Blow up During Warm-up: Introduction of a Novel Method to Improve Athletic Performance

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ABSTRACT

Short periods of transient blood flow restriction or ischaemia, known as ´ischaemic preconditioning´ (IPC), are known to enhance both vasculature function and muscle function, which are important factors in sport performance. In this study, adapted from two papers published in the American Journal of Physiology and Medicine and Science in Sport and Exercise, the authors investigate the possibility that IPC could enhance performance in endurance running, and examine the potential underlying mechanisms related to lactate metabolism and changes in vascular function. After exposure to four cycles of five-minute bilateral cuff inflation on their upper thighs, 13 moderately training male participants performed running tests (to assess blood lactate accumulation), followed by a 5km time trial (to assess the impact of IPC on endurance running performance + vascular function). A significantly better performance was found in the mean 5km performance after the IPC condition. It was also found that IPC 1) attenuates blood lactate accumulation during submaximal exercise and 2) prevents impairment in vascular function that is typically associated with strenuous running exercise. The authors conclude that, with practical development, IPC may offer an inexpensive, easy applicable and non-invasive strategy to improve running exercise performance.

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Introduction

The ultimate goal for all athletes is to achieve their individual maximal performance. To a large extent, maximal performance level is determined by physiological function and it is axiomatic that all legal avenues optimising physical function should

be investigated. The Fick equation describes that physiological function is determined by the weakest link in the chain of central and peripheral factors that contribute to oxygen delivery and extraction, starting in the lungs by oxygen uptake and ending in the peripheral tissue by oxygen consumption. Interventions that improve oxygen delivery and/or extraction, therefore, are likely to improve exercise performance (e.g. "live high–train low" regimens, sleep in hypoxic chambers, increasing oxygen carrying capacity of erythrocytes).

The intervention introduced here relates to *´ischaemic preconditioning´* (IPC). This technique represents a novel, simple, cheap, legal and easy applicable method that immediately improves peripheral vascular and muscular function. In this report, we describe a series of experiments that provide the first data in humans to support the potential of IPC to enhance athletic performance, but also to reveal underlying mechanisms of these benefits of IPC.

What is ischaemic preconditioning?

IPC was introduced in the mid-1980's by cardiologists[41]. It describes the fact that arteries are protected from injury when they are repeatedly exposed to short periods of transient blood flow restriction or ischaemia. Exposure of a dog's coronary artery to four cycles of five minutes of ischemia (i.e. IPC) results in a 75% reduction in cardiac injury after a 40-minute ischemic insult[41]. Such procedures are associated with obvious practical limitations for clinical use in humans. However, cardioprotective effects of IPC are also present when the repeated bouts of ischemia are applied to a remote vascular bed. For example, a previous study published in ***The Lancet,*** found that repeated cuff inflation around the forearm in patients with an acute myocardial infarction (performed in the ambulance) is associated with a significantly smaller infarction area (Figure 1)[7]. Studies also found beneficial effects when IPC is applied before cardiac surgery[49].

The upper panel of Figure 1 represents the situation in which prolonged occlusion of an artery is followed by necrosis of cardiac tissue. When occlusion is preceded by ischaemic preconditioning (four periods of 5-min occlusions of a limb) cardiac injury is at least partly reduced (lower panel).

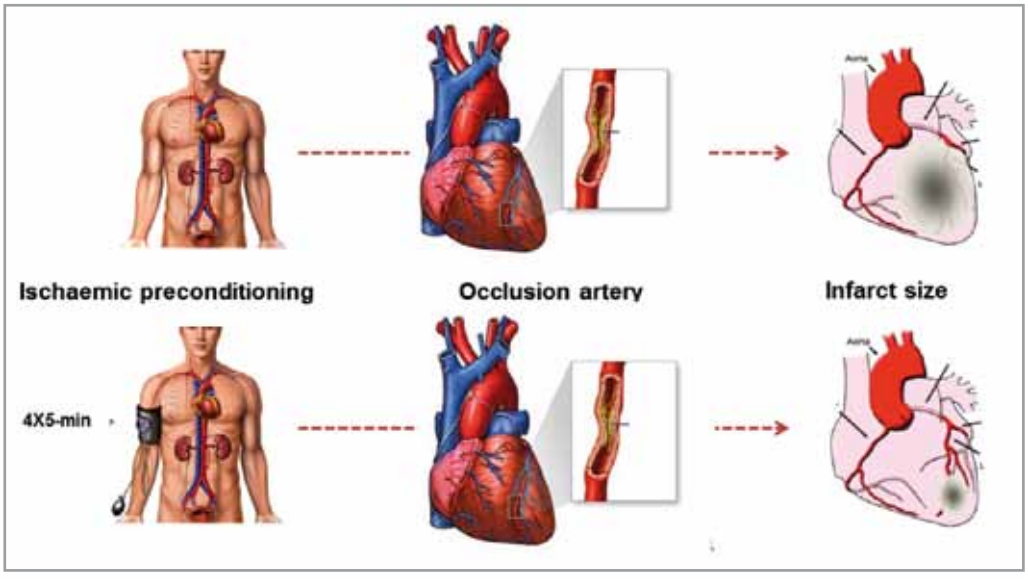

Figure 1: Effects of ischaemic preconditioning

Although the exact mechanisms for IPC are unclear, studies have found that IPC has well-established effects on the vasculature (e.g. adenosine), resulting in an increased blood supply[46]. In addition, previous studies in animals have shown that IPC can enhance muscle efficiency in ATP-usage via ATP-sparing, augmented function of the mitochondrion or increased efficiency in the excitation-contraction coupling[27, 34, 43]. Based on the effect of IPC on the vasculature and muscle function, IPC may potentially contribute to beneficial effects of IPC to exercise performance.

