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Short communication

Post-exercise accumulation of interstitial lung water is greater in hypobaric than normobaric hypoxia in adults born prematurely

Tadej Debevec[a,b,1,*], Mathias Poussel[c,d,1], Damjan Osredkar[e], Sarah J. Willis[d], Claudio Sartori[f], Grégoire P. Millet[d]

[a] Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia
[b] Department of Automation, Biocybernetics and Robotics, Jozef Stefan Institute, Ljubljana, Slovenia
[c] Department of Pulmonary Function Testing and Exercise Physiology, CHRU de Nancy, Nancy, France
[d] Institute of Sport Sciences, University of Lausanne, Lausanne, Switzerland
[e] Department of Pediatric Neurology, University Children's Hospital Ljubljana, Ljubljana, Slovenia
[f] Department of Internal Medicine and the Botnar Center for Extreme Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

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ABSTRACT

We aimed to gauge the interstitial lung water accumulation following moderate-intensity exercise under normobaric and hypobaric hypoxic conditions in a group of preterm born but otherwise healthy young adults.

Sixteen pre-term-born individuals (age = 21±2yrs.; gestational age = 29±3wk.; birth weight = 1160±273 g) underwent two 8 -h hypoxic/altitude exposures in a cross-over manner: 1) Normobaric hypoxic exposure (NH; F_IO_2 = 0.142±0.001; P_IO_2 = 90.6±0.9 mmHg) 2) Hypobaric hypoxic exposure (HH; terrestrial high-altitude 3840 m; P_IO_2 = 90.2±0.5 mmHg). Interstitial lung water was assessed via quantification of B-Lines (using lung ultrasound) before (normoxia) and after 4-h and 8-h of respective exposures. At each time point, B-Lines were quantified before (Pre) and immediately after (Post) a 6-min moderate-intensity exercise.

The baseline B-lines count were comparable between both conditions (P = 0.191). A higher B-lines count was noted at Pre-H4 in HH versus NH (P = 0.0420). At Post-H8 B-lines score was significantly higher in HH (4.6 ± 1.6) than in NH (3.1 ± 1.4; P = 0.0073). Furthermore, at this time point, a significantly higher number of individuals with B-line scores ≥5 was observed in HH (n = 7) than in NH (n = 3; P = 0.0420).

These findings suggest that short moderate-intensity exercise provokes a significant increase in the interstitial lung water accumulation after 8 h of exposure to terrestrial but not simulated altitude (≈3840 m) in prematurely born adults. Further work is needed to elucidate the exact mechanisms of (moderate-intensity) exercise-induced interstitial lung water accumulation in this population and directly compare the obtained data to full-term born adults.

1. Introduction

The number of individuals travelling and/or residing at high-altitude regions for both, work, and leisure is constantly increasing. Accordingly, there is a growing number of people exposed to altitude-related hypoxia along with its physiological effect, with some of them having a higher risk for deleterious physiological responses. Individuals born prematurely might represent one such cohort. Indeed, premature birth is known to be associated with numerous long-term respiratory and cardiovascular dysfunctions that present during both rest and exercise (Duke and Lovering, 2020; Lovering et al., 2014). However, whether these long-term impairments result in higher susceptibility for high-altitude ailments or compromised altitude adaptation capacity remains unclear. For example, some evidence from our lab and others suggest that preterm born individuals exhibit reduced hypoxic ventilatory response (Bates et al., 2014; Debevec et al., 2019) which has been associated with the development of high-altitude pulmonary oedema (HAPE), a life-threatening form of non-cardiogenic oedema (Hackett et al., 1988). However, several other studies do not suggest any clear influence of prematurity on hypoxia-related changes on gas exchange

* Corresponding author at: Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia.
E-mail address: tadej.debevec@fsp.uni-lj.si (T. Debevec).

[1] These authors contributed equally to the present work.

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(Duke et al., 2014) and/or pulmonary vascular responses (Laurie et al., 2018) during exercise. While the prevailing evidence does suggest that pre-term born as compared to full term-born individuals exhibit altered pulmonary responses to normoxic exercise, the potential additive effects of hypoxia remain uncertain.

