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Case Report of a Remote Ischemic Preconditioning Intervention during Aerobic Exercise in a 44-year-old Amateur Triathlete Male with a History of Acute Myocardial Infarction

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ABSTRACT

International Journal of Exercise Science 13(3): 924-937, 2020. Over the years, exercise has become increasingly important in patients with acute myocardial infarction (AMI). However, AMI patients need to be closely monitored since they maintain cardiovascular disease risks, such as ventricular repolarization abnormalities in electrocardiograms during exercise and rest. A recent study showed the need to focus on the different potential mechanisms and the applicability of remote ischemic preconditioning (RIPC) for cardiac patients engaged in exercise rehabilitation. This is the first case report that explores the effectiveness of an RIPC intervention in a 44-year-old amateur triathlete male with a history of AMI during a moderate (75% of gas exchange threshold) and high (115% of gas exchange threshold) intensity steady-state cycling aerobic exercise. Prior to aerobic exercise, the participant was allocated to either RIPC intervention or CTL (control) with four cycles of five minutes of ischemia followed by five minutes of reperfusion. ECG was continuously recorded during the protocol. These findings showed that RIPC improved participant's oxygen uptake response and shortened his ventricular repolarization during steady-state aerobic exercises. By measuring the physiological and electrophysical parameters, this case report adds new evidence for the benefits of RIPC. This study also demonstrates the safety of the intervention for cardiac patients in addition to showing that the intervention is not dangerous or harmful. This provides a new approach to cardiac rehabilitation programs. Future studies with cardiac patients are needed to provide a safe, standardized exercise intervention in cardiac rehabilitation.

KEY WORDS: RIPC, O_2 kinetics, ventricular repolarization, aerobic exercises

INTRODUCTION

Cardiovascular disease is the main cause of death in the world, with about 17.5 million deaths each year (43). The risk of cardiac arrest in participants running long distances is 1.01 out of 100,000 participants and 1.41 out of 100,000 men (28). Triathlon (e.g., middle/long distance Ironman) is an endurance sport, mainly performed under aerobic conditions. Cardiac issues have been reported in athletes performing triathlons (19, 31). Moreover, it appears that many deaths in triathlons are related to cardiac events, mainly cardiac arrest (2.40 per 100,000 men participants) (22). In this sense, exercise has become, over the years, increasingly important in patients with acute myocardial infarction (AMI) (3, 7). Indeed, exercise-based cardiac rehabilitation has been shown to improve health-related quality of life and regular physical activities, which contribute to patients' autonomy (3, 7, 32).

There are studies of patients with a history of AMI who participated in major physical challenges such as climbing Mount Everest or doing long-distance triathlons after their rehabilitation (37). However, these patients with a history of AMI need to be closely monitored during exercise since they maintain cardiovascular disease risks, such as ventricular repolarization abnormalities in electrocardiograms, with a QT prolongation (1, 46). To counteract these potential issues, revascularization procedure (i.e., percutaneous coronary intervention and coronary artery bypass grafting) has been demonstrated to play an important role in the care of AMI patients (42). Revascularization procedure also allows an improvement in cardiac patients' exercise time (14).

In the last decade, it has been proposed that remote ischemic preconditioning (RIPC) intervention also has an effect on aerobic exercise (AE) performance in healthy population, notably by improving muscle oxygenation, vasculature and blood flow delivery to active tissues and organs (13). When RIPC intervention is applied prior to AE, a positive effect during AE on electrophysiological parameters (ECG parameters) is also reported (9, 10). The RIPC intervention is considered to be a non-invasive procedure induced by a pressure cuff, applied to the right arm, to cause three to four brief cycles of ischemia followed by a period of reperfusion on skeletal muscle (10). In the cardiology research, RIPC intervention is an attractive method to induce a protective effect on the myocardium and a reduction in the presence of inflammatory markers in patients with a cardiovascular disease (27, 38).

To the best of the authors' knowledge, there are no case reports that have explored the effects of RIPC intervention during AE in cardiac patients with a history of AMI. Despite this observation, it is clearly specified in the literature that future research on RIPC may take interest in the applicability of RIPC for patients engaged in exercise rehabilitation (24). This is all the more important since RIPC intervention was observed to induce heart rate independent shortening of QT intervals that has been revealed during different steady-state AE in healthy participants (9). Case reports on the effect of RIPC interventions in cardiac patients could allow the development of preventive and supportive measures through a detailed description of a patient's episode of care (15). Thus, this case report explores the effectiveness of a RIPC

intervention in a 44-year-old amateur triathlete male with a history of AMI during a moderate and high intensity steady-state cycling AE.

