach statistical significance ( $p = 0.084$ ).

$HR_{\text{peak}}$  and  $Sa_{O_2}$  at peak were both significantly lower at HA than SL in control and IPC conditions ( $p < 0.05$ ), but  $SV_{\text{peak}}$ ,  $Q_{\text{peak}}$ , and  $RPE_{\text{peak}}$  were not significantly different between SL and HA (Table 2). IPC did not significantly affect peak cardiovascular hemodynamics,  $Sa_{O_2}$ , or RPE at SL or HA.  $HR_{\text{peak}}$  at HA tended to be higher with IPC than control, but failed to reach statistical significance ( $p = 0.064$ ).

## Chapter 4: DISCUSSION

The purpose of this study was to examine the effects of IPC of the legs on  $W_{\text{peak}}$ , submaximal and peak cardiovascular hemodynamics, and  $\text{SaO}_2$  in trained males at SL and HA. Our hypotheses were partially supported in that IPC resulted in small improvements in  $W_{\text{peak}}$  at SL only. However, in the face of considerable arterial hypoxemia at HA, IPC failed to significantly improve any variable measured. These results provide important information regarding the effects of IPC on systemic oxygen delivery and the practical implications of IPC for exercise that will be subsequently discussed.

### *$W_{\text{peak}}$ and systemic oxygen delivery*

The significant improvement in  $W_{\text{peak}}$  at SL with IPC compared to control in this study (1.9%) is consistent with the findings of similar studies involving IPC of both legs prior to cycling exercise at SL (2-4%) (de Groot et al. 2010; Crisafulli et al. 2011). The mechanism behind these small improvements in  $W_{\text{peak}}$  is still unclear, as there is little evidence from this study and others that IPC improves Q and  $\text{SaO}_2$ , and thus systemic oxygen delivery, during maximal exercise at SL. While some have reported that IPC results in significantly higher maximal HR values (Crisafulli et al. 2011), we and others have failed to find a significant effect of IPC on peak HR, SV, or Q compared to control (Table 2) (de Groot et al. 2010). Additionally, while IPC in this study resulted in  $\text{SaO}_2$  values at rest and during steady state exercise that were slightly higher than control (Fig. 4),  $\text{SaO}_2$  at peak was unaffected by IPC (Table 2). Future studies will need to include measurements of blood flow, oxygen delivery, and arteriovenous oxygen difference across the working limb in order to determine whether IPC results in any local

improvements in these variables that may be responsible for small improvements in  $W_{\text{peak}}$  at SL.

The ability of IPC to reduce ischemia-reperfusion injury has led to the belief that it may be especially beneficial to intense exercise performance that results in arterial hypoxemia and mimics ischemic injury (Jean-St-Michel et al. 2011). It was for this reason that we hypothesized that IPC would result in greater improvements in  $W_{\text{peak}}$  at HA than SL. The HA condition of this study resulted in significant arterial hypoxemia with  $\text{SaO}_2$  values at rest, during steady state exercise, and at  $W_{\text{peak}}$  that were 11-22% lower than corresponding values at SL (Table 2, Fig. 4). This significant arterial hypoxemia corresponded with 21% lower  $W_{\text{peak}}$  values at HA than SL (Fig. 5). Similar reductions in  $\text{SaO}_2$  (21-24%) and  $W_{\text{peak}}$  (19-23%) were noted previously in trained male subjects tested at a similar simulated altitude (Jacobs et al. 2011; Kressler et al. 2011). However, IPC did not significantly improve  $W_{\text{peak}}$  under these conditions (Fig.5). While the difference in  $W_{\text{peak}}$  at HA with IPC compared to control was greater than that at SL ( $4.7 \pm 2.3$  vs.  $1.9 \pm 0.8\%$ ), it failed to reach statistical significance likely due to the more variable individual responses to IPC at HA than SL (Fig. 6). IPC at SL and HA resulted in either small individual improvements or no change in  $W_{\text{peak}}$  compared to control, but at HA this was countered by several instances of decreases in  $W_{\text{peak}}$  with IPC compared with control. In order to try to further explain the results, we examined the correlation between  $\text{VO}_{2\text{max}}$  and change in  $W_{\text{peak}}$  with IPC at SL and HA, but found no significant relationship ( $r = 0.16$  and  $0.07$ , respectively). There remains the possibility that a larger subject pool may be necessary to verify the effect of IPC on  $W_{\text{peak}}$  at HA.

