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The effect of remote ischemic pre-conditioning on pulmonary vascular pressure and gas exchange in healthy humans during hypoxia

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ABSTRACT

This study investigated whether rIPC alters the typical changes in pulmonary arterial pressure, pulmonary gas exchange associated with exercise in hypoxia.

Methods: 16 healthy adults were randomized to either rIPC treatment (n = 8) or control (n = 8). Afterward, subjects performed supine ergometry at constant load (30 W, 40˜50 rpm) for 25 min during hypoxia (12.5% O_2). Following a 90˜120 min rest, either rIPC or sham treatment was performed, which was then followed by post-assessment exercise. Throughout exercise, pulmonary arterial systolic pressure (PASP) and mean pulmonary arterial pressure (mPAP) were measured via echocardiography, while pulmonary gas exchange was being assessed.

Results: The rICP group demonstrated improved PASP and mPAP ($p < 0.05$), whereas the control group did not. Additionally, breathing efficiency (V_E/V_{CO2}) and end-tidal CO_2 (PET_{CO2}) were improved in rIPC group ($p < 0.05$), but not in controls.

Conclusion: These data suggest that rIPC contributes to reduced pulmonary arterial pressure, and improved pulmonary gas exchange during hypoxic exercise. However, follow-up studies are needed to apply these findings to patient care settings.

1. Introduction

Compared with breathing normoxic air, breathing hypoxic air can lead to an impaired ability to perform physical activity (e.g., exercise) because of marked decreases in arterial oxygen saturation (SaO_2) and content. In otherwise healthy adults, hypoxia does not typically occur at sea-level, however, unique settings such as during high intensity aerobic exercise can provoke signs and symptoms of hypoxia at both sea-level and high altitude (Dempsey and Wagner, 1999; Hackett and Roach, 2001). In contrast, it has been observed that patient populations such as heart failure (HF) and/or pulmonary hypertension (PH) may demonstrate hypoxemia even while breathing room air at sea-level (De Boer et al., 2003; Taylor et al., 2013). This is relevant because it has been suggested there is a link between the amount of hypoxemia and pulmonary vasoconstriction (Dinh-Xuan et al., 1993; Sweeney and Yuan, 2000; Taraseviciene-stewart et al., 2001), which may contribute to ventilation-perfusion (V_A/Q) mismatch and ventilatory inefficiency, both of which may be exacerbated during physical activity (e.g., exercise) (Woods et al., 2011a, b; Kim et al., 2012, Kim et al., 2015). Although underlying pathophysiological mechanisms remain unclear, it has been suggested that both alveolar and systemic forms of hypoxia are key contributors to pulmonary vasoconstriction in patients with cardiovascular diseases (e.g., HF, PH, etc.) (Dinh-Xuan et al., 1993; Sweeney and Yuan, 2000; Taraseviciene-stewart et al., 2001).

In this context, ischemic pre-conditioning (IPC) is defined as brief episodes of ischemic-reperfusion, which provides endogenous protection against ischemia-reperfusion injury. By administering ischemic pre-conditioning on one organ, it has also been suggested there may be a therapeutic downstream influence on a 'remote' organ. This application of ischemic pre-conditioning has been termed remote ischemic pre-conditioning (rIPC). Several studies conducted in animals have indeed demonstrated rIPC as a therapy may elicit protective effects on the heart (i.e., myocardial infarction), stomach, kidneys, liver, and skeletal muscle (Brzozowski et al., 2004; Konstantinov et al., 2005; Moses et al., 2005; Kristiansen et al., 2005; Lai et al., 2006). Although the exact underlying mechanisms have yet to be fully elucidated, it has been proposed that improved endothelial function via enhanced nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) bioavailability plays a key role in the therapeutic benefit linked to rIPC (Kuntscher et al., 2002; Abu-Amara et al., 2011; Veighey and Macallister, 2012). As

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such, it is possible that with favorable effects on endothelial function following rIPC, particularly at tissue of the central circulation, pulmonary-arterio coupling may improve leading to more closely matched hemodynamics, ventilation, and gas exchange. Therefore, as a hypothesis generating study, we aimed to assess whether acute delivery of rIPC is associated with blunted increases in pulmonary arterial pressure concurrent with improved ventilatory and gas exchange function during hypoxic submaximal exercise in healthy adults.

