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Interstitial lung fluid balance in healthy lowlanders exposed to high-altitude

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ABSTRACT

We aimed to assess lung fluid balance before and after gradual ascent to 5150 m. Lung diffusion capacity for carbon monoxide (DLCO), alveolar-capillary membrane conductance (Dm_{CO}) and ultrasound lung comets (ULCs) were assessed in 12 healthy lowlanders at sea-level, and on Day 1, Day 5 and Day 9 after arrival at Mount Everest Base Camp (EBC). EBC was reached following an 8-day hike at progressively increasing altitudes starting at 2860 m. DLCO was unchanged from sea-level to Day 1 at EBC, but increased on Day 5 (11 ± 10%) and Day 9 (10 ± 9%) vs. sea-level ($P \leq 0.047$). Dm_{CO} increased from sea-level to Day 1 (9 ± 6%), Day 5 (12 ± 8%), and Day 9 (17 ± 11%) (all $P \leq 0.001$) at EBC. There was no change in ULCs from sea-level to Day 1, Day 5 and Day 9 at EBC. These data provide evidence that interstitial lung fluid remains stable or may even decrease relative to at sea-level following 8 days of gradual exposure to high-altitude in healthy humans.

1. Introduction

The volume of extravascular pulmonary fluid is determined by Starling's Law and is a function of pulmonary capillary fluid extrusion relative to the rate of fluid reabsorption from the pulmonary interstitial compartments (Bates et al., 2011; Butler et al., 1999). Fluid flux across the pulmonary vasculature is reflected by the balance between the hydrostatic pressure in the pulmonary capillaries and the hydrostatic pressure in the interstitial space, as well as the permeability of the pulmonary capillaries to fluid. Fluid clearance or reabsorption from the pulmonary interstitium is largely dependent on the activity of the thoracic lymph ducts (Bates et al., 2011) and Na^{2+} transport systems located apically on the alveolar surface that actively reabsorb lung fluid that has permeated the alveolar-capillary membrane (Matthay et al., 2002; Mutlu et al., 2004).

Exposure to high-altitude is associated with a substantial increase in pulmonary capillary hydrostatic pressure due to hypoxic pulmonary vasoconstriction (Maggiorini et al., 2001; Naeije et al., 2010), increased pulmonary vascular leakage secondary to endothelial dysfunction (Richalet, 1995), and inhibition of the epithelial Na^{2+} transport systems central to lung fluid clearance (Sartori et al., 2010). In combination, these changes in the pulmonary system associated with high-altitude would be expected to disturb lung fluid balance such that a subclinical increase in interstitial lung fluid should occur.

Despite the aforementioned considerations, the evidence for a change in lung fluid balance in healthy lowlanders who sojourn at high-altitude remains equivocal (Cogo and Miserocchi, 2011; Swenson, 2011), with some but not all reporting a subclinical increase in interstitial lung fluid (Agostoni et al., 2013; Bouzat et al., 2013; Cremona et al., 2002; de Bisschop et al., 2012; Dehnert et al., 2010; Pratali et al., 2010). It has, however, been suggested that very rapid, acute exposure to high-altitude causes a transient, but significant, accumulation of lung fluid (Agostoni et al., 2013; Bouzat et al., 2013; Cremona et al., 2002). For example, Bouzat et al. (Bouzat et al., 2013) reported an increase in the number of ultrasound lung comet-tails, a robust index of changes in alveolar-interstitial fluid (Agricola et al., 2005; Picano and Pellikka, 2016), in healthy subjects transported by helicopter to 4250 m (~10 min). Interestingly, prolonged exposure and gradual adaptation to high-altitude appears to be associated with a progressive normalisation (after ~2 weeks) (de Bisschop et al., 2012) and subsequent reduction in lung fluid relative to sea-level values (after ~3 weeks) that may be related to an increase in sympathetic tone (Agostoni et al., 2011). Taken together, these previous findings suggest that rapid exposure to high-altitude may facilitate a transient, asymptomatic increase in lung fluid in healthy humans that reverses with a period of acclimatization, possibly due to a sympathetically mediated upregulation of lung fluid clearance mechanisms (Agostoni et al., 2011; Sartori et al., 2002).

