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Severe hypoxic exercise does not impair lung diffusion in elite swimmers

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Abstract

Background: Exercise performed at high-altitude may cause a sub-clinical pulmonary interstitial edema which can worsen gas exchange function. This study aimed to evaluate whether there are changes in alveolar-capillary diffusion after exercise during a short-term exposure to hypobaric hypoxia in elite swimmers.

Materiols & Methods: Seven elite swimmers [age: 20.4 ± 1.4 years, height: 1.78 ± 10.8 m, body mass (BM): 69.7 ± 11.1 kg] participated in the study. Diffusing capacity of the lungs for carbon monoxide (DL_{CO}), transfer coefficient of carbon monoxide (K_{CO}), pulse oximeter oxygen saturation (S_pO_2) and heart rate (HR) were measured at sea level at rest (SL-R), and after a short-term hypobaric hypoxia exposure (4,000 m), both at rest (HA-R) and at the end of moderate interval exercise (HA-E).

Results: The combined exposure to high-altitude and exercise did not change DL_{CO} from SL-R to HA-R, or HA-E (43.8 ± 9.8 to 41.3 ± 10.5 to 42.4 ± 8.6 $ml \cdot min^{-1} \cdot mmHg^{-1}$, P = 0.391). As expected, elite swimmers showed large decrease in S_pO_2 (72 ± 5; P < 0.001) and increase in HR (139 ± 9 $beats \cdot min^{-1}$; P < 0.003) after HA-E.

Conclusions: An acute high-altitude exposure combined with submaximal exercise does not change alveolar-capillary diffusion in elite swimmers.

Key Words: diffusing capacity, intermittent hypoxic exercise (IHE), high-altitude pulmonary edema (HAPE), hypoxic training, lung diffusing capacity for carbon monoxide (DL_{CO})

Introduction

Evidence is accumulating on the growth limitations of the pulmonary system as fitness level increase (Sheel et al., 2004). Endurance training does not improve the structural and functional properties of the lungs to the same extent as the cardiovascular or muscular system in land-based athletes (Dempsey, 1986; McKenzie, 2012). However water-based athletes, such as swimmers, have larger lungs and higher diffusing capacity than other athletes (Armour et al., 1993; Mickleborough et al., 2008) probably due to repeated exposure to mechanical strain and hypoxia during swimming (Wagner, 2005). Altitude training camps are extensively utilized by elite swimming coaches (Lundby and Robach, 2016), but the possible modifications of the alveolar–capillary exchange are still unknown. Under severe altitude exposure and/or high intensity exercise, the O_2 delivery to active tissues may not sufficient to ensure an adequate function, leading to hypoxemia (Naeije and Chesler, 2012), diffusion limitation (Mairbäurl et al., 2019) and lung interstitial edema (Anholm et al., 1999; Eldridge et al., 2006; Marabotti et al., 2017). In particular, the practice of swimming has been associated to the occurrence of pulmonary edema (Hohmann et al., 2018), with an specific denomination *(swimming-induced pulmonary edema, SIPE)*.

Different modalities of altitude training have been proposed although Living High - Training High (LHTH) protocol is still the most feasible modality among swimmers (Rodríguez et al., 2015). However, the application of intermittent hypoxic exercise (IHE) in hypobaric hypoxic chamber or normobaric hypoxic tents at severe altitude (> 3,000 m) are becoming popular among elite athletes to enhance exercise performance (Viscor et al., 2018). The exposure to severe hypoxia may provoke changes in the diffusing capacity of the lungs for carbon monoxide (DL_{CO}) although there are no consensus about the conditions needed to provoke these changes in lung diffusing parameters (de Bisschop et al., 2012; Clarenbach et al., 2012; Coffman et al., 2017; Taylor et al., 2016). Recently, we showed that a session of moderate cycling at normobaric hypoxia (3,000 m) during a 14-day altitude training camp at moderate altitude (1,850 m) decrease acutely DL_{CO} in elite swimmers (García et al., 2020).