Effect of ischaemic preconditioning on human performance

We performed a pilot study in 15 moderate-to-highly trained subjects who performed two maximal cycling tests; 1. Control test, 2. Test preceded by IPC (Figure 2). Remarkably, cycling exercise preceded by IPC was associated with an immediate 3% higher maximal oxygen consumption and 1.6% higher maximal workload. To put these numbers in perspective, such improvements are normally observed after prolonged, intensive exercise training of several weeks. These pilot data were recently published and represent the first description of the effect of IPC to enhance performance in the literature[17].

Aims of this research project

The general aim was to gain further insight into the potential of IPC to enhance performance in humans. First, we were interested whether, in addition to cycling exercise[17], IPC could also improve running exercise, i.e. the most common type of exercise during sports. Therefore, Aim 1 is to *examine the impact of IPC to enhance running exercise performance*.

No previous study has attempted to understand the potential mechanisms that underlie the remarkable effects of IPC on exercise performance. Data from animal studies indicate that improvement in mitochondrion function is a key mechanism underlying the beneficial effect of IPC[45,51]. Such changes may alter ATP usage and, therefore, the build-up of lactate in muscle tissues. In addition, IPC improves muscle blood flow[46], potentially improving removal of lactate[11,31]. Finally, IPC improves muscle contraction efficiency, possibly by enhancing muscle force and contractility[34] and/or via increased efficiency of excitation-contraction

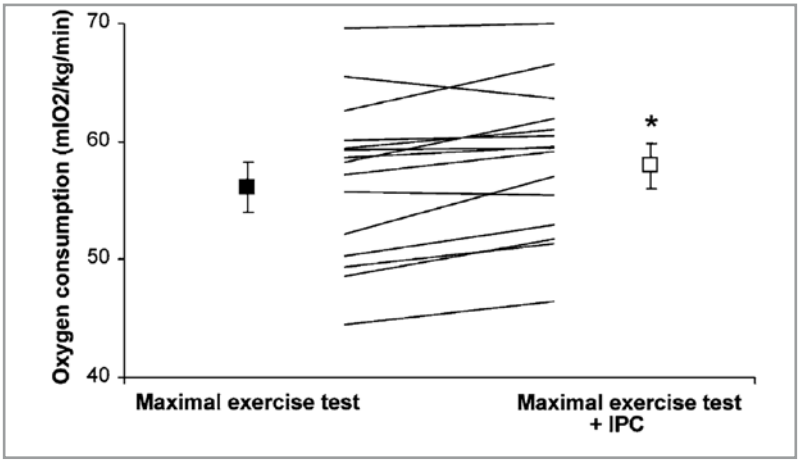

*Figure 2: Individual and mean maximal oxygen consumption (VO_2max in mlO_2/min/kg, n=15) during the maximal exercise test without (black square) and with ischaemic precondioning (open squares) (Both tests were given in a randomised order to prevent potential improvement in oxygen consumption induced by familiarisation. Error bars represent SE. *P=0.003.)*

coupling[43]. This suggests that IPC may alter lactate production and/or removal, consequently contributing to an improved exercise performance. Therefore, Aim 2a of the present study was to ***examine the potential of IPC to alter the onset of blood lactate accumulation***.

High-intensity, strenuous exercise is associated with immediate vascular injury, leading to a decrease in vascular function[16]. A reduction in function of vessels may potentially be detrimental for exercise performance[22], but also seems to be associated with a lower blood flow to the exercising limb[9]. Previous studies found that vascular injury after prolonged ischemia can be prevented by IPC[29,37]. Similarly, IPC may prevent vascular injury associated with strenuous exercise. Therefore, Aim 2b was to examine the ***effect of IPC on brachial artery vascular function after running exercise***.

In general, this series of experiments will improve our understanding of the impact of IPC to enhance exercise performance and provides insight into the underlying mechanisms. Specifically, we will examine:

AIM 1 ('*performance*'): the impact of IPC on running performance (5km time trial) in healthy subjects

AIM 2a ('*mechanism: lactate*'): the impact of IPC on the onset of blood lactate accumulation during running exercise in healthy subjects

AIM 2b ('*mechanism: vascular*'): the impact of IPC on the acute impairment in vascular function in healthy subjects after strenuous running exercise

How is this series of experiments relevant for the development of athletics?