2. Methods

Sixteen healthy adults participated in this study. Subjects were asked to refrain from caffeine intake and eating food < 2h prior to participation. Additionally, individuals who had been exposed to hypoxia within 6 month prior to the present study were excluded. All participants provided written informed consent prior to participation in this study. All aspects of this study were approved by the Mayo Clinic Institutional Review Board.

2.1. Protocol overview

Prior to experimental measurement, participants underwent a baseline assessment at rest in normoxia. Thereafter, participants were randomly assigned to either the rIPC group (n = 8) or a control group (n = 8) (Table 1, characteristics). The experimental protocol included 3 phases as follows; 1) pre–assessment during hypoxia, 2) rIPC treatment during normoxia, and 3) post-assessment during hypoxia. During hypoxia participants continuously breathed via mask an O_2 concentration equal to 12.5% (Fig. 1).

During pre-assessment, participants were asked to perform constant intensity submaximal exercise on a stress echocardiographic supine ergometer (Ergoselect 1200 P ergometer, CareFusion, New Zealand) for 30 min. This protocol included: 5 min of rest, 5 min of warm-up unloaded exercise, and 20 min of constant workload (30 W) exercise. Pedaling rate was maintained at 40 ~ 50 rpm during exercise. Following the pre-assessment phase, participants underwent a 90 min rest, which constituted the washout period. Immediately after the washout period, participants underwent rIPC treatment. For individuals randomized to the rIPC group, a 5 inch width cuff was placed on the upper arm at the brachial artery level and inflated to 200 mmHg to elicit an ischemic condition at the brachial artery for 5 min, which was followed by a 5 min deflation period for reperfusion. This brief ischemia-reperfusion process was repeated 4 times. The presence of a pulsed-wave form was continually monitored via pulse-oximetry to confirm the occurrence of ischemia. In contrast, for individuals randomized to the control group, the same cuff used in the rIPC group was inflated to 20 mmHg on the upper arm at the brachial artery level.

Following completion of the rIPC treatment phase in both groups, subjects were instructed to rest for 60 min. This rest period timing was selected based on the fact that the acute effect of rIPC would be maximized approximately 60 ~ 90 min post-treatment (Yellon and Dana, 2000; Carini and Albano, 2003; Loukogeorgakis et al., 2005). Thus, following the 60 min rest period, post-assessment was performed at an optimal 'treatment' timing in an identical manner as the pre-assessment phase.

Table 1
Subject characteristics and baseline assessment.

	rIPC group	Control group
Sex (M/F)	3 / 5	5 / 3
Age (years)	25.8 ± 9.5	30.8 ± 8.0
Height (cm)	171.3 ± 6.9	175.4 ± 8.7
Weight (kg)	67.3 ± 8.1*	83.0 ± 11.1*
BMI (kg/m^2)	22.9 ± 2.5*	27.1 ± 3.7*

Body mass index (BMI). * denotes significant difference between groups.

2.2. Echocardiographic assessment

To determine pulmonary arterial pressure, pulmonary arterial systolic pressure (PASP) and mean pulmonary arterial pressure (mPAP) were quantified via calculation with echocardiographic parameters (Kitabatake et al., 1983). Tricuspid regurgitation velocity (TRV) was obtained to estimate PASP [$PASP = 4(TRV)^2 + 5mmHg$]. In addition, the ratio of acceleration time to the total duration of systolic ejection time (AT/ET) in the right heart was obtained to estimate mPAP [$mPAP = -\log_{10}(2.8(AT/ET) + 2.4$], where AT was defined as the time to peak flow velocity and ET was defined as the time from onset of ejection to that of zero flow. This measurement was performed at 15 min after starting exercise and at least 3 ~ 5 beats were obtained and averaged. An investigator responsible for echocardiographic assessment was blinded to whether rIPC or the control treatment.