Significant increases in PASP with hypoxia are known to reduce arterial oxygen content and Q by hindering ventilation/perfusion matching and right ventricular afterload, respectively (Ghofrani et al. 2006). IPC was previously shown to significantly attenuate the hypoxia-induced increase in PASP at rest compared to control. Unfortunately, these measures were not taken during exercise when arterial hypoxemia is most severe and IPC may have the greatest benefits. It was for these reasons that we hypothesized that IPC would result in significant improvements in cardiovascular hemodynamics and Sa<sub>O2</sub> at HA during steady state exercise and at W<sub>peak</sub>. However, IPC did not significantly influence cardiovascular hemodynamics or Sa<sub>O2</sub> at rest, during submaximal exercise, or at W<sub>peak</sub> at HA (Table 2, Fig. 1-4). It is possible that any reductions in PASP with IPC were not great enough to result in significant improvements in cardiovascular hemodynamics or Sa<sub>O2</sub>. Foster et al. (2011) found that a 72.8% reduction in PASP at rest only resulted in a trend for an improvement in Q compared to control ( $4.6 \pm 0.7$  vs.  $4.2 \pm 0.7$  L/min,  $p = 0.09$ ) and no change in Sa<sub>O2</sub>. Alternatively, IPC may not be potent enough to significantly reduce PASP that results from the combined stimuli of hypoxia and exercise. Regardless, these findings indicate that while IPC may benefit surgical outcomes through multifactorial mechanisms, IPC appears to have little effect on systemic oxygen delivery at rest or during exercise at HA.

### *Practical implications*

While this study and others like it (de Groot et al. 2010; Crisafulli et al. 2011) have found that IPC can produce small, but significant improvements in W<sub>peak</sub>, it is difficult to know

whether these changes will result in significant and meaningful improvements in endurance exercise performance. Variables such as lactate threshold, ventilatory threshold, and exercise economy have been shown to be better predictors of endurance exercise performance than  $VO_{2peak}$  or  $W_{peak}$  (Farrell et al. 1979; Ribeiro et al. 1990; Lucia et al. 2004). To date, two studies have examined the effects of IPC on exercise performance and have reported a significant 1.1% improvement in intense swim performance of highly trained swimmers (Jean-St-Michel et al. 2011), and a non-significant 2.6% improvement in time trial performance of experienced cyclists (Foster et al. 2011). The use of older and less well-trained subjects by Foster et al. (2011) may have led to greater variability in time trial performance, thus making the identification of small improvements due to IPC difficult to detect. Additionally, the cyclists studied by Foster et al. (2011) may have not derived a great benefit from IPC because it was only applied to one leg. Future studies will have to determine whether these small changes in exercise performance are likely to be meaningful in the field by taking into account the experience of the competitor, the smallest worthwhile improvement for a particular event, and also the typical error associated with the measurement of a specific exercise task (Hopkins et al. 1999).

Another aspect of the practical application of IPC to exercise is the optimal timing between IPC and the start of exercise. IPC has been found to significantly improve  $W_{peak}$  when performed as little as 5 min (de Groot et al. 2010; Crisafulli et al. 2011) to as much as 45 min from the start of exercise in the current study. The positive effects of IPC may begin to decrease with longer time intervals as it has been found to positively affect

exercise performance after 45 min (Jean-St-Michel et al. 2011), but not 90 min (Foster et al. 2011). However, large methodological differences exist between these studies and future work must systematically alter the time between IPC and the start of exercise to determine if an optimal interval exists.

