Remote Preconditioning Improves Maximal Performance in Highly Trained Athletes

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ABSTRACT

JEAN-ST-MICHEL, E., C. MANLHIOT, J. LI, M. TROPAK, M. M. MICHELSEN, M. R. SCHMIDT, B. W. MCCRINDLE, G. D. WELLS, and A. N. REDINGTON. Remote Preconditioning Improves Maximal Performance in Highly Trained Athletes. *Med. Sci. Sports Exerc.*, Vol. 43, No. 7, pp. 1280–1286, 2011. **Background**: Remote ischemic preconditioning (RIPC) induced by transient limb ischemia releases a dialysable circulating protective factor that reduces ischemia–reperfusion injury. Exercise performance in highly trained athletes is limited by tissue hypoxemia and acidosis, which may therefore represent a type of ischemia–reperfusion stress modifiable by RIPC. **Methods and Results**: National-level swimmers, 13–27 yr, were randomized to RIPC (four cycles of 5-min arm ischemia/5-min reperfusion) or a low-pressure control procedure, with crossover. In study 1, subjects (n = 16) performed two incremental submaximal swimming tests with measurement of swimming velocity, blood lactate, and HR. For study 2, subjects (n = 18) performed two maximal competitive swims (time trials). To examine possible mechanisms, blood samples taken before and after RIPC were dialysed and used to perfuse mouse hearts (n = 10) in a Langendorff preparation. Infarct sizes were compared with dialysate obtained from nonathletic controls. RIPC released a protective factor into the bloodstream, which reduced infarct size in mice ($P < 0.05$ for controls and swimmers). There was no statistically significant difference between the effect of RIPC and the low-pressure control protocol on submaximal exercise performance. However, RIPC was associated with a mean improvement of maximal swim time for 100 m of 0.7 s ($P = 0.04$), an improvement in swim time relative to personal best time (−1.1%, $P = 0.02$), and a significant improvement in average International Swimming Federation points (+22 points, $P = 0.01$). **Conclusions**: RIPC improves maximal performance in highly trained swimmers. This simple technique may be applicable to other sports and, more importantly, to other clinical syndromes in which exercise tolerance is limited by tissue hypoxemia or ischemia. **Key Words:** EXERCISE, ISCHEMIA, REPERFUSION INJURY, PRECONDITIONING

Ischemia and reperfusion are key components of many cardiovascular diseases and their treatments. Whether deliberately imposed (e.g., during cardioplegic cardiac arrest during open heart surgery or during balloon coronary angioplasty) or because of the disease itself (e.g., coronary thrombosis), prolonged ischemia may lead to cellular dysfunction, apoptosis, and cell death, which might be amplified by reperfusion injury after restoration of blood flow. Ischemic preconditioning is a potent endogenous mechanism that has been demonstrated to protect tissues against ischemia–reperfusion injury. First described in 1986 by Murry et al. (16), this protective phenomenon was shown to result from short, nonlethal ischemic episodes to the target tissue before a prolonged potentially lethal period of ischemia (13,14,19,23). Whereas the stimuli, signaling mechanisms, and downstream effects of ischemic preconditioning have been described in detail (7,24), its clinical utility has been limited by the need to render the target organ ischemic before a predictable injury. Remote ischemic preconditioning (RIPC) is a more clinically applicable stimulus that has translated into several randomized clinical trials (12). RIPC releases a circulating protective factor into the bloodstream (22), the liberation of which is induced by cycles of inflation and deflation of a standard blood pressure cuff on a limb. RIPC has been shown to protect the heart and lungs against ischemia–reperfusion injury in children undergoing cardiac surgery using cardiopulmonary bypass (5) and has also been shown to reduce evidence of cardiac damage in adults undergoing cardiac (10) and vascular surgery (1), during elective coronary stenting (11), and, most recently, to reduce infarct size after emergency percutaneous coronary intervention in evolving myocardial infarction (3). Recently, local preconditioning of the legs was found to improve maximal performance by 1.6% and maximal oxygen consumption by 3% in healthy subjects undergoing bicycle testing (9). The study of highly trained athletes represents a unique opportunity to study the human adaptation to a form of relative tissue ischemia/hypoxemia, in this case, maximal exercise performance. Swimming, in particular, represents a unique physiological challenge to athletes. During high-intensity swimming,

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Submitted for publication July 2010.
Accepted for publication November 2010.

