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Time course of asymptomatic interstitial pulmonary oedema at high altitude

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ABSTRACT

The time course of asymptomatic pulmonary oedema during high-altitude exposure and its potential relationship with changes in cardiac function remain to clarify.

Eleven volunteers were rapidly exposed to 4350 m during a 4-day period. Each subject received clinical examination and thoracic ultrasonography to assess ultrasound lung comets (USLC) on day 1, 2 and 3 after arrival. Echocardiography was performed on day 2 and 4 at 4350 m.

All subjects had a significant increase in the number of USLC on day 1 ($n = 8 \pm 3$), day 2 ($n = 7 \pm 4$) and day 3 ($n = 3 \pm 2$) compared to sea level ($n = 1 \pm 1$) ($P < 0.01$). Although left ventricle diastolic function and systolic tricuspid regurgitation gradient were significantly different at altitude compared to sea level, they did not correlate with the number of USLC ($P > 0.05$).

Asymptomatic pulmonary oedema seems to be transiently present in fast-ascending recreational climbers. The lack of correlation between the number of USLC and indices of cardiac changes suggest that non-cardiogenic mechanisms may underlie this transient increase in lung water.

1. Introduction

High-Altitude Pulmonary Oedema (HAPE) is the leading cause of death from high-altitude illness in recreational climbers (Hackett and Roach, 2001). Few high-altitude climbers only have clinical symptoms requiring medical attention whereas asymptomatic extravascular lung water accumulation is probably more common (Cremona et al., 2002; Cogo and Miserocchi, 2011; Swenson, 2011). Initially devoted to diagnose alveolar-interstitial syndrome (Lichtenstein et al., 1997) in pathological situations such as acute respiratory distress syndrome or cardiogenic acute pulmonary oedema (Gargani et al., 2008), thoracic ultrasonography has been used to show extravascular lung water accumulation at high altitude (Fagenholz et al., 2007; Otto et al., 2009). The main criterion in favour of pulmonary alveolar-interstitial oedema was the presence of ultrasound lung comet (USLC) (Picano et al., 2006) which is particularly robust for assessing changes in alveolar-interstitial fluid (Jambrik et al., 2004; Agricola et al., 2005).

Pulmonary extravascular fluid accumulation in HAPE depends on the quantity of liquid escaping from the pulmonary vasculature and on the ability of the alveolar respiratory epithelium to reabsorb flood overload (Scherrer et al., 2010). It is well established that hypobaric hypoxia increases pulmonary capillary hydrostatic pressure (Maggiorini et al., 2001) and causes endothelial dysfunction promoting pulmonary vascular leakage (Stelzner et al., 1988; Richalet, 1995). Hypoxia-induced epithelial sodium-transport inhibition may underlie impaired alveolar fluid clearance at high altitude (Vivona et al., 2001; Sartori et al., 2010). The participation of these phenomena to asymptomatic extravascular lung water accumulation remains unclear. In 26 unacclimatized subjects ascending to Monte Rosa (4559 m), changes in pulmonary function assessed by spirometry, single-breath nitrogen wash-out and diffusion capacity were consistent with extravascular fluid accumulation (Senn et al., 2006) but did not relate to changes in arterial pulmonary pressure. In 18 healthy recreational climbers participating to a 3-week trekking up to 5130 m, the numbers of USLC at rest progressively increased with altitude ascent, even in 14 asymptomatic subjects, with no correlation with pulmonary artery systolic pressure increase (Pratali et al., 2010). In this study, no significant changes in indices of left diastolic or systolic function were observed in high-altitude echocardiography, probably due to medication and progressive ascent. However, changes in left ventricle

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diastolic function have been described in 41 patients ascending to 4559 m within a period of 24 h (Allemann et al., 2004). In pathological condition like heart failure with preserve ejection fraction, diastolic dysfunction could lead to pulmonary congestion (Desai, 2007). Therefore, to clarify the participation of cardiac changes to asymptomatic alveolar-interstitial fluid accumulation in non-acclimatized climbers at rest, the time course of asymptomatic pulmonary oedema in non-acclimatized healthy subjects staying at a constant high altitude without exercise-induced fatigue and its relationship with high altitude cardiac changes remain to be investigated.

In the present study our aim was to assess (i) USLC time course in recreational climbers during a 4-day stay at 4350 m, avoiding the potential confounding effects of physical activity (Swenson, 2011) and/or preliminary acclimatization as during trekking and (ii) the relationship between the number of USLC and echocardiographic indices of left and right cardiac functions. We hypothesized that USLC would peak on day 1 or 2 after arrival at high altitude, and would correlate with changes in cardiac function.

2. Materials and methods

Eleven male subjects (mean age 28 ± 8 years) were examined at the Grenoble University Hospital (altitude: 212 m) to rule out respiratory or cardiac diseases and to establish sea level measurements. Subjects were usual recreational climbers with no history of HAPE during previous high-altitude ascents and were unacclimatized to high altitude (no sojourn above 1500 m of altitude over the past 3 months). All subjects underwent helicopter transport at midday (±2 h) to be dropped 10 min later at 4350 m (*Observatoire Vallot*, Mont Blanc, Chamonix, France). They stayed for the next 4 days in the *Observatoire Vallot* without further ascent or climbing. They received no treatment to prevent or treat acute mountain sickness (AMS). The Regional Institutional Ethics Committee (*Grenoble Sud-Est V*) approved the design of the study and all subjects provided written informed consent.