### *Limitations*

This study was limited by the lack of measurements of blood flow and arteriovenous oxygen difference across the working limb as well as PASP that would have allowed us to further delineate the effects of IPC on local oxygen delivery/use and systemic factors that influence cardiovascular hemodynamics, respectively. Another limitation of the study was the inability to blind subjects to the IPC condition. Others have used low-pressure control conditions in which the blood pressure cuff is only inflated to 10 mm Hg (Jean-St-Michel et al. 2011), but we chose not to employ this technique in the current study because it is easily distinguished from IPC. Finally, while the size of the subject pool of the current study ( $n=15$ ) is similar to those used by previous IPC and exercise studies ( $n = 8$  to  $23$ ) (Groot et al. 2010; Crisafulli et al. 2011; Foster et al. 2011; Jean-St-Michel et al. 2011), it was insufficient to detect some of the small effects of IPC on  $W_{\text{peak}}$ , cardiovascular hemodynamics, and  $\text{SaO}_2$ . With our measured effect size of 0.2 and power of 0.41, we calculated that we would have required a sample size of 22 subjects to find a significant effect of IPC on  $W_{\text{peak}}$  at HA.

### *Conclusions*

The primary findings of this study were that IPC only resulted in small improvements in  $W_{\text{peak}}$  at SL that were not associated with any changes in cardiovascular hemodynamics or  $\text{SaO}_2$ . Contrary to our hypotheses, IPC had no significant effects on  $W_{\text{peak}}$ , cardiovascular hemodynamics, or  $\text{SaO}_2$  during intense exercise at HA that resulted in arterial hypoxemia. These results indicate that IPC performed 45 min prior to exercise has little effect on systemic oxygen delivery and future studies must examine its influence on local factors such as working limb blood flow, oxygen delivery, and arteriovenous oxygen difference.



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## TABLES AND FIGURES

**Table 1. Subject characteristics.**

Variable	
Age, year	29.9 ± 1.7
Height, cm	175.9 ± 1.6
Weight, kg	75.8 ± 2.5
Absolute VO <sub>2peak</sub> , L/min	4.6 ± 0.1
Relative VO <sub>2peak</sub> , ml/kg/min	61.1 ± 2.0

Values are mean ± SE; *n* = 15.

**Table 2. Cardiovascular hemodynamics, SaO<sub>2</sub>, and RPE at W<sub>peak</sub>**

Variable	SL		HA	
	Control	IPC	Control	IPC
HR <sub>peak</sub> , beats/min	176 ± 3	175 ± 2	167 ± 3‡	172 ± 3‡
SV <sub>peak</sub> , ml/beat	105 ± 5	108 ± 4	114 ± 6	108 ± 5
Q <sub>peak</sub> , L/min	17.5 ± 1.0	18.2 ± 0.8	18.0 ± 1.2	17.7 ± 1.0
SaO <sub>2</sub> at peak, %	93 ± 1	93 ± 1	73 ± 1‡	73 ± 2‡
RPE <sub>peak</sub>	18 ± 1	19 ± 1	18 ± 1	18 ± 1

Values are mean ± SE; *n* = 15.

IPC, ischemic preconditioning; SL, sea level; HA, simulated high altitude; HR<sub>peak</sub>, peak heart rate; SV<sub>peak</sub>, peak stroke volume; Q<sub>peak</sub>, peak cardiac output, SaO<sub>2</sub> at peak, arterial oxygen saturation at test termination; RPE<sub>peak</sub>, rating of perceived exertion at test termination.

‡Significantly different from corresponding SL value (*p* < 0.05).

## FIGURE LEGEND

Fig.1. Heart rate at rest and during steady state exercise. Values are means  $\pm$  SE;  $n = 15$ .  $W_{\text{peak}}$ , peak exercise capacity; SL, sea level; HA, simulated high altitude; IPC, ischemic preconditioning. \*Significantly different from rest ( $p < 0.05$ ). †Significantly different from minutes 4-6 (all conditions) ( $p < 0.05$ ).

