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Original Research

Ischemic Preconditioning Does Not Improve Time Trial Performance in Recreational Runners

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ABSTRACT

International Journal of Exercise Science 13(6): 1402-1417, 2020. Some evidence indicates that ischemic preconditioning (IPC) may positively affect endurance exercise performance, but IPC's effect on running performance is unclear. This study's purpose was to examine the effect of IPC on running performance in recreational runners. Participants (n=12) completed IPC, a sham (SH) condition, and a leg elevation without blood restriction (LE) control condition on separate days (order randomized). For IPC, blood was restricted using blood pressure cuffs inflated to 220 mmHg at the thigh. For SH, the cuffs were inflated to only 20 mmHg. For LE, participants positioned their legs at 90 degrees against a wall while laying supine. The duration of each protocol was 30 minutes (three 5-minute bouts with 5-minute breaks). Following each protocol, participants ran 2.4 kilometers as fast as possible on a motorized treadmill. Run time, heart rate, and perceived exertion were measured and statistically compared, using repeated-measures ANOVA, each 0.8 kilometers. There were no differences in heart rate or time trial performance across protocols ($p>0.05$; IPC, 612.5±61.2 sec; SH, 608.1±57.9 sec; LE, 612.7±59.1 sec). Rating of perceived exertion at 0.8 kilometers was significantly lower for the IPC protocol than SH in females only (~5.7%, or ~0.8 points on a 6-20 scale; $p<0.05$). Our IPC protocol did not improve running performance or physiological parameters during a time trial run in recreational runners. The performance benefit seen in this study's most fit individuals suggests that fitness level may influence IPC's efficacy for improving endurance running performance.

KEY WORDS: Running, amateur athletes, ergogenic aid, IPC

INTRODUCTION

Ischemic preconditioning (IPC) is the occlusion of blood flow to the limbs followed by reperfusion, and in recent years researchers have tested this technique prior to exercise as a potential ergogenic aid (39). Early evidence of physiologic benefits of IPC was found by Murry et al. (43), who identified the protective effect of 5-minute ischemic bouts, followed by reperfusion, on canine cardiac tissue. In essence, an "acute training effect" occurs, temporarily increasing the cardiac tissue's ability to handle the stress of surgery and ischemic periods. Such ischemic periods also occur in skeletal muscle during high-intensity exercise, providing a

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theoretical explanation for how IPC may improve endurance exercise performance. However, currently the specific physiological mechanisms behind IPC's ergogenic benefits remain only partly understood, rendering it unclear when (e.g., for what type of exercise, what populations) IPC may serve as an effective ergogenic aid.

Repeated bouts of IPC induce a localized reactive hyperemia. The ensuing vasodilation results in an increased delivery of oxygen to and shuttling of metabolites away from the previously occluded skeletal muscle tissue (38). Kido et al. (33) found that IPC significantly affected muscle oxygenation kinetics during moderate-intensity exercise, suggesting that the increased blood supply to the working muscle as a result of IPC may improve exercise performance, especially if exercise limitations were due to lack of blood to the working muscle (e.g., low oxygen availability or excess lactate production). Others have suggested that IPC affects the metabolic substrate pathways, specifically creatine phosphate production and anaerobic glycolysis, improving the energy yielding capacity of the tissue (41). Several studies have also shown a benefit of remote IPC, the occlusion of blood to a tissue other than the target tissue, on cardioprotection and exercise performance (29,36); these findings suggests that IPC releases humoral factors into the blood, thereby triggering a systemic response and increasing tissues' resistance to ischemia (2,54). Alternately, it is possible that the impact of IPC on athletic performance is psychological rather than physiological.