We propose a novel and potentially efficacious approach to enhance the benefits of training to improve performance for athletes at all levels. Combining this novel intervention into sports is unique and it will not interfere with normal preparations for a match/race or with race (pacing) strategy. Another advantage is that this technique can be implemented immediately during the daily practice of athletes. Therefore, IPC directly relates to the most important aspect of athletics: i.e. performance improvement. In addition to the clear beneficial effects for daily practice of athletes, this study also provides important and novel mechanistic insight into pathways that eventually limit human performance. Such novel knowledge may mark an important and significant step forward in exercise physiology.

Methods

Participants

In a randomised, single-blind, crossover study, thirteen healthy moderately-trained males (25±6 years; 176±4cm; 77±7kg) volunteered to participate. Based on their medical history, participants were free of health problems and did not use any medication. Prior to testing, all participants were informed of the methods of the study, but remained naive of study rationale to prevent any placebo effect of IPC. All subjects provided written informed consent before participation. The study was approved by the Liverpool John Moores University ethics committee and adhered to the Declaration of Helsinki (2000).

Experimental Design

All participants refrained from alcohol, caffeine and additional nutritional training supplements for 24 hours prior to all exercise testing. Participants reported twice to the laboratory to perform the same testing procedure, either preceded by four cycles of five-minute bilateral cuff inflation to 220 mmHg (i.e. IPC-intervention) or cuff inflation to 20 mmHg (i.e. SHAM-intervention). In a randomised, single-blind, crossover study, participants performed five three-minute stages of treadmill running at 10-14 km/h to assess blood lactate accumulation (Aim 2a), which was then followed by one km/h increments every two min until voluntary exhaustion. Heart rate and oxygen consumption was continuously monitored throughout exercise. Following a 45-minute rest in the supine position, subjects performed a 5km running

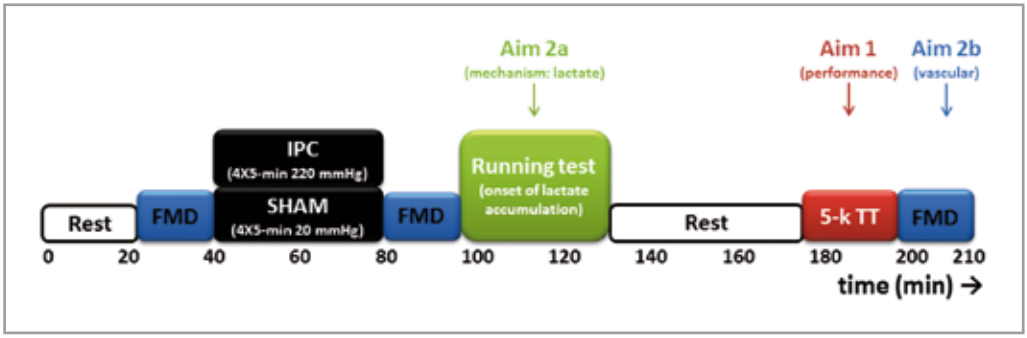

Figure 3: Experimental design to assess Aim 1 (performance), 2a ('lactate') and 2b ('vascular')

time trial on a treadmill (after being familiarised with this time trial three to four times before performance of this test) (Aim 1). For Aim 2b, brachial artery endothelial function was examined before and after the IPC- or SHAM-intervention as well as immediately after the 5km time trial (Figure 3).

Ischemic Preconditioning: IPC was performed in the supine position using bilateral arterial occlusion[18]. Automated occlusion cuffs were placed proximally around the upper thigh and inflated to 220 mmHg to block arterial inflow for five minutes. The ischemic procedure was repeated four times bilaterally, with each ischemic episode separated by five minutes of rest. On another occasion, participants followed an identical protocol, but instead the cuff was inflated to 20 mmHg (without affecting arterial inflow). The latter procedure represented the SHAM-intervention, whilst the order of days was counterbalanced.

Blood lactate accumulation (Aim 2a): A discontinuous incremental test was used to assess accumulation of blood lactate. The test commenced following a five-minute warm-up ranging between 6-10 km/h (this was standardised for all tests). Five cycles of three-minute submaximal stages (10-14 km/h) were performed, interspersed with 30 sec of passive recovery to obtain lactate measurements (5). During the test, breath-by-breath expired gases were continuously monitored (Oxycon IV, Jaeger, Germany) for oxygen consumption ($\dot{V}O_2$ ml·kg^{-1}·min^{-1}), ventilation ($\dot{V}E$ L·min^{-1}) and respiratory exchange ratio (RER) and were averaged over the last 15 sec of each stage. Heart rate was measured continuously with a chest strap and monitor (RS800, Polar, Finland), whilst ratings of perceived exertion (RPE) were measured at the end of each stage using Borg's 6-20 scale. A 2.5 ml venous blood sample was collected via a forearm cannula at rest and after each submaximal stage. Upon collection, each sample was immediately placed on ice and spun in a refrigerated centrifuge. Plasma was stored at -80°C and were later analysed for lactate concentration (Daytona, Ireland). Blood lactate concentration (in mMol^{-1}) was plotted against workload (intensity) during the incremental running test. The absolute increase in blood lactate was plotted against time and compared between both conditions. The onset of blood lactate accumulation (OBLA) was analysed as the point (km/h) that was associated with a lactate level that first exceeded the 4 mMol^{-1} threshold[28]. OBLA represents a marker of endurance capacity which is frequently used to predict endurance ability[42] and performance[4]. The reproducibility of the OBLA at a given intensity has been reported as high (r=0.88) and is able to detect meaningful changes in training status[21].

