Durand, Fabienne, Gaston, Anne Fleur, Vicenzi, Marco, Deboeck, Gaël, Subirats, Enric, & Faoro, Vitalie

Noninvasive Pulmonary Hemodynamic Evaluation in Athletes With Exercise-Induced Hypoxemia

Article. Version publiée - Published version.

© ELSEVIER

Citation APA:

Durand, F., Gaston, A. F., Vicenzi, M., Deboeck, G., Subirats, E., & Faoro, V. (2020). Noninvasive Pulmonary Hemodynamic Evaluation in Athletes With Exercise-Induced Hypoxemia. *Chest*, 18. doi:10.1016/j.chest.2020.01.037

DOI: 10.1016/j.chest.2020.01.037

Also available at: <http://hdl.handle.net/2013/ULB-DIPOT:oai:dipot.ulb.ac.be:2013/303110>

Cet article publié par ELSEVIER provient du Dépôt institutionnel de l'Université Libre de Bruxelles, DI-fusion <http://difusion.ulb.ac.be>. Il n'est accessible qu'aux membres de la communauté universitaire de l'ULB sur le réseau sécurisé de l'ULB.

Tout utilisateur autorisé peut lire, télécharger ou reproduire cet article à des fins d'usage privé ou à des fins non commerciales d'enseignement ou de recherche scientifique. Il ne peut être atteint à l'intégrité de l'article, et les noms des auteurs et de l'éditeur doivent être conservés. Tout téléchargement systématique des articles publiés par ELSEVIER mis à disposition dans DI-fusion est interdit.

This article published by ELSEVIER comes from the Institutional repository of Université Libre de Bruxelles, DI-fusion <http://difusion.ulb.ac.be>. It is accessible only to the members of the university community of ULB on the ULB secure network.

Any authorized user may read, download or reproduce this article for private usage, or for non commercial research or educational purposes. The integrity of the article and identification of the author and copyright owner must be preserved. Systematic downloading of articles published by ELSEVIER that are available in DI-fusion is not permitted.

NON-INVASIVE PULMONARY HEMODYNAMIC EVALUATION IN ATHLETES WITH EXERCISE-INDUCED HYPOXEMIA

Fabienne Durand, Ph.D, Anne-Fleur Gaston, Ph.D, Marco Vicenzi, MD, Gael Deboeck, Ph.D, Enric Subirats, MD, Vitalie Faoro, Ph.D

PII: S0012-3692(20)30274-9

DOI: <https://doi.org/10.1016/j.chest.2020.01.037>

Reference: CHEST 2899

To appear in: *CHEST*

Received Date: 31 July 2019

Revised Date: 22 December 2019

Accepted Date: 31 January 2020

Please cite this article as: Durand F, Gaston AF, Vicenzi M, Deboeck G, Subirats E, Faoro V, NON-INVASIVE PULMONARY HEMODYNAMIC EVALUATION IN ATHLETES WITH EXERCISE-INDUCED HYPOXEMIA, *CHEST* (2020), doi: <https://doi.org/10.1016/j.chest.2020.01.037>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2020 Published by Elsevier Inc under license from the American College of Chest Physicians.

NON-INVASIVE PULMONARY HEMODYNAMIC EVALUATION IN ATHLETES WITH EXERCISE-INDUCED HYPOXEMIA

Durand Fabienne, Ph.D^{1,2}, Gaston Anne-Fleur, Ph.D^{1,3}, Vicenzi Marco, MD^{4,5}, Deboeck Gael, Ph.D⁴, Subirats Enric, MD^{1,2}, Faoro Vitalie, Ph.D⁴

¹, Laboratoire Européen Performance, Santé, Altitude, EA4604 - Université de Perpignan Via Domitia, Département STAPS, Font-Romeu, France

², Catedra de medicina de muntanya I del medi natural I de simulacio clinica, Universitat de Girona, Spain

³, Unité de Physiologie des Exercices et Activités en Conditions Extrêmes, Institut de Recherche Biomédicale des Armées, Brétigny-sur-Orge, France.

⁴, Cardio-Pulmonary Exercise Laboratory, Faculty of Motorskill Science, Université Libre de Bruxelles, Brussels, Belgium

⁵, Cardiovascular Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Department of Clinical Sciences and Community Health, Milan, Italy

Corresponding author:

Pr Fabienne Durand. Laboratoire Européen Performance, Santé, Altitude, EA4604. Université de Perpignan Via Domitia, Département STAPS. 7 Avenue Pierre de Coubertin, 66120 Font-Romeu, France. Email: fdurand@univ-perp.fr. Tel: (+33) 468 300 151

Conflicts of interests: The authors have no conflicts of interests to declare

ABSTRACT

Background: Pulmonary capillary stress failure is potentially involved in exercise-induced hypoxemia *i.e.*, a significant fall in hemoglobin O₂ saturation (SpO₂) during sea level exercise in endurance-trained athletes. Whether there may be specific properties of the pulmonary vascular function in athletes exhibiting O₂ desaturation is unknown.

Methods: 10 endurance trained athletes with exercise induced O₂ desaturation (EIH), 9 endurance trained athletes without (NEIH) and 10 untrained controls underwent an incremental exercise stress echocardiography coupled with lung diffusion capacity for CO (DLCO) and NO (DLNO). Functional adaptation of the pulmonary circulation was evaluated with measurements of mean pulmonary arterial pressure (mPAP), pulmonary capillary pressure (Pcap), pulmonary vascular resistance (PVR), cardiac output (Qc) and pulmonary vascular distensibility (α) mathematically determined from the curvilinearity of the multipoint mPAP-Qc relationship.

Results: EIH exhibited lower exercise induced PVR decrease compared to untrained and NEIH groups ($p < 0.001$). EIH athletes showed higher maximal mPAP as compared to NEIH (45.4 ± 0.9 mmHg vs 41.6 ± 0.9 mmHg, $p = 0.003$, respectively) while no difference appeared between NEIH and untrained. Alpha was lower in EIH compared to NEIH ($p < 0.05$). Maximal mPAP, Pcap and alpha were correlated with the fall of SpO₂ during exercise ($p < 0.01$, $p < 0.01$ and $p < 0.05$ respectively). DLNO and DLCO increased with exercise in all groups without difference between groups while DLNO/Qc was correlated to the exercise induced SpO₂ changes ($p < 0.05$).