Fig.2. Stroke volume at rest and during steady state exercise. Values are means  $\pm$  SE;  $n = 15$ .  $W_{\text{peak}}$ , peak exercise capacity; SL, sea level; HA, simulated high altitude; IPC, ischemic preconditioning. \*Significantly different from rest ( $p < 0.05$ ). †Significantly different from minutes 4-6 (SLcontrol only) ( $p < 0.05$ ).

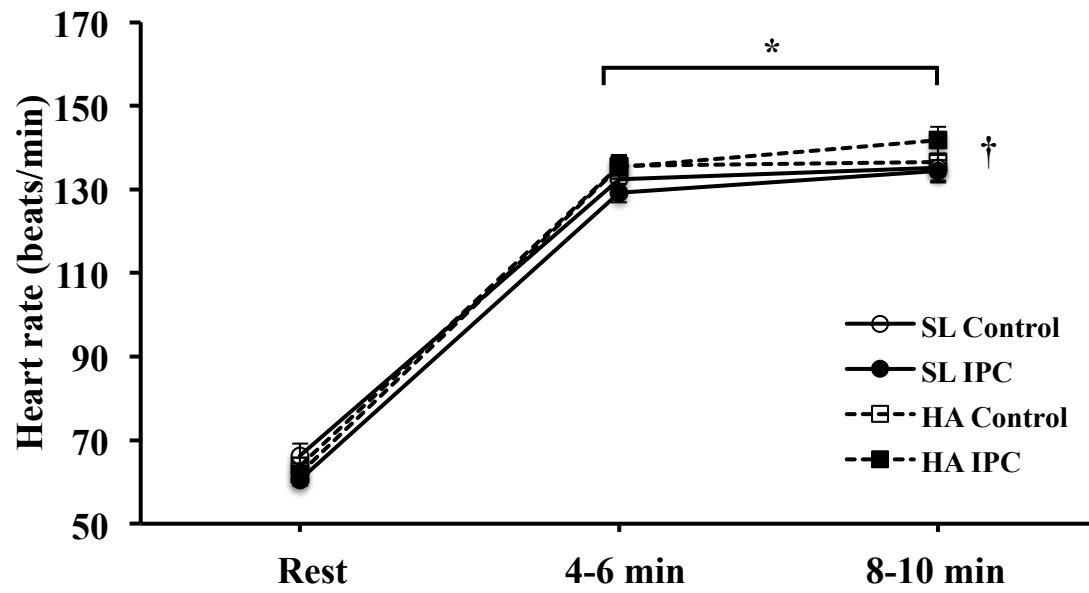
Fig.3. Cardiac output at rest and during steady state exercise. Values are means  $\pm$  SE;  $n = 15$ .  $W_{\text{peak}}$ , peak exercise capacity; SL, sea level; HA, simulated high altitude; IPC, ischemic preconditioning. \*Significantly different from rest ( $p < 0.05$ ). †Significantly different from minutes 4-6 (all conditions) ( $p < 0.05$ ). ‡Significantly different from SL ( $p < 0.05$ ).