As a result of these new approaches in hypoxic training (Viscor et al., 2018), the main goal of this study was to evaluate the lung diffusing response during exercise under

acute hypobaric hypoxia exposure in unacclimated elite swimmers. These include exposures of this kind to exercise at high-altitude while they reside at sea level. So, we aimed to evaluate the possible changes in DL_{CO} after a short term ~~exposure~~ bout of exercise at 4,000 m high-altitude (HA). We evaluate DL_{CO} at rest at sea level (SL-R), and then at 4,000 m, both at rest (HA-R) and after moderate intensity interval exercise (HA-E). We hypothesized that there will be an increase in lung diffusion at rest in HA (HA-R) due to a recruitment and distension of the pulmonary vasculature, but there will be a decrease after exercise at HA (HA-E) due to an accumulation of interstitial fluid.

Materials & Methods

Participants

Seven elite swimmers, including 2 females and 5 males, were the participants of the study [age: 20.4 ± 1.4 years, height: 1.78 ± 10.8 m, body mass (BM): 69.7 ± 11.1 kg]. The participants had an average FINA (Fédération Internationale de Natation) points in their best event of 781 FINA points at the time of the study and five of them have participated in European and World junior championships. The training schedule of the swimmers were composed by 10 swimming training sessions and 5 dry land sessions per week, amounting 25 hours of training per week. None of them had asthma and none were smokers.

Experimental design

The study was performed in a hypobaric chamber sited at the University of Barcelona. The participants performed two DL_{CO} measurements before the start of the study to become familiar with the procedure. A cycle ergometer (Corival Lode BV, Groningen, Netherlands) was used to do the exercise protocols, and a computerized spirometer (Easy One Pro, ndd Medical Technologies, Zurich Switzerland) was used to evaluate DL_{CO} and other pulmonary parameters.

Lung diffusing capacity was evaluated in relation to exercise during a short-term exposure to hypobaric HA at 4,000 m. The participants performed a basal measurement in resting condition at sea level (SL-R). They reached the target barometric pressure of 462 torr (equivalent to 4,000 m of altitude) in the hypobaric chamber in a time lapse of 30 minutes of pressure stabilization. Then, measurements were performed in a resting condition at high-altitude (HA-R), and immediately at the end of 30 minutes of moderate

interval exercise at the same high-altitude (HA-E). The exercise interval protocol consisted of 5 sets with 3 minutes at moderate intensity (2 W per kilogram of individual body mass; 139 ± 23 W) and 3 minutes of active recovery (25 W). The computerized spirometer utilized to measure DL_{CO} was placed within the hypobaric chamber during the HA measurements. The subjects were instructed to perform the DL_{CO} manoeuvre less than one minute after the exercise. Exercise at HA was monitored by pulse oximeter oxygen saturation (S_pO_2) and heart rate (HR) to ensure an optimal health status during exercise.

All measures considered in this study were "grade A" manoeuvres, as identified by the system (Graham et al., 2017). In addition, the haemoglobin (Hb) concentration was determined from a small blood sample obtained by venepuncture to adjust DL_{CO} to individual parameters before the beginning of the study and DL_{CO} was also corrected to actual barometric pressure (DL_{CO}adj) in the HA-R and HA-E conditions.

Pulmonary function measurements

The procedure used to obtain diffusion lung capacity parameters was the single-breath method, for which a computerized spirometer was attached to a gas mixture cylinder. This method involves measuring the uptake of CO from the lungs over a short breath-holding period. The recommendations made in a recent joint statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) were followed (Graham et al., 2017). The participants were placed in a seated position, with a mouthpiece and nose-clip in place throughout the test procedure. The test started with tidal breathing for 2–4 breaths until the subject felt comfortable with the mouthpiece. Then the DL_{CO} manoeuvre began with an unforced exhalation to residual volume (RV). At residual volume (RV) the subject's mouthpiece was connected to the source of test gas, and the subject inhaled rapidly to maximal inspiration. After that, the participant was asked to hold their breath for 10 s and then exhale completely without interruption in less than 4 s and to continue with a tidal breath to finish the test. The test gases mixture used to calculate pulmonary function and diffusion capacity was composed of 0.3% of carbon monoxide (CO), 11% of a tracer inert gas (He) used to measure alveolar volume (VA) and the initial alveolar CO, a mixture of 20.9% of oxygen (O_2) and the rest was nitrogen (N_2). In addition to DL_{CO} and VA, transfer coefficient of the lung for carbon

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monoxide (K_{CO}), total lung capacity (TLC), vital capacity inspired (VC_{IN}) and RV were calculated.