IPC is appealing as a potential ergogenic aid for exercise performance due to the inexpensive, non-invasive nature of the protocol coupled with promising results in early studies investigating its efficacy. A 2019 review (39) identified 45 studies that examined the effect of IPC on exercise performance. The majority (n=32) were published since 2015 with many focusing on IPC's effect on cycling performance. Cycling is heavily dependent on lower-body, quadriceps muscles' fitness and ability to utilize oxygen. IPC, which has been shown to acutely improve vascular function (1) and increase blood flow and muscle oxygenation in the previously occluded region (13), has the potential to increase oxygen availability in the legs and thereby enhance high-intensity cycling performance. For example, De Groot et al. (20) found that 3x5 minute bouts of IPC prior to a cycling test increased the maximal exercise performance among a group of cyclists along with oxygen consumption ($\dot{V}O_2$) peak (56.8 to 58.4 ml/kg/min). Additional studies have observed increases in maximal aerobic power (11) and exercise capacity (24), whereas others have found no difference between IPC and a placebo protocol and some even observing an ergolytic effect on peak power (18,19,46). Despite the mixed findings, IPC does appear to have a positive impact on cycling performance. Studies of IPC at altitude, where oxygen availability is also limited, predominantly show increased oxygen saturation and improved exercise performance with IPC (17,47), suggesting that improved $\dot{V}O_2$ kinetics by the working muscle may partly explain the improvement in cycling performance with IPC.

Fewer studies have examined the impact of IPC on running performance, and results are mixed and inconclusive. Bailey et al. (3) utilized 4x5 minute IPC bouts prior to a graded maximal treadmill running test and subsequent 5 kilometer time trial. Participants' average time trial completion was 34 seconds faster following IPC compared to a control protocol. The authors also observed an attenuated blood lactate response during the graded exercise test and posited

this reduced rate of lactate accumulation could be responsible for the improved time trial performance. If IPC increases blood flow to the musculature during exercise (as previously indicated) (61), it stands to reason it could aid in lactate removal/buffering. Tocco et al. (58) performed a similar study, where participants underwent a 3x5 minute IPC protocol and then performed a 5 kilometer time trial on an outdoor track. However, the authors observed no differences in blood lactate nor run performance compared to a control condition. Additional studies also failed to find significant improvements in running economy, blood lactate, $\dot{V}O_2$, and perceived exertion compared to a placebo protocol (27, 32, 49). Running utilizes more muscles of the lower body than cycling (42) which poses less oxygen demand on any one muscle tissue or group. It may be that IPC provides less benefit in running activities than in cycling, especially if a main ergogenic mechanism is improved oxygen delivery to the previously occluded tissue. However, there are considerable differences across study methodologies and populations, which makes the evidence on IPC's effective more difficult to interpret. Thus, more research is needed as to the effect of IPC on endurance running performance.

Additionally, studies have used mostly or exclusively males as research participants (6). More research is needed to better understand the effect of IPC in females, ideally in a mixed sample of males and females so that results can be directly compared between sexes. Finally, it is unclear if IPC's effectiveness is influenced by training status. A review by Salvador et al. (51) recently suggested that the effectiveness of IPC may be higher in highly-trained individuals compared to those with lower fitness. Conversely, the ability to make improvements with intervention is often thought to be inversely related to initial training status (25), making it unclear if and how training status may affect IPC's effectiveness. Given the ease of administering the IPC protocol and the low cost of occlusion cuffs, such a technique is accessible to individuals of all skill levels and not restricted solely to highly trained athletes. However, more research is need to understand efficacy of IPC in recreationally active populations. Accordingly, the purpose of the study was to examine the effect of IPC on running performance among a group of recreational male and female runners completing a 2.4 kilometer time trial run.

METHODS

Participants

Twelve apparently healthy individuals (7 female, 5 male) were recruited through word of mouth. Inclusion criteria included requiring that participants were between the ages of 18-40 years, self-identified as runners, and were currently running at least 3 days per week. Participants were required to complete the Physical Activity Readiness Questionnaire (PAR-Q) Plus (60) and a university-developed health screening questionnaire. A "yes" to any question on the PAR-Q Plus or a listed health condition on the questionnaire resulted in exclusion from the study. Additional questions specific to risks of deep vein thrombosis (DVT) were added to the questionnaire. Participants were excluded if they had a history of DVT, were currently taking hormonal birth control, had undergone extensive travel (car or plane) in the past 2 weeks, or had a history of pulmonary embolism, stroke, myocardial ischemia/infarction, and/or any blood-related disorders.