Conclusions: EIH athletes exhibit higher maximal pulmonary vascular pressures, lower vascular distensibility or exercise induced changes in PVR compared to NEIH subjects, in keeping with pulmonary capillary stress failure or intra-pulmonary shunting hypotheses.

INTRODUCTION

Performance in endurance trained athletes is dependent on the functional interdependence of the physiological components of the convectional and diffusional oxygen (O_2) transport system from ambient air to the mitochondria. While cardiac and skeletal muscle can easily adapt to endurance training, the healthy pulmonary system has no structural adaptability to physical training¹. Recently, research interest on pulmonary system limitations to endurance exercise performance has intensified^{2,3}. It is well accepted that the capacity of the pulmonary system exceeds the demands required for ventilation and gas exchange during endurance and intensive exercise in normal conditions. However, it must be emphasized that, in specific conditions, the healthy pulmonary system can be a limiting factor of whole-body endurance exercise performance. Accordingly, endurance-trained athletes may develop respiratory muscle fatigue, intrathoracic and extrathoracic obstruction, expiratory flow limitation and O_2 arterial desaturation during exercise^{2,3}. Oxygen arterial desaturation during exercise in highly-trained athletes is called exercise-induced hypoxemia (EIH) and is described according to the level of desaturation. This phenomenon occurs in ~50% of endurance male trained athletes⁴. Physiopathology of the phenomenon is still debated but major explanations are relative hypoventilation, ventilation/perfusion (VA/Q) inequality and diffusion limitation⁵. It seems that diffusion limitation is responsible for gas exchange abnormalities occurring from exercise intensities of 75 to 100% of maximal oxygen uptake (VO_{2max}) in athletes exhibiting EIH^{4,6}.

Exercising at sea level is associated with an increase in pulmonary diffusing capacity for CO (DLCO) and NO (DLNO) attributed to increased pulmonary capillary blood volume (V_c) and better matching between tissue and erythrocyte surfaces, and to a lesser extent the expansion of the alveolar–capillary membrane surface area¹⁶. Previous measurements of V_c showed linear increase with exercise intensity without ceiling effect, suggesting unlimited recruitment or distention of pulmonary capillaries. Indeed, recruitment and distention of pulmonary capillaries are known to appear during conditions that raise pulmonary blood flow and pulmonary vascular pressure and are crucial to maintain capillary pressure low during intense exercise⁷. In numerous studies, West et al. highlighted that an abnormal increase in capillary pressure at exercise above a 20–25 mmHg threshold could possibly lead to a capillary stress

failure known to elicit interstitial lung edema and altered ventilation/perfusion relationships leading to hypoxemia ⁸.

We therefore hypothesized that athletes exhibiting O₂ desaturation at exercise have a distinctive pulmonary vascular response to exercise, namely elevated pulmonary vascular pressures which could consequently alter the normal lung diffusion capacity response. We therefore compared the pulmonary vascular response to exercise using non-invasive echocardiographic and lung diffusing capacity measurements, in athletes exhibiting EIH, in athletes without EIH and in a control group of untrained subjects.

MATERIALS AND METHODS

Study Population

Twenty-nine healthy non-smoking males volunteered to participate were recruited for this study. Nineteen subjects were endurance trained athletes in running or cycling, performing at least 5 training sessions per week. The other ten subjects were sedentary or active in recreational sports but had never been engaged in systematic endurance training. Characteristics of all participants are reported in Table 1 (values of $\text{VO}_{2\text{max}}$ were obtained from an incremental cardio-pulmonary exercise testing realized in a preliminary visit). Each subject was informed about the procedures to be followed and the potential risks inherent with the experiments and signed a written informed consent form. All procedures were approved by the ethics committee of Consell General de l'Esport, Catalunya (0099S/2046/2013).

Design of the study

All subjects underwent a clinical examination with measurements of systemic blood pressure (sphygmomanometry), hemoglobin concentration (EKF diagnostics, Penarth, Cardiff), heart rate (HR) and hemoglobin O_2 saturation (SpO_2) with a finger pulse oximeter (Nonin, Minnesota, USA). This examination was successively followed by an echocardiographic examination at rest and an incremental exercise test with echocardiography coupled with lung diffusion capacity measurements.

Stress echocardiography and diffusion capacity measurements

After resting measurements, subjects performed an incremental exercise test on a semi recumbent braked cycle ergometer (Ergoline, model 900 EL, Bilz, Germany) laterally tilted by 20 to 30 degrees to the left. The work rate was increased by 30 to 50 Watts every 2 minutes, according to the previously measured physical capacity of the subject. Echocardiography and lung diffusion measurements were made at each exercise step using a repeated sequence of measurement. This protocol allowed us to have: 1) at least 5 levels of exercise with echocardiographic measurements, and 2) a time of exercise between 12-14 minutes to reach optimal exercise capacity.

Echocardiography measurements: The echocardiographic measurements were performed with a portable ultrasound system (CX50 Compact Xtreme Ultrasound System Philips, Amsterdam, Netherlands). Stroke volume (SV) was calculated with the following equation: $SV = 3.14 \times (LVOT \text{ diameter}/2)^2 \times TVI$ where LVOT is the left ventricular outflow tract cross sectional area measured at rest and TVI the pulsed Doppler time-velocity integral measurements ⁹. Cardiac output (Qc) was calculated as the product of SV and HR. Systolic pulmonary arterial pressure (sPAP) was calculated from the maximum velocity of the continuous-Doppler tricuspid regurgitation jet (TRV) and corrected for right atrial pressure as $sPAP = 4 \text{ TRV}^2 + RAP$, where RAP is the right atrial pressure estimated from the dimension and the collapsibility of the inferior vena cava. Subjects have been selected according to the TRV to obtain a good quality signal in all subjects. Mean pulmonary arterial pressure (mPAP) was calculated as $mPAP = 0.61 * sPAP + 2$, as previously reported ¹⁰. Pulmonary vascular resistance (PVR) was defined as the ratio of the difference between mPAP and left atrial pressure (LAP) divided by Qc ¹¹. LAP was estimated from the ratio of Doppler mitral early flow-velocity wave (E) and tissue Doppler mitral annulus early diastolic velocity (E') with the following equation: $LAP = 1.9 + 1.24 \text{ E/E'}$ ¹². Pulmonary capillary pressure (Pcap) was calculated as $0.4 \times (mPAP - LAP) + LAP$ ¹³. This non-invasive evaluation of the pulmonary circulation at exercise has been validated *i.a.* in athletes and untrained healthy subjects but also in patients, and present reasonable accuracy compared to exercise cardiac magnetic resonance imaging with simultaneous invasive pressure records ^{14,15}.