Ethics

The study was developed in accordance with the Helsinki Declaration concerning the ethical principles of human experimentation and approved by the Institutional Ethical Committee from the University of Barcelona (Institutional Review Board number IRB00003099), in accordance with current Spanish legislation. The participants were informed and familiarized with all the experimental procedures, as well as the risks and benefits of the study. They signed an informed consent form and were free to withdraw from the experimental protocol at any time.

Statistical analysis

Data are reported as mean values ± standard deviation (SD). Differences in pulmonary parameters among different conditions (SL-R, HA-R and HA-E) were analysed using a one-way repeated measures analysis of variance (ANOVA), and in case of detecting statistical effects ($p<0.05$), Bonferroni corrections were performed. Effect sizes as partial eta squared (η^2_p) values were employed to present the magnitude of differences and statistical power (sp) was also described. The analyses were performed using the SPSS v. 26 (IBM SPSS Statistics, Armonk, New York, USA).

Results

Basal lung capacity and diffusing capacity of elite swimmers were higher than predicted by age and height, including DL_{CO} (139 ± 6%), K_{CO} (120 ± 7%) and VA (116 ± 8%).

Table 1 shows the response in pulmonary functional and structural parameters to HA conditions. At the hypobaric chamber, there were no differences between SL-R, HA-R, and HA-E in any of the main pulmonary parameters evaluated such as DL_{CO}adj (43.8 ± 9.8 to 41.3 ± 10.5 to 42.4 ± 8.6 ml·min^{-1}·mmHg^{-1}, P = 0.319), K_{CO}adj (6.02 ± 0.48 to 5.79 ± 0.52 to 5.77 ± 0.84 ml·min^{-1}·mmHg^{-1}·l^{-1}, P = 0.541), and VA (7.22 ± 1.34 to 7.10 ± 1.57 to 7.31 ± 0.92 l, P = 0.787).

Figure 1 shows the response in the cardiovascular parameters during the different conditions studied and Figure 2 shows the individual changes in S_pO_2, HR and DL_{CO}adj from HA-R to HA-E in the sample of elite swimmers.

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Regarding S_pO_2, there were a significant interaction between S_pO_2 and the studied conditions ($F = 124.17$, $P < 0.001$, $\eta^2_p = 0.95$, sp = 1.000). There were a significant decrease in S_pO_2 from SL-R to HA-R ($P < 0.001$), and there were a significant decrease from SL-R to HA-E ($P < 0.001$) and from HA-R to HA-E ($P = 0.004$), respectively 99 ± 1 to 84 ± 4 to 72 ± 5 %.

Regarding HR, there were a significant interaction between HR and the studied conditions ($F = 175.86$, $P < 0.001$, $\eta^2_p = 0.96$, sp = 1.000) .There were a significant increase from SL-R to HA-R ($P > 0.001$), and there were a significant increase from SL-R to HA-E ($P < 0.001$) and from HA-R to HA-E ($P < 0.001$), respectively 60 ± 6 to 68 ± 11 to 139 ± 9 beats·min^{-1}.

Discussion

The main finding of this study is that there were no changes in any lung diffusion parameter during the exposure to 4,000 m in the hypobaric chamber (HA-R and HA-E), suggesting that the cardio-pulmonary system of healthy subjects cope well with a short-term exposure to exercise at high altitude.