Demographics data for the sample are shown in Table 1. All but one participant had a body mass index in the normal weight range (18.6-24.9 kg/m^2). Additionally, all but one participant was a full-time college student aged 18-20 years. Participants ran 3-5 days each week. Based on the results of the 2.4 km time trial, females had higher relative fitness than males despite a lower weekly training volume; both groups were well above average for $\dot{V}O_2$max (31).

Table 1. Participant demographic information.

	All (N=12)	Female (n=7)	Male (n=5)
Age (years)	20.4 (3.7)	19.3 (0.8)	22.0 (5.6)
Height (cm)	171.3 (10.7)	163.2 (3.5)	182.5 (5.0)
Weight (kg)	68.1 (14.9)	58.8 (6.6)	81.2 (13.2)
Body mass index (kg/m^2)	23.0 (2.8)	22.1 (2.3)	24.3 (3.2)
Predicted $\dot{V}O_2$max (ml/kg/min)	51.6 (4.7)	48.8 (2.8)	55.4 (4.2)
Predicted $\dot{V}O_2$max percentile	79.6 (11.2)	83.6 (6.9)	74.0 (14.3)
Training volume (running km/week)	26.5 (22.7)	17.0 (5.3)	39.8 (31.6)

Data presented as mean (standard deviation).

A necessary sample size of n=11 was determined using a power analysis (G*Power version 3.0.10,) (15) with an alpha of 0.05, a desired power of 0.8, and an expected effect size of 0.9 (based on the work of Bailey et al. (3), who found an effect size of 0.95 for change in running time with IPC), and we oversampled by one due to the possibility of drop-out associated with multiple testing days. The study protocol was approved by the college's institutional review board (reference number: 5e28afdb72f8f) and adhered to the ethical standards of the Helsinki Declaration. This research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (44).

Protocol

Participants reported for three testing sessions, spaced at least 48 hours apart and at similar times of day to avoid successive fatigue, second-wave preconditioning effects (45), or variations in circadian rhythms (48) from influencing results. Participants were instructed to report to the laboratory wearing their typical running attire. They were also instructed to maintain a similar regimen prior to each testing day (e.g., diet, sleep) and to refrain from caffeine 12 hours prior to testing and strenuous exercise 24 hours prior to testing. Height and body mass were measured using a standard scale and stadiometer (Detecto, Webb City, MO, USA). Body mass was measured to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm. Participants were then outfitted with a Polar A360 wrist-worn heart rate (HR) monitor (Polar Electro Oy, Kempele, Finland). This device has been validated previously for HR assessment during treadmill exercise (49). The Polar A360 was fitted to the participant's non-dominant wrist, above the styloid process of the ulna and fastened tightly so as to eliminate any movement during exercise (in accordance with manufacturer specifications).

This study was a randomized control trial with three pre-exercise protocols, which are described below. The order of pre-exercise protocols was randomized and counterbalanced using a balanced Latin square design with each participant serving as his/her own control.

For the IPC protocol, participants lay supine on a padded, athletic training table for 30 minutes with legs fully extended. Blood pressure cuffs (Elite Medical Instruments, Orange County, CA) were secured on the most proximal portion of the thigh and inflated to 220 mmHg for 5 minutes and then deflated for 5 minutes to allow for reperfusion. Only one cuff was inflated at a time. This procedure was repeated for a total of three, 5-minute bouts of IPC on each leg. Cuffs were specifically designed for the thigh and measured between 40.6-66.0 cm length and 20.3 cm width. The cuff pressure of 220 mmHg was chosen in accordance with the majority of past research examining IPC protocols (39) and evidence suggesting it is well above the threshold for occlusion of blood to the lower leg (53).

Participants underwent a sham (semi-occlusion) protocol (SH). It was identical to the IPC protocol; however, the cuffs were inflated to only 20 mmHg, allowing for full perfusion of the lower limb even during cuff inflation. A similar sham protocol has been used in past work to account for a possible placebo effect (22,30).