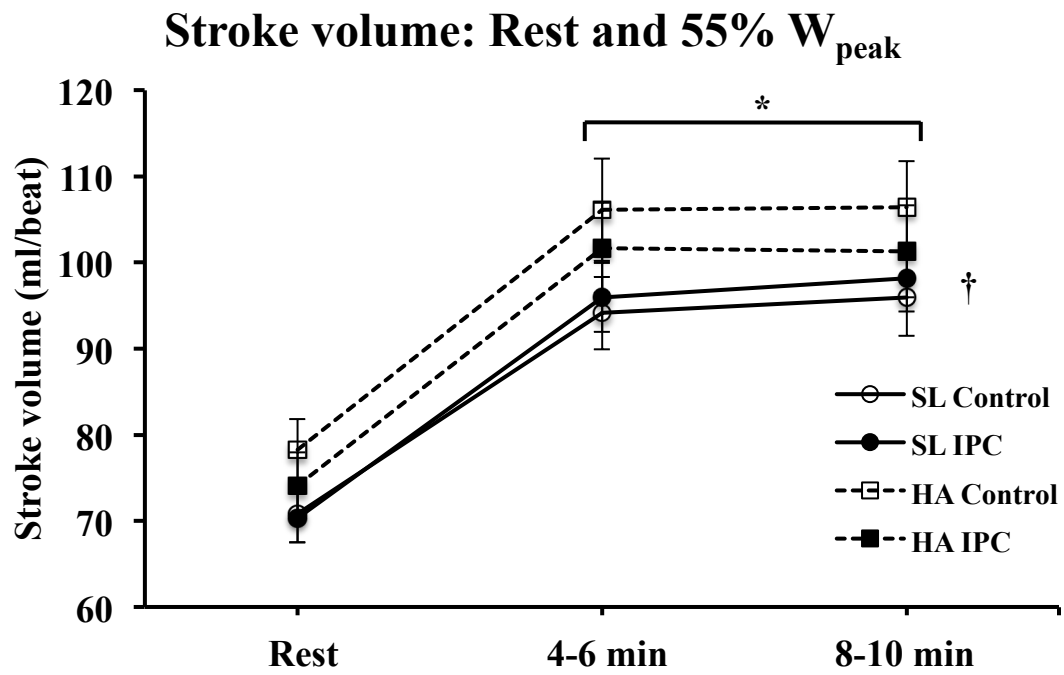
Fig.4. Arterial oxygen saturation at rest and during steady state exercise. Values are means  $\pm$  SE;  $n = 15$ .  $W_{\text{peak}}$ , peak exercise capacity; SL, sea level; HA, simulated high altitude; IPC, ischemic preconditioning. \*Significantly different from rest. ‡Significantly different from SL ( $p < 0.05$ ). +Significantly different from control ( $p < 0.05$ ).

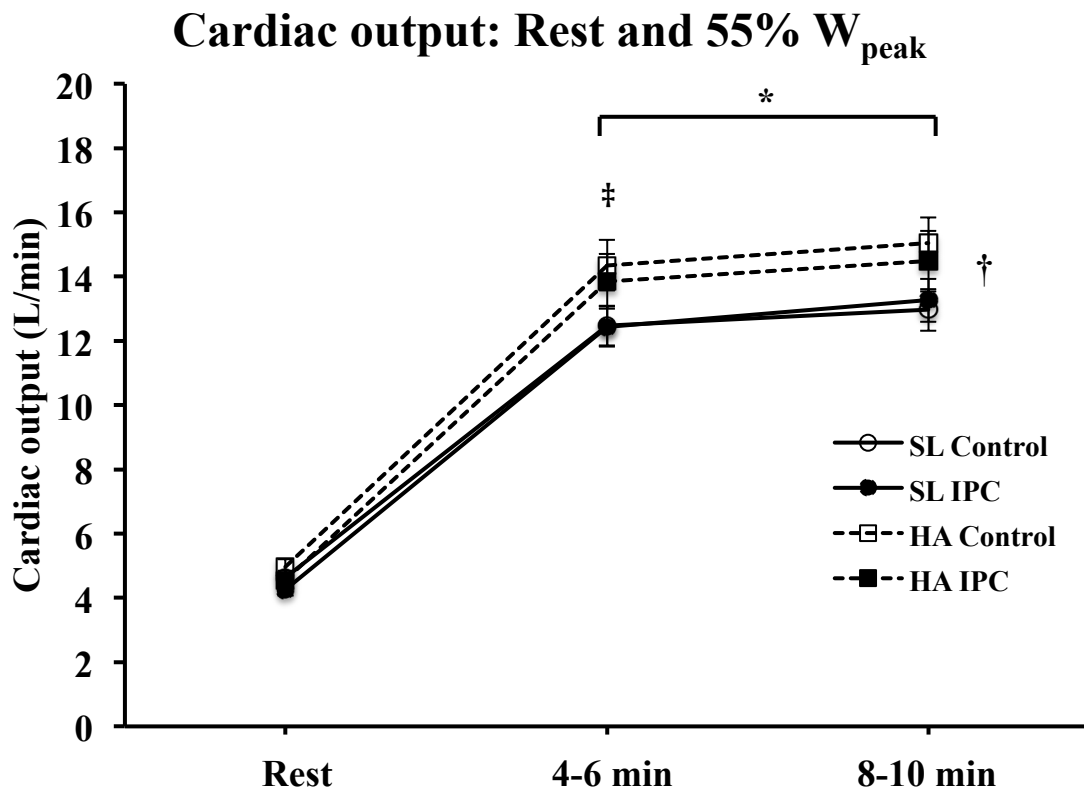
Fig.5. The effect of IPC on  $W_{\text{peak}}$ . Values are means  $\pm$  SE;  $n = 15$ .  $W_{\text{peak}}$ , peak exercise capacity; W, watts; SL, sea level; HA, simulated high altitude; IPC, ischemic preconditioning. ‡Significantly different from SL ( $p < 0.05$ ). +Significantly different from control ( $p < 0.05$ ).

