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Original Research

Remote Ischemic Preconditioning Does Not Improve the Six Minutes Walk Test Performance in Chronic Heart Failure Patients: a Randomised Pilot Trial

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ABSTRACT

International Journal of Exercise Science 14(2): 1354-1362, 2021. Cycles of ischemia and reperfusion induced with a pressure cuff on a skeletal muscle, also know as remote ischemic preconditioning (RIPC), appears to improve performance in different time-trial events in healthy individuals. Our primary goal was to assess the effect of RIPC in heart failure (HF) patients' functional capacity using the six-minute walk test (6MWT). A randomized crossover design comparing RIPC (4 x five-minutes of upper arm ischemia) to the SHAM procedure was done in 15 patients prior to a 6MWT. The primary outcome measure was the total distance walked in a standardized 6MWT (20m corridor). Metabolic and hemodynamic responses were measured using gas exchange analysis with a portable metabolic analyzer and peripheral skeletal muscle oxygen saturation (smO_2) with near-infrared spectroscopy. The total distance travelled during 6MWT was not significantly different between the RIPC (347 ± 63 m) and the SHAM procedure (352 ± 65 m; p = 0.514). Relative oxygen uptake did not change when comparing interventions: 10.26 ± 2.01 ml/kg/min vs 10.69 ± 2.51 ml/kg/min (RIPC vs SHAM, respectively, p = 0.278). As well, no significant differences were observed for heart rate, respiratory exchange ratio, smO_2, and ventilation. Even though HF patients tolerated well the RIPC intervention, it did not provide any significant improvement in functional capacity and other physiological parameters in our sample of patients.

KEY WORDS: Remote ischemic preconditioning, heart failure, rehabilitation, exercise, walk

INTRODUCTION

Remote ischemic preconditioning (RIPC) consists of creating cycles of transient ischemia and reperfusion on a skeletal muscle using a pressure cuff (9). Brief ischemia of the upper arm has systemic effects that contribute to protect distant organs such as the myocardium from ischemic insult (Hausenloy, 2007). This low cost and simple method is used in different research settings, such as heart surgery or physical performance. RIPC is used prior to physical activity as a means of increasing performance. A meta-analysis study claimed that RIPC improves performance, whereas different large trials refute that hypothesis (3, 14). Some investigators, however,

reported that RIPC improved performance on time trial events, such as a 5-km run (1), during swimming trials (6, 10), and during incremental cycling tests (4, 5). Different physiological mechanisms were tested to explain the potential increase in exercise performance either with explosive exercise, associated with the anaerobic metabolism and with oxidative exercise, associated with the aerobic metabolism (3). Nevertheless, to this date, there is no clear mechanism that can explain the effect of RIPC on sports performance. Most studies investigated the effect of RIPC with a healthy and active population that were not elite athletes (14). The RIPC method, however, could have an interesting impact in a clinical context when applied to patients with cardiovascular conditions.

It is well established that patients with heart failure (HF) face exercise intolerance, dyspnea, and fatigue during both physical activity and resting due to diminishing cardiac output and to alteration in skeletal muscle function (13, 18). Since RIPC is triggered by different factors that provide cardioprotection against subsequent ischemic insults (such as exercise), RIPC may be an interesting option for HF patients prior to exercise (22). Therefore, RIPC could be used as a simple means to increase exercise tolerance or performance in that HF population. RIPC has already been investigated as a means of improving clinical outcomes in patients undergoing cardiac surgery. A meta-analysis that included 7036 patients reported that RIPC reduced troponin I and troponin T release after cardiac surgery (21). A recent study investigated this question and did not report any beneficial effects of RIPC in HF patients using a VO_2peak cycle ergometer progressive protocol where the load was increased 10 Watts per minute (15). On the other hand, time-trial type exercise testing (e.g., 5-km run, 100-m swim, or reaching 100-Kj as fast as possible on a cycle ergometer) seems to better reflect the effects of RIPC on sport performance than incremental protocols, as demonstrated in healthy active subjects (3). Thus, we hypothesized that RIPC in HF patients would be beneficial when performing the six-minute walk test (6MWT), a simple and reliable field-test for HF patients that is comparable to a self-paced effort, such as a time trial used in healthy populations (7). Our primary hypothesis was that upper limb RIPC in chronic HF patients before exercise would increase the total distance covered during the 6MWT. A secondary hypothesis was that RIPC would improve metabolic responses.

