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Research article

Effect of Ischemic Preconditioning on Endurance Running Performance in the Heat

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Abstract
Ischemic preconditioning (IPC) is a strategy that may enhances endurance performance in thermoneutral environments. Exercising in the heat increases thermoregulatory and cardiovascular strain, decreasing endurance performance. The current study aimed to determine whether IPC administration improves endurance performance in the heat. In a randomized crossover design, 12 healthy subjects ($\dot{V}O_{2max}$: 54.4 ± 8.1 mL·kg^{-1}·min^{-1}) underwent either IPC administration (220 mmHg) or a sham treatment (20 mmHg), then completed a moderate-intensity 6-min running (EX1) and a high-intensity time-to-exhaustion running test (EX2) in a hot environment (35 °C, 50 % RH). Cardiac function, oxygen consumption ($\dot{V}O_2$), and core body temperature (T_{CORE}) were measured. During EX2, IPC administration increased the total running time in the heat compared to the sham treatment (IPC: 416.4 ± 61.9 vs. sham 389.3 ± 40.7 s, P = 0.027). IPC administration also increased stroke volume (IPC: 150.4 ± 17.5 vs. sham: 128.2 ± 11.6 ml, P = 0.008) and cardiac output (IPC: 27.4 ± 1.7 vs. sham: 25.1 ± 2.2 ml·min^{-1}, P = 0.007) during 100% isotime of EX2. End-exercise $\dot{V}O_2$ (IPC: 3.72 ± 0.85 vs. sham: 3.54 ± 0.87 L·min^{-1}, P = 0.017) and slow phase amplitude (IPC: 0.57 ± 0.17 vs. sham: 0.72 ± 0.22 L·min^{-1}, P = 0.016) were improved. When compared with the baseline period, an increase in T_{CORE} was less in the IPC condition during EX1 (IPC: 0.18 ± 0.06 vs. sham: 0.22 ± 0.08 °C, P = 0.005) and EX2 (IPC: 0.87 ± 0.10 vs. sham: 1.03 ± 0.10 °C, P < 0.001). IPC improves high-intensity endurance performance in the heat by 6.9 %. This performance benefit could be associated with improved cardiac and thermoregulatory function engendered by IPC administration.

Key words: IPC, heat stress, aerobic performance, cardiac function, thermoregulation.

Introduction

Ischemic preconditioning (IPC) consists of brief periods of ischemia followed by reperfusion and is well-known to promote cardiac and vascular protection against future ischemic events (Cocking et al., 2017; Murry et al., 1986). Previous studies have suggested that administering IPC before exercise is a promising strategy to improve endurance exercise performance, such as in swimming (Jean-St-Michel et al., 2011; Williams et al., 2021), cycling (Crisafulli et al., 2011; Cruz et al., 2015; de Groot et al., 2010; Kido et al., 2015), and running (Bailey et al., 2012b; Paull and Van Guilder, 2019). The proposed mechanisms underpinning these improvements in exercise performance include improved cardiac contractility (Cocking et al., 2017; Mulliri et al., 2016), increased blood flow to the exercising muscles (Cruz et al., 2015; Kido et al., 2015), and improved oxygen extraction capacity (Kilding et al., 2018; Paull and Van Guilder, 2019).

Recently, researchers have investigated the impact of IPC on exercise performance under environmental stresses such as systemic hypoxia and external heat. It has been well documented that endurance diminishes at high altitudes because of low oxygen availability for aerobic metabolism (Amann et al., 2006; Amann et al., 2007). IPC mitigates the performance decrement in moderate hypoxia (fraction of inspired oxygen of 16%, ~2400 m) through higher blood O_2 saturation, peripheral oxygen utilization, and reduced perception of fatigue (da Mota et al., 2019; Paradis-Deschenes et al., 2018).

Unlike systemic hypoxia, exercising in the heat induces thermoregulatory strain, ultimately impairing exercise capacity particularly during prolonged endurance exercise (Cheuvront et al., 2010; Ely et al., 2010; Gonzalez-Alonso et al., 2008; Racinais et al., 2015). Multifactorial mechanisms - encompassing cardiovascular, neurological, psychological, and metabolic alterations - underlie the heat-induced decline in exercise performance (Gonzalez-Alonso et al., 2008; Sawka et al., 2011). Exercising in the heat is also characterized by competition for blood flow between the muscles and skin (Gonzalez-Alonso et al., 2008). Increased blood flow is directed to the active skeletal muscles and the myocardium to meet metabolic and oxygen demands, while elevated blood flow to the skin is also required for heat dissipation (Cheuvront et al., 2010; Gonzalez-Alonso et al., 2008). Due to the combined metabolic and thermoregulatory demands, exercise in the heat imposes an exceptional burden on the circulation system (Johnson, 2010), resulting in increased cardiovascular strain for any given exercise intensity (Otani et al., 2016). This increased cardiovascular strain appears to be the foremost factor precipitating fatigue during moderate- and high-intensity endurance exercise in the heat (Periard et al., 2012).

IPC enhances vascular function in various anatomical regions, including the coronary and peripheral arteries, as well as the cutaneous microvasculature. Human (Zhou et al., 2007) and animal studies (Shimizu et al., 2007) have reported increased coronary blood flow in response to IPC of the lower limbs. Endogenous vasoactive substances such as adenosine and nitric oxide were suggested to be responsible for coronary vasodilation, while this effect ap-

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pears to be caused by remote IPC rather than a direct preconditioning effect (Shimizu et al., 2007). In addition, IPC improves the endothelium-dependent vasodilation of the brachial artery (Enko et al., 2011; Moro et al., 2011) as well as skin microcirculation (Jones et al., 2014; Kim et al., 2021; Lang et al., 2019) potentially via increased nitric oxide production. Collectively, IPC's potent vascular effects could optimize hemodynamic adjustment to facilitate internal heat dissipation while maintaining exercise performance under heat stress.

Only one study has so far examined the effectiveness of IPC on incremental intensity running performance in mild heat (32 °C), reporting no observable improvements following IPC (James et al., 2016). However, during the incremental intensity exercise, energy source shifts from aerobic to anaerobic metabolism, potentially reducing the effectiveness of IPC, as IPC is known to be more beneficial for enhancing performance in aerobic exercise compared to other types of exercise (Salvador et al., 2016). Thus, further investigation with different exercise protocols (incremental vs. constant intensity) and environment settings (higher ambient temperature) is warranted to provide insight to this field.

The current study aimed to determine 1) whether IPC improves endurance running performance in a hot environment (35 °C), and 2) whether IPC enhances cardiovascular and thermoregulatory function during endurance exercise in the heat. We hypothesized that IPC could enhance high-intensity exercise performance in the heat by improving cardiovascular and thermoregulatory functions.