5km time trial (Aim 1): Upon completion of the running test to assess the OBLA, a 45 min rest period in the supine position followed, then a 5km running time trial was performed on a

motorised treadmill (Pulsar 4.0, H/P Cosmos, Germany). Participants were instructed to run five kilometres as quickly as possible. The running time and running speed were blinded to the participant. The speed of the treadmill was set at 8 km/h, and once the participant was ready the time trial was started. Throughout the time trial, participants were allowed to alter running speed, but were kept blinded for running speed and running time. The only information available to the participants during each time trial was total distance covered (m) as to adjust work-output to pace towards the known endpoint[1]. No further information or encouragements were provided. Heart rate was monitored continuously, with RPE was recorded at the end of each 1000m. All trials were performed with a fan placed 0.5m in front of the treadmill to provide air circulation and cooling to the participant to match field conditions. The 5km time trial has previously shown to have a greater absolute reliability, compared to time-to-exhaustion tests of the same relative intensity[33]. Before the beginning of the experimental trials participants received at least three supervised familiarisation trials. The 5km time trial revealed a coefficient of variation (CV) of 2.2% test-retest in participants after familiarisation. This finding is in line with previous studies[24,33].

Brachial artery endothelial function (Aim 2b): Brachial artery endothelial function was measured using the flow-mediated dilation (FMD) technique[48]. This method provides an index of vascular function of the brachial artery. This measure was performed before and after the IPC/SHAM-intervention to examine the potential immediate effect, but also after the 5km time trial to examine whether IPC can prevent the decline in FMD after strenuous exercise. For this purpose, participants were instructed to abstain from strenuous exercise for 24 hrs and from caffeine and alcohol ingestion for 18 hrs before attending the laboratory. Measurements were performed in the supine position. Baseline assessment was performed after resting for 20 minutes, followed by assessment of heart rate and blood pressure using an automated sphygmomanometer (GE Pro 300V2, Dinamap, Tampa, FL). This was followed by assessment of brachial artery diameter and velocity.

To examine brachial artery FMD, the arm was extended and positioned at an angle of ~80° from the torso. A rapid inflation and deflation pneumatic cuff (D.E. Hokanson, Bellevue, WA) was positioned on the forearm, immediately distal to the olecranon process to provide a stimulus to forearm ischemia. A 10MHz multi-frequency linear array probes, attached to a high-resolution ultrasound machine (T3000; Terason, Burlington, MA) was then used to image the brachial artery in the distal 1/3rd of the upper arm. Continuous Doppler velocity assessments were obtained using the ultrasound and were collected using the lowest possible isonation angle (always <60°). Following baseline assessments, the forearm cuff was inflated (>200 mmHg) for five minutes. Diameter and flow recordings resumed 30 sec prior to cuff deflation and continued for three minutes thereafter, in accordance with recent technical specifications[6,50]. Post-test analysis was performed using custom-designed edge-detection and wall-tracking software, which is largely independent of investigator bias[6,50]. From synchronised diameter and velocity data, blood flow (the product of lumen cross- sectional area and Doppler velocity) and shear rate (four times mean blood velocity/vessel diameter) were calculated at 30Hz. Reproducibility of diameter measurements using this semi-automated software is significantly better than manual methods[50].

Statistics

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) software. All data are reported as means (±SD), and statistical significance assumed at $P<0.05$. For all analyses, trial order (IPC or C first) was entered into the statistical model as a between subjects factor. According to recent advice, the least significant difference (LSD) test was used for pair-wise multiple comparisons[44,47].

For Aim 1 ('performance'), A ***Students'*** paired ***t***-test was used to compare 5km time trial performance (IPC ***versus*** C). In addition, a 2-factor repeated measures GLM (trial x time) was also used to examine differences in parameters during the 5km time trial (RPE, running speed and heart rate).

For Aim 2a ('mechanism: lactate'), a 2-factor (trial x time) repeated measures GLM with 95% confidence intervals was used to assess differences in parameters (blood lactate levels, oxygen consumption and heart rate) during the five stages of the incremental test to examine our primary hypothesis. Also, a one-factor repeated measures GLM was used to compare OBLA (IPC versus C).

For Aim 2b ('mechanism: vascular'), we deemed it important to control for the influence of moderators of FMD (shear rate and baseline diameter). We therefore analysed the effects of trial and time on logarithmically-transformed diameter changes using a Generalised Estimating Equation (GEE) which incorporated baseline diameter and shear rate as covariates. Mean and 95% confidence intervals (95% CI) for the effect magnitudes of brachial artery FMD are cited.