2.3. Pulmonary gas exchange

Breath-by-breath ventilation and gas exchange was assessed via metabolic measurement system (Medgraphics, Saint Paul, MN) integrated with gas mass spectrometry (Perkin Elmer, Kansas City, MO) during exercise. Key parameters measured to test our study aim were end tidal carbon dioxide (PET_{CO2}) and breathing efficiency for carbon dioxide (V_E/V_{CO2}) because of their relevance in being used to assess patient prognosis in the clinical setting. Thus, an increase in V_E/V_{CO2} is associated with higher dead space ventilation that is related to increased breathing frequency (Woods et al., 2011a; Kim et al., 2012; Kim et al., 2015). In contrast, PET_{CO2} is associated with V_A/Q mismatch, and thereby decreases when V_A/Q is impaired (Woods et al., 2011a; Kim et al., 2012; Kim et al., 2015). Additionally, an index of inspiratory drive (the ratio of tidal volume to inspiratory time, Vt/Ti) and respiratory rate (RR) were obtained (Olson et al., 2016).

2.4. Statistical analysis

To observe the changes in echocardiographic and pulmonary gas exchange variables following treatment, the primary analysis was conducted via a two-factor (group randomization by measurement time period) repeated measure analysis of variance (ANOVA). Subsequently, post-hoc analysis was conducted to observe specific difference via a paired-sample, an independent or non-parametric t-tests. Additional calculations of standardized mean differences (i.e., effect sizes, ES) between conditions were also performed (large ES ≥ 0.80). Two-tailed statistical significance was determined using an alpha level set a 0.05. All statistical analyses were performed using SPSS (version 22).

3. Results

All subjects completed all aspects of this study in the absence of adverse events. At baseline prior to the experimental phase, no significant difference in PASP between rIPC and the control groups (19.58 ± 6.53 vs. 15.10 ± 6.25 mmHg respectively, p = NS) was observed, whereas there was a significant difference in mPAP (15.60 ± 5.13 vs. 10.60 ± 1.82 mmHg respectively, $p < 0.05$). The rIPC and the control groups demonstrated no significant group difference in V_E/V_{CO2} (35.74 ± 4.92 vs. 32.02 ± 7.38, respectively, p = NS), PET_{CO2} (40.08 ± 3.39 vs. 44.07 ± 6.74 mmHg, respectively, p = NS) and Vt/Ti (571 ± 113 vs. 716 ± 426 respectively, p = NS).

During pre-assessment, hypoxic exercise resulted in an elevation in PASP ($p < 0.05$), but no difference between rIPC group and the control was observed (p = NS). Similarly, mPAP was increased during hypoxic exercise ($p < 0.05$), however, there was no difference between rIPC group and the control group (p = NS). This trend remained same for key gas exchange variables including PET_{CO2} (p = NS), V_E/V_{CO2} (p = NS), $V_E/V_{CO2\ slope}$ (p = NS) and Vt/Ti (p = NS). Table 2 illustrates pulmonary pressure and gas exchange at pre- and post-assessments.

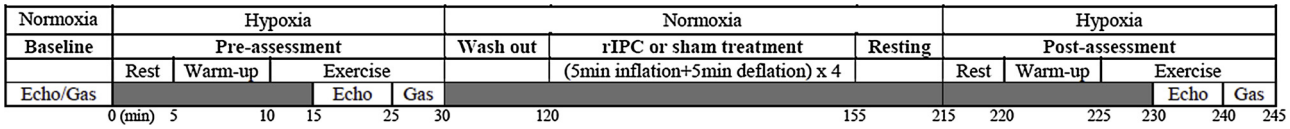

Fig. 1. The overall study protocol. Subjects inhaled ~21% of O_2 during normoxia and ~12.5% of O_2 during hypoxia. Echocardiographic assessment (Echo), respiratory gas exchange assessment (Gas).