METHODS

Case Presentation

We present the case of an amateur triathlete volunteer of 44 years with a history of AMI. The participant was initially part of a study protocol in healthy amateur triathletes (8) and was later excluded from the original study data analysis due to his health status of which he informed us at the end of the study. The initial project was approved by the institutional ethics committee of the University of Montreal (Certificate number: 13-091-CERES-D) that accepted secondary data presentation in order to produce a case report. This investigation was conducted in accordance to the World Medical Association Declaration of Helsinki and the International Journal of Exercise Science (36). The participant gave his written informed consent that was reviewed and signed before his participation. Participant's clinical characteristics are presented in Table 1.

Table 1. Clinical Characteristics of the 44-year-old amateur triathlete male with an history of AMI.

Variables	Value
Height (cm)	181
Weight (kg)	80.3
Body mass index (kg/m^2)	24.5
Resting heart rate (bpm)	76
Resting systolic blood pressure (mmHg)	126
Resting diastolic blood pressure (mmHg)	71
$\dot{V}O_2$ max (mL.O_2^{-1}.kg^{-1})	40.5
Maximal heart rate at $\dot{V}O_{2max}$ (bpm)	150
Maximum systolic blood pressure at $\dot{V}O_{2max}$	180
Maximum diastolic blood pressure at $\dot{V}O_{2max}$	66
Power at $\dot{V}O_2$ max (Watts)	275
$\dot{V}O_2$ at GET (mL.kg^{-1}.min^{-1})	27.9
Power at GET (Watts)	175
Power at 75 % of GET(Watts)	131
Power at 115 % of GET (Watts)	201

$\dot{V}O_2$ max = maximal oxygen uptake; GET = gas exchange threshold; 75% = moderate intensity; 115% = high intensity.

In the initial project, inclusion criteria required that participants were aged >18 years, with no known cardiopulmonary conditions and without contraindications to exercise as assessed by the Physical Activity Readiness Questionnaire (41). In this sense, at the beginning of the initial project, the participant presented himself as a healthy amateur triathlete without an unhealthy medical history or cardiovascular events. However, at the end of the protocol, he revealed his medical condition to the exercise physiologist in charge of executing the protocol.

In February 2013, nine months before his participation in the study (October 2013), the participant had a cardiac catheterization after an AMI that revealed that the right coronary artery was functioning at 100%, while the left coronary artery was at 90% and that the lateral coronary artery was at 65%. Following his AMI, the participant took the following medication: statin, anticoagulant, and hypertension drugs. He was regularly monitored by his cardiologist who had given him permission to resume physical activity without restrictions. In April 2013, the participant participated in his first marathon (42.195km) and continued to be regularly monitored by his cardiologist. The participant had no counter indications to exercise, as assessed by the Physical Activity Readiness Questionnaire. On October 22nd, 2013, prior to the maximal aerobic capacity test, no abnormalities on the electrocardiogram were observed, as well as, no ischemia and no arrhythmia. Also, during the maximal aerobic capacity test, no cardiac or functional abnormalities were detected on the electrocardiogram.

Protocol

The participant was randomly assigned to a sequence of procedures either starting with RIPC intervention or control (CTL), separated by a washout period of at least one week (29, 30, 45). The participant was asked to abstain from drinking alcohol, drinking caffeine and smoking forty-eight hours prior to all interventions, and to avoid high-intensity training (more than 7.5 METS or anaerobic intervals or strength training) during the week before tests and the week between tests (8, 9). He was also asked to arrive at the laboratory fully hydrated, rested and was at least four hours post prandial.

During the first laboratory visit, exercise physiologists collected data on participant's resting blood pressure, heart rate, body weight and height. His maximal oxygen consumption ($\dot{V}O_{2max}$) was evaluated on a cycle ergometer (Corival 906 900, LODE Medical Technology BV, Groningen, the Netherlands) to establish the individual exercise intensities for the steady-state AE test. Oxygen uptake ($\dot{V}O_2$) measurements were made with a breath-by-breath system (Ultima CardiO2, 790705-006, 12-lead ECG Test CPX, MedGraphics Cardiorespiratory Diagnostics, St. Paul, MI). The gas analyzers were calibrated with calibration gas (25% O_2 and balance N_2; and 16% O_2, 5% CO_2 and balance N_2) and air volume before each test and before each intervention with a 3L syringe (Roxon). The software to display $\dot{V}O_2$ max and ECG was the Breeze Suite (software version. 7.2.0.52, 2001-2011, MedGraphics Cardiorespiratory Diagnostics, St Paul, MN).