RESULTS

5km time trial (Aim 1)

Mean time trial performance significantly improved following the IPC-intervention (34±49 sec, 95% CI five to 64 sec, *P*=0.027) (Figure 4). Running speed and heart rate gradually increased during the 5km time trial, but these increases were similar between conditions (Table 1). Post-hoc analysis showed that the RPE was significantly lower during the first 1000m of the 5km time trial after IPC compared to the control intervention, but this difference disappeared when continuing exercise (Table 1).

Blood lactate accumulation (Aim 2a)

Heart rate, oxygen consumption, ventilation and ratings of perceived exertion increased across the five incremental stages, but these increases were of similar magnitude in both conditions (Table 2). Resting blood lactate levels were similar between both tests (Figure 5).

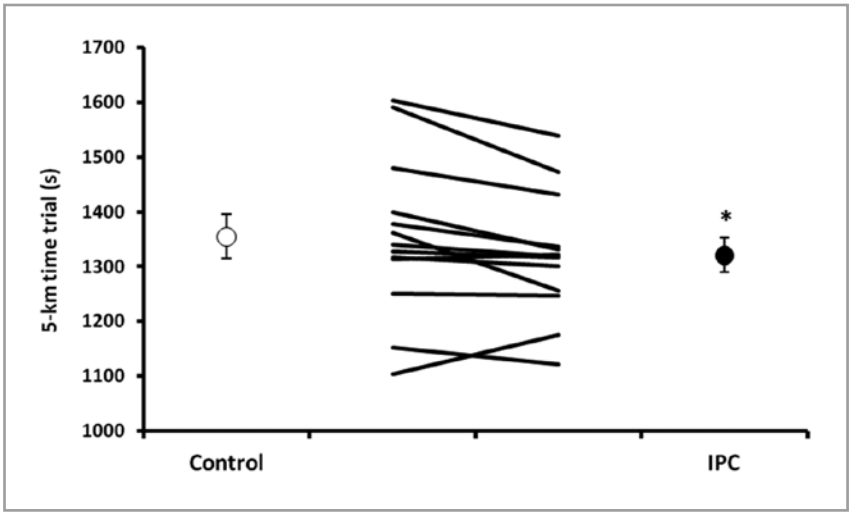

Figure 4: Aim 1: Performance (Individual and mean (error bars represent SD) data on 5km time trial performance after IPC and control interventions in healthy young men (n=13) (denotes a significant treatment effect of IPC, P=0.027.)*

Table 1: Exercise characteristics during the 5km time trial in healthy subjects (n=13)

Heart rate (b·min^{-1})	**1000m**	**2000m**	**3000m**	**4000m**	**5000m**	**P-values**
Control	167±8	173±7	176±5	177±5	185±6	Time: <0.001
IPC	166±11	172±6	177±8	179±5	189±7	IPC: 0.159
						Time*IPC: 0.180
RPE						
Control	14±3	15±2	16±1	17±1	19±1	Time: <0.001
IPC	13±3*	15±2	16±1	17±1	19±1	IPC: 0.136
						Time*IPC: 0.030
Running speed (km·h^{-1})						
Control	12.8±1.5	13±1.5	13.2±1.5	13.7±1.6	14.3±2.2	Time: <0.001
IPC	13±1.0	13.5±1.2	14.1±1.3	14±1.5	14.7±1.6	IPC: 0.371
						Time*IPC: 0.387

*Significantly different between IPC and C at P<0.05. RPE; ratings of perceived exertion.

Blood lactate concentration increased over time in both conditions (P<0.001). When exercise was preceded with IPC, a smaller increase in blood lactate was observed, resulting in a difference between both tests of 1.07±0.11 mMol^{-1} at 14 km/h (Figure 5). A later OBLA was evident when exercise was preceded with IPC, but did not reach statistical significance (13.1±1.9 and 14.6±1.4 km/h, mean difference 1.5-km/h, 95% CI -0.18 to 3.87, ***P***=0.071).

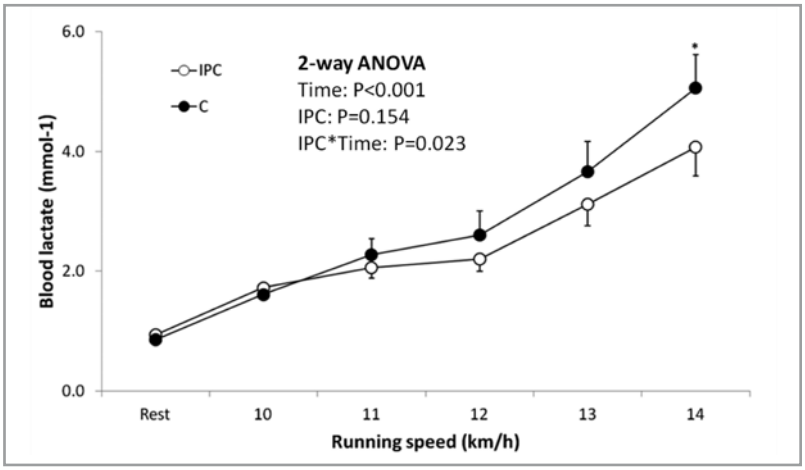

*Figure 5: Aim 2a: lactate (Blood lactate levels at rest at all five submaximal stages during the incremental running tests. Exercise preceded by IPC shown with solid circles and exercise preceded by control intervention shown with open circles. Error bars represent SE. *Post hoc significantly different between C and IPC.)*