METHODS

Participants

This study was approved by the hospital ethics committee (CRCHUM # CE.16.068) and was conducted in accordance to the World Medical Association Declaration of Helsinki and the accordance with the ethical standards of the International Journal of Exercise Science International Journal of Exercise Science (17). Fifteen patients from the heart failure clinic of the University of Montreal hospital center (CHUM) signed their informed consent form prior to participating in the study. The inclusion criteria were: age 18 years and older, NYHA functional class from III to IV, or II with NT- proBNP above 1000 pg/m in the last 30 days. Patients were excluded if they were hospitalized for heart failure during the previous 30 days, if they were incapable of giving their informed consent, or if they had any of the following conditions: neurological or orthopedic conditions, use of a walking aid, pregnancy, uncontrolled

hypertension (systolic BP ≥ 160 mmHg at rest and/or diastolic BP of ≥ 100 mmHg at rest), unstable angina, severe peripheral vascular disease, surgery for breast cancer with lymph node dissection, a pulmonary disease under use of home-based oxygenotherapy, severe anemia (hemoglobin less than 90 g/L), chronic atrial fibrillation, symptomatic obstructive cardiomyopathy or angina or syncope, and symptomatic tight aortic stenosis. Patients were enrolled from January 2017 to May 2019. To recruit patients, we had access to the patient files treated at the CHUM heart failure clinic (via the Oacis software). We analyzed each file and contacted patients that met the project inclusion criteria. All patients agreeing to participate in the project came to the two meetings within approximately 96 hours.

Protocol

An acute intervention was performed in a randomized crossover design, where each participant was exposed to a RIPC intervention and a control intervention (SHAM). The expected effect of the intervention was not disclosed to the participants in order not to influence their performance. The two days of testing were separated by a period of at least 96 hours to avoid potential carryover effect (22).

The RIPC intervention consisted of four five-minute cycles of ischemia of the right arm using an insufflated cuff pressure of 20 mmHg higher than their resting systolic blood pressure followed by 5 minutes of reperfusion as performed in a previous study with heart failure(15). The presence of ischemia was validated by a portable near-infrared spectroscopy (NIRS) device (Moxy-3, Fortiori Design LLC) placed on the anterior brachial muscle. The 6MWT was performed 10 minutes after the RIPC.

The SHAM intervention was similar to the experimental intervention, but only a slight insufflated pressure of 10 mmHg was applied to the cuff (12).

The 6MWT took place in a hospital corridor of 20m in length. A portable metabolic analyzer (Metamax 3B) coupled to a heart-rate monitor (Polar H10) placed at the level of the 6th rib and a portable NIRS device (Moxy) placed on the rectus femoris (10 cm above the proximal border of the patella) were worn by the participant during the 6MWT. The test administrator recorded all of the patients' symptoms for exertion (fatigue, dyspnea and dizziness). Upon finishing the 6MWT, the participant remained standing while the test administrator brought a chair to sit on. The participant was then asked to express their perception of breathlessness and muscle fatigue on a scale of 0 to 10 using a modified Borg scale. After a two-minute recovery, the Metamax 3B and NIRS were removed from the participant.

Table 1. Participant characteristics.