For echocardiographic variables, the rIPC group demonstrated a greater reduction in PASP from pre- to post-treatment compared to the control group (Fig. 2A, $p < 0.05$). Similarly, mPAP also decreased in rIPC group following treatment, but not in the control group (Fig. 2B, $p < 0.01$). For pulmonary gas exchange variables, rIPC group showed a significant improvement in PET_{CO2} and a reduction in V_E/V_{CO2}, whereas there were no changes in the control group (Fig. 3A, $p < 0.05$ and 3B, $p < 0.05$, respectively). Moreover, $V_E/V_{CO2\ slope}$ was a trend toward improvement in the rIPC group from pre- to post-treatment (Fig. 3D, $p = 0.052$), but not in the control group. In addition, neither group demonstrated differences in Vt/Ti (Fig. 3C, p = NS) and RR (p = NS) between-within groups. Subsequently, the change in V_E/V_{CO2} was significantly related to the change in mPAP in all 16 subjects regardless of groups ($r = 0.554$, $p < 0.05$).

4. Discussion

In this single blind randomized controlled study, these data suggest that healthy adults demonstrate blunted increases in pulmonary arterial pressure paralleled by improved ventilatory efficiency during hypoxic submaximal exercise following acute administration of rIPC.

Although several studies have demonstrated favorable effects of acute administration of rIPC, a majority of previous studies have primarily focused on the cardio-protective therapeutic potential of this technique. Despite this central hemodynamic interest, there is limited knowledge of what potential effect rIPC may have on changes in pulmonary vascular pressure accompanied by ventilation and gas exchange. This is relevant as with heart-lung interactions, > 90% of cardiac output (Q) typically is perfused into the pulmonary circulation needed for effective gas exchange. Therefore, due to this intrinsic pulmonary-arterio coupling mechanism and because others have demonstrated a potential cardio-protective effect of rIPC, we sought to test whether physiological effects of this technique translates to the pulmonary circulation while also affecting ventilatory efficiency.

Hypoxia is often associated with increases in pulmonary vascular pressure via pulmonary vasoconstriction (Sylvester et al., 2012), which is consistent with these data. Increased pulmonary vascular pressure can commonly arise as a consequence of neuro-humoral pathway activation linked to exposure to high altitude environments in the absence of supplemental O_2 and/or pathologic conditions such as HF or PH . In the present study, these data confirm, what has been demonstrated by others, hypoxic air breathing during exercise provokes increases in PASP and mPAP in otherwise healthy adults. However, while we are not able to identify the underlying mechanism based on these data, acute administration of rIPC appeared to play a role in attenuating the hypoxia induced elevation in PASP and mPAP. Others propose that key mechanisms influential to the physiological effects of rIPC involve an enhanced nitric oxide (NO), cyclic guanosine monophosphate (cGMP), and protein kinase G (PKG) signaling cascade (Moses et al., 2005; Lai et al., 2006; Abu-Amara et al., 2011) including potent vasodilatory mediators such adenosine (Pell et al., 1998), bradykinin (Schoemaker and van Heijningen, 2000), endocannabinoid (Hajrasouliha et al., 2008), and calcitonin gene related peptide (CGRP) Wolfrum et al., 2005).

This hypothesis is supported by previous studies demonstrating that delivery of NO or phosphodiesterase-5 inhibitor therapy led to attenuated hypoxia induced vasoconstriction and pulmonary hypertension in healthy human and animal models (Pison et al., 1993; Zhao et al., 2001). Others report that endothelial function improves following rIPC in healthy adults, cardiac patients (Zhao et al., 2001), and hypertensive elderly (Moro et al., 2011). Consistent with this, a study by Kono et al. observed that rIPC led to improved coronary microcirculation in both healthy adults and heart failure patients (Kono et al., 2014), whereas Zagidullin et al. suggested rIPC can be used to improve arterial compliance and systolic blood pressure in patients with coronary heart disease (Zagidullin et al., 2016). In this context, we hypothesize that rIPC contributed to suppressed hypoxic pulmonary vasoconstriction and pulmonary vascular resistance followed by increased pulmonary circulation.