Finally, participants underwent a legs elevated control protocol (LE). For the LE control, participants lay supine for 30 minutes; in 5-minute increments, both legs were elevated parallel against a wall. After 5 minutes, the participant's legs returned to the resting supine position. Participants underwent three, 5-minute bouts of leg elevation. The LE protocol was included as a control protocol as this technique can be used for exercise recovery (7).

Following each pre-exercise protocol, participants had 5 minutes of self-directed warm-up, which could include stretching, walking, or light jogging. Participants were instructed to keep their warm-up consistent across all trials. Following warm-up, they completed a 2.4 kilometer time trial run at 0% grade on a motorized treadmill (Life Fitness, Rosemont, IL) with the stated objective to complete the time trial as quickly as possible. The 2.4 kilometer distance was chosen as it is of sufficient duration to rely heavily on oxidative metabolic energy pathways and because $\dot{V}O_2$max can be estimated using 2.4 kilometer times (9). Participants were allowed to adjust speed as often as necessary during the time trial but were instructed not to hold the handrails at any time. Run time and rating of perceived exertion (RPE; Borg 6-20 scale) (4) were recorded at 0.8, 1.6, and 2.4 kilometers, and heart rate was collected every 0.16 kilometers. The laboratory where all testing took place was kept in a thermoneutral range of 19.4±0.4° C and 19.7± 8.5% humidity.

Statistical Analysis

The dependent variables of interest were run time, HR, and RPE at 0.8, 1.6, and 2.4 kilometers into the time trial. These variables were each compared across the three groups (IPC, SH, LE) using repeated-measures analysis of variance (RMANOVA), with $p \leq 0.05$ used to denote statistical significance and a least significant difference correction used for post hoc, pairwise comparisons. Heart rate was also compared across groups each 0.16 kilometers using RMANOVA. Effect sizes were calculated to determine the magnitude of potential differences across conditions, and values of <0.20, 0.20-0.49, 0.50-0.79, 0.80-1.29, and ≥1.30 were used to denote trivial, small, medium, large, and very large effect sizes, respectively (8). Additionally, the smallest worthwhile change was calculated for each variable as 0.2*standard deviation and

0.6*standard deviation to determine if the magnitude of difference between IPC and the two comparison conditions (SH and LE) was physiologically meaningful for high-fitness and low-fitness athletes, respectively, as suggested by previous research (5,39).

Sub-analyses were performed by converting HR to percentage of age-predicted maximum (using HR=208-(0.7*age) (57) for determining maximum HR), stratifying the dataset by sex, and performing a median split the dataset based on age- and sex-specific fitness level (using 2.4 kilometer run time to predict $V\dot{O}_2max$) (9). All analyses were conducted in SPSS version 24.0 (IBM Corp., Armonk, NY).

RESULTS

Data for run times, HR, and RPE during the 2.4 kilometer time trial are shown in Table 2. There were no differences among protocols at any interval (0.8, 1.6, and 2.4 kilometers) for run time or for HR. RPE was significantly lower (~5.5%, or ~0.7 points on the 6-20 scale) for the IPC protocol than the SH and LE protocols at 0.8 kilometers, but there were no significant differences among protocols at 1.6 or 2.4 kilometers.

Subanalyses using percentage of age-predicted maximal HR (rather than raw HR values) as well as stratifying analyses by median split based on age- and sex-specific fitness level revealed no differences among groups. However, stratifying by sex revealed that in females only, RPE was significantly lower (~5.7%, or ~0.8 points) for the IPC protocol than the SH and LE protocols at 0.8 kilometers only (Table 2).

Effect sizes for differences across the protocols are shown in Table 3. All effect sizes were trivial except for the effect sizes between IPC and the other two protocols for HR and RPE at 0.8 km, which were small in magnitude. Additionally, effect sizes for all variables were trivial when comparing SH and LE protocols. Using the smallest worthwhile change analysis for assessing the potential effects of IPC (Table 4), none of the differences among protocols were of a physiologically relevant magnitude if the sample were deemed of low fitness. Conversely, if the sample were deemed to be of high fitness, then both HR and RPE were meaningfully lower for IPC than the other two conditions at 0.8 kilometers and meaningfully lower than the LE condition at 1.6 kilometers.

