Respiratory Physiology & Neurobiology 190 (2014) 96–104

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Inter-individual differences in control of alveolar capillary blood volume in exercise and hypoxia

Manuela Bartesaghi[a], Egidio Beretta[a], Luca Pollastri[a], Valentina Scotti[a], Gaia Mandolesi[b], Francesca Lanfranconi[a], Giuseppe Miserocchi[a,*]

[a] Laboratory of Clinical Physiology and Exercise, Department of Health Sciences, University of Milano Bicocca, Via Cadore 48, 20900 Monza, Italy
[b] Centro Studi Biomedici Applicati allo Sport, University of Ferrara, Via Gramicia 35, 44123 Ferrara, Italy

ARTICLE INFO

Article history:
Accepted 29 August 2013

Keywords:
Lung diffusion
Microvascular filtration
High altitude pulmonary edema
Respiratory impedance
Lung ultrasound

ABSTRACT

We compared by non-invasive technique the adaptive response of alveolar capillary network to edemagenic conditions (exercise and high altitude [HA, P_IO_2 107 mm Hg] in subjects with different resting sea level (SL) capillary blood volume (normalized to alveolar volume, Vc/Va): Group 1 (N = 10, Vc/Va = 16.1 ± 6.8 ml/L- mean ± SD) and Group 2 (N = 10, Vc/Va = 25 ± 7.7). In Group 1 Vc/Va remained unchanged in HA at rest and increased during exercise at SL (26.3 ± 8.6) and HA (28.75 ± 10.2); in Group 2 Vc/Va significantly decreased in HA (19 ± 6) and did not increase in exercise at SL and HA. We hypothesize that Group2 exerts a tight control on Vc/Va being more exposed to the risk of lung edema due to inborn greater microvascular permeability. Conversely, Group 1 appears more resistant to lung edema given the large capillary recruitment in the most edemagenic condition. The 4-fold increase in frequency dependence of respiratory resistance in Group2 in HA stems for greater proneness for lung water perturbation compared to Group 1.

1. Introduction

The surface area of air-blood barrier is in the range of 2000 cm^2/g of lung tissue. This incredible extension serves the gas diffusion function that amounts for O_2, to about 15×10^{-2} ml/min cm^2 in resting conditions. Notably, over the same surface area, fluid is continuously filtered from capillaries to the interstitial space at a rate of 6×10^{-10} ml/min cm^2 (Miserocchi, 2009). Thus, the air-blood barrier presents 2 peculiar features: a very high conductance for gas exchanges and a very low conductance for microvascular filtration. Extravascular lung water is normally maintained at minimum volume and this optimizes the gas diffusion processes. Precapillary pulmonary vasoconstriction is a potential efficient mechanism controlling the lung extravascular volume (Miserocchi, 2009) being regarded as a reflex limiting microvascular filtration, in particular in edemagenic conditions (Moudgil et al., 2005; Negrini, 1995; Negrini et al., 2001) through a decrease in vascular perfusion, filtration surface area and capillary pressure (see Appendix). In humans, edemagenic conditions characteristically occur when the need for O_2 delivery and extraction from the tissues is increased, as during exercise and exposure to hypobaric hypoxia, due to the increase of lung perfusion, capillary filtration coefficient, capillary surface area and water and protein permeability (Hansen et al., 1994; Miserocchi et al., 2001b; Ogawa et al., 1992). Furthermore, many evidences indicate that in humans the efficiency of the mechanisms controlling extravascular lung water substantially differs among individuals as, notably, some subjects are more exposed to the risk of lung edema. Our primary interest was that to derive indications, by non-invasive techniques, concerning the control of the lung microvascular district after exposure to edemagenic conditions. We hypothesize that the adaptive response of the alveolar capillary network might reflect the inborn microvascular permeability. We reason that subjects endowed with a more extended alveolar capillary network, that implies a greater capillary filtration coefficient, would develop a strong precapillary vascocontriction to challenge the greater risk of developing lung edema. Conversely, this would not be the case for subjects having a less extended alveolar capillary network at rest at SL, and thus a lower filtration coefficient. We relied on the measurement of lung capillary blood volume (Vc), a subcomponent of lung diffusion, as an index of the extension of the alveolar pulmonary network (Miserocchi et al., 2007).