Altitude-related reduction in ambient and partial O_2 pressure are recognised to provoke pulmonary vasoconstriction, thereby augmenting pulmonary artery pressure and can subsequently, due to related capillary stress failure, result in interstitial lung water accumulation (Bartsch et al., 2005). These pathological responses could sometimes, principally in more susceptible individuals lead to the development of HAPE and/or other altitude-related illnesses (Maggiorini et al., 2001). Up-to-date research in this regard suggests that HAPE susceptible individuals (those having at least one episode of HAPE previously) display both, greater exercise-related pulmonary artery pressure increase (Eldridge et al., 1996) and greater pulmonary artery occlusion pressure reactivity (Maggiorini, 2006). These phenomena, interestingly, do not seem to be directly related to hypoxia and/or oxygenation but exercise *per se*.

The above-mentioned interstitial lung water accumulation can be assessed using the non-invasive lung ultrasound technique (Pratali et al., 2010; Wimalasena et al., 2013). Limited up-to-date research data suggests that interstitial lung water accumulation correlates to exercise intensity in hypoxia (Pratali et al., 2012). Furthermore, recent evidence indicates that high-intensity exercise increases pulmonary interstitial oedema at terrestrial high-altitude (hypobaric hypoxia, HH) but not at comparable simulated altitude (normobaric hypoxia, NH) (Edsell et al., 2014). Whether the same holds for moderate-intensity exercise is currently unclear. Accordingly, the present work aimed to test the hypothesis that short-term moderate-intensity exercise results in significantly greater interstitial lung water accumulation following exercise under terrestrial (HH) as opposed to simulated (NH) high-altitude conditions in prematurely born young adults. A potential difference between the two conditions is of interest, particularly in clinical populations that might have higher altitude-related illness susceptibility, which is often estimated solely using exercise testing under NH conditions (Richalet et al., 2012).

2. Methods

The present work was part of a larger (PreTerm) project aiming to comprehensively assess the effects of hypoxia/altitude exposure on physiological responses of prematurely born individuals with methodological details published previously (Debevec et al., 2019, 2020). The protocol and employed procedures were approved by the National Ethics committee (0120−101/2016−2), preregistered at ClinicalTrials.gov (NCT02780908) and conducted following the Declaration of Helsinki guidelines.

Briefly, 16 healthy pre-term-born participants (age = 21±2yrs.; gestational age = 29±3wk.; birth weight = 1160±273 g; BMI = 22.9±3.3 kg·m^2; VO_{2peak} = 47±7 mL kg^{-1} min^{-1}) underwent a pre-screening session and two 8 -h hypoxic/altitude exposures in a cross-over manner: 1) Normobaric hypoxic exposure (NH; F_IO_2 = 0.142±0.001; P_IO_2 = 90.6±0.9 mmHg; Planica normobaric hypoxic facility, Rateče, Slovenia) and 2) Hypobaric hypoxic exposure (HH; terrestrial high-altitude 3840 m; P_IO_2 = 90.2±0.5 mmHg; Aiguille du Midi High-Altitude Laboratory, Chamonix, France). The participants underwent interstitial lung water assessment by quantification of B-Lines (using lung ultrasound) before (in normoxia) and after 4-h (H4) and 8-h (H8) of respective hypoxic exposures.

At each time point, lung ultrasound assessments were conducted before (Pre) and immediately after (Post) a 6-min moderate-intensity exercise, performed on a bicycle ergometer at a workload corresponding to 50 % of the baseline VO_{2peak}. Lung ultrasound assessments were always performed in a supine position in a quiet laboratory using an ultrasound transducer (2.5–3.5 MHz; 3V2c Acuson, Siemens Medical Solutions USA, Inc. Moutain View, US). Each intercostal space from the second to the fifth on the right and the second to the fourth on the left was scanned in four different positions (para-sternal, midclavicular, anterior axillary, and mid-axillary). A total of 28 different zones were examined (16 on the right and 12 on the left). Examinations were always carried out by the same trained operator (MP, a respiratory physician) during both exposure sessions with particular caution to prevent respiration-induced movement and double-counting (asking the patient to hold his breath). B-lines were, defined as hyperechogenic vertical lines arising from the pleural line and extending to the edge of the ultrasound screen. The analysis was conducted in a blinded manner. For each ultrasound zone, the highest number of B-lines in a single intercostal space was recorded. The sum of the number of B-lines measured at each of the 28 zones was then calculated. A total number of <5 B-lines was considered normal (i.e. below clinical significance) (Platz et al., 2012). Data are reported as mean ± SD and were analysed using two-way repeated-measures ANOVA (time x condition) with post-hoc analysis only conducted when a main effect or an interaction was noted.