During a exposure to HA, a hypobaric pulmonary vasoconstriction (HPV) and a raise in pulmonary arterial pressure (PAP) are produced (West, 2012), conditions that may be aggravated by the high cardiac output and high pulmonary flow induced by exercise (Marabotti et al., 2017; Naeije and Chesler, 2012). In some cases an additional functional reserve can be recruited to improve membrane O_2 diffusing capacity during exercise in hypoxia (Hanson et al., 1989; Taylor et al., 2016).

Regarding the literature, hypoxic exercise does not impair acutely neither lung diffusion (de Bisschop et al., 2012; Guenette et al., 2007), although some studies has found a slight increase (Snyder et al., 2006; Taylor et al., 2016) or decrease (Agostoni et al., 2013; Senn et al., 2006).

The DL_{CO} response to short-term hypobaric hypoxia may be complex. Several hypotheses can explain our results. The hypobaric exposure could have been too short to induce interstitial fluid accumulation and thus a reduction in DL_{CO}, although some relevant risk factors to the development of pulmonary edema were induced in our experimental design such as rapid ascent rate, high-altitude and intense exercise. However, the proposed exercise protocol could have been insufficient to present a

challenge in the respiratory system. Therefore, the HR got during exercise (139 ± 9 bpm) could not be enough to stress lung diffusion. The time of exposure to hypoxia and the intensity of the exercise may be decisive to find an increase, no changes or a decrease in DL_{CO}. In a recent study, elite swimmers acclimated to 1,850 m had a significant decrease in DL_{CO} after a similar exercise protocol even at lower simulated altitude (García et al., 2020). However, that cycling session was conducted after a swimming training within a 14-day altitude training camp and under normobaric hypoxia conditions (3,000 m). In addition, in this previous study, a lower HR in acclimated athletes may result in less lung perfusion and therefore greater diffusion limitation.

Dynamics of lung diffusing equilibrium may change depending on intensity, duration of the stimulus and inter-individual physiological status. In addition, the similarity between hypobaric and normobaric hypoxia stimuli are still under discussion (Viscor et al. 2018, Millet and Debevec, 2020; Richalet, 2020) which could have affected the divergent results.

Apart from that, a maintained balance between the reduction in alveolar-capillary diffusion secondary to interstitial fluid accumulation and the increase in capillary lung perfusion due to the presented increase in HR (Bates et al., 2011; Taylor et al., 2014) could also explain the lack of changes in DL_{CO}. Therefore, the induced increase in interstitial lung fluid could have been masked by the additional recruitment of the pulmonary vasculature during hypoxic exercise. The appearance of pulmonary edema or the reduced transit time under specific conditions of low PO_2 and high flow of the blood such as exercise may provoke diffusion disequilibrium (Ayappa et al., 1998; Torre-Bueno et al., 1985), limiting the O_2 uptake in the lungs and the supplementary increases in DL_{CO}. In our study, we did not measure SIPE with direct techniques (CT-scan or X-ray), but it cannot be dismissed that some interstitial fluid was still accumulating. The partition of DL_{CO} into its components, D_M and capillary blood volume (V_C) (Roughton and Forster, 1957) is necessary to understand whether the absence of changes in lung diffusion capacity is related to changes in alveolar-capillary diffusion from basal to post-exercise in hypoxia.

Regarding the response in S_pO_2, there was an expected decrease in S_pO_2 during the studied conditions. Aquatic athletes such as artistic swimmers (Bjurstrom and Schoene, 1987) and divers (Foster and Sheel, 2005) have a low hypoxic ventilatory response (HVR)

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which is associated with HAPE-susceptible individuals (Hohenhaus et al., 1995). That is why, in some cases, elite athletes have been described as more susceptible to HAPE than control subjects (Hohenhaus et al., 1995). However, we could not associate this serious decrease in S_pO_2 (72 ± 5 %) to a diffusion limitation.

One concern of the study is the use of indirect measures of interstitial lung fluid. Although DL_{CO} has been consistently associated with an increase in extravascular lung water (Snyder et al. 2006; Clarenbach et al. 2012), a combined study of DL_{CO} and diffusion capacity of the lung for nitric oxide (DL_{NO}) would be more accurate to detect very mild interstitial fluid accumulation (Dehnert et al. 2010), since DL_{NO} reflects more sensitively the changes in membrane diffusing capacity (Zavorsky and Lee, 2017). Additional measurements of cardiac output or stroke volume could also explain the disassociation between the raise in HR and the unchanged DL_{CO} after HA-E.