Each point of the mPAP – Qc relationship was fitted to the equation:

$$mPAP = [((1 + \alpha LAP)^5 + 5\alpha R_0 Qc)^{1/5} - 1] / \alpha$$

where R_0 is total PVR at rest, to calculate a distensibility α index expressing the percentage of diameter change in resistive pulmonary vessel per mmHg increase in transmural pressure during exercise ¹¹.

Recordings were stored on optical disks and analyzed twice blindly by a cardiologist experienced in stress echocardiography with a reliability above 80%.

Lung diffusion measurements: The Roughton and Forster equation states that $1/DL = 1/Dm + 1/\theta Vc$, where DL is the diffusing capacity of the lung, Dm its membrane component, θ blood-gas affinity and Vc capillary blood volume ¹⁶. The transposition of the equation to two

different gas tracers (NO and CO) after the measurement of their respective diffusion capacity (DLNO and DLCO) allows for the calculation of Dm, and hence Vc. Single breath measurements of DLCO and DLNO were performed at rest and every other exercise level in the echocardiographic position. An automated device, including automated calibrations, mixing of gases and online calculations, and corrections for hemoglobin and inspired partial pressure of oxygen was used (Hyp'Air compact, Medisoft, Dinant, Belgium) in agreement with recent recommendations of an expert Task Force of the European Respiratory Society ¹⁶. The concentrations of inspired gases were 40 ppm of NO, 1600 ppm of CO, 8% of helium and 19% of O₂ in nitrogen. The breath holding time was 4 sec. The first 0.8 L of expired gas was discarded. The coefficient relating DLNO and Dm was set at 1.97 according to the solubility and molecular weights of both gases ¹⁷. Measurements were repeated two to three times at rest, with the aim to obtain DLCO values within 5% and DLNO values within 10% of each other.

SpO₂ measurement and O₂ desaturation: SpO₂ was measured continuously during tests using a finger pulse oximeter (Nonin, Minnesota, USA). This method has been reported to deliver high precision, reproducibility and validity for O₂ saturation above 85% when compared to O₂ saturation measured from arterial blood gases in highly trained athletes ¹⁸. The instrument's conducting cable was secured to prevent movement artefacts and before the probe was placed, the finger was warmed up by massage to active arterialized circulation. SpO₂ fall $\geq 4\%$ observed between rest and maximal condition during at least 3 minutes of the test was defined as a significant O₂ desaturation ⁴.

Statistical analysis

Results are expressed as mean $\pm$ standard error of mean (SEM). The data were screened for normality of the distribution and homogeneity of variances using the Shapiro–Wilk normality and Levene tests, respectively. Differences between the three groups with unrepeated measures (anthropometric data, VO_{2max}, FEV₁, training volume, workload, Δ PVR, mPAP/Qc slope, mPAP/CI slope) were analysed using one-way analysis of variance (Anova). Kruskal-Wallis test has been used when normality of the distribution and homogeneity of variances failed (SpO_{2max} and Δ SpO₂ variables). Other hemodynamic and diffusion parameters were analysed using Anova for repeated measures during exercise (rest vs max) as the within-subject factor and groups (EIH vs. NEIH vs. untrained) as the between-subject factor. When

overall significance was obtained, differences between means were identified using a Student-Newman-Keuls post-hoc analysis. Correlation analysis (Pearson's coefficient for normal distribution variables or Spearman's coefficient for non-normal distribution variables) were performed to test the linear relationships between data, especially to identify the specific variables associated to SpO_2 at maximal exercise or exercise-induced ΔSpO_2 . For all statistical tests, the level of significance was set at $p < 0.05$ and analyses were conducted using SigmaStat software (Ver 3.5).

RESULTS

Incremental exercise test on the semi recumbent braked cycle allowed us to identify two different groups of endurance-trained athletes: one exhibiting O₂ exercise desaturation (EIH group) and another without O₂ exercise desaturation (NEIH group). Figure 1 reports the fall of SpO₂ measured during exercise in the three groups. SpO₂ values at the end of exercise were significantly lower in EIH group than in NEIH or untrained groups ($94.2 \pm 0.3\%$; $96.1 \pm 0.3\%$; $96.2 \pm 0.5\%$; $p = 0.001$, respectively). Delta SpO₂ (difference of SpO₂ between rest and maximal exercise) level measured in EIH signed a physiological desaturation which is not found in NEIH or untrained groups. Semi recumbent braked cycle test was performed at $95 \pm 1.8\%$ of HR_{max} achieved during the incremental cardio-pulmonary exercise test realized during the preliminary visit.

Hemodynamic parameters were reported in Table 2. No between group difference was observed at rest except in PVR: NEIH presented a slightly higher PVR compared to EIH and untrained (Anova interaction $p = 0.004$, post hoc analyses $p = 0.029$ and $p = 0.005$, respectively). PVR decreased with exercise in NEIH only ($p = 0.001$) while maximal LAP did not change. Delta PVR reflecting the fall of PVR during exercise was significantly higher in NEIH group than in EIH and in untrained subjects (Anova interaction $p = 0.002$, post hoc analyses $p = 0.025$ and $p = 0.003$ respectively). The same effect between EIH and NEIH was observed for the coefficient of arteriolar distensibility alpha ($p = 0.045$). Qc, cardiac index (CI), HR, SV, mPAP and Pcap increased with exercise in all groups (Anova exercise effect $p < 0.001$). Qc and CI at maximal exercise were significantly higher in endurance trained athletes (EIH and NEIH) compared to untrained subjects (Anova interaction $p = 0.041$ and $p = 0.010$, post hoc analyses $p = 0.016$ and $p = 0.003$, respectively). EIH reported significant greater values of maximal mPAP and maximal Pcap compared to NEIH and untrained groups (Anova interaction $p = 0.033$, post hoc analyses $p = 0.003$ and $p = 0.002$, respectively) without difference between NEIH and untrained subjects. Alpha and the increase in mPAP from rest to maximal exercise were correlated with delta PVR ($r = -0.79$, $p < 0.001$ and $r = 0.45$, $p = 0.022$ respectively).