Pulmonary gas exchange is often impaired in hypoxia partly attributable to low alveolar PO_2 and hyperventilation followed by V_A/Q inhomogeneity. With the potential for abnormal pulmonary blood flow redistribution during hypoxia, it is also possible V_A/Q mismatch can be exacerbated because of poor perfusion during exercise while breathing hypoxic air. Although we are not able to identify with these data a clear underlying mechanism regarding direct relationships between high pulmonary vascular pressure and gas exchange function, others demonstrate increased pulmonary arterial pressure is highly associated with impaired pulmonary gas exchange in hypoxia (Reindl et al., 1998; Maggiorini et al., 2001). In addition, although further investigations are needed, we observed that the change in V_E/V_{CO2} during exercise was significantly related to the change in mPAP. Therefore, we propose that improved ventilation and gas exchange in those administered rIPC may be attributable to effects of this therapy on attenuated hypoxic

Table 2
Pulmonary pressure and gas exchange at pre- and post-assessments.

	rIPC group		Control group	
	Pre	Post	Pre	Post
PASP (mmHg)	28.91 ± 14.13	20.56 ± 10.02	20.92 ± 6.18	20.86 ± 7.96
mPAP (mmHg)	19.27 ± 5.44	15.76 ± 3.55	14.83 ± 4.64	16.06 ± 3.77
PETCO2 (mmHg)	38.39 ± 3.11	39.06 ± 3.33	42.27 ± 7.91	41.29 ± 8.20
VE/VCO2	31.52 ± 2.75	30.66 ± 2.87	29.27 ± 6.63	30.43 ± 6.92
VE/VCO2 slope	31.62 ± 3.42	29.01 ± 4.39	26.89 ± 6.25	28.91 ± 8.77
Vt/Ti (ml/sec)	1309 ± 247	1219 ± 198	1372 ± 398	1329 ± 338
RR (br/min)	26.35 ± 6.67	25.53 ± 5.30	22.38 ± 8.03	23.07 ± 8.12

Pulmonary arterial systolic pressure (PASP), mean pulmonary arterial pressure (mPAP), end-tidal CO_2 (PET_{CO2}), breathing efficiency (V_E/V_{CO2}), breathing efficiency slope ($V_E/V_{CO2\ slope}$), an index of inspiratory drive (Vt/Ti) and respiratory rate (RR).

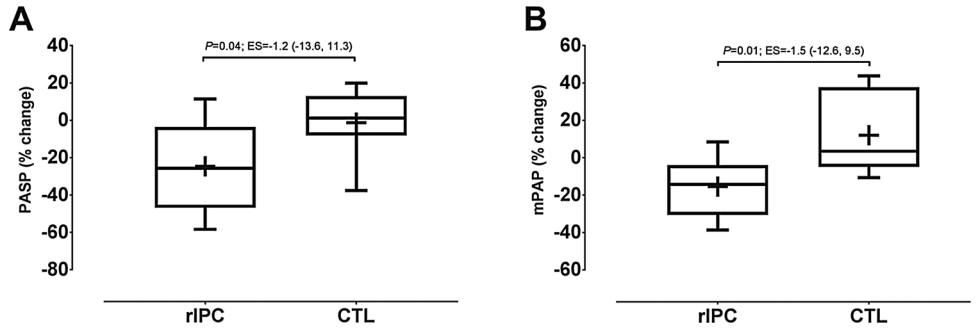

Fig. 2. The percent changes in pulmonary systolic arterial pressure and mean pulmonary arterial pressure from pre- to post-assessments. PASP (pulmonary arterial systolic pressure), mPAP (mean pulmonary arterial pressure).