0195-9131/11/4307-1280/0
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DOI: 10.1249/MSS.0b013e318206845d

the entrained nature of the breathing cycle results in breath holding, which can result in significant decreases in the arterial partial pressure of oxygen (PaO_2) resulting in exercise-induced arterial hypoxemia and decreased blood pH (increased [H^+]) relative to non–frequency-controlled breathing exercise (6,18,21). Exercise-induced arterial hypoxemia may be a significant contributor to the development of fatigue in skeletal, respiratory, and cardiac muscles (17) responsible for the physiological limitation in maximal swimming exercise.

Therefore, we examined the possibility that RIPC before extreme exercise could render tissues more resistant to the adverse metabolic effects of high-intensity exercise, in much the way it modifies tissue responses to clinical ischemia. It was hypothesized that RIPC would improve maximal and submaximal swimming exercise performance of highly trained swimmers. The primary aim of this study was to evaluate the effect of RIPC on exercise performance in highly trained swimmers. Our secondary aim was to determine whether highly trained athletes have the same preconditioning potential as control nonathletic subjects using a mouse model of global myocardial infarction.

METHODS

Subjects

A double-blind crossover randomized control trial was performed. The Hospital for Sick Children Research Ethics Board approved the protocol that was registered before study initiation (identifier: NCT00761566, registered November 2008). Subjects were selected from Canadian competitive swimming teams at both the national and international levels. Healthy male or female swimmers between 13 and 27 yr who had previously achieved a swimming performance time within national championship qualification standards were included in the study. The swimmers' best performances were evaluated using an international point score system (15) recognized by the International Swimming Federation (FINA), which permits the comparison of performance by male and female swimmers in any of the different swimming events (freestyle, backstroke, breaststroke, butterfly, and individual medley). This system ascribes a point score to each swim scaled to 1000 points (a score of 1000 points is equal to the mean of the eight fastest times in the history for that event). Subjects with scores above 700 were included in the study. The participants in the submaximal protocol (n = 17) also completed the maximal study, and an additional six subjects completed the maximal protocol (n = 23). Subjects with diabetes mellitus, a recent illness, recent surgery, or any medical intervention in the 48 h before any of the study days were excluded. Informed written consent was obtained from subjects or from minor subjects' parents or guardians before enrollment in the study. On a separate occasion, we performed an experimental study in a subgroup of control subjects and swimmers to assess the release of humoral preconditioning factors during RIPC. Blood samples were obtained before and after RIPC, using an identical RIPC protocol, and prepared for *in vitro* validation using our previously described Langendorff method (22).

Procedures

Randomization and preconditioning protocol. The randomization list was computer generated. The randomization codes were sealed in opaque envelopes and assigned to the athletes after their enrollment in the study. Subjects were randomized to the order by which they received either four 5-min cycles of upper limb ischemia interspaced with 5 min of reperfusion or a control procedure with low-pressure cuff inflation, with crossover at the second study period. Ischemia was achieved by one of the investigators inflating a blood pressure cuff to a pressure of 15 mm Hg greater than measured systolic arterial pressure. For the low-pressure control procedure, the blood pressure cuff was inflated to only 10 mm Hg. The "reperfusion" period consisted of 5 min after full cuff deflation. On the subsequent study date, separated by 1 wk from the previous one, the subjects were submitted to the intervention they had not received; therefore, the data from each subject are reported as a comparison. All other study investigators and participants were blinded to treatment assignment for the duration of the study. The group allocation was not revealed to the investigators until the end of the statistical analysis, and the athletes were not told which inflation could be beneficial to their swimming performance. The participants completed the preconditioning immediately before beginning their standardized warm-up, which lasted approximately 40–45 min. The test procedures were then completed after the warm-up. Figures 1 and 2 show the details of subjects' recruitment and randomization for both the submaximal and maximal exercise test protocols (see below). There were no adverse events or adverse effects associated with the real or low-pressure control remote preconditioning intervention.