Fig.6. Individual  $W_{\text{peak}}$  at SL (A) and HA (B).  $W_{\text{peak}}$ , peak exercise capacity; W, watts; SL, sea level; HA simulated high altitude; IPC, ischemic preconditioning. Each line represents a different subject.

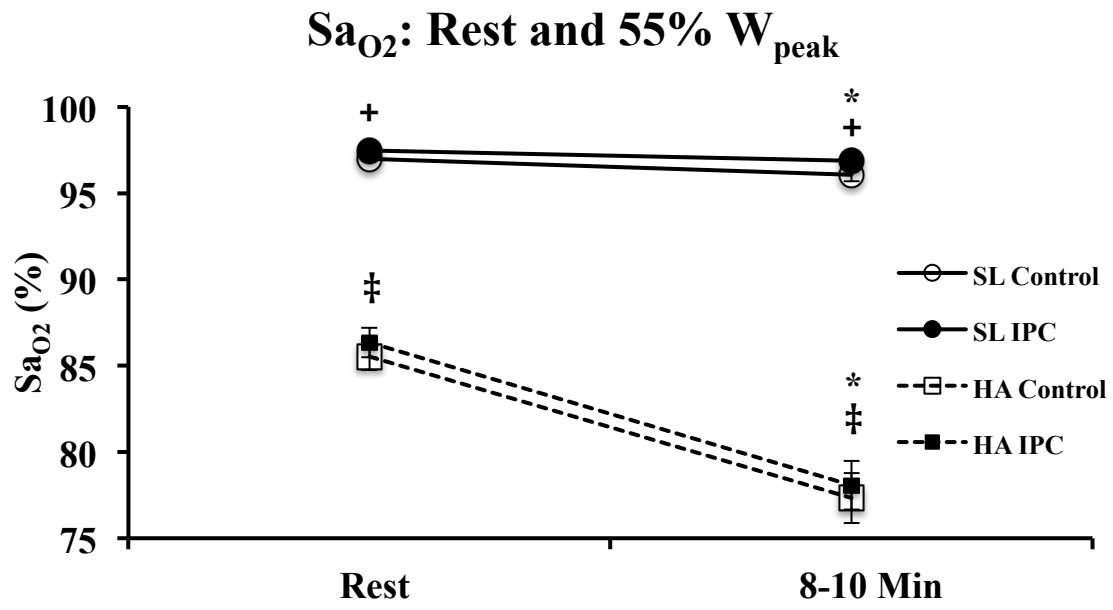
### Heart rate: Rest and 55% $W_{peak}$

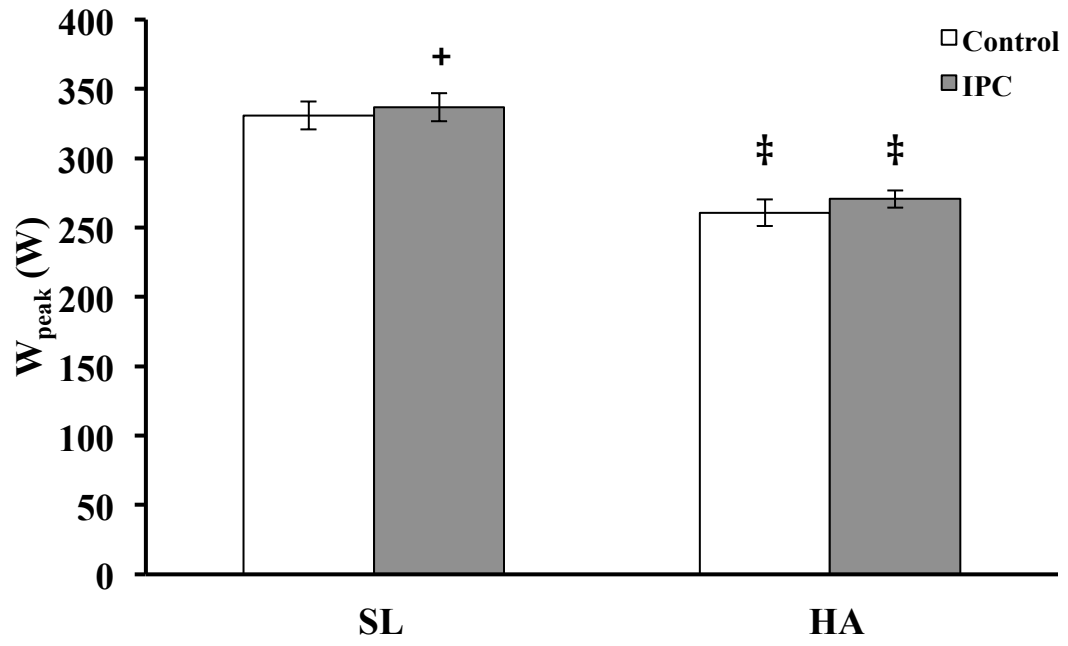




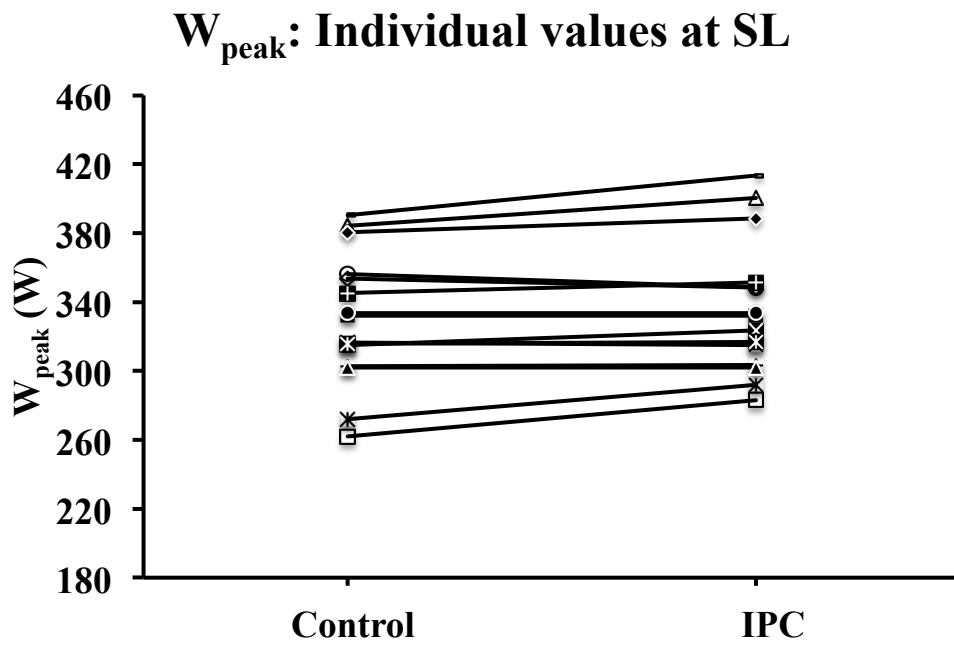








A.



B.