None of the subjects exhibited mPAP/Qc or maximal TPR above 3 WU. No between groups differences were observed for the mPAP/Qc or mPAP/CI slopes. Delta SpO₂ and SpO₂ at maximal exercise were significantly correlated with maximal mPAP ($r = -0.60$, $p = 0.002$ and $r = -0.58$, $p = 0.002$, respectively). The significant correlation between mPAP and delta SpO₂

was reported in Figure 2. Maximal Pcap was significantly correlated with the delta of SpO₂ ($r = -0.55$, $p = 0.005$) and with SpO₂max ($r = -0.44$, $p = 0.027$). In athletes, the alpha coefficient of pulmonary arteriolar distensibility was also correlated to delta SpO₂ ($r = 0.43$, $p < 0.05$).

Dm and Vc calculated with θ_{NO} assumed to be finite as $4.5 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$ are shown in Table 3. Maximal exercise was associated with increase in VA, DLCO, DLNO, KCO, KNO, Dm, Vc corrected for Hb, in all groups (Anova exercise effect $p < 0.05$). The ratio DLNO/DLCO did not change. No group effect was observed at any time. However, DLCO and preponderantly DLNO corrected for Qc at rest or maximal exercise were correlated to delta SpO₂ in athletes. Figure 3 shows that DLNO/Qc at maximal exercise decreases with exercise induced SpO₂ changes ($r = 0.41$, $p = 0.032$).

DISCUSSION

To our knowledge, this study is the first to highlight specific pulmonary vascular adaptations to exercise consisting in higher maximal pulmonary arterial and capillary pressures with concomitantly lower vascular distensibility and decreased PVR reduction at exercise in athletes exhibiting O₂ desaturation compared with athletes without O₂ desaturation and control group, *i.e.* untrained subjects.

Methodological consideration

For ethical reasons this study used pulse oximetry, a non-invasive method for estimation of SpO₂ rather than blood arterial gases. Pulse oximetry method has been reported to deliver high precision, reproducibility and validity for O₂ saturation above 75% when compared to O₂ saturation measured from arterial blood gases at rest and exercise^{18–20}. All the quoted references define exercise induced O₂ desaturation in athletes, *i.e.* EIH during an upright exercise^{4,21}. In our study, subjects performed a stress echocardiography in semi supine position laterally tilted by 20 to 30 degrees to the left for optimal echocardiographic acquisition. Pedersen et al.²² reported that despite a lower VO₂max and a suggested improvement in VA/Q distribution, there was no difference in O₂ desaturation during exercise between upright and supine position. This reference allowed us to use the Prefaut's team definition to determine a significant physiological O₂ desaturation⁴.

Invasive studies in the recumbent position previously reported a lower resting PVR compared with upright position explained by a better vascular recruitment when venous return is increased with gravity ²³. However, the differences disappeared with exercise because of vascular recruitment/dilation with pulmonary blood flow elevation. Accordingly, Forton et al. compared stress echocardiography in the upright-seated position vs the same semi-recumbent position as used in the present study and showed no body position effect on pulmonary hemodynamic parameters such as maximal PVR, PAP/Qc relationships and no alteration of exercise capacity (identical maximal Qc and VO₂max) ²⁴. In the present study, end-exercise HR in a semi recumbent position reached 95% of maximal upright HR as suggested by Forton et al ²³.

While echocardiographic evaluation of E/e' was found sensitive to LAP during exercise ¹², insufficient accuracy at high levels of exercise has previously been addressed ^{25,26}. In the present study and in agreement with previous echocardiographic studies, LAP did not increase significantly during exercise ²⁷⁻³⁰. Accordingly, an invasive study in 5 athletes achieving a maximal VO₂ similar to the present study reported no or limited RAP or LAP elevation for exercise intensities under a Qc of 20 L.min⁻¹ ³¹. At higher Qc, exercise induced LAP elevation was delayed and smoothened in athletes compared to sedentary subjects reaching a moderate value around 15 mmHg ³¹. This may be explained by a right shifting of the hyperbolic relationship between LV diastolic pressure and volume in athletes. In the present study, the LAP/Qc ratio, quantifying the post-capillary pressure elevation throughout exercise with less imprecisions than maximal LAP, was very low in all groups suggesting no or little influence of LAP on the exercise induced PAP increase ³². It is therefore reasonable to think that insufficient accuracy of LAP estimations may not account for the presently observed Pcap and mPAP elevation in EIH athletes.

Results discussion

The present results show that athletes with EIH present distinctive pulmonary vascular adaptations to exercise. Even if it is not known whether it is a cause or a consequence, these results are in keeping with the hypothesis that some pathophysiological explanations of EIH may be in relation with pulmonary hemodynamic adaptations to exercise.

Echocardiographic estimations of pulmonary vascular pressures and Qc are advantageous because being noninvasive, flexible and validated ^{15,30}. However, those estimations rely on a series of assumptions in the calculations of pressures and flows. The physiologic range of

pulmonary pressures is affected by different hemodynamic, clinical and anthropometrics factors: cardiac output, age, gender, race, body dimensions, body mass index, type and level of exercise training, posture and/or exercise. Kovacs et al.³³ reported in a systematic review that normal mPAP resting values in healthy subjects were not more than about 20.6 mmHg. A study of D'Andrea et al.³⁴ showed that 1) training status should be taken into account and 2) the upper physiologic limit of resting sPAP in endurance athletes may reach 40 mmHg in line with the increased SV. In the present study, resting mPAP values are in good agreement with previous invasive and noninvasive studies. Substantial increase in mPAP occurs during intense exercise as a result of marked increase in cardiac output and pulmonary blood flow along with increase in left ventricular filling pressure³⁵. Argiento et al.³⁰ have estimated that for a $10 \text{ L} \cdot \text{min}^{-1}$ increase in Q_c , from 10 to $20 \text{ L} \cdot \text{min}^{-1}$, pulmonary hypertension is defined by mPAP exceeding an absolute value of 45 mmHg. However invasive or echocardiographic studies reported on considerable variations in pulmonary vascular response to exercise from one subject to another³⁰. In the present study, EIH athletes reached significantly higher values of maximal mPAP and P_{cap} than NEIH and untrained groups. As the maximal mPAP value depends on the achieved exercise level or Q_{cmax} ³⁰, our results could suggest that EIH group exhibit a higher Q_c at the end of exercise. However, this observation cannot be attributed to higher maximal Q_c or maximal LAP as identical values were reached in both athletes groups. If the measured maximal Q_c may seem low for endurance athletes, we must not forget that i) the mean age of the present athletes is around 40 years old and ii) it is well reported that exercise echocardiography underestimates Q_c at exercise in comparison with the exercise cardiac magnetic resonance imaging with simultaneous invasive pressure registration¹⁴. This bias is due to underestimation of SV, particularly at maximal exercise in a stress echocardiographic position when peak HR is lower²³. However, the reported maximal values of Q_c are higher as compared to previous stress echocardiography in athletes²⁵. Moreover, the present maximal Q_c coincide with predicted values calculated from previous Q_c vs workload relationships established during stress echocardiography in healthy subjects²³. As identical maximal Q_c was reached in EIH and NEIH groups with identical V_c , the hypothesis that a reduction in capillary transit time altering the O_2 saturation of the passing red blood cells can be excluded.