One strength from this study is that all the DL_{CO} measurements were taken 30-s to 1-min after exercise. Most of the studies assess DL_{CO} 30 to 120 min after exercise suggesting that the potential decrease in DL_{CO} is due to blood volume redistribution to the peripheral organs after exercise, a hypothesis that may be dismissed in our study.

In conclusion, this study shows that submaximal exercise during acute exposure to high-altitude does not change lung diffusing capacity in elite swimmers, suggesting that healthy participants can deal with this type of combined environmental stressors without compromise of respiratory exchange. However, this study does not definitively show that submaximal exercise during acute exposure to altitude does not impair alveolar-capillary diffusion in the lungs, due to the possible interference between the V_C and D_M in our exercise protocol. ~~This finding could help coaches and medical doctors assure that hypoxic exercise is safe to the respiratory interface during altitude training camps or under severe hypoxic exposure in elite swimmers while residing at sea level.~~ Some methodological limitations in this study do not allow to completely rule out the possibility of the unchanged lung gas diffusion not being also due, at least in part, to the small number of subjects studied, the relatively short duration and intensity of the exercise performed at simulated altitude and the intrinsic inaccuracy of this type of gas exchange measurements. Further studies should consider measurements of CT-scan, DL_{NO}, D_M and V_C to fully understand the physiological implications of severe acute hypoxic exercise in the lungs.

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References

Agostoni P, Swenson ER, Fumagalli R, Salvioni E, Cattadori G, Farina S, Bussotti M, Tamplenizza M, Lombardi C, Bonacina D, Brioschi M, Caravita S, Modesti P, Revera M, Giuliano A, Meriggi P, Faini A, Bilo G, Banfi C, and Parati G (2013). Acute high-altitude exposure reduces lung diffusion: Data from the HIGHCARE Alps project. Respir Physiol Neurobiol 188:223–228.

Anholm JD, Milne ENC, Stark P, Bourne JC, and Friedman P (1999). Radiographic evidence of interstitial pulmonary edema after exercise at altitude. J Appl Physiol 86:503–509.

Armour J, Donnelly PM, and Bye PTP (1993). The large lungs of elite swimmers : an increased alveolar number? Eur Respir J Respir J 6:237–247.

Ayappa I, Brown L V., and Lai-Fook SJ (1998). Effects of hypoxia, blood PCO2 and flow on O2 transport in excised rabbit lungs. Respir Physiol 112:155–166.

Bates ML, Farrell ET, and Eldridge MW (2011). The Curious Question of Exercise-Induced Pulmonary Edema. Pulm Med 2011:1–7.

de Bisschop C, Martinot JB, Leurquin-Sterk G, Faoro V, Guénard H, and Naeije R (2012). Improvement in lung diffusion by endothelin A receptor blockade at high altitude. J Appl Physiol 112:20–25.

Bjurstrom RL and Schoene RB (1987). Control of ventilation in elite synchronized swimmers. J Appl Physiol 63:1019–1024.

Clarenbach CF, Senn O, Christ AL, Fischler M, Maggiorini M, and Bloch KE (2012). Lung function and breathing pattern in subjects developing high altitude pulmonary edema. PLoS One 7:3–8.

Coffman KE, Carlson AR, Miller AD, Johnson BD, Bryan J, Affiliations A, Clinic M, Clinic M, and Taylor BJ (2017). The effect of aging and cardiorespiratory fitness on the lung diffusing capacity response to exercise in healthy humans. J Appl Physiol 122:1425–1434.

Dempsey JA (1986). Is the lung built for exercise? Med Sci Sports Exerc 18:143–155.

Eldridge MW, Braun RK, Yoneda KY, and Walby WF (2006). Effects of altitude and exercise on pulmonary capillary integrity: Evidence for subclinical high-altitude pulmonary edema. J Appl Physiol 100:972–980.