However, whether extravascular lung fluid accumulation occurs in healthy, recreational climbers gradually exposed to high-altitude (i.e.

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over 6-10 days) remains uncertain and requires further investigation. Accordingly, the aim of the present study was to assess changes in 1) lung diffusing capacity and alveolar-capillary membrane conductance, 2) ultrasound lung comets, and 3) pulmonary function in healthy lowlanders from before to after gradual exposure to 5150 m. We hypothesised that gradual exposure to high-altitude would not change lung fluid balance relative to at sea-level, as evidenced by no change in lung diffusing capacity, alveolar-capillary membrane conductance, ultrasound lung comets, and pulmonary function. Importantly, it has been suggested that each of these measures provide an accurate index of changes in lung fluid balance (Agostoni et al., 2003; Agricola et al., 2005; Cremona et al., 2002; Dehnert et al., 2010; Jambrik et al., 2004; Picano and Pellikka, 2016; Snyder et al., 2006). In addition, heart-rate variability was measured as an index of autonomic tone before, during and after the expedition.

2. Materials and methods

2.1. Subjects

Twelve healthy non-smoking adult lowlanders (2 female) with no history of cardiorespiratory or metabolic disease participated in the study (mean ± SD; age = 36 ± 11 years, stature = 178 ± 8 cm, body mass = 79.7 ± 12.7 kg). The subjects were physically active (≥30 min physical activity/day, ≥5 days/week; self-reported) and had normal forced vital capacity (FVC = 109 ± 12% of predicted), forced expiratory volume in 1 s (FEV_1 = 103 ± 9% of predicted), FEV_1/FVC ratio (95 ± 7% of predicted) and maximal mid-expiratory flow (MMEF = 106 ± 14% of predicted) at sea-level. Each participant gave written informed consent after being provided a detailed description of the study requirements. The experimental procedures were approved by the Mayo Clinic Institutional Review Board and were performed in accordance with the ethical standards of the Declaration of Helsinki. All study participants were prohibited from prophylactic administration of any medication to aid altitude acclimatization (e.g., sildenafil, acetazolamide). Moreover, no subject required emergent pharmaceutical treatment (e.g., dexamethasone) for high altitude illness.

2.2. Experimental procedures

Arterial oxygen saturation (SaO_2) (via transcutaneous pulse oximetry) and heart-rate (HR) (via telemetry) were measured with the participants at rest in the supine position before pulmonary function was assessed using a spirometer according to standard procedures (Miller et al., 2005). Next, systolic pulmonary artery pressure (sPAP) and the number of ultrasound lung comets (ULCs) were obtained using transthoracic sonography. Finally, lung diffusing capacity for carbon monoxide and nitric oxide (DLCO and DLNO) were measured. This sequence of measurements was performed in each participant at sea-level (Rochester, MN, USA; elevation 401 m), on Day 1 (within 24 h), Day 5 and Day 9 after arrival at Mount Everest Base Camp (elevation 5150 m), and within 2 weeks of returning to sea-level after the expedition. To reach Everest Base Camp, each participant travelled to Kathmandu, Nepal (elevation 1400 m) before being transported by airplane to Lukla, Nepal (elevation 2860 m). From Lukla, the participants completed an 8-day hike at progressively increasing altitudes to reach Everest Base Camp. Once at Everest Base Camp, the participants were free to move about the camp but were instructed to avoid strenuous exercise activities. All meals were served by local support staff and the intake of water was allowed ad libitum.

2.3. Pulmonary artery pressure

sPAP was estimated from the peak velocity of tricuspid regurgitation (TR) using a modified Bernoulli equation as described previously (Taylor et al., 2011; Yock and Popp, 1984). With the participants in the left lateral supine position, the TR jet was located using 2D-color Doppler echocardiography (SonoSite Edge, FUJIFILM SonoSite Inc., Bothell, WA, USA). To determine the maximal velocity of the TR jet, the continuous wave sampler was positioned within and parallel to the regurgitation jet and sPAP was computed as $4TR^2$ added to an assumed right atrial pressure of 5 mmHg.