Exercise protocols. ***Submaximal incremental swimming test.*** The submaximal exercise swimming protocol has been previously reported (20,25). The test was conducted in a long course pool (i.e., 50 m in length). Before the swimming test, participant's weight and height were measured (26). Each submaximal swim test consisted of seven sequential 200-m swims. Each 200-m swim commenced at 6-min intervals and began from a push start. The coach calculated the required speed for each 200-m swim before the test, and the participants were informed of these target speeds before the test began. Each target speed was based on a fixed percentage of the participant's best time. For example, the first 200 m were swum at a speed that would result in a time equal to the individual's best time + 35 s. Thereafter, each subsequent 200 m was completed approximately 5 s faster than the preceding swim. Time, HR (RS 800; Polar Electro, Inc., Kempele, Finland), stroke rate, and blood lactate were measured and recorded for each swimming increment. Blood samples were obtained from a

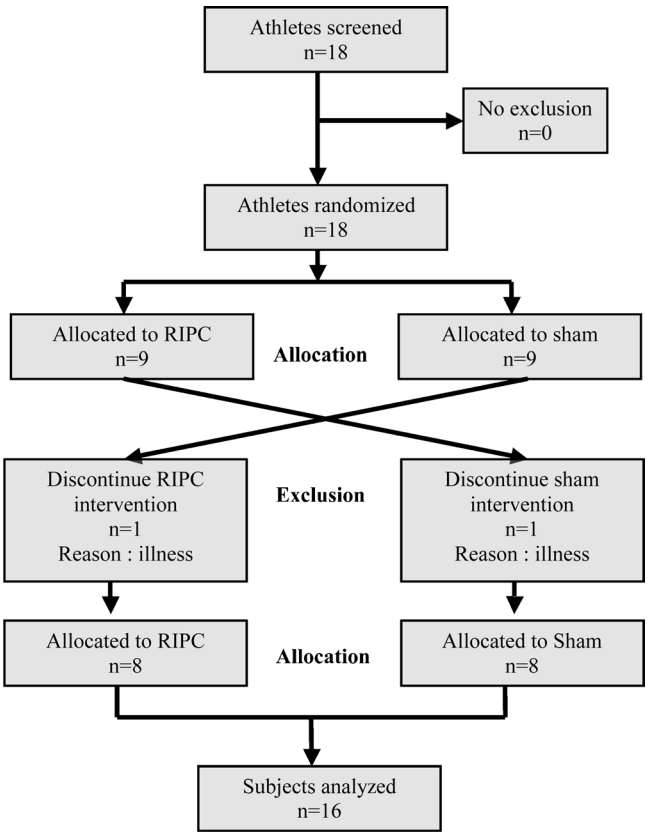

FIGURE 1—Submaximal exercise testing protocol flow diagram.

finger stick and analyzed using the Lactate Pro LT-1710 Analyzer (Arkray, Inc., Kyoto, Japan) approximately 2 min after the completion of each swim. The swimmers were asked to swim the performance test in their best stroke style (e.g., freestyle, backstroke, breaststroke, fly, individual medley).

Maximal competitive swimming test. The maximal swimming performance test was also completed in a long course pool. The swimmers swam their preferred swim length, 100 m (n = 16) or 200 m (n = 2), using their best stroke style at 100% effort. Blood lactates were measured before and after the test. Time, blood lactate, and stroke rate were also measured. Blood samples were obtained from a finger stick and analyzed using the Lactate Pro LT-1710 Analyzer (Arkray, Inc.) approximately 2 min after the completion of the swim. The maximal swimming performance testing was done either in a competitive or in a simulated competitive environment. In both cases, warm-up procedures were identical in both test conditions. The primary end point of the submaximal study was an improvement in the critical velocity, defined as the extrapolated intersection between the maximal HR and swimming velocity of preconditioned subjects during incremental exercise testing. The primary end point for the maximal exercise test was the swim time. Our secondary end points were change in peak blood lactate level and change in stroke rate.