The present study highlights elevated pulmonary vascular pressures during exercise in EIH compared with NEIH and untrained groups suggesting a specific hemodynamic response linked to O_2 desaturation during exercise, as illustrated in Figure 2. Indeed, all EIH athletes

present mPAP above 42 mmHg and are all included in a clustering. The significant correlation found between the exercise induced mPAP increase and changes in PVR suggests that high pulmonary pressure increase occurs when reduction of PVR with exercise is low. Moreover, the present study also shows impaired exercise induced pulmonary arteriolar distensibility in EIH correlated to ΔSpO_2 . The reason why this intrinsically particular pulmonary circulation difference exists remains unknown, but it may be hypothesized that it contributes to the excessive exercise-induced PAP elevation and lower exercise-induced PVR reduction in EIH. During maximal exercise, Durand et al.³⁶ have observed an attenuated release of atrial natriuretic factor (pulmonary vasodilator) in athletes with EIH compared to athletes without. Moreover, Verges et al.³⁷ reported reduced nitric oxide (NO) concentrations in EIH athletes. Indeed, pulmonary vascular tone is in part mediated by NO response to exercise. However, controversial results have been reported on NO production and O_2 exercise desaturation in endurance-trained athletes^{38,39}. In fact, NO response has been reported to be increased by endurance training but also limited by intensive endurance training susceptible to induce vascular remodeling⁴⁰, vascular smooth muscle desensitization for NO⁴¹ and/or elevate reactive oxygen species production⁴². These references are in keeping with the present observation of a lower decrease of PVR in EIH athletes compared to NEIH. In numerous studies, West et al. pointed out the fact that EIH could be due to increase in PAP and then Pcap, leading to interstitial pulmonary edema via stress failure process^{8,43}. Indeed, it is well described that during intense exercise, capillary transmural pressure at the base of the lung can exceed 25 mmHg⁴⁴. Such pressures may cause very high hoop stress in the thin-walled capillaries. In the present study, Pcap increased during exercise in all groups but with higher values reached in the EIH group compared with NEIH while no inter-group difference was reported between the EIH and the untrained group. Furthermore, it has been previously suggested that during exercise, the opening of small intra-pulmonary arteriovenous anastomoses could allow blood to bypass the air-exchange zone of the lung in relation to exercise induced PAP elevation⁴¹. Even if a correlation between intra-pulmonary shunts and the increase of D(A-a)O_2 in exercise in healthy humans has been reported⁴⁵, Vogiatzis et al. suggested that pulmonary shunts were not significantly involved in the PaO_2 drop in trained athletes during maximal exercise⁴⁶. However, the present results cannot exclude the presence of intra-pulmonary shunts and its role in the observed exercise hypoxemia.

Our results are thus in agreement with the literature on the topic and confirm the implication of a high pulmonary pressure in EIH physiopathology, as it was often previously suggested

but never measured in humans. However, it is to acknowledge that, due to small sample size, a type I error cannot be excluded and could possibly influence the present results.

In the present study and in keeping with previous studies, lung diffusion capacity increased linearly with exercise intensity without ceiling effect and with no or minor changes in the DLNO/DLCO ratio, suggesting no limitation of recruitment and distention of pulmonary capillaries even at high exercise intensities. However, the membrane and the capillary component of the diffusive response to exercise were similar between groups. As physiopathology of EIH suspects abnormalities in gas exchange diffusion from 75% to 100% of $\text{VO}_{2\text{max}}$ ⁶, we hypothesized that some diffusion abnormalities could occur during maximal exercise in EIH athletes. Indeed, previous studies reported a post-exercise decrease in DLCO in endurance-trained athletes associated with O_2 desaturation during exercise^{46,47}. This exercise-induced diffusion limitation has been attributed to changes in the membrane diffusion properties such as interstitial extra-vascular water accumulation. Despite those evidences, the present study did not show any obvious diffusion capacity alteration in EIH athletes compared to NEIH or untrained subjects. However, a type II error could not be excluded in this small sample size study and in the presence of an end-exercise desaturation that could be qualified as “mild”²⁰. It is also possible that some occurred changes are not detectable during our short exercise protocol or by the measure of DLCO and DLNO. Mechanisms such as pulmonary blood flow redistribution and/or lymphatic fluid reabsorption could act and hid some diffusion limitation despite nascent pulmonary interstitial edema. Notwithstanding, even if the present study could not highlight a specific diffusion alteration in EIH subjects at exercise, the DLNO corrected for Q_c was found to be correlated to the exercise induced O_2 desaturation (Figure 3). As DLNO is mainly dependent on the membrane component of diffusion, it indicates that subjects desaturating the most at maximal exercise have a less diffusible alveolo-capillary membrane regarding the maximal exercise level reached. This could possibly be explained by extra-capillary fluid accumulation impairing the membrane component of the diffusion limitation. However, further studies need to be established to increase the power of the present observations and confirm the possible pulmonary capillary stress failure or intra-pulmonary shunting hypotheses in EIH endurance athletes.

CONCLUSION

This study is the first to demonstrate that athletes exhibiting O₂ arterial desaturation during exercise present distinctive pulmonary vascular response to exercise. Indeed, decreased pulmonary vascular distensibility and smoothened reduction of PVR at high levels of exercise seems to induce higher levels of maximal PAP and Pcap. Although it could not be demonstrated directly and no causality can be proven, the present results are in favor of the pulmonary capillary stress failure theory to explain O₂ arterial desaturation of athletes during exercise, while intra-pulmonary shunting cannot be excluded.