2.4. Lung diffusing capacity

DLCO, DLNO, alveolar-capillary membrane conductance (Dm_{CO}) and pulmonary capillary blood volume (Vc) were assessed as we have described previously (Coffman et al., 2016b; Taylor et al., 2016). With subjects in the sitting position, DLCO and DLNO were assessed by simultaneously measuring the disappearance of CO and NO via a rapid single breath technique using an automated device for performing gas calibrations, extemporaneous mixing of gases and calculations (Hyp'air Compact, Medisoft, Dinant, Belgium) (de Bisschop et al., 2012; Pavelescu et al., 2013). For each single breath maneuver, the participants were instructed to breathe normally on environmental air for 4–5 breaths before exhaling slowly and completely down to residual volume (RV). Once at RV, the participants were switched to an inspiratory reservoir filled with 2600 ppm CO, 40 ppm NO, 8% He, 21% O_2 and N_2 balance, and told to inspire rapidly and fully to total lung capacity before holding their breath for 4 s. After the breath hold, the participants then exhaled steadily and swiftly back to RV. The first 0.9 l of the expired gas was discarded to ensure dead-space wash out with the next 0.9 l of the expirate collected for subsequent analysis. The single breath maneuver was performed in triplicate at sea-level (pre-expedition), on Day 1, Day 5 and Day 9 after arrival at Mount Everest Base Camp (elevation 5150 m), and within 2 weeks of returning to sea-level after the expedition. Each measure of DLCO and DLNO was separated by four minutes (Macintyre et al., 2005).

Following the assessment of lung diffusing capacity, Dm_{CO} and Vc were computed as described previously (de Bisschop et al., 2012; Glenet et al., 2007; Pavelescu et al., 2013). Based on the molecular weight and solubility of CO and NO, the coefficient relating DLNO to Dm_{CO} was set at 1.97 (Aguilaniu et al., 2008) such that Dm_{CO} was calculated as the measured DLNO/1.97. Then, to solve the Roughton and Forster equation (Roughton and Forster, 1957), $1/\theta_{CO}$ was calculated using an equation proposed by Forster expressing the blood conductance of CO (i.e. θ_{CO}) as a function of capillary PO_2 (Forster, 1987):

$$1/\theta_{CO} = 1.3 + 0.0041 \times PcapO_2$$

where $PcapO_2$ is the capillary pressure of O_2, estimated as alveolar PO_2–$\dot{V}O_2$/(DLCO × 1.23) with partial pressures in mmHg, $\dot{V}O_2$ in ml/min, and DLCO in ml/min/mmHg. Based on the measured barometric pressure (~400 mmHg) and the expired fraction of O_2, the calculated alveolar PO_2 at Everest Base Camp ranged from 52 to 60 mmHg. $\dot{V}O_2$ was calculated using the mass balance of O_2 between inspiration and expiration during the single breath maneuver and DLCO × 1.23 was used as a surrogate for DLO_2 (Forster, 1987). Using this equation, $PcapO_2$ was calculated at ~116 mmHg and ~50 mmHg at sea-level and Everest Base Camp, respectively; these values are similar to those recently reported under similar conditions (de Bisschop et al., 2012). Venous blood was sampled for haemoglobin (Hb) concentration and Vc was corrected accordingly for standard concentrations of Hb in men (14.6 g/dl) and women (13.4 g/dl) (Macintyre et al., 2005) as measured Vc × (standard Hb concentration/measured Hb concentration). To allow comparison between DLCO measured at sea-level and at high-altitude, DLCO at Everest Base Camp was recalculated using the Dm_{CO} and Vc values computed at high-altitude and the sea-level (i.e. normoxic) θ_{CO} as follows (Pavelescu et al., 2013):

$$1/DLCO_{ALT} = 1/Dm_{COALT} + 1/\theta CO_{SL} \cdot Vc_{ALT}$$

where, Dm_{COALT} and Vc_{ALT} are the alveolar-capillary membrane