Langendorff protocol. All animal protocols were approved by the Animal Care and Use Committee of the Hospital for Sick Children in Toronto and conformed with the *Guide for the Care and Use of Laboratory Animals* published by National Institutes of Health (publication No. 85-23, revised 1996). Blood samples (30 mL) were obtained before and after RIPC in nine of the national-level swimmers and four control healthy nonathletic subjects. Our experimental method has been described in detail in a previous publication (22). Briefly, the blood was collected in heparinized tubes and immediately put on ice before centrifuging at 3000 rpm for 20 min at room temperature. The plasma fraction was carefully removed without disturbing the buffy coat, and it was placed in a 12- to 14-kDa dialysis tubing (SpectraPor) and dialysed against a 10- or 20-fold volume of Krebs–Henseleit solution. For use in the Langendorff system, the dialysate was made isotonic by adjusting the salts: 130 mmol·L^{-1} NaCl, 0.5 mmol·L^{-1} $MgSO_4 \cdot 7H_2O$, 4.7 mmol·L^{-1} KCl, 1.0 mmol·L^{-1} $CaCl_2$, 1.2 mmol·L^{-1} KH_2PO_4, and 20 mmol·L^{-1} HEPES in a 10× Krebs–Henseleit buffer stock. Finally, the pH was adjusted to 7.4 by adding sodium bicarbonate ($NaHCO_3$) and glucose. The dialysate was equilibrated to 37°C and oxygenated for 20 min before use in the mouse Langendorff. The mice were anesthetized with pentobarbital (60 mg·kg^{-1}, intraperitoneally), and the hearts were excised, chilled with

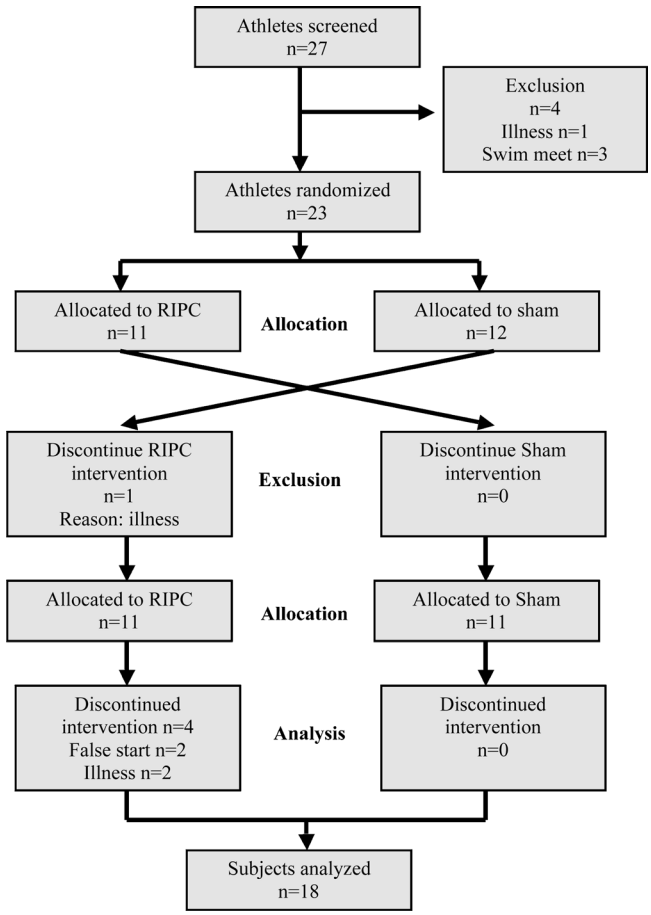

FIGURE 2—Maximal exercise testing protocol flow diagram.

cold saline, and cannulated under a microscope via the aorta. The hearts were then perfused in the Langendorff mode with modified Krebs–Ringer buffer at 37°C consisting of 119 mmol·L^{-1} NaCl, 4.8 mmol·L^{-1} KCl, 1.3 mmol·L^{-1} $CaCl_2$, 1.2 mmol·L^{-1} KH_2PO_4, 1.2 mmol·L^{-1} $MgSO_4$, and 25 mmol·L^{-1} $NaHCO_3$. A water-filled latex balloon was placed in the left ventricular cavity via the mitral valve. This balloon was connected to a pressure transducer and kept a constant pressure of 6 mm Hg. The peak left ventricular developed pressure was continuously monitored. Each heart underwent an initial 20-min stabilization period. The hearts were then perfused with the human dialysate, and subsequently subjected to 30 min of global zero-flow ischemia, followed by 60 min of postischemia reperfusion. The hemodynamic measurements, including HR, peak left ventricular pressure, the maximum rate of pressure increase ($+dP/dt_{max}$), the maximum rate of pressure decrease ($-dP/dt_{max}$), and the coronary flow were recorded throughout the experiment. After completion of the Langendorff protocol, the hearts were frozen with liquid nitrogen after being submerged in a high-potassium solution and stored at −80°C. The hearts were put into a slicer matrix and cut into 1- to 2-mm-thick slices (approximately five slices per heart). The slices were immersed in a 1.25% 2, 3, 5-triphynyltetrazolium chloride (T8877; Sigma, St. Louis, MO) and kept in a water bath at 40°C for 15 min to allow us to distinguish between dead tissue areas that become white or tan in color from viable tissue area that becomes a brick red color. The slices were fixed in 10% formalin and scanned. Using Photoshop, the different areas were traced, and the percentage of infarcted area was expressed as a ratio of the total left ventricular area (22). Intraobserver reliability was assessed. We found a high level of agreement (correlation 98%, $P < 0.001$) and no evidence of significant bias (mean bias = −1.12 ± 4.62, 95% confidence interval (CI) = −10.20 to +7.96, $P = 0.25$). Our primary end point for the Langendorff protocol was percentage of infarcted area. Our secondary end points were peak left ventricular developed pressure, HR, maximum rate of pressure increase ($+dP/dt_{max}$), the maximum rate of pressure decrease ($-dP/dt_{max}$), and the coronary flow.