Table 2: Exercise characteristics during incremental stages during running test in healthy subjects (n=13)

	10 km/h	11 km/h	12 km/h	13 km/h	14 km/h	P-values
VO_2($mLO_2 \cdot kg^{-1} \cdot min^{-1}$)						
Control	34.1±2.58	36.5±2.2	39.4±2.5	42.1±2.4	45.3±2.8	Time: <0.001
IPC	34.4±1.2	36.6±1.2	39.5±1.8	41.9±2.3	45.0±2.8	IPC: 0.971
						Time*IPC: 0.796
VE ($L \cdot min^{-1}$)						
Control	65±9	72±11	81±15	94±18	107±19	Time: <0.001
IPC	65±9	73±10	81±13	94±19	106±18	IPC: 0.88
						Time*IPC: 0.630
RER						
Control	0.84±0.03	0.88±10.4	0.91±0.03	0.94±0.05	0.99±0.04	Time: <0.001
IPC	0.83±0.03	0.86±0.04	0.91±0.03	0.94±0.07	0.98±0.03	IPC: 0.378
						Time*IPC: 0.521
Heart rate ($b \cdot min^{-1}$)						
Control	136±12	152±14	166±8	175±7	181±12	Time: <0.001
IPC	136±13	150±12	166±11	176±5	182±14	IPC: 0.761
						Time*IPC: 0.540
RPE						
Control	10±2	12±2	13±2	14±1	16±1	Time: <0.001
IPC	10±2	12±2	13±2	14±2	16±2	IPC: 0.357
						Time*IPC: 0.841

RPE; ratings of perceived exertion, VE; ventilation, RER; respiratory exchange ratio

Brachial artery endothelial function (Aim 2b)

No differences in baseline diameter and SR_{AUC} were found at baseline between testing days or after the IPC- or SHAM-intervention (all P>0.05). At baseline, differences in FMD were negligible and non-significant between the SHAM [5.3% (4.5-6)] and IPC [4.8 (3.6-5.9)] trials (P>0.05). FMD changed by less than 0.6% immediately after both the IPC and SHAM interventions (P>0.30, Table 3). In the SHAM trial, FMD decreased following the 5km time trial (P=0.02). However, in the IPC trial FMD was similar post-IPC and post-5km time trial, with an FMD of 5.4% (4.4-6.4) and 5.7% (4.6-6.8) (P=0.60; Figure 6), respectively. IPC had no effect on the change in baseline diameter and SR_{AUC} (Table 3).

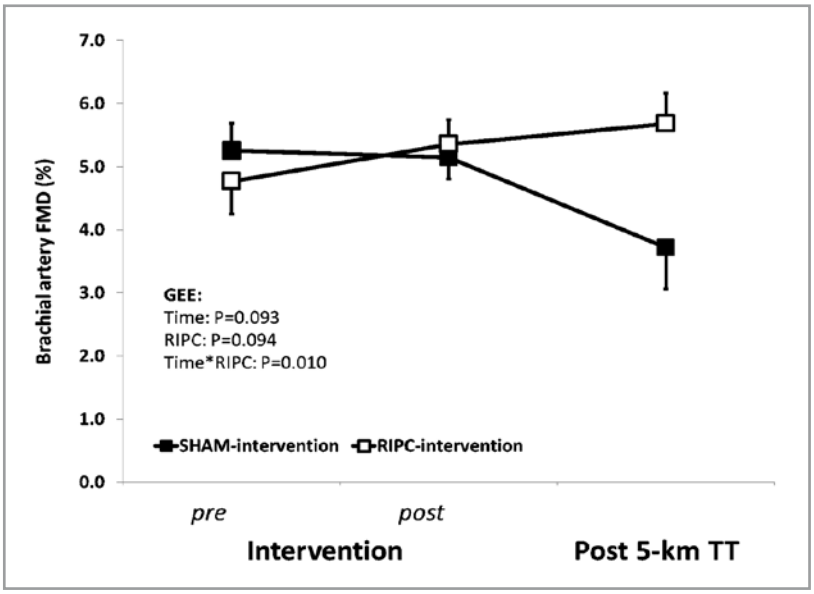

Figure 6: Aim 2b: vascular (Brachial artery flow-mediated dilation (FMD) before (pre) and after (post) the intervention (IPC or SHAM) as well as post 5km time trial in health, volunteers (n=11, two participants were not included due to technical problems) during the SAHM- (solid squares) and IPC-intervention (open squares). Error bars represent 95% CI. Data from the GEE were included in the figure.)