	N (%)
Total number of patients	15 (100)
Participants starting with RIPC	10 (66.6)
Participants starting with SHAM	5 (33.4)
Participants with pacemaker	2 (13.3)
Participants with defibrillator	4 (26.6)
Gender (M/F)	14/1
Age (years)	69.60 ± 9.13
Height (cm)	171.20 ± 6.00
Weight (kg)	86.67 ± 16.21
Body mass index ($kg*m^{-2}$)	29.48 ± 4.46
HR rest (bpm)	74.46 ± 12.34
SBP rest ($mm*Hg^{-1}$)	115.27 ± 20.63
DBP rest ($mm*Hg^{-1}$)	66.67 ± 12.55
SBP during RIPC ($mm*Hg^{-1}$)	145.00 ± 38.17
NYHA functional class	
II	12 (80)
III	3 (20)
Left ventricular ejection fraction (%)	33.87 ± 9.10

Values are presented as means ± SD. N, absolute number; RIPC, Remote Ischemic Preconditioning; M: male; F: female; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; NYHA: New-York Heart Association.

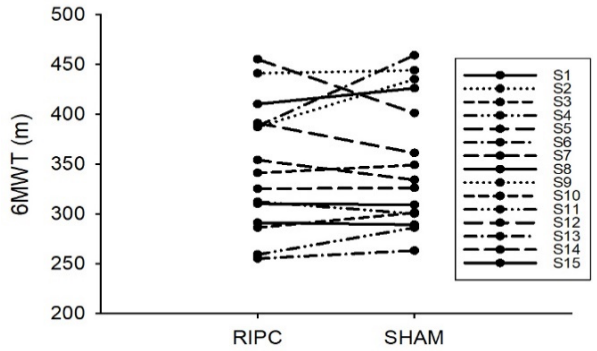
Statistical Analysis

Results are expressed as means and SD, or number of cases and proportions (%). All data were screened for outliers to ensure that means were representative of the group. Significant differences between RIPC and SHAM were measured with Student's paired t-test. A two factor (intervention x time) ANOVA with repeated measures (GLM) was used to detect significant differences between RIPC and SHAM during the 6MWT and the three-minute recovery period. If significant differences were detected, a post-hoc analysis (LSD) was performed. Statistical significance was set at an alpha level of .05 and were performed using SPSS version 24. As well, a sample size calculation was performed (Gpower ver. 3.1.9.7) using a within subject improvement of 22.5-m and a between intervention (RIPC vs SHAM) improvement of 32-m on the 6MWT. Using a statistical power of 90% (β = 10%) and a = .05 a sample of n = 14 was required to reach significance between interventions.

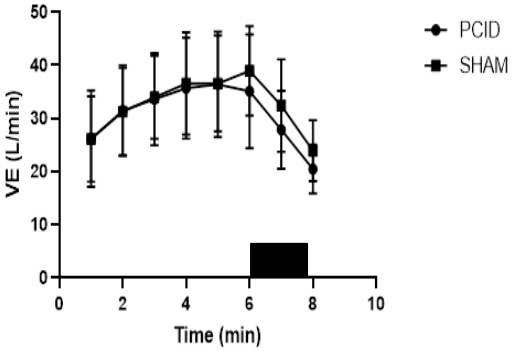
RESULTS

A total of 15 participants were included in the study. Table 1 shows the participants characteristics. Mean age, weight and BMI were 69.6 ± 9.13 years, 86.67 ± 16.21 kg and 29.48 ± 4.46 $kg*m^{-2}$ respectively. Most participants (n=12) were considered stage 2 in the NYHA functional class and 3 were considered stage 3.

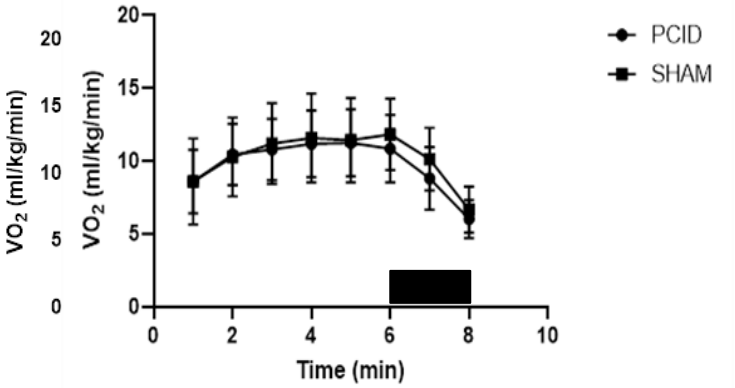
A) Total distance achieved during 6MWT after RIPC and after SHAM