Methods

Subjects and ethical approval

Twelve healthy young subjects, including 8 males (age: 27.1 ± 4.3 years, body mass: 73.3 ± 4.0 kg; stature: 1.8 ± 0.1 m, body fat percentage: 14.5 ± 2.1 %; $\dot{V}O_{2max}$: 56.0 ± 7.7 mL·kg^{-1}·min^{-1}) and 4 females (age: 25.5 ± 0.6 years, body mass: 51.8 ± 1.5 kg; stature: 1.6 ± 0.1 m, body fat percentage: 22.3 ± 1.3 %; $\dot{V}O_{2max}$: 51.6 ± 9.2 mL·kg^{-1}·min^{-1}), participated in this study. All subjects were nonsmokers and regularly participated in endurance training (>1 h/day, 5 days/week or more). None of the subjects were acclimated to heat stress, and to account for seasonal variation in environmental temperatures, experimental procedures were halted during the summer (from June to September) (Bennett et al., 2023; James et al., 2016). All experimental procedures were approved by the Jeonbuk National University Ethics Committee (JBNU 2023-02-007-001) and conformed to the standard set by the Declaration of Helsinki (2013). The participants were verbally informed of the risks and discomforts associated with experimental trials, and written informed consent was obtained from all the subjects prior to their participation.

Experimental design

This study employed a randomized crossover design. Subjects visited the laboratory for two preliminary visits and two experimental trials (a total of 4 visits), separated by 7 days between visits. They were asked to maintain their regular diet but not to consume any food in the 2 h before a study visit. They were also requested to refrain from strenuous physical activity, alcohol, and caffeine consumption for 24 h prior to a visit. To minimize potential diurnal variation in exercise performance, all testing sessions were conducted at the same time of day (± 1 h).

The first preliminary visit to the laboratory involved a graded maximal exercise test (GXT) on a treadmill. This test was conducted to assess cardiopulmonary function and determine if participants qualified for the study. The qualifying criterion was a $\dot{V}O_{2max}$ greater than 50 mL·kg^{-1}·min^{-1} (Paradis-Deschenes et al., 2020; Wiggins et al., 2019). Ventilatory kinetics, including the first and second ventilatory thresholds (VT_{1st} and VT_{2nd}), were also obtained during the GXT (Bellini et al., 2023). Before the GXT, subjects' body mass and body fat percentage were measured using a bioelectrical impedance analysis (InBody 720, InBody Co., Seoul, South Korea). During the second preliminary visit, participants completed a standardized trial in a thermoneutral environment (24 °C) to familiarize themselves with the experimental procedures and validate the accuracy of the ventilatory threshold data collected during the first visit. This trial did not involve any specific treatment and was therefore considered a control group. As the decline in exercise performance due to heat is well established (Bennett et al., 2023; Gonzalez-Alonso et al., 2008), statistical analyses comparing performance outcomes between the thermoneutral (control) and hot environments (IPC or sham) were not conducted.

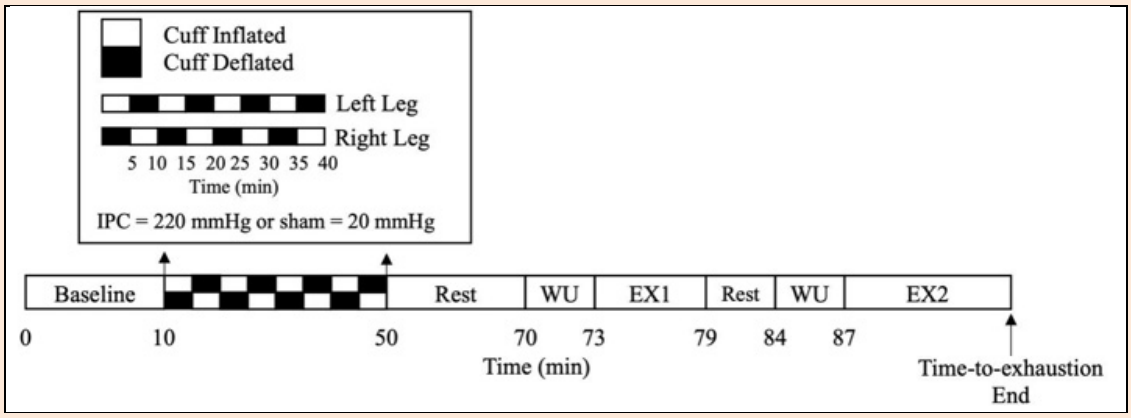

Figure 1. Experimental protocol. IPC, ischemic preconditioning; WU, warm-up; EX1, 6-min running at constant moderate intensity; EX2, time-to-exhaustion running test at high intensity.

Following the preliminary sessions, participants were randomly assigned and counterbalanced in a crossover experimental protocol (Figure 1). During the two experimental visits, subjects were first asked to provide a urine sample to determine their hydration status. They then entered the temperature-controlled chamber (35 °C, 50% RH) and completed either an IPC protocol (4 × 5 min occlusion at 220 mm Hg) or a sham protocol (4 × 5 min occlusion at 20 mm Hg) on their legs after a 10-min baseline period (Wiggins et al., 2019). Briefly, 5-cm-wide cuffs (KAATSU C3, Sato Sports Plaza, Tokyo, Japan) were placed around the participant's upper thighs and alternately inflated for 5-min bouts, whereby the cuffs were deflated on one leg and immediately inflated on the other throughout the intervention. Circulatory occlusion was confirmed using a Doppler ultrasound (Ultrasound system DP-20, Mindray, Shenzhen, China) on the posterior tibial artery (James et al., 2016; Kilding et al., 2018) until no pulse was detected during cuff inflation. A sufficient rest interval of 20 min was given between the treatment and exercise (da Mota et al., 2019). Subjects performed a 3-min warm-up, which included jogging and stretching, then undertook a 6-min moderate-intensity run (EX1) at a power output equivalent to the VT_{1st} determined by the GXT. After a 5-min rest, subjects performed a high-intensity time-to-exhaustion test (EX2) with a constant speed at a power output equivalent to the VT_{2nd}. Participants were not informed of the potential benefit of IPC on performance to minimize psychophysiological effects (Bellini et al., 2023).

Graded Maximal Exercise Test (GXT)

All exercise testing sessions were performed using a treadmill (Trackmaster, Full Vision Inc, Newton, United States). The Bruce treadmill protocol (Bruce et al., 1973) was employed for the GXT to determine $\dot{V}O_{2max}$ and the power output corresponding to the ventilatory thresholds (Driver et al., 2022; Ogawa et al., 2022). The treadmill speed and incline were increased every 3 min after the onset of exercise until exhaustion was reached in a thermoneutral environment (24 °C and 50 % RH). Subjects had prior experience of this test protocol.