Foster GE and Sheel AW (2005). The human diving response, its function, and its control. Scand J Med Sci Sport 15:3–12.

García I, Drobnic F, Galera T, Pons V, and Viscor G (2020). Lung diffusion in a 14-day swimming altitude training camp at 1850 meters. Int J Environ Res Public Health 17:1–12.

Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, Macintyre NR, Thompson BR, and Wanger J (2017). 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 49:1–31.

Guenette JA, Sporer BC, MacNutt MJ, Coxson HO, Sheel AW, Mayo JR, and McKenzie DC (2007). Lung density is not altered following intense normobaric hypoxic interval training in competitive female cyclists. J Appl Physiol 103:875–882.

Hanson WL, Emhardt JD, Bartek JP, Latham LP, Checkley LL, Capen RL, and Wagner WW (1989). Site of recruitment in the pulmonary microcirculation. J Appl Physiol 66:2079–2083.

Hohenhaus E, Paul . A, McCullough RE, Kucherer H, and Bartsch P (1995). Ventilatory and pulmonary vascular response to hypoxia and susceptibility to high altitude pulmonary oedema. Eur Respir J 8:1825–1833.

Hohmann E, Glatt V, and Tetsworth K (2018). Swimming induced pulmonary oedema in athletes – a systematic review and best evidence synthesis. BMC Sports Sci Med Rehabil 3:1–10.

Lundby C and Robach P (2016). Does 'altitude training' increase exercise performance in elite athletes? Exp Physiol 101:783–788.

Mairbäurl H, Dehnert C, Macholz F, Dankl D, Sareban M, and Berger MM (2019). The hen or the egg: Impaired alveolar oxygen diffusion and acute high-altitude illness? Int J

Mol Sci 20:1–13.

Marabotti C, Cialoni D, and Pingitore A (2017). Environment-induced pulmonary oedema in healthy individuals. Lancet Respir Med 5:374–376.

McKenzie DC (2012). Respiratory physiology: Adaptations to high-level exercise. Br J Sports Med 46:381–384.

Mickleborough TD, Stager JM, Chatham K, Lindley MR, and Ionescu AA (2008). Pulmonary adaptations to swim and inspiratory muscle training. Eur J Appl Physiol 103:635–646.

Millet GP and Debevec T (2020). CrossTalk proposal: Barometric pressure, independent of PO2, is the forgotten parameter in altitude physiology and mountain medicine. J Physiol 598:893–896.

Naeije R and Chesler N (2012). Pulmonary circulation at exercise. Compr Physiol 2:711–741.

Richalet JP (2020). CrossTalk opposing view: Barometric pressure, independent of PO2, is not the forgotten parameter in altitude physiology and mountain medicine. J Physiol 598:897–899.

Rodríguez FA, Iglesias X, Feriche B, Calderón-Soto C, Chaverri D, Wachsmuth NB, Schmidt W, and Levine BD (2015). Altitude Training in Elite Swimmers for Sea Level Performance (Altitude Project). Med Sci Sports Exerc 47:1965–1978.

Roughton FJW and Forster RE (1957). Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol 11:290–302.

Senn O, Clarenbach CF, Fischler M, Thalmann R, Brunner-La Rocca H, Egger P, Maggiorini M, and Bloch KE (2006). Do changes in lung function predict high-altitude pulmonary edema at an early stage? Med Sci Sports Exerc 38:1565–1570.

Sheel AW, Richards JC, Foster GE, and Guenette JA (2004). Sex differences in respiratory exercise physiology. Sport Med 34:567–579.

Snyder EM, Beck KC, Hulsebus ML, Breen JF, Hoffman EA, and Johnson BD (2006). Short-term hypoxic exposure at rest and during exercise reduces lung water in healthy humans. J Appl Physiol 101:1623–1632.

Taylor BJ, Carlson AR, Miller AD, and Johnson BD (2014). Exercise-induced interstitial

pulmonary edema at sea-level in young and old healthy humans. Respir Physiol Neurobiol 191:17–25.