During the second laboratory visit, one-week post-evaluation of the $\dot{V}O_2$ max, the participant participated in two steady-state eight minutes AE tests at 75% and 115% of the established gas exchange threshold (GET) (8, 9). The steady-state AE test took place five minutes after RIPC intervention or CTL to take advantage of the first protective window that occurs ten to sixty minutes after RIPC (45). The two interventions were separated by a week to eliminate the potential effects of the second window of protection which occurs 24 to 96 hours post-intervention (29, 30, 45). Finally, the protocol was repeated on the third visit, using RIPC intervention or CTL depending on the randomized assignment.

Maximal aerobic capacity test: A five minutes unloaded warm-up was performed prior to the $\dot{V}O_2$ max test, which is a standard incremental procedure (8, 9). The maximal aerobic capacity test started at 50 watts (W) for three minutes and the load was increased of 25 W each minute until the participant was no longer able to maintain the required pedalling cadence (60-90 rpm) despite strong verbal encouragement (6). The participant had to reach two out of three of the following criteria in order to establish $\dot{V}O_2$ max: a plateau in $\dot{V}O_2$ despite an increased workload, a respiratory exchange ratio value >1.15, and when cadence could not be kept.

RIPC intervention and CTL: The RIPC intervention consisted of four five minutes cycles of ischemia to the right arm, with a pressure cuff (Standby Model, Baumanometer, W.A. Baum Co Inc., Copiague, NY) inflated to 50 mmHg above resting systolic blood pressure, followed by five minutes of reperfusion. The RIPC method, as used by researchers in a previous study (26) was used to establish ischemia and confirmed by the absence of a pulse during the occlusion phase by palpation of the radial artery. The participant was also asked to rate on a scale of ten their perceived pain due to limb ischemia (40). The CTL intervention, which was insufficient to induce ischemia, was similarly administered in four cycles of five minutes in the right arm with a pressure cuff inflated at 10 mmHg, followed by five minutes of cuff deflation.

Steady-state AE tests: From the results of the VO_2max test, two working intensities were individually determined. Exercise at 75% (under GET) and 115% (above GET) of GET always has important cardiovascular and hemodynamic responses independently of exercise intensity. However, the role of the central nervous system in mediating fatigue is different (17). The synthesis of dopamine and the increase of the dopaminergic activity of the brain differs, depending on exercise intensity (17). Moreover, exercise at 115% of GET is associated with a greater cardiac sympathetic stimulation, with a higher $\dot{V}O_2$ and heart rate. In order to obtain the moderate (75% of GET) and high (115% of GET) intensity workloads, the GET was visually determined by two physiologists as the point of the incremental exercise during which ventilation ($VE/\dot{V}O_2$) increased without any change in the ventilatory equivalent for CO_2 (VE/VCO_2) (2). Steady-state AE tests were composed of two blocks: the first block was a five minutes warm-up (unloaded), followed by an effort of eight minutes at 75% of GET (moderate intensity) and by a five minutes cool down period, and the second block was a five minutes warm-up, followed by an effort of eight minutes at 115% of GET (high intensity) and by a five minutes cool down period. During all warm-ups and effort periods, the participant was asked to maintain a pedalling cadence between 60 to 90 rpm. Blocks were separated by a twenty minutes interval of passive recovery. The participant was also asked to rate their perceived exertion on a modified Borg scale (range from zero to ten) at each minute during each of the eight minutes AE period (34). During steady-state AE tests, 12-lead ECG tracings were acquired by using an ambulatory monitor (Txxx series Transmitter T12-60, Mortara Instruments Milwaukee, WI).