2. Methods

We recruited 20 healthy subjects, average age 35.2 ± 7.3, BMI 22.0 ± 3.1, who regularly practiced mountaineering in Italian Alps

* Corresponding author at: Department of Health Sciences, University of Milano Bicocca, Via Cadore 48, 20900 Monza, Italy. Tel.: +39 02 64488309; fax: +39 02 64488068.
E-mail address: giuseppe.miserocchi@unimib.it (G. Miserocchi).

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http://dx.doi.org/10.1016/j.resp.2013.08.021

reaching at times altitudes higher than 3500 m. All subjects were not involved in regular, structured sport activity (defined as three times per week training or more and up to regional race level). The subjects attended the laboratory at SL, where normoxia experiments were carried out (Pb 749.8 ± 6.62 mmHg, P_IO_2 157 mmHg) and there was no exclusion on medical grounds for infective, cardiovascular, pulmonary or neurologic diseases. In the 4 months before the study subjects abstained from reaching altitude higher than 1500 m. Experiments at HA were done at Casati Refuge (Valtellina, Italy), situated at 3269 m (Pb 516 ± 3.36 mmHg, P_IO_2 107 mmHg). Reaching the refuge required about 3 h walking to cover an altitude difference of 1100 m.

The project was approved by the ethical committee of University of Milano Bicocca. Subjects were instructed about the experimental procedure and related discomfort, as well as of the risks of acute exposure to hypoxia, and signed an informed consent.

2.1. Total lung diffusion

Measurements of DLCO were done in sitting position at total lung capacity (TLC) by single breath method (QUARK PFT, Cosmed, Italy) by having subjects to inspire a gas mixture containing 0.3% CH_4, 0.3% CO and 20% O_2. A quality evaluation was performed by visual inspection of the expected curves and, just in case, the measurement was repeated. Alveolar volume (Va) was determined by CH_4 dilution and represented a normalizing parameter for diffusion components. DLCO data were standardized to a haemoglobin concentration of 14.6 g/dl in men and 13.4 g/dl in women. Measurements were done at SL and HA in resting condition and at moderate intensity constant load exercise on a cycloergometer under the gas exchange threshold (GET) that was individually determined.

To compare DLCO values at SL to those obtained at HA, the latter were corrected with the following equation (Macintyre et al., 2005):

$$DLCO_{corr} = DLCO_{meas} \cdot [1.0 + 0.0031(PIO_{2ALT} - 150)]$$

2.2. Diffusion subcomponents

Diffusion subcomponents Dm and Vc were determined at TLC (Roughton and Forster, 1957). Subjects inspired gas mixtures containing 0.3% CH_4, 0.3% CO and different O_2 percentages: 20, 40 and 60% at SL and 40 and 60% at HA. Each maneuver was performed at least 6 min after the previous one. Values of DLCO were considered valid only when Va measurements did not differ by more than 5%; maneuvers were repeated in case of intra-individual discrepancy.

The subcomponent Dm and Vc and DLCO are considered to be in the following relationship (Roughton and Forster, 1957):

$$\frac{1}{DLCO} = \frac{1}{Dm} + \frac{1}{\theta Vc}$$

where θ represents the chemical reaction rate of CO with hemoglobin.