Subjects were considered to have reached $\dot{V}O_{2max}$ if they attained 2 of the following 4 criteria: 1) a plateau in oxygen consumption despite an increase in intensity; 2) a respiratory exchange ratio value > 1.10; 3) a heart rate within 10 % of predicted maximal HR that was calculated as 220 - age; and 4) volitional exhaustion. $\dot{V}O_{2max}$ was defined as the highest value achieved over a 30-s period (Crisafulli et al., 2011). VT_{1st} was determined using the criteria of an increase in both the ventilatory equivalent of oxygen ($\dot{V}_E/\dot{V}O_2$) and end-tidal partial pressure of oxygen ($P_{ET}O_2$) with no concomitant increase in the ventilatory equivalent of carbon dioxide ($\dot{V}_E/\dot{V}CO_2$). VT_{2nd} was determined using the criteria of an increase in both the $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ and a decrease in $P_{ET}O_2$ (Bellini et al., 2023; Cerezuela-Espejo et al., 2018; Lucia et al., 2000). VT_{1st} and VT_{2nd} were detected by two independent observers, with a third investigator consulted in case of disagreement. In subsequent experimental trials, moderate- and high-intensity were determined by the power output equivalent to the VT_{1st} and VT_{2nd}, respectively (Cerezuela-Espejo et al., 2018; Kilding et al., 2018).

Cardiac output monitoring

Electrical impedance cardiography (PhysioFlow Enduro; Manatec Biomedical, Petit Ebersviller, France) was used to assess stroke volume (SV), heart rate (HR), and cardiac output (CO). Six electrodes were placed on the subject by an experienced researcher: two at the left base of the neck above the supraclavicular fossa, two in the middle of the back at the same level as the xiphoid process, one on the right upper chest and one on the left lower chest. An alcohol swab was used to clean these areas prior to placement, followed by the application of electrode gel (NuPrep, Weaver and Company, Aurora, CO, United States) to these areas. The skin was further cleaned with a paper towel. Arterial blood pressure was measured to calibrate the PhysioFlow software before and at the conclusion of each stage (HEM-770A, Omron Healthcare, Kyoto, Japan). SV, CO, and HR data were recorded beat-by-beat and averaged every 5 s throughout the experiment. Data collected during every 1-minute window of EX1 period were averaged to obtain steady-state measurements. Since the exercise duration differed between IPC and sham trials, data were compared at 20%, 40%, 60%, 80% and 100%, relative to the time of task failure in the shorter trial each individual (*i.e.*, isotime points) (Barbosa et al., 2015). The validity and reliability of this data collection technique during running exercises have been previously documented (Ogawa et al., 2022; Stucky et al., 2018).

Pulmonary $\dot{V}O_2$ kinetics

Pulmonary $\dot{V}O_2$ kinetics were measured on a breath-by-breath basis using a gas analyzer (Quark CPET, Cosmed, Italy). The gas analyzers were calibrated according to the manufacturer's specifications, using ambient air and gases with known concentrations (16.0 % O_2 and 4 % CO_2). The flowmeter was calibrated using a 3-L syringe. The breath-by-breath $\dot{V}O_2$ data were smoothed by removing aberrant data (two standard deviations from the mean of a 15-breath window). The $\dot{V}O_2$ data were interpolated to give second-by-second values and then were averaged into 5-s bins. To characterize the on-transient $\dot{V}O_2$ kinetics, data were modelled from 20 s post-onset of exercise, thereby excluding the cardiodynamic response, until end-exercise by nonlinear least-squares regression (Kido et al., 2015; Kilding et al., 2018). A single-exponential model was used to characterize the $\dot{V}O_2$ responses to moderate-intensity exercise (Eq. 1), and a biexponential model (Eq. 2) was used for high-intensity exercise, as described in the following equations:

$$\textit{(Eq. 1)}\ \dot{V}O_2(t) = \dot{V}O_2(b) + A_p\left[1 - \exp^{-(t-\delta_p/\tau_p)}\right]$$

$$\textit{(Eq. 2)}\ \dot{V}O_2(t) = \dot{V}O_2(b) + A_p\left[1 - \exp^{-(t-\delta_p/\tau_p)}\right] + A_s\left[1 - \exp^{-(t-\delta_s/\tau_s)}\right]$$

where $\dot{V}O_2(t)$ represents the absolute $\dot{V}O_2$ at a given time; $\dot{V}O_2(b)$ represents the mean $\dot{V}O_2$ in the last 60 s of the baseline period; A_p, δ_p, and τ_p represent the amplitude, time delay, and time constant, respectively, describing the phase II increase in $\dot{V}O_2$ above baseline; and A_s, δ_s, and τ_s represent the amplitude, time delay, and time constant describing the

development of the $\dot{V}O_2$ slow component, respectively. Furthermore, the end-exercise $\dot{V}O_2$ was defined as the mean $\dot{V}O_2$ measured over the last 30 s of exercise both for moderate- and high-intensity exercise (Kilding et al., 2018).

Near-Infrared Spectroscopy (NIRS)

Muscle oxygen saturation (SmO_2) was assessed on the right vastus lateralis (VL) and the right gastrocnemius muscle (GA) using portable, spatially resolved, dual wavelength NIRS apparatus (Idiag Moxy, Idiag, Fehraltorf, Switzerland). One NIRS probe was placed on the VL, a third of the distance from the top of the patella to the greater trochanter, while another was placed on the belly of the GA medialis muscle. Subcutaneous skinfold thickness has been reported to affect NIRS measurement sensitivity (van Beekvelt et al., 2001); therefore, the skinfold thickness (VL: 11.9 ± 3.0 mm; GA: 11.0 ± 3.3mm) was measured where the NIRS was applied, using a digital ultrasonic imaging system (DP-20, Mindray, Shenzhen, China) during the first visit, and was less than half the distance between the emitter and the detector (Feldmann et al., 2020; Wang et al., 2023).

The NIRS data analysis was conducted with reference to previous research using the same device (Wang et al., 2023). All NIRS signals were acquired at a default sampling rate, which sampled the four wavelengths over 80 cycles for an averaged output every 2 s. This consistent sampling approach ensured accurate measurement. For analysis, a bin-averaging strategy was used to determine the signal at the time points of interest. The NIRS data were averaged over the last 1 min within each phase, using a Butterworth lowpass filter to smooth the NIRS signal. Additionally, the amplitude of SmO_2 was normalized individually for each session, with the baseline amplitude representing 100%.

Skin Blood Flux (SkBF) and Cutaneous Vascular Conductance (CVC)

Changes in skin blood flux (SkBF) were measured using laser-Doppler flowmetry via two multifiber integrating probes (VP7A/T with moorVMS-LDF2, Moor Instruments, Wilmington, DE, United States) that were placed on the left VL and GA (see NIRS section for detailed location). At both sites, the probes were placed in areas where blood vessels were not visually apparent in order to obtain SkBF from cutaneous capillaries rather than major vessel readings (Hinds et al., 2004). Once affixed, the probes remained in situ throughout the entire procedure. All data were acquired at 40 Hz, and a Butterworth lowpass filter was applied to smooth the data. SkBF values were calculated from 1 min averages at the end of each period. Mean arterial pressure (MAP) was determined as one-third pulse pressure plus diastolic blood pressure at the end of the period. Cutaneous vascular conductance (CVC) was calculated as the ratio of SkBF to MAP.