Statistical Analysis

The data of each period of AE was first examined in order to exclude potential outliers. They were then fitted to a curve having a one- (moderate exercise) or two-component (heavy exercise) exponential model. The breath-by-breath data was scrutinized for noisy/errant

breaths (outliers) and then interpolated to second-by-second values. Furthermore, values >4 SDs from the mean of the predicted regression value, where $\dot{V}O_2$ was in $mL \cdot kg^{-1} \cdot min^{-1}$, were removed before being expressed in $L \cdot min^{-1}$ (12). The first twenty seconds after the onset of exercise were excluded from the analysis (i.e. the cardiodynamic phase was omitted). The baseline was the measured value of the last sixty seconds of the warm-up at 0 W. For the moderate exercise (below GET), a mono-exponential model was used and for heavy exercise (above GET), a bi-exponential model was used as follows, respectively (4, 5, 39).

1) Mono-exponential model: $\Delta \dot{V}_{O2}(t) = A_1 \left[1 - e - \frac{t - TD_1}{\tau_1}\right]$

2) Bi-exponential model: $\Delta \dot{V}_{O2}(t) = A_1 \left[1 - e - \frac{t - TD_1}{\tau_1}\right] + A_2 \left[1 - e - \frac{t - TD_2}{\tau_2}\right]$

where in these formulas, t is the time in seconds; A_1 and A_2 are the gain of the primary and slow components in $L.min^{-1}$; τ_1 and τ_2 are the time constants of the primary and slow components in seconds; TD_1 and TD_2 are the time delays of primary and slow components in seconds. The amplitude of the slow component was additionally described as the amplitude of the slow component at eight minutes of exercise (A_2). The parameters of the models were determined by minimizing the sum of residual squares using a non-linear least-square algorithm.

RESULTS

Results of the oxygen uptake response during steady-state AE: Data from the oxygen uptake response were analyzed and are presented in Table 2.

Data from the mono-exponential model (steady-state exercise at 75% of GET) showed that the participant's time constants and gain in the primary component was faster with RIPC intervention (40.93sec and $0.81 L.min^{-1}$, respectively) than with the CTL (22.70sec and $0.70 L.min^{-1}$, respectively), while the time delay of the primary component was slower with RIPC intervention (25.47sec) than with the CTL (16.81sec). Data from the bi-exponential model (steady-state exercise at 115% of GET) showed that the participant's time constant in the primary components was faster with RIPC intervention (29.2sec) than with the CTL (30.02sec), while the time constant of the slow components was slower with RIPC intervention (329.32sec) than with the CTL (309.87sec). The time delays in the primary and slow components were faster with RIPC intervention (13.21sec and 134.0sec, respectively) than with the CTL (13.69sec and 179.99sec, respectively). The gain in the primary and slow components, as well as, the amplitude of the slow component was increased with RIPC intervention than with the CTL. The pulmonary oxygen response analysis during steady-state AE test at 75% of GET and 115% of GET with control or RIPC intervention are modeled in Figure 1 and Figure 2, respectively.

Table 2. Data analysis from the mono- and bi-exponential model during steady-state AE tests at 75% of gas exchange threshold and 115% of gas exchange threshold with RIPC intervention and CTL.

	CTL intervention	RIPC intervention
Mono-exponential model (75% of gas exchange threshold)		
Baseline $\dot{V}O_2$ (L.min^{-1})	1.00	0.97
τ_1 (s)	40.93	22.70
D_1 (s)	16.81	25.47
A_1 (L.min^{-1})	0.70	0.81
RPE	2	1
Bi-exponential model (115% of gas exchange threshold)		
Baseline $\dot{V}O_2$ (L.min^{-1})	0.86	0.60
τ_1 (s)	30.02	29.20
D_1 (s)	13.69	13.21
A_1 (L.min^{-1})	1.42	1.68
τ_2 (s)	309.87	329.32
D_2 (s)	179.99	134.00
A_2 (L.min^{-1})	0.21	0.30
A'_2 (L.min^{-1})	0.14	0.19
RPE	3	4.4

RIPC = remote ischemic preconditioning; CTL = control; $\dot{V}O_2$ = oxygen uptake; 75% = moderate intensity; 115% = high intensity; RPE = Rated Perceived Exertion; t is the time in seconds; A_1 and A_2 are the gain of the primary and slow components in L.min^{-1}; τ_1 and τ_2 are the time constants of the primary and slow components in seconds; TD_1 and TD_2 are the time delays of primary and slow components in seconds; the amplitude of the slow component was additionally described as the amplitude of the slow component at eight minutes of exercise (A'_2).