*Table 3: Brachial artery FMD before (pre) and after (post) the IPC or SHAM intervention as well as after the 5km time trial (TT) in healthy volunteers (n=11, one subject was missing because of technical problems) (Data is presented as mean (95% Confidence Intervals). P-values refer to a Generalised Estimating Equation (effect of 'time', 'IPC' and 'time*IPC').)*

	Intervention		Post 5km TT	P-values
	pre	*Post*		
D_{rest} (mm)				
SHAM	0.41(0.38-0.44)	0.41(0.39-0.43)	0.44(0.41-0.47)*	Time: <0.001
IPC	0.41(0.39-0.44)	0.41(0.38-0.43)	0.44(0.41-0.47)*	IPC: 0.688
				Time*IPC: 0.607
SR_{AUC} (s, 10^3)				
SHAM	15.7 (12.4-19.0)	16.3 (12.8-19.7)	32.8 (24.6-41.0)*	Time: <0.001
IPC	11.4 (7.8-15.1)	13.8 (11.5-16.1)	26.8 (20.5-33.1)#	IPC: 0.009
				Time*IPC: 0.262

Post-hoc significantly at P<0.05 different from *pre-intervention or #SHAM

Discussion

The general aim of this study was to examine the potential of IPC to enhance exercise performance and to elucidate potential underlying mechanisms for this effect. First, our study is the first to demonstrate that IPC can improve running exercise performance. Moreover, we provided the first insight into potential mechanisms, providing strong evidence that IPC is associated with a reduction in blood lactate accumulation during submaximal running exercise. In addition, IPC was associated with the prevention of impaired vascular function that is typically observed after strenuous exercise. Therefore, our results may have important consequences for athletes to improve exercise performance.

Impact of IPC on performance

Recent studies, including from our laboratory, have highlighted the potential of IPC to improve cycling and swimming exercise performance[14,18,27]. Our data add novel information that IPC also improves running performance; i.e. the most common mode of exercise in athletics and during (team) sports. Due to our experimental set-up, our data provides important practical insight into the application of IPC for athletes. First, previous researchers have observed beneficial effects of IPC when applied immediately before exercise, which is associated with obvious practical limitations for athletes. In our study, the faster 5km time trial was performed 90 min ***after*** IPC. This indicates that the benefits of IPC on exercise performance have a longer time-window than initially anticipated. In addition, the benefits of IPC were apparent in the 5km time trial, despite performing a running test prior to this time trial. This suggests that the effects of IPC remain, even after an initial exercise bout. Practically, these observations are highly important, as application of IPC during athletic competitions will likely be performed well before the actual performance event, even before the warm-up stage.

Impact of IPC on mechanisms: lactate

Oxygen uptake at the lactate threshold represents the strongest predictor for maximal oxygen uptake [12, 39]. Lower blood lactate concentrations at a given workload are therefore associated with improved exercise economy, including in highly trained athletes [36, 39]. Interestingly, data in our study indicates that IPC attenuates the accumulation of blood lactate during an incremental running test, a finding that is supported by the trend for a later onset of blood lactate accumulation. More specifically, we found significantly lower blood lactate levels after IPC at submaximal running speed of 14 km/h, which may relate to the improved exercise performance during the 5km time trial (performed at average speed of 13.7 km/h after IPC, compared to 13.1 km/h after SHAM).

It is important to note that the attenuated accumulation of lactate during exercise is not explained by differences in absolute or relative exercise intensity level between tests (Table 2). Moreover, due to our randomisation procedure and statistical analysis, familiarisation or order-effects are unlikely explain our findings. A potential explanation for the altered lactate levels may relate to a faster removal and/or lower production of lactate during exercise. For example, IPC may work through improvements in vascular function, which regulates blood flow to remove blood lactate, but also enhances blood flow to ensure sufficient O_2 supply (resulting in dominance of aerobic glycolysis and less lactic acid production). Also, increases in mitochondrial capacity importantly contribute to endurance performance[25]. Previous studies in animals and humans indicate that IPC enhances mitochondrial capacity, most likely via ATP-sensitive potassium channels located on the inner membrane[46]. An alternative but not mutually exclusive explanation could relate to a reduction in muscle lactate production after IPC. Animal studies have shown previously that IPC can enhance muscle efficiency in ATP-usage via ATP-sparing, augmented function of the mitochondrion or increased efficiency in the excitation-contraction coupling[27, 34, 43].

Nevertheless, within the bounds of our current data we can only speculate about the mechanisms underlying the lower blood lactate levels at submaximal workload with IPC

Impact of IPC on mechanisms: vascular

Based on the importance of blood flow control during exercise, changes in performance after IPC may also relate to the vasculature. First, we confirmed findings from previous studies[16, 23, 35] that brachial artery endothelial function (i.e. vascular function) is reduced after strenuous running exercise. More importantly, a unique and novel finding in our study is that the decrease in vascular function was abolished when exercise was preceded by IPC. Several previous studies have established that IPC can prevent vascular injury after prolonged periods of ischemia[30, 37, 38] or prevent cardiac damage in clinical groups, as evidenced by smaller increments in ischemic biomarkers and infarct size[7, 10]. In line with these observations, we add the novel observation that IPC also protects against the acute decrease in vascular function observed after strenuous exercise. Our findings may have clinical consequences, as an attenuated vascular function is associated with an impaired exercise-induced blood flow[9]. Although speculative, prevention of the impaired vascular function and blood flow response during strenuous exercise by IPC may contribute to the enhanced exercise performance.