Core temperature

Core temperature (T_{CORE}) was monitored using an ingestible telemetry sensor capsule (CorTemp®, HQ Inc, Palmetto, FL, United States; weight 2.75 g, length 23 mm, and diameter 10.25 mm) that the subjects ingested at least 2 h before the start of each experiment (Byrne and Lim, 2007; Domitrovich et al., 2010; Wilkinson et al., 2008). The capsules' temperature reactivity was tested prior to ingestion by comparison with a digital thermometer. As the capsule transited through the gastrointestinal tract, it transmitted the temperature every 10 s via radio signal to an external data recorder worn around the subject's waist. T_{CORE} values were calculated from 1 min averages at the end of the baseline and each exercise period. Data points were excluded manually if they were greater than 2 standard deviations from the mean of the nearest 4 values excluding the outlier value.

Hydration status

A urine sample was collected at each visit, and the urine specific gravity (USG) was measured to ensure appropriate hydration. Two drops of urine were placed on a digital refractometer (DR501, Huaqin Co. Ltd, Shanghai, China), then the sample was analyzed using the 'read' setting. Euhydration was achieved when the USG was below 1.020 (Casa et al., 2000). The instrument was cleaned after every sample and calibrated to 1.000 using distilled water after every three samples.

Statistical analyses

All data values are reported as means ± standard deviation (SD). The normality of the dependent variables was determined using the Shapiro-Wilk test and the homogeneity of variance using the Brown-Forsythe and Welch ANOVA tests. A two-way repeated ANOVA (condition × time) was used to test for differences in cardiovascular parameters (CO, SV, and HR), CVC, and SmO_2. A priori simple main effects were examined with a Bonferroni correction for multiple planned comparisons where applicable. Paired samples t-tests were used to detect differences between baseline physiological variables (USG, T_{CORE}, and BP), total running time (endurance running performance), and pulmonary $\dot{V}O_2$ kinetics. The alpha for significance was set a priori at $P < 0.05$ for all comparisons. Consistent with an a priori sample size calculation (G*Power 3.1) from a previous study (James et al., 2016), a sample of 10 was required to achieve the targeted statistical power of $\beta = 0.80$ at $\alpha = 0.05$ for the endurance tests (actual power = 0.84 at $n = 10$). To account for potential dropouts, 12 participants were recruited.

Partial eta-squared (η^2) was calculated to estimate the effect size of the two-way ANOVA (main effects and interaction), in which values of 0.01, 0.06, and above 0.14 represent small, medium, and large effects, respectively. In addition, effect size was calculated (mean difference divided by the pooled standard deviation) to determine the practical relevance (if $P < 0.05$ was found) and classified as small (0.2 - 0.49), moderate (0.5 - 0.79), or large (≥ 0.8). All statistical calculations were performed using Prism 10 software (GraphPad Software, San Diego, CA, USA).

Results

During the baseline period, no differences in physiological variables, namely, USG, T_{CORE}, SBP, and DBP were found between the IPC and sham conditions (Table 1).

Table 1. Physiological variables during the baseline period.

	IPC	Sham	*P*-value
USG (g/ml)	1.010 ± 0.005	1.012 ± 0.005	0.348
T_{CORE} (°C)	37.07 ± 0.20	37.12 ± 0.17	0.362
SBP (mmHg)	115 ± 10	114 ± 10	0.679
DBP (mmHg)	74 ± 10	73 ± 8	0.731

USG, urine specific gravity; T_{CORE}, core body temperature; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are presented as mean ± SD, n = 12.

Endurance performance

Endurance performance, as indexed by total running time, during EX2 is shown in Figure 2. The total running time was considerably greater under the IPC condition compared to the sham condition (IPC 416.4 ± 61.9 vs. sham 389.3 ± 40.7 s, P = 0.027, ES = 0.25). Specifically, endurance performance following IPC administration improved by 6.9 % compared to after the sham treatment (Figure 2A). The scatter plot analysis in Figure 2B shows that 8 of 12 subjects performed better after IPC administration than after the sham treatment.

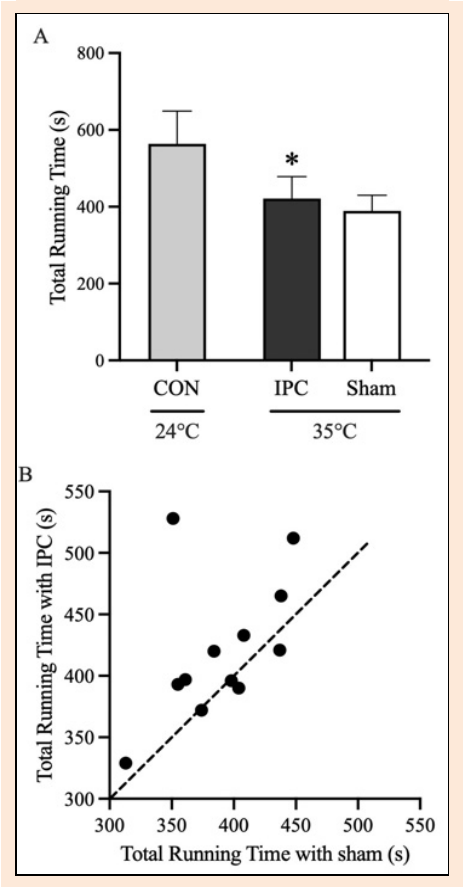

Figure 2. Endurance running performance. (A) Total running time during EX2 and (B) a scatter plot of running times in IPC and sham conditions are shown. Individuals who performed better with IPC administration (vs. sham) fall above the dashed line and those who performed worse fall below the line. Data are presented as mean ± SD; n = 12. *P < 0.05 vs. sham.

Cardiac function

Figure 3 presents indices of cardiac function, including SV, HR, and CO. In EX1, significant main effects of time were observed for SV, HR, and CO (P < 0.001 for all, η^2 = 0.307, 0.945 and 0.788); however, no significant differences were found between IPC and sham at each minute (all p > 0.05). In EX2, SV, HR and CO increased throughout the exercise (time effect: P = 0.005, P < 0.001 and P < 0.001, η^2 = 0.210, 0.804, 0.722) Post-hoc analyses showed higher SV (IPC: 150.4 ± 17.5 vs. sham: 128.2 ± 11.6 ml, P = 0.008, ES = 0.60) and CO (IPC: 27.4 ± 1.7 vs. sham: 25.1 ± 2.2 ml·min^{-1}, P = 0.007, ES = 0.50) in the IPC condition at 100% isotime of EX2 (high-intensity exercise). No significant differences were observed in HR between conditions at any stage (P > 0.05 for all).