Statistical Analysis

Data are described as means with SD, median with minimum and maximum values, and frequencies as appropriate. Differences between exercise performances between RIPC and low-pressure control procedure were assessed in paired *t*-tests. Difference in infarct size between mice hearts perfused with highly trained athletes' dialysate and normal controls' dialysate were assessed using Student's *t*-tests. The effects of potential confounders including subjects' age, gender, personal best time, FINA ranking, competitive level, stroke, and order of randomization were assessed in linear regression models adjusted for repeated measures through a compound symmetry covariance structure. All statistical analyses were performed using SAS statistical software v9.1 (SAS Institute, Cary, NC).

RESULTS

Athletes were recruited between November 2008 and January 2010. A total of 27 athletes from four different swimming teams across Canada (Vancouver, Toronto, and Guelph) were eligible for randomization. The submaximal exercise test was completed by 16 athletes (Fig. 1), and 22 subjects completed the maximal exercise intervention (Fig. 2). Three athletes were unable to participate in the maximal performance testing because of a conflict with their competition schedule and one subject because of illness. Six swimmers were excluded from the analysis because of false starts and/or illnesses on the second study day. Subjects with false starts ($n = 2$) were excluded from the study because, by not starting on time, they modified significantly their swim time independent of actual performance. Table 1 provides the characteristics of the highly trained swimmers included in the study analysis of the submaximal exercise protocol (7 × 200-m protocol) and also describes the characteristics for those completing the maximal exercise protocol (100-m protocol). For the submaximal exercise protocol, 44% of subjects used freestyle ($n = 7$), 13% used breaststroke ($n = 2$), 25% used fly ($n = 2$), 13% used individual medley ($n = 2$), and 5% used backstroke ($n = 1$). Of the subjects, 50% were randomized to RIPC intervention on the first study day. For the maximal exercise protocol, 39% of subjects used freestyle ($n = 7$), 17% used breaststroke ($n = 3$), 22% used fly ($n = 4$), 17% used individual medley ($n = 3$), and 5% used backstroke ($n = 1$). Of the subjects, 61% were randomized to RIPC intervention on the first study day. There were no protocol deviations. There was no significant difference in occurrences of respiratory illnesses between the two groups. There was also no difference in average blood pressure between the groups.

Submaximal incremental swimming test results. We did not demonstrate any significant effect of RIPC on any of the indicators of submaximal exercise performance. In particular, there were no significant differences between RIPC and the low-pressure control protocol on our primary end point, critical velocity, or maximal HR. The velocity achieved at a lactate concentration of 4 mmol·L^{-1} was also unaffected.

Maximal competitive swimming test results. RIPC was associated with an improvement in competitive swim

TABLE 1. Characteristics of the athletes enlisted.