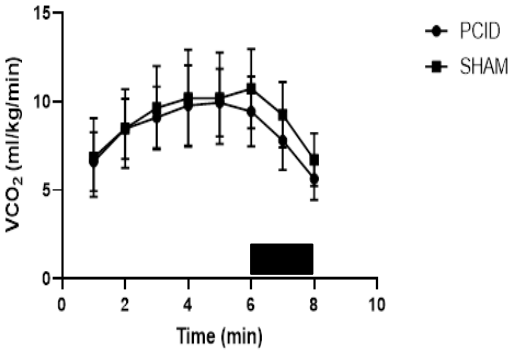
B) Ventilation during and after 6MWT



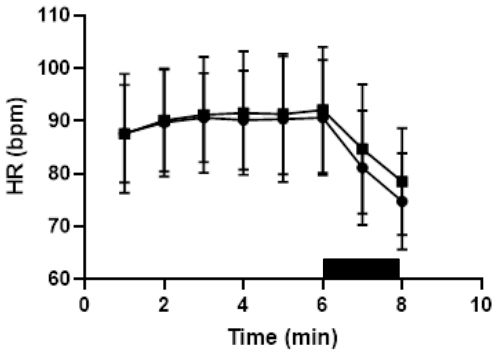
C) Relative oxygen uptake during and after 6MWT



D) Relative expired carbon dioxide during and after 6MWT



E) Heart rate during and after 6MWT



F) Expiratory exchange ratio during and after 6MWT

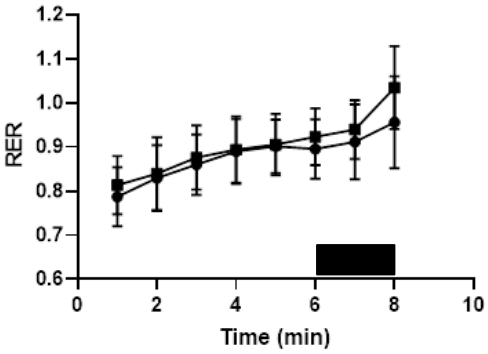


Figure 1. Shows the total distance achieved during 6MWT after RIPC and after SHAM for each participant (Panel A). The other panels, B-F, show, respectively, during and after (recovery black bar) the 6MWT, ventilation (VE) (B), relative oxygen uptake (VO_2) (C), relative expired carbon dioxide (VCO_2) (D), heart rate (HR) (E), and the expiratory

exchange ratio (RER) (F). In all panels (except panel A), the black circles and squares represent the RIPC and SHAM interventions, respectively. The time from 0 to 6 minutes represents the active portion of the 6 minute-walk test (6MWT). The time from six to eight minutes represents the passive recovery time following the 6MWT (black rectangle on the x axis). In panel A, the first column of dots represents the distance achieved by each participant after the RIPC intervention. The second column of dots represents the distance achieved by each participant after the SHAM intervention.