Kinetic parameters derived from the $\dot{V}O_2$ during moderate- and high-intensity exercise under the IPC and sham conditions are shown in Table 2. No significant differences in kinetic parameters were observed during moderate-intensity exercise (P > 0.05 for all). During high-intensity exercise, higher $\dot{V}O_2$ at the end-exercise (IPC: 3.72 ± 0.85 vs. sham: 3.54 ± 0.87 L·min^{-1}, P = 0.017, ES = 0.10) and lower slow phase amplitude (IPC: 0.57 ± 0.17 vs. sham: 0.72 ± 0.22 L·min^{-1}, P = 0.016, ES = 0.37) were found in the IPC condition when compared with the sham condition.

Muscle oxygen saturation (SmO_2)

Changes in SmO_2 on the VL and GA are shown in Table 3. Significant main effects of time were observed for VL and GA (P < 0.001 for both, η^2 = 0.537 and 0.677, respectively). There were no significant main condition effects or interactions for VL and GA (P > 0.05 for all). During the intervention period, a lower SmO_2 in the VL (IPC: 89.7 ± 7.1 vs. sham 101.5 ± 1.4%, relative to BL, P < 0.001, ES = 0.75) and GA (IPC: 96.2 ± 4.6 vs. sham: 103.6 ± 3.6%, P = 0.001, ES = 0.67) was observed in the IPC condition compared to the sham condition. During the recovery period, the VL SmO_2 was significantly higher in the IPC condition (IPC: 106.6 ± 5.9 vs. sham: 100.5 ± 2.8%, P = 0.028, ES = 0.40). In subsequent exercises (EX1 and EX2), there were no significant differences in the VL and GA SmO_2 between the two conditions (P > 0.05 for all).

Cutaneous vascular conductance (CVC)

The changes in CVC are shown in Figure 4. Figure 4A presents representative SkBF data from one subject in the IPC condition. During the IPC's occlusion period, CVC was significantly lowered in the VL relative to during the sham procedure (IPC: 0.59 ± 0.33 vs. sham: 1.04 ± 0.38 SkBF·mmHg^{-1}, P < 0.001, ES = 0.53) (Figure 4B). Similar to the VL, a decrease in CVC was seen in the GA during IPC administration (IPC: 0.40 ± 0.20 vs. sham: 0.68 ± 0.49 SkBF·mmHg^{-1}, P < 0.001, ES = 0.74) (Figure 4C). A significant main effect of time as well as interaction were found in the VL (P < 0.001 for both, η^2 = 0.765 and 0.668) and GA (P < 0.001 for both, η^2 = 0.706 and 0.556) (Figs. 4B and 4C). There were no main condition effects in the VL or GA (P > 0.05 for both, η^2 = 0.149 and 0.220).

A higher CVC was observed in the VL during the recovery phase and post-EX1 after IPC administration compared to the sham treatment (recovery, IPC: 1.45 ± 0.46 vs. sham: 1.07 ± 0.36 SkBF·mmHg^{-1}, P = 0.0006, ES = 0.85; post-EX1, IPC: 1.67 ± 0.53 vs. sham: 1.19 ± 0.40 SkBF·mmHg^{-1}, P < 0.0001, ES = 0.45) (Figure 4B). No differences in CVC during the recovery phase and post-

EX1 were found for the GA ($P > 0.05$ for both) (Figure 4C).

Core body temperature (T_{CORE})

The delta changes of T_{CORE} during EX1 and EX2 are shown in Figure 5. A smaller increase in T_{CORE} was observed in the IPC condition during EX1 (IPC: 0.18 ± 0.06 vs. sham: 0.22 ± 0.08 °C, $P = 0.005$, ES = 0.27) (Figure 5A). Interestingly, the difference in T_{CORE} between the two conditions became greater during EX2 (IPC: 0.87 ± 0.10 vs. sham: 1.03 ± 0.10 °C, $P < 0.001$, ES = 0.62), such that T_{CORE} was lower in the IPC condition by 0.16 ± 0.06 °C by the end of EX2 (Figure 5B).

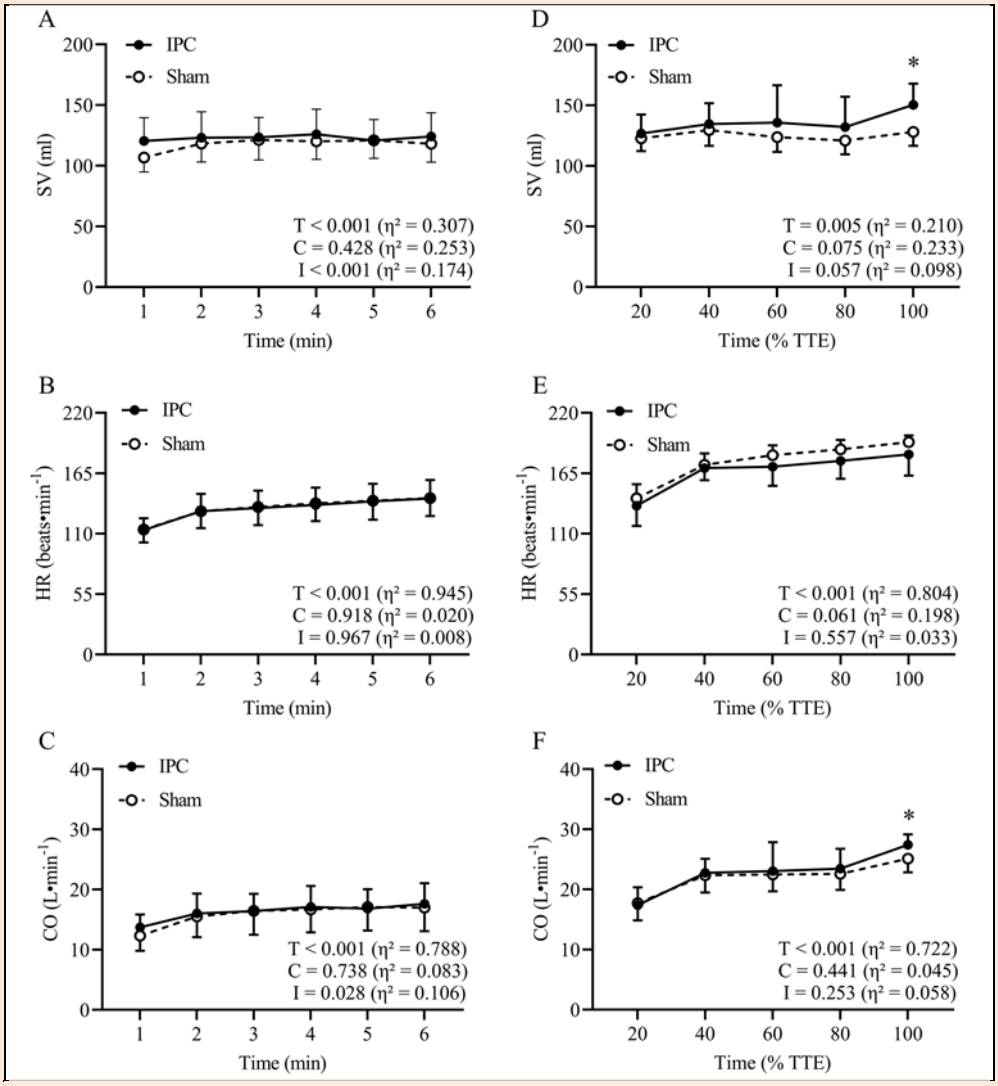

Figure 3. Cardiovascular parameters. (A) Stroke volume (SV), (B) heart rate (HR), and (C) cardiac output (CO) during each 1-minute window of EX1 are shown. (D) SV, (E) HR and (F) CO at 20%, 40%, 60%, 80% and 100% isotime are shown. Data are presented as mean ± SD, $n = 12$. * $P < 0.05$ vs. sham.