Table 2. Run times, heart rate, and rating of perceived exertion for the full sample and split by sex at 0.8, 1.6, and 2.4 kilometers during time trials across each protocol.

	Ischemic preconditioning	Sham	Legs elevated
Total sample (N=12)			
Run time (seconds)			
0.8 km	217.2 (23.7)	214.8 (20.0)	215.4 (21.0)
1.6 km	421.5 (43.2)	417.3 (38.1)	419.9 (40.3)
2.4 km	612.5 (61.2)	608.1 (57.9)	612.7 (59.1)
Heart rate (beats/minute)			
0.8 km	165.3 (12.5)	167.8 (11.7)	169.6 (9.7)
1.6 km	172.8 (14.4)	173.6 (12.5)	175.8 (13.7)
2.4 km	176.6 (14.7)	178.3 (14.2)	177.6 (15.3)
Rating of perceived exertion			
0.8 km	12.6 (1.7)*	13.3 (1.6)	13.3 (1.6)
1.6 km	15.3 (1.4)	15.5 (1.2)	15.6 (1.6)
2.4 km	17.4 (1.8)	17.4 (1.2)	17.3 (1.6)
Females (n=7)			
Run time (seconds)			
0.8 km	224.3 (18.4)	224.4 (13.5)	219.4 (13.7)
1.6 km	438.7 (34.2)	438.3 (27.2)	430.1 (28.0)
2.4 km	641.7 (43.7)	641.4 (39.8)	630.4 (42.3)
Heart rate (beats/minute)			
0.8 km	164.9 (10.4)	168.3 (8.1)	171.1 (6.5)
1.6 km	175.7 (12.3)	178.3 (7.8)	182.7 (7.8)
2.4 km	179.9 (12.3)	183.0 (11.3)	184.3 (11.5)
Rating of perceived exertion			
0.8 km	12.2 (1.1)*	13.0 (1.0)	13.0 (0.8)
1.6 km	15.0 (1.3)	14.9 (0.9)	15.3 (1.5)
2.4 km	17.0 (1.6)	16.9 (1.1)	17.3 (1.7)
Males (n=5)			
Run time (seconds)			
0.8 km	207.2 (28.6)	201.2 (20.9)	209.8 (29.4)
1.6 km	397.4 (46.3)	388.0 (32.2)	405.6 (53.4)
2.4 km	571.6 (62.0)	561.4 (46.7)	587.8 (74.9)
Heart rate (beats/minute)			
0.8 km	166.0 (16.3)	167.2 (16.6)	167.4 (13.6)
1.6 km	168.8 (17.5)	167.0 (15.6)	166.2 (15.0)
2.4 km	172.0 (18.0)	171.8 (16.3)	168.2 (15.9)
Rating of perceived exertion			
0.8 km	13.1 (2.3)	13.8 (2.3)	13.8 (2.8)
1.6 km	15.8 (1.6)	16.4 (1.1)	16.0 (1.9)
2.4 km	18.0 (2.0)	18.2 (1.1)	17.4 (1.7)

*Indicates significant difference from all other protocols.

Table 3. Effect sizes across protocols for run time, heart rate, and rating of perceived exertion.

	IPC – Sham	IPC – Legs elevated	Sham – Legs elevated
Run time (seconds)			
0.8 km	0.11	0.08	0.03
1.6 km	0.10	0.04	0.07
2.4 km	0.08	0.00	0.08
Heart rate (beats/minute)			
0.8 km	0.21	0.38	0.17
1.6 km	0.06	0.22	0.17
2.4 km	0.12	0.07	0.05
Rating of perceived exertion			
0.8 km	0.45	0.43	0.00
1.6 km	0.13	0.17	0.06
2.4 km	0.00	0.05	0.06

IPC: ischemic preconditioning protocol.

Table 4. Smallest worthwhile change for physiological significance for run time, heart rate, and rating of perceived exertion.