3. Results

The sums of B-line count along with the number of participants demonstrating ≥5 B-lines at each time point are depicted in Table 1. The baseline B-lines count were comparable between both conditions (P = 0.191). Even though none of the participants displayed a clinically significant number of B-lines, a slightly higher B-lines count was noted at Pre-H4 in HH versus NH (P = 0.042), with no differences observed at Post-H4 (P = 0.080). Also, no significant differences were observed between NH and HH at Pre-H8 (P = 0.279) with only one participant in HH demonstrating B-lines score >5. In contrast, the Post-H8 score was significantly higher in HH (4.6±1.6) than in NH (3.1±1.4; P = 0.0073). Furthermore, at this time point, a significantly higher number of individuals with B-line scores ≥5 was observed in HH (n=7) than in NH (n=3; P = 0.042). As reported previously (Debevec et al., 2020), significantly lower resting (83±2% vs. 86±3%) and exercise (77±3 vs. 81±4%) capillary oxyhemoglobin saturation was noted at 4-h time point in HH vs. NH (P = 0.010) with no differences between conditions observed in respiratory parameters, heart rate, or blood pressure.

4. Discussion

In the present report, we show, for the first time, a significant increase in the interstitial lung water accumulation following a short moderate-intensity exercise after 8 h of exposure to terrestrial high-altitude (3840 m) but not during simulated altitude corresponding to

Table 1
Ultrasound B-lines count before (Baseline) and at 4 -h (H4) and 8 -h (H8) time points during the normobaric hypoxic (Planica; NH) and the hypobaric hypoxic (Chamonix; HH) exposures. At each time point the B-line assessments were performed before (Pre) and after (Post) 6-minute moderate-intensity exercise.

	Planica (*NH*)	Chamonix (*HH*)	*P*
Baseline (*Score*)	0.2±0.4	0.4±0.5	NS (0.19)
Baseline (*CS*)	0	0	–
Pre – H4 (*Score*)	1±0.8	1.62±1.0	0.04
Pre – H4 (*CS*)	0	0	–
Post – H4 (*Score*)	1.9±1.1	2.6±1.0	NS (0.08)
Post – H4 (*CS*)	1	1	NS (0.93)
Pre – H8 (*Score*)	2±1.1	2.4±1.0	NS (0.28)
Pre – H8 (*CS*)	0	1	NS (0.22)
Post – H8 (*Score*)	3.1±1.4	4.6±1.6	0.01
Post – H8 (*CS*)	3	7	0.04
Δ - H4 (*Score*)	0.9±0.8	0.9±0.8	NS (0.87)
Δ - H4 (*CS*)	1	1	NS (0.93)
Δ – H8 (*Score*)	1.3±1.0	2.2±1.5	NS (0.05)
Δ – H8 (*CS*)	3	6	NS (0.07)

Data presented as mean ± SD. CS, Clinically Significant (i.e. B-lines score ≥ 5); Δ - H4, Score change from Baseline to H4; Δ – H8, Score change from H4 to H8.

the same partial oxygen pressure. Indeed, in line with previous work (Edsell et al., 2014), the obtained data further confirm the independent effect of barometric pressure on interstitial lung water accumulation during acute high-altitude exposure and lend support to the notion that HH and NH should not be used interchangeably within clinical high-altitude medicine (Millet and Debevec, 2020).

While higher interstitial lung water accumulation in HH as opposed to NH was previously shown only in healthy individuals following high-intensity exercise (Edsell et al., 2014), the fact that an increase in lung B-lines in preterm born individuals was observed after only 6-minute moderate-intensity exercise at altitude is a new finding. It is of note that, in the present study, the differences in interstitial lung water accumulation between NH and HH were observed upon acute (8-h) exposure whereas Edsell et al. (2014), albeit at a similar altitude, tested the effects of HH upon six days of high-altitude sojourn which might have significantly modulated the subsequent pulmonary responses to exercise. Accordingly, a direct comparison between the two studies and subsequent assessment of the relative risk for developing lung comets at terrestrial altitude is not feasible. The fact that a significantly lower number of preterm born individuals exhibited interstitial lung water accumulation following exercise in HH in the present study (seven out of 16 participants), as opposed to almost all healthy controls (12 out of 13) in the study by Edsell et al. (2014) does not necessarily indicate that preterm born individuals have a lower risk of interstitial lung water accumulation but can be related to differences in exercise intensity (moderate vs. high) and HH exposure duration (8-h vs. six days). There, however, exists clear evidence that exercise at altitude - similar to that employed in the present study (3,500−3,600 m) - induces a significantly higher accumulation of interstitial lung water in some clinical populations (i.e. chronic mountain sickness patients) as opposed to healthy age-matched controls (Pratali et al., 2012).