Table 2. Pulmonary $\dot{V}O_2$ kinetic parameters. Pulmonary VO_2 kinetic indexes during EX1 and EX2 are shown.

		IPC	Sham	*P*-value (ES)
Moderate-intensity exercise (EX1)	Baseline (L·min^{-1})	0.93 ± 0.11	0.91 ± 0.10	0.275 (0.09)
	End-exercise (L·min^{-1})	1.98 ± 0.48	2.05 ± 0.36	0.332 (0.08)
	Primary amplitude (L·min^{-1})	1.00 ± 0.21	1.10 ± 0.19	0.797 (0.24)
	Primary time delay (s)	20.30 ± 8.30	19.90 ± 7.60	0.909 (0.03)
	Primary time constant (s)	17.50 ± 6.30	18.50 ± 7.90	0.619 (0.07)
High-intensity exercise (EX2)	Baseline (L·min^{-1})	0.97 ± 0.17	0.98 ± 0.14	0.666 (0.03)
	End-exercise (L·min^{-1})	3.72 ± 0.85*	3.54 ± 0.87	0.017 (0.21)
	Primary amplitude (L·min^{-1})	2.01 ± 0.66	1.98 ± 0.75	0.822 (0.02)
	Primary time delay (s)	14.30 ± 2.70	15.90 ± 4.70	0.136 (0.20)
	Primary time constant (s)	26.20 ± 11.50	30.30 ± 16.90	0.342 (0.14)
	Slow phase time delay (s)	128.90 ± 23.20	134.90 ± 22.40	0.503 (0.13)
	Slow phase amplitude (L·min^{-1})	0.57 ± 0.17*	0.72 ± 0.22	0.016 (0.36)

Data are presented as mean ± SD, $n = 12$. * $P < 0.05$ vs. sham.

Table 3. Muscle oxygen saturation (SmO_2). SmO_2 in the vastus lateralis (VL) and gastrocnemius (GA) during each stage are presented.

		SmO_2 (% of BL)		
		IPC	Sham	*P*-value (ES)
Vastus Lateralis (VL)	BL	100	100	
	INT	89.7 ± 7.1*	101.5 ± 1.4	0.001 (0.76)
	REC	106.6 ± 5.9*	100.5 ± 2.8	0.028 (0.55)
	EX1	95.7 ± 4.8	91.6 ± 10.2	0.701 (0.25)
	EX2	69.2 ± 25.2	63.5 ± 36.5	0.974 (0.09)
Gastrocnemius (GA)	BL	100	100	
	INT	96.2 ± 4.6*	103.6 ± 3.6	0.001 (0.67)
	REC	105.7 ± 1.4	102.1 ± 4.4	0.085 (0.48)
	EX1	79.1 ± 18.9	74.2 ±21.3	0.984 (0.12)
	EX2	55.0 ± 32.8	51.0 ± 29.3	0.999 (0.06)

BL, baseline; INT, intervention; REC, recovery; EX1, 6-min running at constant moderate intensity; EX2, time-to-exhaustion running test at high intensity. Data are presented as mean ± SD, $n = 12$. * $P < 0.05$ vs. sham.

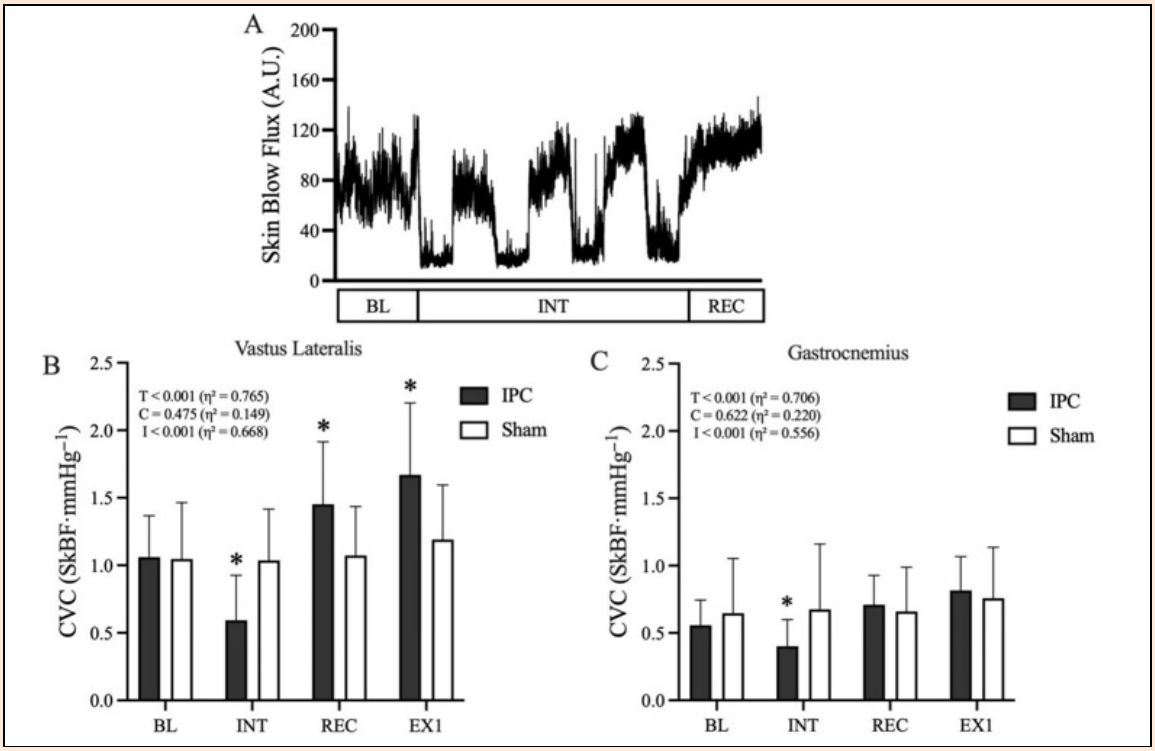

Figure 4. Cutaneous vascular conductance (CVC). (A) a representative raw data for SkBF from one subject, (B and C) CVC in the vastus lateralis (VL) and gastrocnemius (GA) during each stage are presented. Data are presented as mean ± SD, $n = 12$. * $P < 0.05$ vs. sham.