	SWC low-fit (SD*0.6)	SWC high-fit (SD*0.2)	Mean difference IPC – Sham	Mean difference IPC – Legs elevated
Run time (seconds)				
0.8 km	14.2	4.7	2.4	1.8
1.6 km	25.9	8.6	4.2	1.6
2.4 km	36.7	12.2	4.4	-0.2
Heart rate (beats/min)				
0.8 km	7.5	2.5	-2.5*	-4.3*
1.6 km	8.6	2.9	-0.8	-3.0*
2.4 km	8.8	2.9	-1.8	-1.0
Rating of perceived exertion				
0.8 km	1.0	0.3	-0.8*	-0.8*
1.6 km	0.9	0.3	-0.2	-0.3*
2.4 km	1.1	0.4	-0.0	0.1

*Indicates that difference from IPC protocol met smallest worthwhile change threshold for high-fitness individuals.
SWC: smallest worthwhile change.
SD: standard deviation.
Low-fit: the smallest worthwhile change in a sample deemed to have low fitness.
High-fit: the smallest worthwhile change in a sample deemed to have high fitness.
IPC: ischemic preconditioning protocol.

Finally, heart rate kinetics are shown in Figure 1. While heart rate was not significant across protocols at any distance, the point estimates are lower for IPC than the other two protocols at virtually every distance measured.

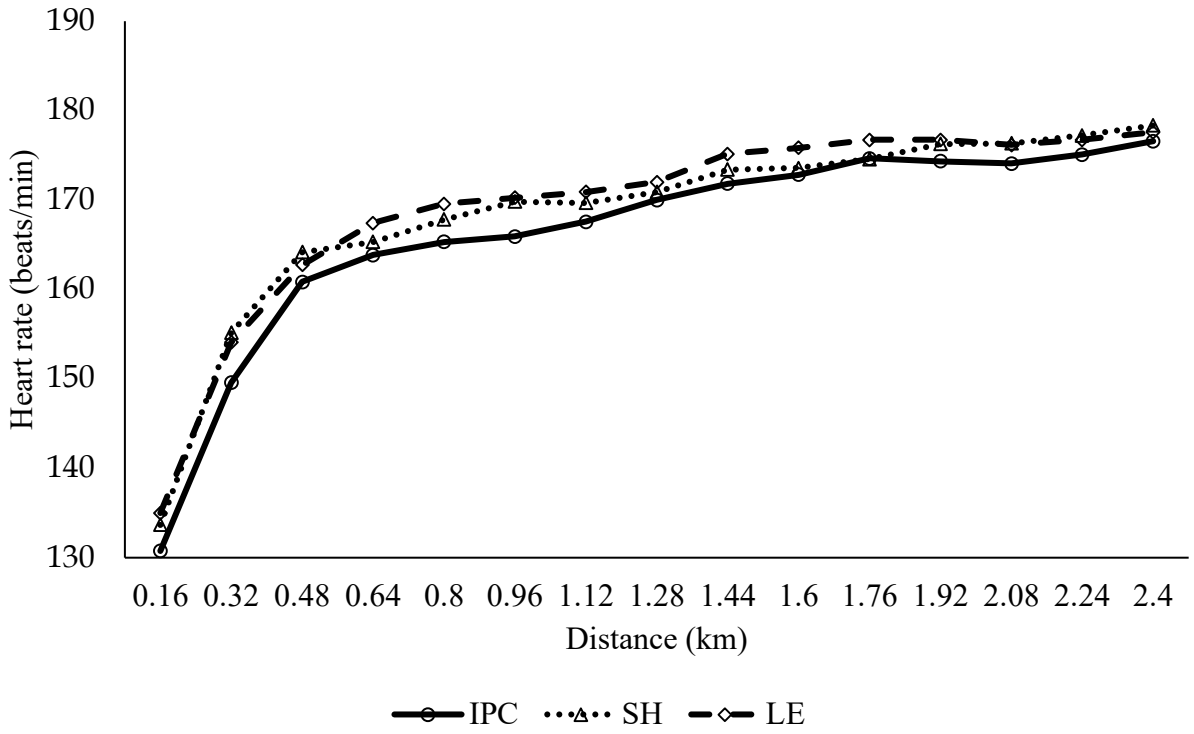

Figure 1. Heart rates at each 0.16 kilometer distance for ischemic preconditioning, sham, and legs elevated protocols.
IPC: ischemic preconditioning protocol.
SH: sham protocol.
LE: legs elevated protocol.