Taylor BJ, Coffman KE, Summerfield DT, Issa AN, Kasak AJ, and Johnson BD (2016). Pulmonary capillary reserve and exercise capacity at high altitude in healthy humans. Eur J Appl Physiol 116:427–437.

Torre-Bueno JR, Wagner PD, Saltzman HA, Gale GE, and Moon RE (1985). Diffusion limitation in normal humans during exercise at sea level and simulated altitude. J Appl Physiol 58:989–995.

Viscor G, Torrella JR, Corral L, Ricart A, and Javierre C (2018). Physiological and Biological Responses to Short-Term Intermittent Hypobaric Hypoxia Exposure : From Sports and Mountain Medicine to New Biomedical Applications. Front Physiol 9:1–20.

Wagner PD (2005). Why doesn't exercise grow the lungs when other factors do? Exerc Sport Sci Rev 33:3–8.

West JB (2012). High-Altitude Medicine. Am J Respir Crit Care Med 186:1229–1237.

Zavorsky GS and Lee I Van Der (2017). Can the measurement of pulmonary diffusing capacity for nitric oxide replace the measurement of pulmonary diffusing capacity for carbon monoxide? Respir Physiol Neurobiol 241:9–16.

Figure legends

Figure 1. Pulse oximeter oxygen saturation (black circles, left scale) and heart rate (white circles, right scale) at the different conditions. Statistical significance ($P<0.05$) is denoted by asterisks (*) for the comparison to sea level at rest (SL-R) and by cross (†) for the comparison between rest (HA-R) and after exercise (HA-E) at simulated altitude (4,000 m). Two symbols indicate $P<0.01$ and three symbols mean $P<0.001$.

Figure 2. Individual changes in pulse oximeter oxygen saturation (S_pO_2), heart rate (HR) and diffusing capacity of the lungs for carbon monoxide ($DL_{CO}adj$) from resting position at high-altitude (HA-R) to post-exercise at high-altitude (HA-E) in each one of the 7 unacclimated elite swimmers.

Table 1. Pulmonary parameters of swimmers and control subjects under different environmental and exercise conditions: Sea level at rest (SL-R), simulated high-altitude at rest (HA-R) and simulated high-altitude immediately at the end of exercise (HA-E).

	Elite swimmers (n = 7)		
	SL-R	HA-R	HA-E
DL_{CO}adj ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	43.8 ± 9.8	41.3 ± 10.5	42.4 ± 8.6
DL_{CO}adj (%-predicted)	139 ± 6	133 ± 10	137 ± 12
K_{CO}adj ($ml \cdot min^{-1} \cdot mmHg^{-1} \cdot l^{-1}$)	6.02 ± 0.48	5.79 ± 0.52	5.77 ± 0.84
K_{CO}adj (%-predicted)	120 ± 7	115 ± 10	115 ± 16
VA (l)	7.22 ± 1.34	7.10 ± 1.57	7.31 ± 0,92
VA (%-predicted)	116 ± 8	113 ± 12	119 ± 16
TLC (l)	7.37 ± 1.34	7.25 ± 1.57	7.46 ± 0.92
TLC (%-predicted)	116 ± 8	113 ± 12	118 ± 15
VC_{IN} (l)	5.46 ± 1.28	5.48 ± 1.24	5.19 ± 1.03
RV (l)	1.91 ± 0.34	1.77 ± 0.50	2.27 ± 1.03 * †

* Significantly different than SL-R ($P<0.05$). † Significantly different than HA-R ($P<0.05$).