ACKNOWLEDGEMENTS

We thank all subjects who volunteered to participate in this study. Moreover, we are grateful to Masella ski resort and the Medicine Faculty of Gerona.

Author's Contributions:

- Significant manuscript writer: FD/AFG/VF
- Significant manuscript reviewer/reviser: MV/GD/ES
- Concept and design: FD/ES/VF
- Data acquisition: FD/AFG/MV/GD/VF
- Data analysis and interpretation: FD/AFG/MV /VF
- Statistical expertise: AFG
- Guarantor of the paper: FD/VF

REFERENCES

1. Dempsey JA, Johnson BD, Saupe KW. Adaptations and limitations in the pulmonary system during exercise. *Chest* 1990;97(3 Suppl):81S-87S.
2. Amann M. Pulmonary system limitations to endurance exercise performance in humans. *Exp Physiol* 2012;97(3):311–318.
3. McKenzie DC. Respiratory physiology: adaptations to high-level exercise. *Br J Sports Med* 2012;46(6):381–384.
4. Prefaut C, Durand F, Mucci P, Caillaud C. Exercise-induced arterial hypoxaemia in athletes: a review. *Sports Med Auckl NZ* 2000;30(1):47–61.
5. Hopkins SR, Gavin TP, Siafakas NM, et al. Effect of prolonged, heavy exercise on pulmonary gas exchange in athletes. *J Appl Physiol* 1998;85(4):1523–1532.
6. Durand F, Mucci P, Préfaut C. Evidence for an inadequate hyperventilation inducing arterial hypoxemia at submaximal exercise in all highly trained endurance athletes. *Med Sci Sports Exerc* 2000;32(5):926–932.
7. Hanson WL, Emhardt JD, Bartek JP, et al. Site of recruitment in the pulmonary microcirculation. *J Appl Physiol Bethesda Md* 1985 1989;66(5):2079–2083.
8. West JB. Invited Review: Pulmonary capillary stress failure. *J Appl Physiol* 2000;89(6):2483–2489.
9. Christie J, Sheldahl LM, Tristani FE, Sagar KB, Ptacin MJ, Wann S. Determination of stroke volume and cardiac output during exercise: comparison of two-dimensional and Doppler echocardiography, Fick oximetry, and thermodilution. *Circulation* 1987;76(3):539–547.
10. Naeije R, Huez S, Lamotte M, et al. Pulmonary artery pressure limits exercise capacity at high altitude. *Eur Respir J* 2010;36(5):1049–1055.
11. Naeije R, Vanderpool R, Dhakal BP, et al. Exercise-induced Pulmonary Hypertension: Physiological Basis and Methodological Concerns. *Am J Respir Crit Care Med* 2013;187(6):576–583.
12. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30(6):1527–1533.
13. Cope DK, Grimbert F, Downey JM, Taylor AE. Pulmonary capillary pressure: a review. *Crit Care Med* 1992;20(7):1043–1056.
14. Claessen G, La Gerche A, Voigt J-U, et al. Accuracy of Echocardiography to Evaluate Pulmonary Vascular and RV Function During Exercise. *JACC Cardiovasc Imaging* 2015;
15. Caravita S, Yerly P, Baratto C, et al. Noninvasive versus invasive pressure-flow relationship of the pulmonary circulation: bias and error. *Eur Respir J* 2019;54(5).

16. Zavorsky GS, Hsia CCW, Hughes JMB, et al. Standardisation and application of the single-breath determination of nitric oxide uptake in the lung. *Eur Respir J* 2017;49(2).
17. Aguilaniu B, Maitre J, Glénet S, Gegout-Petit A, Guénard H. European reference equations for CO and NO lung transfer. *Eur Respir J* 2008;31(5):1091–1097.
18. Martin D, Powers S, Cicale M, Collop N, Huang D, Criswell D. Validity of pulse oximetry during exercise in elite endurance athletes. *J Appl Physiol Bethesda Md* 1985 1992;72(2):455–458.
19. Trivedi NS, Ghouri AF, Lai E, Shah NK, Barker SJ. Pulse oximeter performance during desaturation and resaturation: a comparison of seven models. *J Clin Anesth* 1997;9(3):184–188.
20. Mollard P, Bourdillon N, Letournel M, et al. Validity of arterialized earlobe blood gases at rest and exercise in normoxia and hypoxia. *Respir Physiol Neurobiol* 2010;172(3):179–183.
21. Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. *J Appl Physiol* 1999;87(6):1997–2006.
22. Pedersen PK, Mandøe H, Jensen K, Andersen C, Madsen K. Reduced arterial O₂ saturation during supine exercise in highly trained cyclists. *Acta Physiol Scand* 1996;158(4):325–331.
23. Reeves JT, Taylor AE. Pulmonary Hemodynamics and Fluid Exchange in the Lungs During Exercise [Internet]. In: Comprehensive Physiology. American Cancer Society; 2011 [cited 2019 Jul 9]. p. 585–613. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/cphy.cp120113>
24. Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. *J Appl Physiol* 2016;121(5):1145–1150.
25. Gerche AL, MacIsaac AI, Burns AT, et al. Pulmonary transit of agitated contrast is associated with enhanced pulmonary vascular reserve and right ventricular function during exercise. *J Appl Physiol* 2010;109(5):1307–1317.
26. Olsen MH, Wachtell K, Hermann KL, et al. Maximal exercise capacity is related to cardiovascular structure in patients with longstanding hypertension. A LIFE substudy. *Am J Hypertens* 2001;14(12):1205–1210.
27. Vríz O, Argiento P, D'Alto M, et al. Increased pulmonary vascular resistance in early stage systemic hypertension: a resting and exercise stress echocardiography study. *Can J Cardiol* 2015;31(4):537–543.
28. Groepenhoff H, Overbeek MJ, Mulè M, et al. Exercise pathophysiology in patients with chronic mountain sickness exercise in chronic mountain sickness. *Chest* 2012;142(4):877–884.
29. Lalande S, Yerly P, Faoro V, Naeije R. Pulmonary vascular distensibility predicts aerobic capacity in healthy individuals. *J Physiol* 2012;590(17):4279–4288.