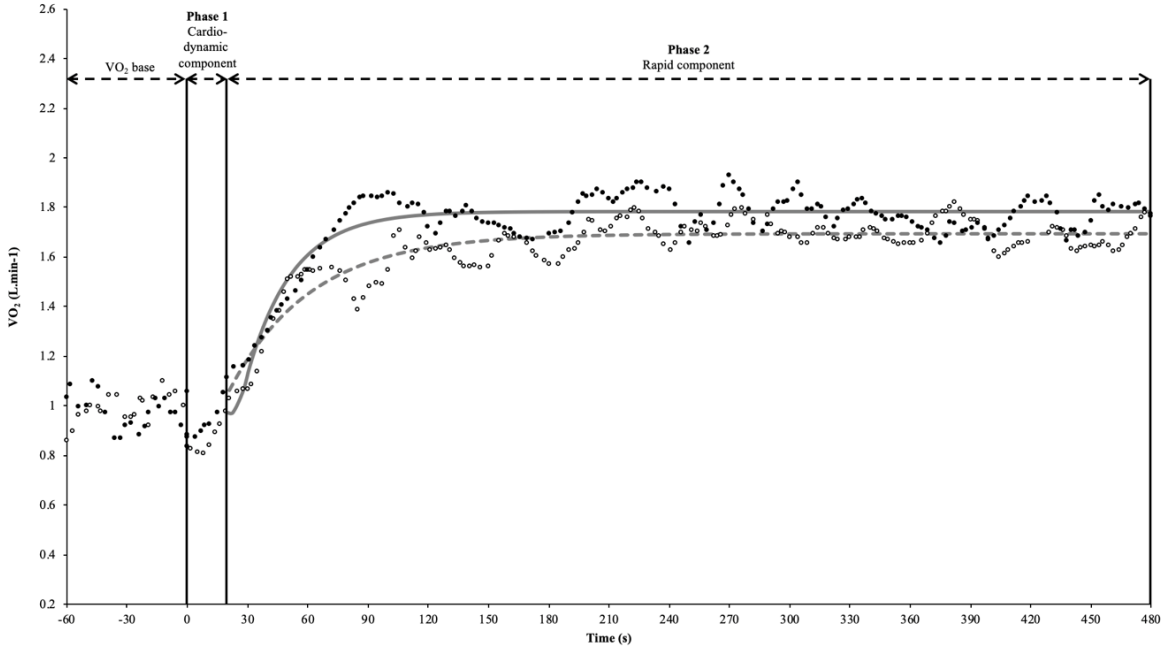

Figure 1. Pulmonary oxygen response at 75 % of gas exchange threshold. The RIPC intervention is represented with a black dots and the control intervention with white dots. The filled line represents the best fit curve for RIPC and the dashed line represents the best fit curve for control intervention.