Collectively, the above-discussed data of higher interstitial lung water accumulation under HH vs. NH conditions bring into question the pertinence and applied value of hypoxic susceptibility tests that are generally conducted under normobaric conditions with a possible underestimation of high-altitude illnesses risk in this group. This is particularly relevant since the exercise intensity corresponds to the one faced by trekkers or mountaineers at high-altitude. Even though the clinical relevance of a small number of B-lines to high-altitude pulmonary oedema and the adaptational specificity of pre-term born individuals remain to be fully clarified, the present data should be considered by clinicians advising an ever-increasing number of individuals (including those born prematurely) visiting/travelling to high-altitude regions for work and/or leisure.

Whilst these data are of interest and novel, we would like to acknowledge a few important limitations. First, due to the lack of a control group, consisting of full-term and age-matched individuals, we cannot discern the independent effect of prematurity on the observed effects, and this should be comprehensively explored in the future. While preterm born individuals might indeed be more prone to high-altitude-related respiratory ailments (including potential higher interstitial lung water accumulation and subsequent higher high-altitude pulmonary oedema incidence) further work is needed to confirm this. Although some up-to-date work suggests that prematurity does not exacerbate hypoxic exercise-related pulmonary vascular responses (Goss et al., 2018; Laurie et al., 2018) there is evidence to suggest that young preterm born adults exhibit endothelial dysfunction (Engan et al., 2021) that can also result in reduced pulmonary vascular compliance and, thereby, augment susceptibility of this cohort to hypoxia and/or HAPE (Khatri et al., 2020). While the observed post-exercise accumulation of interstitial lung water in preterm born individuals might be associated to pulmonary artery pressure and/or compliance-related pathological responses, this remains a speculation as we did not assess pulmonary vasculature responses in the present cohort. With that in mind, further studies are warranted to comprehensively elucidate all potential underlying factors of prematurity-specific vascular and physiological responses that could result in augmented HAPE susceptibility. It also seems reasonable to conduct future studies, investigating the pathophysiology of HAPE in this population, at higher terrestrial altitudes, known to be more conductive to its manifestation (Wilkins et al., 2015). Second, one cannot exclude that some of the observed B-lines in preterm individuals are due to potential lung abnormalities, even if these participants exhibited normal and/or predicted lung function capacities compared to their full-term born counterparts (Debevec et al., 2019) potential structural abnormalities cannot be excluded. Nevertheless, given that clear changes in the number of B-lines were observed between different time points it seems that the observed changes are indeed related to hypobaria and exercise and not to other artefacts. Third, while HAPE does not typically develop within the tested exposure duration (i.e. 8 h) and at the altitude level tested (3840 m), the hypoxic & exercise stimuli were sufficient to induce a measurable increase in interstitial lung water accumulation. Further work to study the incidence of HAPE in this population should employ higher and longer (duration) altitude exposures. Fourth, the study was only conducted with male participants as we were not able to logistically conduct such a study with taking female-specific hormonal variation – known to modulate respiratory adaptation to high-altitude - into consideration. Finally, and as nicely outlined in a recent Cross-Talk debate, perfectly matching the two hypoxic conditions is highly challenging and potential methodological limitations related to that aspect cannot be completely ruled out (Richalet, 2020).

In conclusion, the present findings suggest that even short-term moderate-intensity exercise provokes a significant increase in the interstitial lung water accumulation after 8 h of exposure to terrestrial but not simulated altitude. Further investigations of interstitial lung water accumulation during prolonged high-altitude activities and its relation to high-altitude pulmonary oedema and other altitude-related illnesses susceptibility seem particularly warranted in preterm born individuals to further clarify their capacity for high-altitude adaptation.

Author statement

Tadej Debevec: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing, Funding acquisition Mathias Poussel: Conceptualization, Methodology, Investigation, Data Curation, Writing - Review & Editing Damjan Osredkar: Conceptualization, Methodology, Writing - Review & Editing Sarah J. Willis: Investigation, Writing - Review & Editing Claudio Sartori: Conceptualization, Methodology, Writing - Review & Editing Grégoire P. Millet: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing, Funding acquisition

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