Dm and Vc values were obtained as the reciprocal of intercept and slope of the regressions 1/DLCO vs $1/\theta$ for each subject. The values of $1/\theta$ were obtained from the equation (Foster, 1987):

$$\frac{1}{\theta} = 0.75 + (0.0057 \cdot PcapO_2)$$

where $PcapO_2$ was the average capillary O_2 pressure. $PcapO_2$ was obtained from the following equation (De Bisschop et al., 2012):

$$PcapO_2 = PalvO_2 - \dot{V}O_2 \cdot (1.23 \cdot DLCO)^{-1}$$

where $PalvO_2$ is the end tidal alveolar partial pressure of O_2, $\dot{V}_{O_2}$ is the pulmonary O_2 uptake and 1.23 is the correction factor that accounts for the ratio of O_2 to CO diffusion coefficient. At HA we excluded the use of 20% O_2 to avoid the fall of $PcapO_2$ below 75 mmHg (Foster, 1987).

A blood sample was taken in resting conditions at SL to determine hemoglobin concentration and hematocrit.

2.3. Exercise protocol

Pulmonary ventilation ($\dot{V}_E$, in BTPS), $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ were determined breath-by-breath by a portable metabolic cart, expiratory flow was determined by a mass flow sensor (K4b^2, Cosmed, Roma, Italy). $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ were determined through continuous monitoring of PO_2 and PCO_2 at the mouth throughout the respiratory cycle and from established mass balance equations. Heart rate (HR) was determined from a 12-lead electrocardiographic signal interfaced to Sensor Medics metabolic cart. Arterial blood O_2 saturation (SaO_2) was monitored continuously through the oximetry at the finger (RAD 9 Signal Extraction Pulse Oximeter: Masimo Corporation, Irvine - California, USA) whose validity was based on the visual evaluation of the quality of the pulse wave signal. The environmental temperature during exercise was standardized to 18 °C using an air-conditioning system and the current barometric pressure was recorded. All exercise tests were conducted under close medical supervision and with 12-lead electrocardiography monitoring (Quark C12x, Cosmed, Italy). We assessed that the participants were in a resting condition before the test based on observation of HR and $\dot{V}_E$. An incremental exercise test was performed on a cycloergometer (Ergoline 900, Cosmed, Italy). After 2 min of unloading pedaling, the workload was increased every 60 s until voluntary exhaustion. The initial workload at SL was set at 60–90 W (the exact workload was chosen on the basis of the estimated level of physical fitness of the subject) and increments of 15–25 W/min were given up to exhaustion. At HA, the initial workload was 45–75 W and increments were 10–15 W/min. Exhaustion was defined by the inability to maintain the cycling rate despite vigorous encouragement by the operators. The whole session in normoxia lasted 9.4 ± 2 min. In hypobaric hypoxia, the incremental tests were performed 6 h after reaching the altitude and lasted 7.9 ± 1.8 min. Systemic arterial blood pressure was measured in resting conditions and at peak of exercise and during recovery until return to a resting value. Blood lactate and glucose were determined on capillary blood samples (BIOSEN C line, EKF diagnostic, London, UK) obtained from an ear lobe, at rest and from 1 to 9 min during recovery and the highest value was considered as peak both at SL and in HA.

A constant load exercise corresponding to 70 and 60% of gas exchange threshold (GET) at SL and HA, respectively, was conducted for 20 min in order to evaluate DLCO and subcomponents values. The GET was determined as the breaking point of the $\dot{V}_{O_2}$ vs $\dot{V}_E$ relationship where the slope increased (Beaver et al., 1973).

2.4. Respiratory mechanics

We assessed the mechanical properties of the respiratory system by applying the forced oscillation technique (IOS, Master System, Jeager, Germany) in resting conditions at SL and HA. This technique is based on the superimposition of small pressure impulse oscillations with multiple frequency contents on the spontaneous breathing of the subject. The resulting small changes in pressure and corresponding flow depend on mechanical properties of airways and lung tissue. Based on oscillation frequency imposed, IOS is able to derive indications of the mechanical behavior of the lung without the cooperation of the subject. We considered in particular: a) resistance at 5 Hz (R_5), b) resistance at 20 Hz (R_{20}), c) the difference $R_5 - R_{20}$, expression of the frequency dependence of resistance, d) reactance at 5 Hz (X_5) that reflects the visco-elastic properties of the distal lung (Goldman et al., 2005). We also