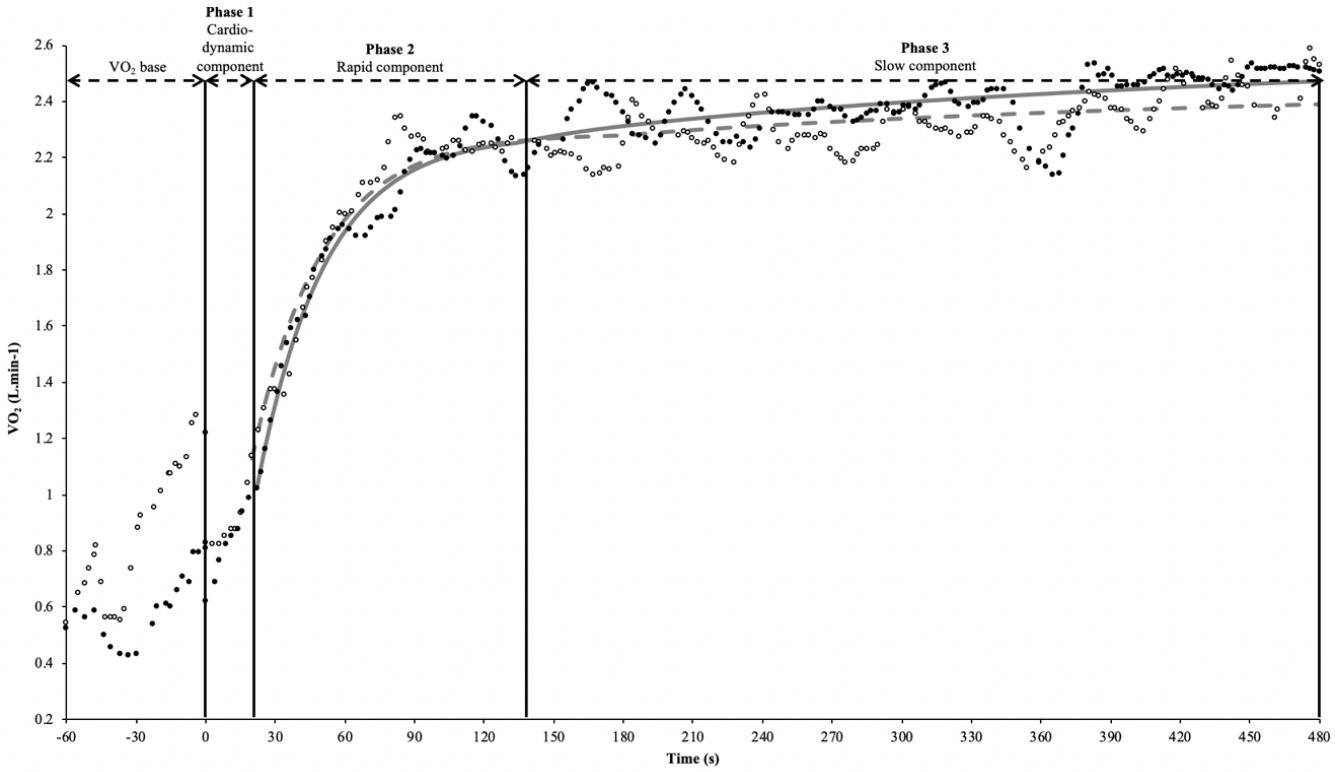

Figure 2. Pulmonary oxygen response at 115 % of gas exchange threshold. The RIPC intervention is represented with a black dots and the control intervention with white dots. The filled line represents the best fit curve for RIPC and the dashed line represents the best fit curve for control intervention.

Analyses and Results of the Electrocardiogram During Steady-State Aerobic Exercise: Data from the 12-lead electrocardiogram measurement were analyzed and are illustrated in Figure 3. To study ventricular repolarization during steady-state AE tests, 12-lead ECG tracings were acquired by using an ambulatory monitor (Txxx series Transmitter T12-60, Mortara Instruments Milwaukee, WI). Each ECG was recorded at a sampling frequency of 250 Hz. Manual readings were made on a computer screen, using Breeze Suite software (version 7.2.0.52, 2001-2011, MedGraphics Corporation, St Paul, MI). All readings, blinded to the intervention, were made by the author and revised by a single experienced observer to verify the reproducibility of the measurements. Offline analysis was realized with a display of waveforms at 10 mm/mV and 25 mm/s. The time resolution of this approach based on Gravel et al (2012) (21) was ± 4 ms. The reproducibility of the measurements was verified by a strict procedure of random measurement by three minutes blocks. Series one was compared to series two (Pearson's correlation coefficient = 1).

Lead V3 was chosen for its large and reliable T wave (11). The QTe interval was defined as the period from the onset of the Q wave to the end of the T wave, measured linearly. The end of the T wave was identified as the intersection of the tangent of the steepest slope of the T wave and the isoelectric line. The QT intervals were also measured from the onset of the Q wave to the peak of the T wave (QTp) which is considered as a reliable parameter for QT analysis during exercise (23). Both QT interval measurements (QTp and QTe) were carried out every 30 seconds (on an average tracing of the preceding ten seconds) during the last three minutes of

baseline (two minutes after the start of the warm-up) and during the first three minutes of exercise and recovery. The time elapsed between two successive R-waves of the QRS signal on the ECG (RR intervals) were subjected to the same processing methodology. The ST-segment level was measured every minute (on an average tracing based on J+60ms) with an accuracy of 0.1mm.

Data presented in Figure 3 A and B highlighted that RR intervals with RIPC intervention or CTL were similar during the baseline, exercise and recovery of the steady-state AE tests (75% and 115% of GET). Also, QTe and QTp data appeared similar between RIPC intervention and CTL during the baseline of the steady-state exercise tests at 75% (Figure 3 C and E) and 115% of GET (Figure 3 D and F). Conversely, QTp and QTe during exercise and recovery were shorter with RIPC intervention than with the CTL whether it be at 75% (Figure 3 C and E) or at 115% of GET (Figure 3 D and F). The ST-segment level at rest (RIPC = 0.5mm v. CTL = 0.6mm, respectively), 75% of GET (RIPC = 1.0mm v. CTL = 1.2mm, respectively) and 115% of GET (RIPC = 1.2mm v. CTL = 1.3mm) appeared lower with RIPC intervention than with the CTL.