30. Argiento P, Chesler N, Mulè M, et al. Exercise Stress Echocardiography for the Study of the Pulmonary Circulation. *Eur Respir J Off J Eur Soc Clin Respir Physiol* 2010;35(6):1273–1278.
31. Stickland MK, Welsh RC, Petersen SR, et al. Does fitness level modulate the cardiovascular hemodynamic response to exercise? *J Appl Physiol Bethesda Md* 1985 2006;100(6):1895–1901.
32. Eisman AS, Shah RV, Dhakal BP, et al. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. *Circ Heart Fail* 2018;11(5):e004750.
33. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009;34(4):888–894.
34. D'Andrea A, Riegler L, Golia E, et al. Range of right heart measurements in top-level athletes: the training impact. *Int J Cardiol* 2013;164(1):48–57.
35. Bossone E, Rubenfire M, Bach DS, Ricciardi M, Armstrong WF. Range of tricuspid regurgitation velocity at rest and during exercise in normal adult men: implications for the diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 1999;33(6):1662–1666.
36. Durand F, Mucci P, Hayot M, Couret I, Bonnardet A, Préfaut C. Attenuated ANF response to exercise in athletes with exercise-induced hypoxemia. *Int J Sports Med* 2004;25(4):252–256.
37. Verges S, Flore P, Favre-Juvin A, Lévy P, Wuyam B. Exhaled nitric oxide during normoxic and hypoxic exercise in endurance athletes. *Acta Physiol Scand* 2005;185(2):123–131.
38. Sheel AW, Edwards MR, McKenzie DC. Relationship between decreased oxyhaemoglobin saturation and exhaled nitric oxide during exercise. *Acta Physiol Scand* 2000;169(2):149–156.
39. Kippelen P, Caillaud C, Robert E, Masmoudi K, Préfaut C. Exhaled nitric oxide level during and after heavy exercise in athletes with exercise-induced hypoxaemia. *Pflüg Arch Eur J Physiol* 2002;444(3):397–404.
40. Petersen SE, Wiesmann F, Hudsmith LE, et al. Functional and structural vascular remodeling in elite rowers assessed by cardiovascular magnetic resonance. *J Am Coll Cardiol* 2006;48(4):790–797.
41. Yamashita H, Tyska MJ, Warshaw DM, Lowey S, Trybus KM. Functional consequences of mutations in the smooth muscle myosin heavy chain at sites implicated in familial hypertrophic cardiomyopathy. *J Biol Chem* 2000;275(36):28045–28052.
42. Sato H, Suzuki K, Nakaji S, Sugawara K, Totsuka M, Sato K. [Effects of acute endurance exercise and 8 week training on the production of reactive oxygen species from neutrophils in untrained men]. *Nihon Eiseigaku Zasshi Jpn J Hyg* 1998;53(2):431–440.

43. West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries as a limiting factor for maximal exercise. *Eur J Appl Physiol* 1995;70(2):99–108.
44. West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. *J Appl Physiol Bethesda Md* 1985 1991;70(4):1731–1742.
45. Stickland MK, Welsh RC, Haykowsky MJ, et al. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J Physiol* 2004;561(Pt 1):321–329.
46. McKenzie DC, Lama IL, Potts JE, Sheel AW, Coutts KD. The effect of repeat exercise on pulmonary diffusing capacity and EI_H in trained athletes. *Med Sci Sports Exerc* 1999;31(1):99–104.
47. Hanel B, Clifford PS, Secher NH. Restricted postexercise pulmonary diffusion capacity does not impair maximal transport for O₂. *J Appl Physiol Bethesda Md* 1985 1994;77(5):2408–2412.

Table 1 : Participant's baseline characteristics

	EIH (n = 10)	NEIH (n = 9)	Untrained (n = 10)
Age (years)	40.3 ± 1.2	39.1 ± 1.3	37.8 ± 1.7
Body mass (kg)	70.1 ± 2.3	71.1 ± 2.4	76.3 ± 1.9
Height (cm)	178 ± 2	179 ± 2	174 ± 1
Body mass index (kg·m⁻²)	22.2 ± 0.4 ^Ψ	22.3 ± 0.7 ^Ψ	24.9 ± 0.6
VO₂max (ml·min⁻¹·kg⁻¹)	60.1 ± 2.0 ^Ψ	58.3 ± 1.8 ^Ψ	43.3 ± 2.0
FEV₁ (% predicted)	119 ± 3	112 ± 7	114 ± 6
Training volume (hours·week⁻¹)	12.0 ± 1.7 ^Ψ	11.3 ± 1.1 ^Ψ	2 ± 0.5

Values are means ± SEM. EIH: athletes exhibiting O₂ desaturation; NEIH: athletes without O₂ desaturation

^Ψ, significantly different from untrained group (p < 0.05)

Table 2: Resting and exercise echocardiography parameters for EIH, NEIH and untrained groups.