Demographic	7 × 200-m Protocol	100-m Protocol
Age, mean ± SD (yr)	18.8 ± 3.3	19.2 ± 2.9
Female, *n* (%)	8 (50%)	8 (50%)
Height, mean ± SD (cm)	179.9 ± 10.1	180.2 ± 8.0
Weight, mean ± SD (kg)	72.7 ± 10.7	71.1 ± 9.4
1000 points ranking, mean ± SD	899 ± 215	899 ± 215

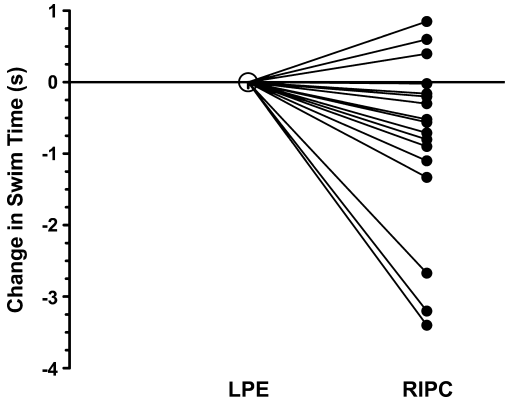

FIGURE 3—The effect of RIPC on maximal swim time expressed as absolute difference (s) from low-pressure experimental intervention, irrespective of treatment order. Values are expressed in seconds. Each *black line* represents different elite swimmers. $n = 18$ for all groups.

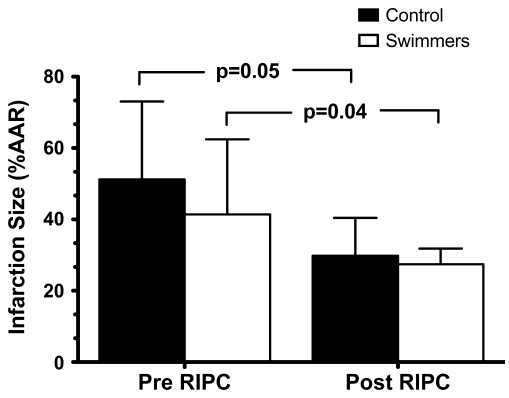

FIGURE 4—The effect of RIPC on infarction size in mouse hearts. Infarct size is expressed as a percentage of area at risk. The *black bar* represents mice perfused with dialysate from control subjects ($n = 4$), and the *grey bar* represents mice perfused with dialysate from elite swimmers ($n = 9$). Values are reported as mean ± SD.

times (Fig. 3). Table 2 shows the effect of RIPC on the indicators of maximal performance. RIPC was associated with a significant improvement in competitive swim time for 100 m of, on average, 0.70 s (95% CI = 0.05–1.35 s, 66.98 ± 21.28 vs 66.28 ± 21.08 s, $P = 0.04$) and a superior swim time relative to personal best time (+4.7% ± 3.8% vs +3.5% ± 3.3%, $P = 0.02$) when compared with the low-pressure control protocol. Moreover, this improvement in swim time was not achieved at the expense of increased lactate production or increased HR. However, there was a nonstatistically significant increase in the number of strokes (20.9 ± 9.3 vs 21.5 ± 9.5, $P = 0.12$) and no increase in HR ($n = 5$) (180 ± 11 vs 180 ± 8 bpm, $P = 0.96$). RIPC was also associated with a smaller mean absolute difference compared with personal best swim time and with a higher average FINA point (627 ± 69 vs 650 ± 64, $P = 0.01$; Table 2). No factors were found to be confounders of the association between race time and RIPC stimulus. In a stratified analysis, the subjects' competitive level (national vs international) did not affect the association between RIPC and improved maximal performance treatment effect (−0.72 s and 95% CI = −1.54 to +0.11 s for the national-level swimmers vs −0.67 s and 95% CI = −2.19 to +0.85 s for international-level swimmers, $P = 0.52$; Table 2).

Langendorff experiments. Athletes and control subjects underwent blood sampling before and after RIPC. Comparing pre-RIPC dialysate with post-RIPC dialysate, the infarct size was reduced from 51.2% ± 18.9% to 27.4% ± 3.8% ($P = 0.05$) for the control subjects and reduced from 41.4% ± 18.9% to 2.8% ± 10.6% ($P = 0.04$) in the swimmers (Fig. 4). There was no significant difference between the control group and highly trained athletes ($P = 0.35$ and $P = 0.46$ for pre-RIPC and post-RIPC dialysate, respectively; Fig. 4). However, left ventricular generated pressure was higher from 25 to 60 min of reperfusion in mice hearts perfused with post-RIPC dialysate from the swimmers (89.9 ± 2.1 to 83.5 ± 2.9 mm Hg, respectively, $P = 0.04$). No other end points were significantly influenced by the RIPC intervention.