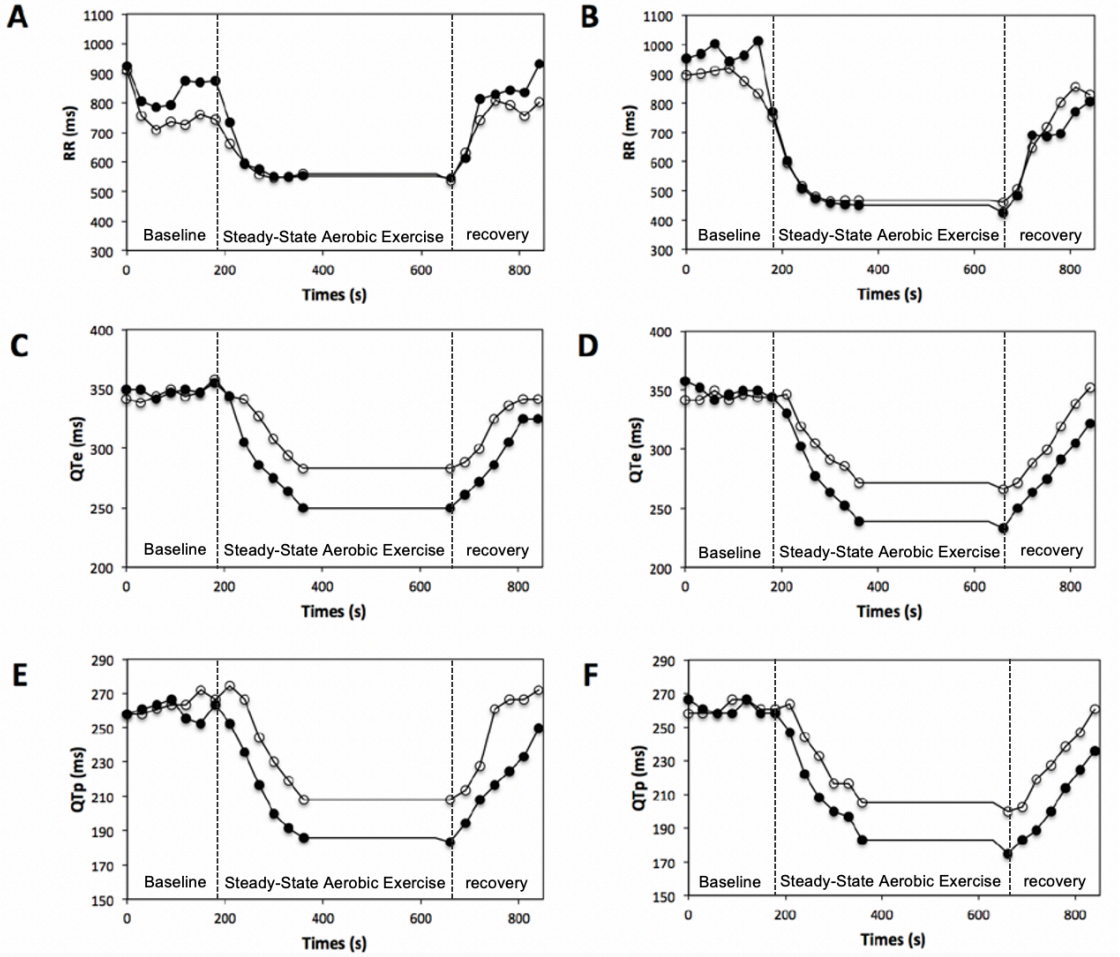

Figure 3. Data analysis for different intervals during three period (baseline, exercise and recovery) with in the first column: exercise at 75% of GET and in the second column: exercise at 115% of GET with RIPC (black dot) or CTL (white dot) interventions. (A) RR at 75% of GET, (B) RR at 115% of GET, (C) QTe at 75% of GET, (D) QTe at 115% of GET, (E) QTp at 75% of GET, (F) QTp at 115% of GET.