2.1. Clinical examination

Clinical examination included measurements of heart rate and non-invasive blood pressure (Dinamap, GE Medical Systems Inc., Milwaukee, WI) every morning at rest in supine position. Arterial oxygen saturation (SpO_2) was measured using finger-pulse oximetry (Biox 3740 Pulse Oximeter, Ohmeda, Louisville, CO) after 30-s signal stabilization and finger warming with a warm glove during 2 min (room air temperature: 23 ± 2 °C at sea level and 21 ± 2 °C at altitude). Subjects were also asked to complete self-reported questionnaires for AMS evaluation according to the Lake Louise Score (LLS, 5 items) (Roach et al., 1993) and the respiratory subscore of the Environmental Symptom Questionnaire (ESQ-III AMS-R, 12 items) (Sampson et al., 1983). The presence of AMS was defined as LLS > 3 and AMS-R ≥ 0.6. Clinical examination took place on the morning at sea level and each morning on days 1 (D1, *i.e.* 20 h after arrival at high altitude), 2 (D2) and 3 (D3).

2.2. Thoracic ultrasonography

Thoracic ultrasonography was performed after clinical examination, using CX-50 (Phillips, Eindhoven, Netherlands) and an abdominal 5–2 MHz probe (curvature 40R, field-of-view 75°) by one trained operator (PB) (Hyacinthe et al., 2011) blinded to clinical and echocardiographic results. The upper, medium and lower parts of the anterior and lateral regions of the two chest walls were sequentially examined with the subject in the supine position. USLC was defined as an echogenic, coherent, wedge-shaped signal with a narrow origin from the hyperechoic pleural line (Picano et al., 2006) (Fig. 1). The comet-tail image described here extends to the edge of the screen (whereas short comet-tail artefacts may exist in other regions) and arises only from the pleural line. This ultrasound sign correlates with alveolar-interstitial oedema assessed by chest radiography, wedge pressure and extravascular lung water measured by thermodilution (Agricola et al., 2005). The number of USLC was recorded through the sequential examination of 28 intercostal lung fields located at the parasternal, midclavicular, anterior axillary and midaxillary lines from the second to the fourth intercostal space on the left side and from the second to the fifth intercostal space on the right side. A number of USLC ≤ 5 is a normal echographic chest pattern since healthy subjects may present a small number of USLC, especially confined laterally to the last intercostal spaces above the diaphragm (Picano et al., 2006).

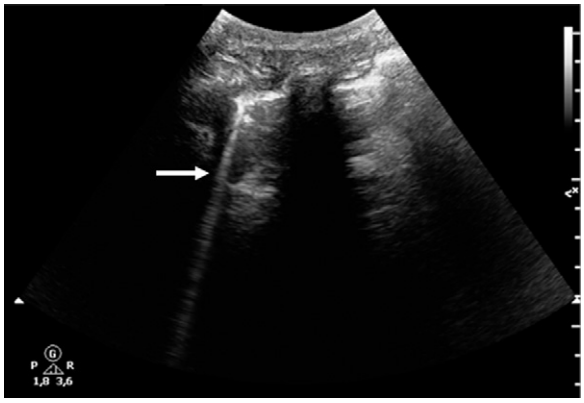

Fig. 1. Ultrasound image of lung-comet tail (USLC, white arrow) in a subject on the first day at 4350 m.

2.3. Echocardiography

Echocardiographic studies were performed using a portable echocardiograph (Vivid Q, GE Healthcare, Horten, Norway) with a 3.5 MHz sector scanning electronic transducer. Bidimensional, Doppler and Doppler tissue imaging measurements were performed by fully trained operator (GW) according to standard procedures recommended by the American Society of Echocardiography (ASE) (Quinones et al., 2002; Lang et al., 2005), and based on the average of 3 cardiac cycles at sea level, on D2 and day 4 (D4) at 4365 m, as previously described (Nagueh et al., 2009; Nottin et al., 2009). Images were acquired in cine loops triggered to the QRS complex and saved digitally for subsequent blinded off-line analysis with dedicated software (EchoPac 6.0, GE Healthcare). Specific recommendations of the ASE (Tamborini et al., 2007) were used to assess systolic tricuspid regurgitation gradient (TR). TR as surrogate of pulmonary artery systolic pressure was calculated with the modified Bernouilli equation as described previously: $TR = 4 \times V^2_{max}$.

2.4. Statistical analysis

Data are expressed as mean ± SD. Analysis of the statistical significance of temporal changes during the study period was performed using one-way analysis of variance for repeated measurements (StatView SE program, SAS Institute, Cary, NC). When a significant main effect was found, *post hoc* analysis was performed with Bonferroni test for multiple comparisons, with sea level taken as the reference time. Correlations were performed using linear regression and Pearson's coefficient. Statistical significance was declared when $P \leq 0.05$.