DISCUSSION

This study's purpose was to assess the effect of IPC on time trial performance in recreationally-trained, male and female runners. Our findings revealed no difference in time trial times or HR across protocols, and RPE was lower following IPC compared to the SH and LE protocols for females at 0.8 kilometers into the 2.4 kilometer time trial. Effect sizes were trivial or small, but the smallest worthwhile change data do indicate some meaningful changes in the early and middle time trial stages for HR and RPE if the high-fitness thresholds are applied.

In contrast to cycling, which has relatively consistent evidence supporting the use of IPC for endurance performance evidence for running is mixed. Several studies have shown improved 5 kilometer time trial performance following IPC (3,52). Conversely, other studies in endurance running showed no improvement in time trial performance, exercise economy, or $\dot{V}O_2$max with IPC (27,32,58). Our study adds support to the evidence showing minimal effect of IPC during a self-paced time trial run.

While our study cannot elucidate the physiological mechanisms behind why running may be minimally affected by IPC, the seemingly greater IPC effect for cycling than running may be informative. One major difference between running and cycling is that cycling is largely

dependent on the quadriceps musculature, whereas running utilizes more musculature in the legs as well as greater arm and core musculature (42). While remote IPC has demonstrated systemic effects which can make tissue more resistant to a hypoxic stimulus (14), the localized effects of IPC (e.g., tissue hyperemia, redistribution of blood to previously occluded area, greater oxygen use by previously occluded tissue) may play a significant role in exercise performance, partly explaining the differences in IPC efficacy by sport. There is mixed evidence as to if remote IPC improves sport performance (29,37), possibly dependent on if the sport outcome is primarily aerobic or anaerobic in nature. Further work evaluating IPC vs. remote IPC in different types and intensities of exercise may help shed light into systemic vs. localized effects of IPC.

Some past research has indicated the potential that there are responders and non-responders to IPC (34,55), which is common with other types of exercise interventions and ergogenic aids (21). More work is needed to understand characteristics of responders to IPC in order to tailor IPC protocols to those most likely to benefit. It also may be that training status of the study participants played a role in our findings. Most current evidence suggests that highly trained athletes may benefit more from IPC than less active individuals due to differences in mechanisms of fatigue between these groups and higher resistance to ischemia of trained individuals (29,40). Our sample was heterogeneous in fitness, but most participants anecdotally classified themselves as recreational rather than competitive runners. Results of the time trial confirm the fitness level of our participants; our sample's overall age- and sex-specific fitness level was above average but non-elite (range 60-90th percentile). Interestingly, the three individuals with the highest age- and sex-specific percentiles for $\dot{V}O_2$max (all 90th percentile) in our sample all had their fastest 2.4 kilometer run times using the IPC protocol, with an average benefit of 19.3 (3.5%) and 26.3 (4.6%) seconds compared to the SH and LE protocols, respectively. While insufficiently powered to make firm conclusions, our study findings lend limited support that runners with higher fitness may be more apt to see positive effects of IPC on time trial performance.

The only difference across protocols which reached statistical significance in our study was a lower RPE during at 0.8 kilometers with the IPC protocol. Additionally, the SWC analysis revealed a physiologically meaningful improvement in RPE at 0.8 and 1.6 kilometers. This finding indicates a potential psychological benefit of IPC, even though it did not persist through the entire time trial. This finding is supported by the work of de Oliveria Cruz et al. (12), who found that RPE rose more slowly during an incremental cycling test following IPC compared to a control protocol (4x5 minutes of 20 mmHg pressure) similar to our SH condition. This finding is encouraging given that the perception of an exercise being slightly less strenuous might lower the barrier to exercise training and/or encourage completion of high-intensity exercise.