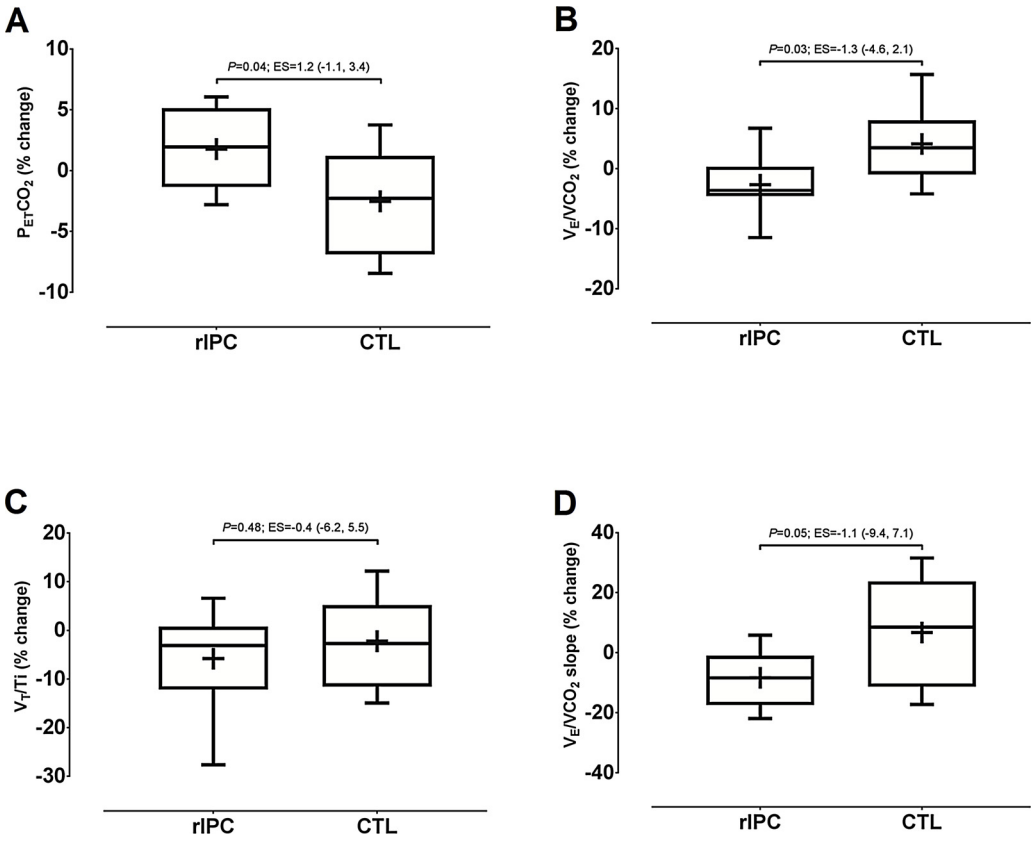

Fig. 3. The percent changes in pulmonary gas exchange from pre- to post-assessments. $V_E/_{VCO2}$ (breathing efficiency), PET_{CO2} (end tidal CO2), $V_E/V_{CO2\ slope}$ (breathing efficiency slope). Vt/Ti (the ratio of tidal volume to inspiratory time). There was a trend of significant difference in $V_E/V_{CO2\ slope}$ between groups (p = 0.052).

mediated pulmonary vasoconstriction, resistance and pressure.

The present study had limitations. We suggested NO-cGMP signaling pathway as a significant underlying mechanism of rIPC for reducing hypoxic vasoconstriction, however, we did not assess the change in NO and cGMP in the present study. Elevations in PASP and mPAP due to hypoxic exercise were relatively small and baseline mPAP was different between groups. These results could influence the outcomes. However, the difference in baseline mPAP between groups was no longer evident at pre-assessment. In addition, difference in baseline BMI between groups could impact PASP and mPAP. However, there was no significant relationship between body weight and PASP (r = -0.382, p = 0.145) and mPAP (r = -0.254, p = 0.343) at rest. The improvement in PASP following treatments was still greater in rIPC group than the control group after correction with body weight (p = 0.042), and this is mirrored for mPAP (p = 0.011). Overall, this provides preliminary evidence to suggest PASP and mPAP were not impacted by body weight in the present study. Lastly, the present study investigated the acute effect of rIPC. Therefore, the findings are limited to acute effect of rIPC only and further studies with larger sample are needed to determine the long term effect and training effect of treatment.

5. Conclusion

The present study demonstrated that compared with a control group, acute administration of a single bout of rIPC resulted in attenuated hypoxic mediated elevations in pulmonary arterial pressure and improved ventilatory efficiency during submaximal exercise. Mechanistic human-based follow-up studies are needed to clarify what underlying physiological and biocellular processes are influenced by administration of rIPC during settings of hypoxia. If, after the mechanistic origins of rIPC are confirmed, future applications of this noninvasive technique may be medically relevant to clinical populations (e.g., heart failure, pulmonary hypertension, etc.) for whom targeted pathways such as relating to NO-cGMP and/or PDE-5 are currently used for pharmacotherapies.

Conflict of interest

None of authors have financial interests in the research project.

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