DISCUSSION

The primary objective of this pilot study was to investigate if RIPC would improve the performance of chronic HF patients during the 6MWT using a randomized controlled crossover design. There were no adverse effects observed for any of our study patients. The results, however, did not show any significant improvement in performance for the total distance covered by participants. Nonetheless, we observed (Figure 1A) that eight participants improved their total distance with the RIPC intervention when compared to the SHAM intervention. The reasons why the results for our first hypothesis were null may be multifactorial, for example, the occlusion site, the small N power, responders vs non-responders, the intensity of exercise, or the fact that HF patients may already be in a preconditioned state (15). Perhaps some patients are non-responders to a RIPC intervention (14). Nevertheless, a larger sample size, with as many participants in NYHA functional Class II as in Class III, may allow us to properly confirm this claim, even though recruitment is laborious. The findings presented herein are consistent with other similar studies using a healthy population doing submaximal self-paced exercise that is comparable to the 6MWT (16). As mentioned by Morocolo et al. (14), maybe the small effect on performance with RIPC can be useful to a specific elite population that target every advantage or the smallest worthwhile improvement to win a race. However, it is very different from the reality of HF patients where objectives may be to engage in a cardiac rehabilitation program or maintain a physically active lifestyle. Thus, a minimal RIPC effect for responders is perhaps sufficient to motivate HF patients to adopt some form of active lifestyle without the unpleasant adverse effects of dyspnea or muscle fatigue. Those small improvements, however, do not meet a clinical improvement that could be useful for patients and their physicians (20). It is noteworthy that there were no adverse effects of impairment in performance with the RIPC intervention suggesting that the intervention by itself is well tolerated by HF patients (15).

Our secondary hypothesis was that RIPC would affect oxygen uptake during exercise. For this variable, we used a portable metabolic analyzer and NIRS during the 6MWT and showed that there was no significant effect of RIPC on VO_2, VCO_2, RER, HR, VE, muscle SpO_2, and RPE. Our results are consistent with McDonald's findings that did not report any significant effects of RIPC for the maximal VO_2 during an incremental cycling test (15). In addition, the majority of the studies using healthy populations did not report any improvement either on maximal oxygen uptake and other derived data provided by from metabolic analyzers (18). Though some studies reported better oxygen uptake during steady-state moderate to high-intensity exercise, no study observed any improvement in oxygen uptake during low steady-state exercise in healthy participants (2, 11). From these findings in healthy populations, we cannot confirm that RIPC affects the oxygen delivery mechanism in HF patients. The hypothesis for a better oxygen extraction was also studied with elite speed skating athletes on a time trial event (19). Similar to

the speed skaters, we did not observe any improvement in the muscle oxygen extraction during the 6MWT. Therefore, we could not conclude that RIPC enhances oxygen extraction during a 6MWT in HF patients. However, since the participants in the current study were at a submaximal exerciser capacity, we can not rule out that results might be different when a maximal exercise is applied. On the other hand, MacDonald's et al. used a maximal exercise protocol on an ergocycle (10 Watt per minute incremental workload) and they did not reported improvement (15). Therefore, our data adds to body of knowledge that RIPC on the arm as no effect in a submaximal exercise performance for HF patients.

One of the main limitations of our study is related to the 6MWT test-retest learning curve. For a participant that never did the test, the learning effect could, by itself, improve the performance of the second test. To avoid this bias, we randomized the interventions. Nevertheless, participants still underwent the same 6MWT except they were under different RIPC or SHAM conditions, so there still is a test-retest effect, and thus may be considered as a limitation in this study. As we interrupted the study before the end of recruitment because of the lack of effect, our randomization resulted in a slightly higher proportion of participants starting with RIPC rather than the SHAM intervention, which may have favoured the SHAM intervention for the total distance travelled. With recruitment issues, we decided to not add a control intervention with our participant cohort (no pressure on the cuff). We also used RIPC on the arm, as previously used by McDonald's et al. (15) with HF patients, and since the arms are not the important locomotion driver for the 6MWT performance, we may have obtained different results using a local IPC approach.

RIPC is well tolerated by patients and is easily applicable in a clinical setting. Nevertheless, our data did not demonstrate any positive or negative significant effects on either performance or metabolic and hemodynamic parameters during the 6MWT amongst HF patients. Even if the potential effect of RIPC remains attractive, it does not provide any substantial functional and physiological improvements to justify clinical application. Further studies, with larger sample sizes, are still needed to validate or dispute the use of RIPC in an exercise rehabilitation setting, especially during submaximal exercise. Future research with other types of patients is also needed to better understand the mechanisms generated by RIPC.

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