DISCUSSION

In this study, RIPC was not associated with an improvement in incremental submaximal exercise but was associated with an improved maximal performance in highly trained swimmers. Our hypothesis was that intense exercise represents a physiologic form of ischemic injury and, therefore, may be amenable to modification by ischemic preconditioning. In this study, we used a simple method of RIPC, by transient upper limb ischemia, in a group of highly trained swimmers. Swimming is an unusual sport in which ventilation is highly entrained and a very high rate of energy

TABLE 2. Effect of RIPC on submaximal and maximal exercises performance indicators.

	LPE	RIPC	EST (95% CI)	*P*
100-m protocol				
Time (s)—100 m only	59.96 ± 6.13	59.29 ± 5.92	−0.664 (−1.235 to −0.093)	0.03
Time (s)—all subjects	66.98 ± 21.28	66.28 ± 21.08	−0.701 (−1.350 to −0.052)	0.04
Mean absolute difference with best time (s)	+2.83 ± 2.47	+2.13 ± 1.83	−0.701 (−1.350 to −0.052)	0.04
National level			−0.718 (−1.542 to +0.105)	
International level			−0.667 (−2.185 to +0.851)	
Mean relative difference with best time (%)	+4.66 ± 3.76	+3.55 ± 3.31	−1.114 (−2.036 to −0.192)	0.02
National level			−1.305 (−2.611 to −0.001)	
International level			−0.732 (−2.266 to +0.803)	
FINA (per 1000) ($n = 21$)	627 ± 69	650 ± 64	+22.3 (+6.1 to +30.5)	0.01
Lactate (mmol·L^{-1})	12.3 ± 2.0	12.8 ± 2.4	+0.45 (−0.60 to +1.50)	0.38
No. strokes	20.9 ± 9.3	21.5 ± 9.5	+0.52 (−0.15 to +1.18)	0.12

LPE, low-pressure experimental group; RIPC, remote ischemic preconditioning group; FINA, International Swimming Federation.

turnover leads to a marked reduction in PaO_2, with measured O_2 saturations falling to between 80% and 85% in highly trained individuals (17), and therefore represents an ideal model to test the effects of RIPC. Indeed, swimming performance is thought to be, at least in part, limited by exercise-induced arterial hypoxemia (25). Associated with this is a fall in arterial pH and a substantial rise in venous lactate (27), reflecting tissue hypoxemia and metabolic acidosis. We hypothesized that RIPC might modify skeletal muscle tolerance to this tissue hypoxia, thereby improving maximal and submaximal exercise performance.

RIPC is a phenomenon that is known to protect tissues against ischemia and reperfusion injury that occurs as a result of cessation of blood flow to a tissue bed, such as during cardiac surgery (4) or myocardial infarction (28). As such, it recapitulates the effects of local preconditioning, albeit in a more facile and clinically relevant way. In the only previous study in human exercise performance, "local" preconditioning of each leg was shown to improve peak oxygen consumption during bicycle exercise testing in normal healthy subjects (9). The current study used transient upper arm ischemia as the stimulus of "remote" preconditioning. We have recently shown that RIPC induced by transient limb ischemia leads to release of a cardioprotective factor, or factors, into the bloodstream of animals and humans (22). The effect of this factor was manifest as an increased tolerance to myocardial ischemia–reperfusion injury in a rabbit Langendorff model. In this study, we confirmed that this humoral mechanism persists in highly trained swimmers and presumably contributes or explains the improved tolerance to exercise-induced hypoxemia and acidosis during intense exercise in the swimmers, where all muscle groups are being used. Interestingly, there was no significant effect on incremental submaximal exercise tolerance in the same individuals. This is perhaps not surprising given the prescriptive nature of the submaximal test (which, by its nature, aims to ensure that the swimmer completes successive swims within defined time limits). Whether the lack of difference reflects the sensitivity of our end points to demonstrate any physiologic change during submaximal exercise or that RIPC has a differential effect on cellular responses during maximal stress remains to be seen. Nonetheless, the effects on maximal performance, in terms of swim time in the face of such cellular responses were clear.