DISCUSSION

This is the first case report that reports the effectiveness of RIPC intervention in a 44-year-old amateur triathlete male with a history of AMI during a moderate and high intensity steady-state cycling AE. The measurement procedure used in this case report was already performed in two of our published studies with healthy amateur triathletes (8, 9). However, because this amateur triathlete male with a history of AMI is a recreational amateur triathlete and not a professional triathlete, his VO_2 peak at the end of the maximal aerobic capacity test (40.5 mL/kg/min) was slightly lower than those of healthy amateur triathletes (44.4±9.3 mL/kg/min). This also explains why his heart rate at VO_2 peak was lower than healthy amateur triathletes. Nevertheless, findings in the case report showed that RIPC intervention improved participant's oxygen uptake response and shortened his ventricular repolarization during steady-state AE. Moreover, it appears that the effect of RIPC intervention is similar between the amateur triathlete who had an AMI and healthy amateur triathletes.

Analyses of the participant's oxygen uptake response showed that RIPC intervention improves his oxygen uptake response during steady-state AE whether it be at 75% or 115% of GET. This improvement appeared to be similar between amateur triathlete who had an AMI and healthy amateur triathletes (8). This result is not surprising since the participant reported at the end of the study that two months after his AMI diagnosis (February 2013 to April 2013), he participated in his first marathon competition with the permission of his cardiologist. Following his first competition after his AMI and until the design of this case report, the participant participated in a total of six marathons (42.195km), two Olympic distance triathlon (swim [1.5km], bike [40km] and run [10km]) and one Ironman 70.3^{tm} (swim [1.9km], bike [90km] and run [21.1km]); in addition to participating in triathlons and running on a regular basis. In order to minimize the risk of a cardiac event, the participant was regularly monitored by his cardiologist.

The follow-up of the participant for his AMI diagnosis played an important role in this case report and could explain why no cardiac or functional abnormalities were detected on the electrocardiogram during the maximal aerobic capacity test. In this sense, the participant's capacity to regain an excellent cardiorespiratory fitness (40.5 mL/kg/min), due to a good cardiac rehabilitation program, allowed him to take full advantage of the effects of RIPC, as observed in healthy participants (8). Our findings showed that participant's oxygen amplitude, time delay reaching steady-state and respiratory exchange threshold were similar to healthy amateur triathletes' (8). The RIPC intervention promoted better oxygen uptake within the working muscle at steady-state based on the faster time constant, as previously reported (8). Also, RIPC intervention contributed to a higher oxygen uptake and an elevated exercise performance in this case report, which is consistent with the literature (18).

No similarities were found in cardiac patients although a study was interested in the potential effect of RIPC on heart failure patients' exercise performance (33). However, this study did not explore the effect of RIPC on electrocardiogram parameters (RR intervals and QT intervals) despite its potential benefits in these patients (33). Due to the lack of data in the literature, our

case report is the first to document the effects of RIPC on the electrophysiological parameters of an amateur triathlete with a history of AMI. This is of interest since one of our articles showed that RIPC could induce heart rate-independent shortening of QT intervals in healthy amateur triathletes (9). It is necessary to provide subsequent evidence to enable patients to benefit from the effects of this innovative intervention. In cardiac patients, especially in AMI patients, ion channel expression is altered (K_{ATP}, sodium, calcium channels) (44), contributing to an abnormal ventricular repolarization (20, 35) and a prolongation in action potential duration (25). In our case report, the effect of RIPC intervention on ventricular repolarization appears to be revealed only during exercise and recovery, which is similar to our findings in healthy amateur triathletes (9). Also, it has been shown that RIPC can help reduce ST-segment elevation among coronary patients (16). This is in accordance to our results since the ST-segment level at rest, 75% of GET and 115% of GET appeared lower with RIPC intervention than with CTL in amateur triathlete with a history of AMI.

By measuring the oxygen uptake response and electrocardiogram parameters, this case report provides new approach to cardiac rehabilitation testing and adds new evidence for the benefits of RIPC. This study also demonstrates the feasibility and safety of the intervention in an amateur triathlete with a history of AMI, in addition to showing that the intervention is not dangerous or harmful. Thus, RIPC intervention improved the oxygen uptake response and shortened ventricular repolarization during AE which is encouraging for this high-risk population. The potential mechanisms and benefits of ischemic preconditioning (10, 16, 24) in AMI patients remain an open question that deserves to be considered in future studies. Future studies with cardiac patients are needed to provide a standard safe RIPC intervention in cardiac rehabilitation.

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