Discussion

This study investigated the effects of IPC on endurance running performance (~6 - 7 min running duration) in the heat. Our data showed that IPC administration improved high-intensity endurance performance in the heat by 6.9 % compared to the sham treatment (small effect, ES = 0.25), with 8 out of 12 subjects performing better after IPC administration. The improvement in endurance performance may be (at least partially) associated with increased cardiovascular and thermoregulatory function. Peripheral oxygen extraction and utilization did not seem to play a role according to our investigation.

To date, the effect of IPC on endurance performance has been extensively studied, though only one study has investigated IPC's impact on endurance performance in hot environments. James and colleagues demonstrated that IPC did not alter the determinants of endurance running performance in the heat (32 °C, 62 % RH) (James et al., 2016). The conflicting results between ours and their findings may be attributed to the different exercise protocols for assessing endurance performance (incremental vs. constant intensity exercises). During incremental intensity exercise, the body predominantly utilizes aerobic metabolism at the onset, which markedly shifts to anaerobic metabolism as the intensity increases (Korzeniewski, 2023). Conversely, a steady state of energy expenditure where energy demands and output are balanced is attained during constant intensity exercise (Korzeniewski,2018; Korzeniewski, 2023). In addition, in incremental intensity exercise, there is either significantly reduced additional ATP usage or increased glycolysis stimulation at high power

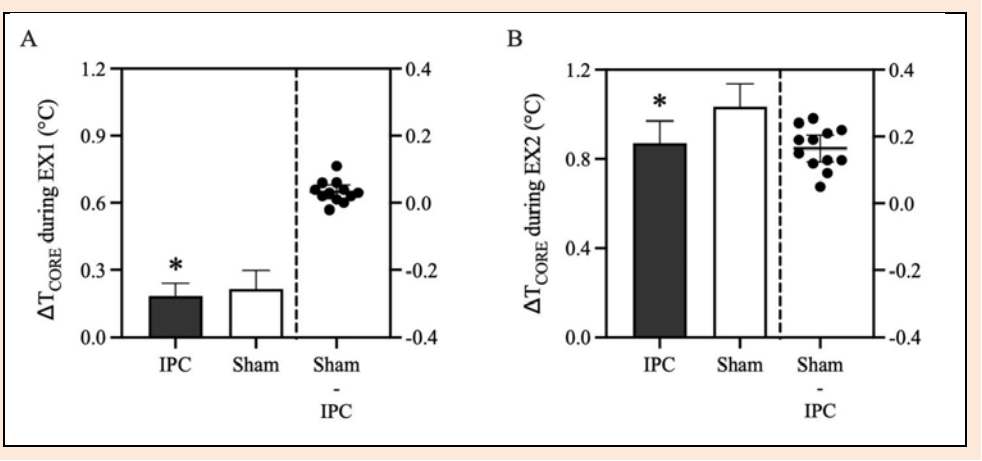

Figure 5. Core body temperature (T_{CORE}). The changes in T_{CORE} (ΔT_{CORE}) before and after (A) EX1 and (B) EX2 are shown. Scatter plots that present the mean difference in TCORE between the IPC and sham conditions are shown on the right panel of each figure. Data are presented as mean ± SD, $n = 12$, * $P < 0.05$ vs. sham.

outputs compared to constant-intensity exercise (Korzeniewski, 2023). A systemic meta-analysis indicated that IPC seems to be more effective for enhancing performance in aerobic exercise rather than other types of exercise (Salvador et al., 2016). In our study, 4 out of 12 subjects in the IPC condition did not exhibit an improved performance compared to the sham condition (Figure 2B). It should be noted that interindividual variability is associated with the ergogenic effects of IPC administration (Incognito et al., 2016). For instance, biological sex may play a role; IPC could improve exercise performance in males but not females (Pereira et al., 2020; Teixeira et al., 2023). Interestingly, 3 out of our 4 nonresponders to IPC administration were female, supporting the idea that a phenotype for responders and nonresponders may exist (Incognito et al., 2016). Further investigation is necessary to elucidate the interindividual variability and responder phenotype associated with IPC.

Cardiac protection is a prominent IPC effect, such that the right and left ventricles function better following IPC intervention in coronary disease patients (Kloner and Rezkalla, 2006). In the context of exercise, cardiac function and hemodynamic indexes could be enhanced by IPC administration during maximal exercise (de Groot et al., 2010). Paradis-Deschenes *et al*. demonstrated that key parameters of cardiac function -including HR, SV, and CO- were elevated by IPC during a cycling time trial in a hypoxic environment (Paradis-Deschenes et al., 2018). In our study, CO significantly increased in response to IPC during high-intensity exercise (EX2) in the heat, mainly due to an elevated SV (Figure 2). IPC's ergogenic effect on cardiac function was not observed in moderate-intensity exercise (EX1) (Figure 2). These results suggest that the effectiveness of IPC is associated with exercise intensity. A plausible explanation for improved cardiac function following IPC may be improved endothelial function in the vasculature. Previous studies have demonstrated that IPC administration increases endothelial function and regulates the main hemodynamic modulators, such as cardiac contractility, preload, and afterload, in coronary disease patients and healthy individuals (Bailey et al., 2012a; Michaelides et al., 2006; Thijssen et al., 2016). Modulators that increase endothelial function in response to IPC include nitric oxide, endothelial-dependent hyperpolarization factors, and prostacyclin. Detailed mechanisms are described in a previous paper (Lang and Kim, 2022). It is also plausible that alterations in autonomic function in response to IPC might contribute to the improved cardiac function. While some studies suggest that sympathetic nervous activity or sympathovagal balance is not altered by a single bout of IPC (Gardner et al., 2020; Incognito et al., 2017), other evidence indicates an improvement in cardiac autonomic function after IPC, independent of any place effect (Sabino-Carvalho et al., 2019). Therefore, the influence of autonomic function in response to IPC administration cannot be excluded as a contributing factor to the the improved cardiac function observed in our study.