Although our study was not designed to explore subcellular mechanisms, it is possible to speculate that the difference observed is related to differences in the pathways of energy utilization during submaximal exercise and at maximal exertion. During submaximal exercise, energy is produced mainly by the aerobic oxidative pathway, whereas during maximal performance, energy is produced not only by the breakdown of phosphocreatinine but also by the anaerobic glycolytic pathway (27) in addition to the aerobic oxidative system. It is known from performance models that predicted exercise capacity is determined by the capacity to produce energy (ATP) by different metabolic pathways (17). Interestingly, *in vivo* studies have shown that ischemic preconditioning leads to opening of mitochondrial ATP-sensitive K channels and uncoupling of oxidative phosphorylation (8). As a result, we speculate that RIPC allows for faster uptake of acetyl-CoA (a breakdown product of glycolysis) by mitochondria, thus maintaining lactate accumulation at a metabolically acceptable level and contributing aerobically generated ATP for exercise. Although it is estimated that 37%–63% of the energy supplied for events of this duration comes from anaerobic glycolysis (27), substantial blood lactate accumulation occurs during these events and aerobic oxidation is a significant contributor to overall ATP production. An improvement in mitochondrial metabolism may explain our observations of faster swimming speeds at a consistent blood lactate level. Our observations of a tendency toward a higher stroke rate and improved swimming time without a change in postswim blood lactate level support this hypothesis.

No matter what the mechanism, the 0.70-s reduction in time not only was statistically significant but also was of major physiologic and competitive significance to the athletes, representing a 1.11% improvement in swim time. It has previously been suggested that an improvement of 0.4% in competition performance is a "competitively significant" change (2). Such improvements are usually generated by a structured training program. In highly trained swimmers, the relationship between the training regimen and the competitive performance is well described (15). From the test data, our observed improvement in simulated competition swim time of 0.7 s would represent, on average, 2 yr of training in these highly trained individuals (2).

One limitation of this study was the fact that we could not completely blind our subjects. We did not explain to the subjects which intervention we thought could improve their performance, but the sensations invoked by the low-pressure control protocol and RIPC intervention were clearly very different. It might be suggested that it was intuitive to the subjects that the beneficial procedure was the one using the high-pressure occlusive protocol, and therefore, a placebo effect might have been induced. Given that the subjects received both interventions in crossover fashion, for both elements of the study, we believe it would be difficult to reconcile a "differential" placebo effect that was only present at maximal, and not at submaximal effort, in our subjects.

Given the limited number of highly trained athletes available this study obviously had limited power, nevertheless, considering the study population, the sample size remains substantial. Finally, it is not possible to infer that similar benefits from RIPC would be obtained under other circumstances. For example, further studies are underway to assess whether the effect is maintained with repeated RIPC stimuli, whether less highly trained swimmers might accrue similar improvement in maximal exercise performance, whether RIPC might be applicable in other sports, and whether RIPC might be useful in the clinical setting such as in those with exercise limitation due to heart failure or

ischemic syndromes (angina, claudication). We recommend that future research be conducted to confirm these observations in specific performance groups such as sprint versus endurance athletes and to elucidate any gender differences in the response to preconditioning.

In summary, RIPC releases a humoral protective factor that modifies skeletal muscle tolerance to extreme exercise that manifests as improved maximal performance. This simple technique may be applicable to clinical syndromes in which exercise intolerance is related to hypoxemia or ischemia.

This study was supported by an unrestricted, peer-reviewed grant from Fondation Leducq, as part of the Transatlantic Networks of Research Excellence program, and from the Canadian Institutes of Health Research.

The sponsor of this study had no role in study design, data collection, data analysis, or writing of the report.

The authors thank the Canadian Sport Centre Ontario, the University of British Columbia Swim Team, the University of Toronto Swim Team, the University of Guelph Swim Team, and the Toronto Swim Club for their support for this study. The authors also thank Gordon Slievert from the School of Exercise Science of University of Victoria, Canada, for his help in data collection.

Andrew N. Redington and Greg D. Wells share senior joint authorship.

Andrew Redington, Michael Schmidt, Cedric Manlhiot, Brian McCrindle, and Michael Tropak are all shareholders in CellAegis, a start-up company with licensed intellectual property (from The Hospital for Sick Children) to develop an automated preconditioning device. This study does not include the use of any automated preconditioning device.

Publication of results of the present study does not constitute endorsement by the American College of Sports Medicine.

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