Our findings that application of IPC to the lower limbs prevents a decrease in upper limb brachial artery vascular function indicate that the effects of IPC are systemic rather than localised. Strenuous exercise in humans is associated with increased levels of oxidative stress, which may be linked to the development of vascular dysfunction after exercise[20]. Interestingly, previous studies provided evidence that IPC upregulates cellular antioxidant defence mechanisms, thereby preventing tissue damage[13, 40]. In addition, IPC has well-established effects on vasodilators, such as adenosine and bradykinin, which may contribute to the protective effects of IPC against cellular damage and increase blood supply to the exercising muscles during strenuous exercise[46]. Although the underlying mechanisms are not fully understood, prevention of vascular damage after strenuous exercise may contribute to the effect of IPC on sport performance and/or recovery from exercise.

What are limitations of our study?

A potential limitation of this study is that we provided limited insight into the practical application of IPC in athletes to enhance performance level. Little is known about optimising the protocol for IPC (number of ischaemic events + duration of ischaemia for an optimal benefit on exercise performance). Based on the findings presented in this series of experiments, logical follow-up studies include the assessment of different (timing of) IPC-protocols. Such knowledge will further improve the practical implication of this technique in daily routine for athletes to enhance sport performance.

Clinical relevance: who will benefit?

An obvious question that arises from our data is whether all athletes benefit from IPC to enhance performance. In a recent study, we examined the impact of IPC during a repeated anaerobic sprint test and repeated cycling sprints in elite rugby players[3]. Interestingly, we found a found a moderate to strong effect size for IPC to enhance power output during high-intensity cycling exercise and attenuate running time and cycling sprint output during repeated sprint exercise. This observation confirms findings from a recent study, which found improved performance of 0.7 sec during the 100m freestyle in elite swimmers after IPC of the upper limbs[15]. In addition to running exercise, evidence (including from our laboratory) supports a potential for IPC to improve cycling performance[14, 18], and swimming times[27]. Finally, the beneficial effects of IPC on exercise performance seems to relate to sprinting[3], short-term exercise (1-2 minutes) [27], moderate-term exercise[14, 18], and to endurance exercise (i.e. 5km time trial). Taken together, our introduction of IPC as a potential strategy to improve exercise may apply to all athletes, which is unique as most interventions are specific for a single sport event only.

Conclusions and Recommendations

In conclusion, we have established the potential of IPC to improve running exercise performance in healthy men. In addition to the remarkable effect on exercise performance, we provided novel mechanistic insight into the potential mechanisms that may explain this effect. First, we found that IPC attenuates blood lactate accumulation during submaximal exercise. Second, IPC prevented impairment in vascular function that is typically associated with strenuous running exercise. The lower blood lactate accumulation and improved vascular function by IPC may contribute to an enhanced exercise performance. Thus, the series of experiments performed in our laboratory have introduced IPC as a novel, cheap, easy applicable and non-invasive strategy to improve exercise performance in humans.

Technical advances have demonstrated value in the history of sport. However, development takes a long time, has problems with implementation (disqualification in the worst case scenario), is associated with high costs, and is always restricted to a single sports event. We have provided strong evidence that a novel, low cost, and easy applicable tool (i.e. repeated cuff inflation during warm-up) can enhance sport performance. Recommendation for application of this novel method in athletes is very broad:

1. IPC has a large potential for most ***Olympic athletes*** and is not restricted to a single event.

2. IPC can be applied ***acutely (short term)*** and therefore is clinically relevant.

3. IPC can be applied at all levels (moderate ***versus*** elite athletes, Paralympics ***versus*** Olympics).

4. IPC is a ***legal, simple, easy accessible and a low cost*** intervention that can easily be applied.

5. IPC can be applied ***without interference*** with the athlete's training programme, development of sport-specific techniques or competition tactics

Whilst the focus of this report is on (elite) athletes, we believe that IPC may benefit various groups. A logical follow-up from this project will be the application of IPC in various patient groups. These groups experience important limitations to perform exercise and benefit from exercise training (such as cardiovascular disease, diabetes mellitus, COPD). Application of IPC may enable these groups to improve their performance and benefit to exercise training. Currently, we are performing the first studies in spinal cord-injured individuals and heart failure patients to examine the potential of IPC. Such interventions could lead to a larger benefit of exercise training for patient groups. *This also marks the potential of IPC to lead to clinically meaningful improvements in health for various patient groups.*

Taken together, the studies performed in our laboratory have resulted in the first description of the potential of IPC to improve performance. The follow-up studies, partly described in this report, consolidate the practical benefit of IPC to improve performance in various groups, whilst we have produced the first mechanistic insight to understand these remarkable effects of 'ischaemic preconditioning'. Therefore, our introduction of IPC represents a large step forward for (applied) exercise physiology and the athlete's benefit. More importantly, our series of experiments have introduced a cheap, non-invasive, legal, easy to apply manner that are suitable for all types (endurance-sprint), levels (moderate vs elite, paralympics vs olympics) and modes (cycling vs running) of exercise to enhance performance which can be implemented immediately.

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