Another important element of our study is that the majority of participants were female. A 2019 review by Caru et al. (6) found that female participants represented only 16.4% of participants in IPC intervention studies. Early studies used primarily male participants, possibly due to a perceived increased risk of blood clotting in females with the occlusion protocol, especially if females were on hormonal contraceptives (10,28,56). However, studies have not reported adverse events related to blood clot formation (12), and literature from blood flow restriction

(23) and flow-mediated dilation (59) fields further supports the safety of using short-duration occlusion protocols in healthy females. While our study was underpowered to make definitive conclusions, IPC was similarly non-effective in males and females for improving time trial performance. However, the lower RPE following IPC in the initial portion of the time trial in our study was driven by the differences seen in only the female participants. Past research suggests that males and females may perceive pain differently during exercise (35), and further research should be conducted to elucidate if sex-specific differences exist in changes in RPE with IPC and how such differences might affect exercise performance following IPC.

In studies evaluating potential ergogenic aids, possible influences of the placebo or nocebo effects need to be taken into consideration (26) as they often affect exercise performance. A recent review by Salvador et al. (51) acknowledged the inability to have a true control group in IPC research due to the inability to blind participants to the IPC protocol (i.e., participants can easily tell when cuffs have 220 mmHg of pressure vs. 0-20 mmHg), rendering the placebo and nocebo effects as important consideration for IPC research. Our findings revealed found no detrimental effect of IPC on performance, which supports the past work showing a lack of nocebo effect of IPC (16). Secondly, a unique aspect of our study was the use of SH and LE protocols for comparison to IPC. Our participants were not told about any potential value or effects of the three protocols on exercise performance, minimizing the potential for placebo or nocebo effects. Additionally, beliefs about the potential value of the SH and LE protocols are unlikely to be the same, so if a placebo or nocebo effect were present, it could have presented in differences in performance between the SH and LE groups or between one of these protocols with IPC. Our study results showed no statistically significant differences and trivial effect sizes between SH and LE protocols, and the comparisons of these two protocols with the IPC protocol revealed virtually identical results (e.g., both were either statistically significant or not for the same variables at the same distances). These findings, coupled with little physiological reasoning why the SH or LE protocols would meaningfully change exercise performance, should give researchers a measure of confidence that the SH protocol can be used as an effective placebo group in IPC research.

Our study had several notable strengths. First, a sample which was majority female is a study strength due to the aforementioned underrepresentation of females in past research in this area. Additionally, the time trial protocol took place indoors and in temperature- and humidity-controlled settings, eliminating the potential influence of environmental factors. Similarly, participants performed all three time trials at similar times of day, eliminating potential differences in circadian rhythms. Finally, the inclusion of two comparison groups (SH and LE) along with blinding of the study purpose to participants limited potential placebo or nocebo effects of the IPC treatment.

Our study also had several limitations which must be acknowledged. We had originally planned to give participants the option to use a treadmill or indoor track for completing the running protocol and so did not build laboratory-based, physiologic data collection such as oxygen consumption, lactate, or muscle oxygenation into our study procedures. Thus, our study cannot shed light into possible mechanisms for the lack of improvement in time trial performance with

IPC. Additionally, our sample, while of similar size to many past IPC trials, did not allow for robust subanalyses by sex or training status. Given the range of fitness levels of the sample, it is also possible that there may have been a learning effect of the repeated time trial runs. While counterbalancing the study removed potential ordering effects, a learning effect may have increased variability in the data and made it harder to detect statistically significant differences across protocols. Future studies should include a familiarization session to minimize potential learning effects. Finally, we necessarily had to constrain our IPC protocol for the current study, but there are many other factors that should be tested in future work. For example, there is evidence that the time duration between completion of IPC and the start of the exercise bout may influence the effectiveness of IPC (39). Also, the number of IPC bouts, and the potential that IPC performed over several consecutive days and/or weeks may augment its effects are intriguing but need further study.

In conclusion, our study found no benefit of IPC on 2.4 kilometer time trial running performance compared with SH or LE protocols. Perception of effort was slightly lower at the beginning of the time trial following the IPC protocol compared to the SH protocol, and further work should explore potential psychological effects of IPC and if these may affect running performance.

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