Prior studies have reported the effects of IPC on the $\dot{V}O_2$ kinetic responses to moderate- and high-intensity exercise (Kido et al., 2015; Kilding et al., 2018), yet this is the first study, to our knowledge, to show the $\dot{V}O_2$ kinetic responses to IPC during exercise at different intensities in a hot environment. We acknowledge the standard practice of averaging multiple rest-to exercise transitions for $\dot{V}O_2$ kinetics analysis (Ozyener et al., 2001). However, due to the high physiological demands and safety concerns associated with exercising in the heat, we opted to use a single transition. During the moderate-intensity exercise, IPC had no significant effects on any temporal or amplitude-based parameters (Table 2), which concurs with previous findings in the thermoneutral environment (Kido et al., 2015; Kilding et al., 2018). During high-intensity exercise, $\dot{V}O_2$ slow phase amplitude reduced, indicating a beneficial priming effect (Kilding et al., 2018). Several lines of evidence evince that the development of the $\dot{V}O_2$ slow component is associated with muscle fatigue, meaning that exercise tolerance can be improved by interventions that reduce or eliminate the $\dot{V}O_2$ slow component (Dimenna et al., 2010; Jones et al., 2011). A potential explanation for the lower $\dot{V}O_2$ slow component would be an increase in NO production in response to arterial occlusion and reperfusion (Bailey et al., 2012a; Kuntscher et al., 2002). Among a range of physiological roles, NO-induced vasodilation in the skeletal muscle vasculature would permit a precise

local matching of blood flow to metabolic rate during strenuous exercise (de Groot et al., 2010). Additionally, NO appears to exert a powerful effect on the recruitment of type II fibers during high-intensity exercise (Pearson and Hussain, 2015; Wang et al., 2023; Wilk et al., 2021). In this regard, an IPC-induced increase in NO production that results in improved blood flow regulation and increased the metabolic efficiency of type II fibers would play a pivotal role in developing the muscle's $\dot{V}O_2$ slow component during high-intensity exercise (Jones et al., 2011; Kilding et al., 2018).

As expected, SmO_2 was decreased by almost 10 % during the IPC occlusion period relative to the sham treatment, which is similar to a finding from another investigation (Patterson et al., 2015). However, our data showed no significant difference in SmO_2 during moderate- and high-intensity exercise between the IPC and sham conditions (Figure 3). Many previous studies have reported that IPC induces reactive hyperemia and an increase in oxygen delivery to exercising muscles (SmO_2) (da Mota et al., 2019; Paradis-Deschenes et al., 2018; Wiggins et al., 2019), but not all research concurred (Paradis-Deschenes et al., 2018). The reason for these inconsistent results might be that muscle blood flow is directed toward the skin to support heat dissipation during exercise in a hot environment (Gonzalez-Alonso et al., 2008), which may mask the independent effect of IPC on oxygen utilization in the muscle. Despite the fact that we found no IPC effects on muscle deoxygenation, we cannot rule out the possibility that the blood flow distribution alters between slow and fast twitch fibers during exercise after IPC administration. Further investigation is warranted.

Prior research has demonstrated that both a single round or repeated IPC in a thermoneutral environment increases endothelium-dependent vasodilatation (Kim et al., 2021). Similarly, our data showed increased CVC during the recovery period as well as at the end of EX1 (post-EX1) (Figure 4). The elevation in CVC in response to the IPC intervention that was seen in the VL was not observed in the GA (Figure 4B), which potentially indicates that the IPC-induced increase in CVC depends on the body's vasculature. We were unable to collect CVC data during EX2, as the data signal was not usable due to the strenuous nature of the exercise. Potentially, the increased CVC following IPC administration facilitates heat dissipation during exercise in the heat, which subsequently elicits a smaller elevation in core temperature (T_{CORE}) following EX1 and EX2 (Figure 5). This interesting finding about the reduced thermal strain following IPC intervention was also observed in a previous investigation, though the underlying mechanisms remain unknown (James et al., 2016). Although the difference in T_{CORE} between the two conditions (0.16 ± 0.06 °C during EX2) does not seem to be physiologically significant, the reduced thermal strain following IPC administration, at least in part, may contribute to the performance improvement during high-intensity exercise in the heat. Although speculative, the altered thermal sensation perceived by participants may play a role, given that thermal sensation itself can be a limiting factor for endurance performance, even in temperate environments (Van Cutsem et al., 2019).

Limitations

The current study has several limitations. Firstly, most IPC studies to date compared IPC with occlusions at low pressure (10–50 mmHg) (Marocolo et al., 2016). However, significant differences in pain, skin color, and limb temperature between IPC and sham procedures may affect exercise performance, potentially due to placebo or nocebo effects based on participant perception (Ley et al., 2011). To account for this, our participants were not informed of the potential benefits of IPC to minimize psychophysiological effects on exercise performance. Nevertheless, the positive effect we observed on aerobic performance may still be influenced by the psychophysiological effect of IPC (Marocolo et al., 2023). Future IPC research should consider using a creative placebo control to better account for the actual IPC effect, or assess participants' expectancy regarding the experimental procedure (Cheung et al., 2020; Gao et al., 2024; Sabino-Carvalho et al., 2017).

Secondly, our data suggested a potential sex difference in the effect of IPC on exercise performance in the heat. However, this interpretation is limited by the fact that our sample included only four females. Due to the small number of female participants, both males and females were analyzed together in the same sample, which should be considered when interpreting our data. Despite this, previous studies have reported sex-related differences in IPC interventions (Gibson et al., 2015; Pereira et al., 2020), highlighting the need for further investigation in this area. Additionally, the use of non-athlete subjects and the time-to-fatigue test resulted in a short exercise duration and a high coefficient of variation (Alghannam et al., 2016; Laursen et al., 2007), making our findings more indicative than definitive. Future studies should evaluating IPC effects in athletes and use exercise protocols with a lower coefficient of variation, such as a time trial test (Laursen et al., 2007).

Thirdly, the accuracy and reliability of impedance cardiography for measuring CO have been debated (Cheung et al., 2020). Various factors, such as electrode placement, perspirations, and movement, can introduce errors that impair the calculation of SV (Stucky et al., 2018). To ensure the reliability, we averaged values over 60 seconds (Ogawa et al., 2022) and found that using waterproof tape to secure electrodes appears to be a practical solution. Nevertheless, the current data obtained from impedance cardiography (*i.e.*, SV and CO) should be interpreted cautiously due to the potential measurement errors. Furthermore, three or four transitions from rest to exercise are typically used to improve the reliability and accuracy of $\dot{V}O_2$ kinetic measurement (Ozyener et al., 2001), while only a single transition was used in our study. Therefore, while the observed improvement in VO_2 is promising, it should be interpreted cautiously due to potential measurement errors. Future studies should incorporate multiple transitions to enhance the reliability and accuracy of $\dot{V}O_2$ kinetic measurements.

Conclusion

This study demonstrated that IPC administration improves endurance exercise performance in the heat by 6.9 %. The

performance benefit could be associated with improved cardiac and thermoregulatory function during high-intensity exercise after IPC administration. The enhanced cardiac function was not observed during moderate-intensity exercise, indicating that the effects of IPC intervention in hot environments depend on the exercise intensity. Future research is needed to determine whether highly-trained endurance athletes would benefit from IPC during exercise or competition in the heat.

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Key points

- Ischemic preconditioning administration improved high-intensity endurance performance in the heat by 6.9 % compared to the sham treatment, with 8 out of 12 subjects performing better after IPC administration.
- The performance benefit could be associated with improved cardiac and thermoregulatory functions during high-intensity exercise after IPC administration.
- The enhanced cardiac function was not observed during moderate-intensity exercise, indicating that the effects of IPC intervention in hot environments depend on the exercise intensity.

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