		EIH (n= 10)	NEIH (n = 9)	Untrained (n = 10)
Workload (W)	<i>Max</i>	270 ± 10 ^Ψ	264 ± 8 ^Ψ	208 ± 11
SV (ml)	<i>Rest</i>	93 ± 6	90 ± 5	83 ± 5
	<i>Max</i>	146 ± 5*	149 ± 9*	124 ± 5*
Qc (l·min⁻¹)	<i>Rest</i>	5.9 ± 0.3	5.2 ± 0.2	5.6 ± 0.2
	<i>Max</i>	23.4 ± 1.1 ^{*Ψ}	22.7 ± 1.2 ^{*Ψ}	19.6 ± 0.9*
CI (l·min⁻¹·m⁻²)	<i>Rest</i>	3.2 ± 0.2	2.8 ± 0.2	2.9 ± 0.1
	<i>Max</i>	12.6 ± 0.5 ^{*Ψ}	12.1 ± 0.6 ^{*Ψ}	10.2 ± 0.5*
HR (bpm)	<i>Rest</i>	63 ± 3 ^Ψ	61 ± 4 ^Ψ	78 ± 5
	<i>Max</i>	168 ± 4*	162 ± 5*	169 ± 5*
mPAP (mmHg)	<i>Rest</i>	18.7 ± 0.4	18.7 ± 0.9	18.1 ± 0.7
	<i>Max</i>	45.4 ± 0.9 ^{*†Ψ}	41.6 ± 0.9*	41.9 ± 0.6*
Pcap (mmHg)	<i>Rest</i>	12.8 ± 0.4	12.2 ± 0.6	12.7 ± 0.4
	<i>Max</i>	24.8 ± 0.4 ^{*†Ψ}	23.3 ± 0.5*	23.4 ± 0.3*
LAP (mmHg)	<i>Rest</i>	8.9 ± 0.5	7.9 ± 0.4	9.2 ± 0.5
	<i>Max</i>	11.1 ± 0.5*	11.3 ± 0.3*	11.1 ± 0.3*
TPR (mmHg)	<i>Rest</i>	3.3 ± 0.2	3.6 ± 0.2	3.3 ± 0.2
	<i>Max</i>	2.0 ± 0.1*	1.9 ± 0.1*	2.2 ± 0.1*
PVR (WU)	<i>Rest</i>	1.7 ± 0.1 [†]	2.1 ± 0.1	1.7 ± 0.1 [†]
	<i>Max</i>	1.5 ± 0.1	1.4 ± 0.1*	1.6 ± 0.1
ΔPVR (WU)		-0.2 ± 0.1 [†]	-0.7 ± 0.2	0.03 ± 0.1 [†]
LAP/Qc slope (mmHg·m⁻²·min⁻¹)		0.01±0.002	0.01±0.002	0.02±0.009
mPAP/Qc slope (mmHg·m⁻²·min⁻¹)		1.6 ± 0.1	1.5 ± 0.1	1.8 ± 0.1
mPAP/CI slope (mmHg·m⁻²·min⁻¹)		3.0 ± 0.2	2.8 ± 0.2	3.5 ± 0.2
Alpha (%)		0.8 ± 0.07 [†]	1.0 ± 0.07	0.8 ± 0.06

Values are means $\pm$ SEM. EIH: athletes exhibiting O₂ desaturation; NEIH: athletes without O₂ desaturation; untrained subjects; SV: stroke volume; Qc: cardiac output; CI: cardiac index; HR: heart rate; mPAP: mean pulmonary arterial pressure; Pcap: pulmonary capillary pressure; LAP: left atrial pressure; TPR: total pulmonary vascular resistance; PVR: pulmonary vascular resistance; Δ PVR: changes of PVR from rest to maximal exercise; Alpha: coefficient of pulmonary arteriolar distensibility

*, significant difference between rest and maximal exercise within group ($p < 0.05$)

†, significantly different from NEIH ($p < 0.05$)

Ψ, significantly different from untrained ($p < 0.05$)

Table 3: Resting and maximal exercise pulmonary diffusing capacity parameters for EIH, NEIH and untrained groups.

		EIH (n = 10)	NEIH (n = 9)	Untrained (n = 10)
VA (l)	<i>Rest</i>	7.3 ± 0.3	7.4 ± 0.3	6.5 ± 0.5
	<i>Max</i>	8.3 ± 0.4*	8.6 ± 0.9*	7.5 ± 0.3*
DLCO (ml·min⁻¹·mmHg⁻¹)	<i>Rest</i>	40 ± 2	42 ± 2	37 ± 2
	<i>Max</i>	54 ± 3*	58 ± 8*	47 ± 2*
DLNO (ml·min⁻¹·mmHg⁻¹)	<i>Rest</i>	198 ± 11	206 ± 10	188 ± 9
	<i>Max</i>	252 ± 167*	267 ± 26*	241 ± 12*
KCO (ml·min⁻¹·mmHg⁻¹)	<i>Rest</i>	5.5 ± 0.2	5.9 ± 0.3	5.7 ± 0.2
	<i>Max</i>	6.7 ± 0.3*	6.7 ± 0.4*	6.2 ± 0.3*
KNO (ml·min⁻¹·mmHg⁻¹)	<i>Rest</i>	27 ± 1	29 ± 1	29 ± 1
	<i>Max</i>	30 ± 1*	32 ± 1*	32 ± 1*
Dm (ml·min⁻¹·mmHg⁻¹)	<i>Rest</i>	212 ± 17	217 ± 15	214 ± 16
	<i>Max</i>	251 ± 24*	242 ± 11*	246 ± 18*
Vc (ml)	<i>Rest</i>	88 ± 5	89 ± 4	79 ± 3
	<i>Max</i>	120 ± 6*	115 ± 6*	105 ± 2*
DLNO/DLCO	<i>Rest</i>	4.9 ± 0.1	4.9 ± 0.1	5.1 ± 0.1
	<i>Max</i>	4.7 ± 0.1	4.7 ± 0.2	5.1 ± 0.1

Values are means ± SEM. EIH: athletes exhibiting O₂ desaturation; NEIH: athletes without O₂ desaturation; VA: alveolar volume; DLCO: pulmonary diffusing capacity for CO; DLNO: pulmonary diffusing capacity for NO; KCO: transfert coefficient for CO; KNO: transfert coefficient for NO; Dm: alveolar-capillary membrane conductance; Vc: pulmonary capillary blood volume; DLNO/DLCO: DLNO/DLCO ratio.

*, significant difference between rest and maximal exercise within group (p < 0.05)

†, significantly different from NEIH (p < 0.05)

Ψ, significantly different from untrained (p < 0.05)

ABBREVIATION LIST

α = pulmonary arteriolar distensibility coefficient

CI = cardiac index

DLCO = pulmonary diffusing capacity for CO

DLNO = pulmonary diffusing capacity for NO

Dm = alveolar-capillary membrane conductance

E = doppler mitral early flow-velocity wave

E' = doppler mitral annulus early diastolic velocity

EIH = exercise-induced hypoxemia

FEV₁ = forced expiratory volume in one second

HR = heart rate

LAP = left atrial pressure

LVOT = left ventricular outflow tract

mPAP = mean pulmonary arterial pressure

NO = nitric oxide

NEIH = endurance trained athletes without exercise-induced hypoxemia

PAP = pulmonary arterial pressure

Pcap = Pulmonary capillary pressure

PVR = pulmonary vascular resistance

Qc = cardiac output

RAP = right atrial pressure

SEM = standard error of mean

sPAP = systolic pulmonary arterial pressure

SpO₂ = haemoglobin O₂ saturation

SV = stroke volume

TVI = time-velocity integral

TRV = tricuspid regurgitation jet

V_A = alveolar volume

V_c = Pulmonary capillary blood volume

$\dot{V}O_{2\max}$ = maximal oxygen uptake