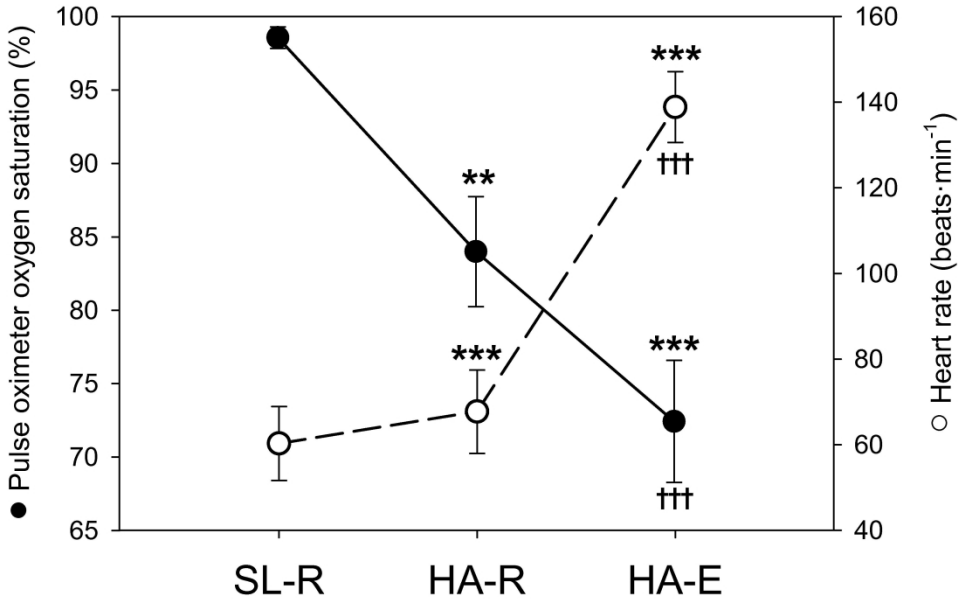

Figure 1. Pulse oximeter oxygen saturation (black circles, left scale) and heart rate (white circles, right scale) at the different conditions. Statistical significance (P<0.05) is denoted by asterisks (*) for the comparison to sea level at rest (SL-R) and by cross (†) for the comparison between rest (HA-R) and after exercise (HA-E) at simulated altitude (4,000 m). Two symbols indicate P<0.01 and three symbols mean P<0.001.

175x119mm (600 x 600 DPI)

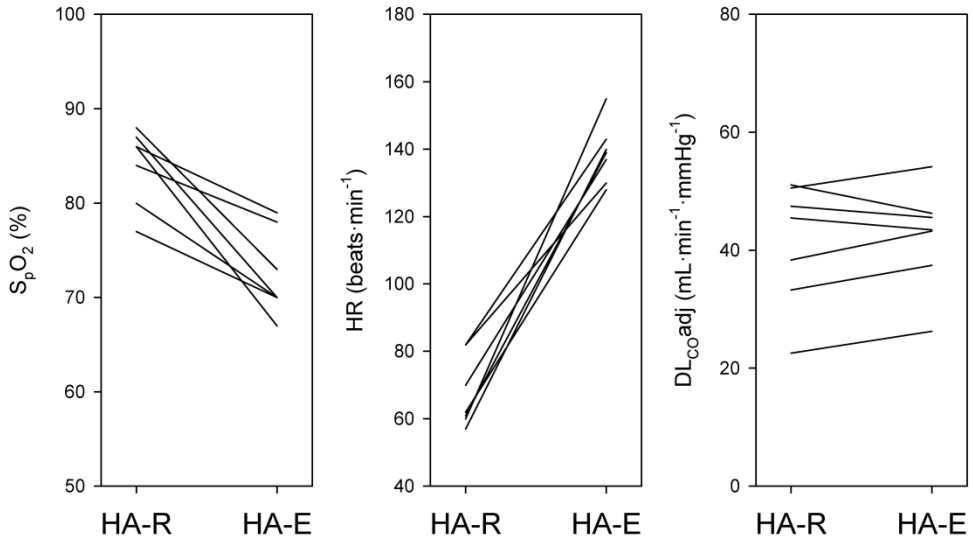

Figure 2. Individual changes in pulse oximeter oxygen saturation (SpO2), heart rate (HR) and diffusing capacity of the lungs for carbon monoxide (DLCOadj) from resting position at high-altitude (HA-R) to post-exercise at high-altitude (HA-E) in each one of the 7 unacclimated elite swimmers.

190x117mm (600 x 600 DPI)