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Transthoracic sonographic assessment of B-line scores during ascent to altitude among healthy trekkers

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ABSTRACT

Sonographic B-lines can indicate pulmonary interstitial edema. We sought to determine the incidence of subclinical pulmonary edema measured by sonographic B-lines among lowland trekkers ascending to high altitude in the Nepal Himalaya. Twenty healthy trekkers underwent portable sonographic examinations and arterial blood draws during ascent to 5160 m over ten days. B-lines were identified in twelve participants and more frequent at 4240 m and 5160 m compared to lower altitudes ($P < 0.03$). There was a strong negative correlation between arterial oxygen saturation and the number of B-lines at 5160 m ($\rho = -0.75$, $P = 0.008$). Our study contributes to the growing body of literature demonstrating the development of asymptomatic pulmonary edema during ascent to high altitude. Portable lung sonography may have utility in fieldwork contexts such as trekking at altitude, but further research is needed in order to clarify its potential clinical applicability.

1. Introduction

High-altitude illnesses include acute mountain sickness (AMS) as well as the more severe and potentially fatal pathologies, high-altitude cerebral edema and high-altitude pulmonary edema (HAPE). HAPE is a form of noncardiogenic pulmonary edema and is responsible for the majority of deaths from altitude illnesses (Schoene, 2008). The main risk factors for developing HAPE during high altitude ascent are the altitude of sleep and the rate of ascent, although there is a high degree of variability in individual susceptibility (Schoene, 2008). The complex pathophysiology involves uneven hypoxic pulmonary vasoconstriction, which leads to both increased pulmonary artery pressures and mechanical damage, initiating vascular leak (Swenson and Bärtsch, 2012). Studies using pulmonary artery catheterization and Doppler echocardiography have found that subjects with HAPE often have abnormally accentuated hypoxic pulmonary vasoconstrictive responses compared to controls (Grunig et al., 2000; Dehnert et al., 2005). Perfusion becomes less uniform in states of hypoxia (Hopkins et al., 2005; Dehnert et al., 2006), and greater hypoxic pulmonary vasoconstriction can lead to greater increases in capillary pressure (Dehnert et al., 2007). However, it is clear that there is more than one mechanism involved in the pathogenesis of HAPE, as the correlation between increased pulmonary artery pressure and measures of interstitial fluid at altitude have been inconsistent (Senn et al., 2006; Pratali et al., 2010; Dehnert et al., 2015). Indeed, impaired fluid clearance from alveoli is also implicated in the development of HAPE (Bärtsch et al., 2005; Schoene, 2008; Swenson and Bärtsch, 2012; Betz et al., 2015).

Early symptoms of HAPE include dyspnea, cough, and reduced exertional capacity, which can progress to respiratory failure and death. While HAPE remains a clinical diagnosis, the presence of B-lines on lung sonography can potentially confirm its presence and indicate the severity of pulmonary edema (Fagenholz et al., 2007). A B-line (also known as "comet tail") is a sonographic sign that may arise from interlobular septal thickening (Lichtenstein et al., 2009). Such thickening may result from excessive extravascular lung water (EVLW) or other processes such as fibrosis or infections (Volpicelli et al., 2012). While there is an abundance of literature on the reliability of lung sonography for the detection of cardiogenic pulmonary edema (Jambrik et al., 2004; Picano et al., 2006; Cogo and Miserocchi, 2011; Al Deeb et al., 2014; Pivetta et al., 2015), less data exists around the use of lung sonography in the context of HAPE. Fagenholz et al. (2007) published the first study using lung sonography to detect B-lines in eleven patients

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with HAPE. Recently, Ma et al. (2017) demonstrated a significant negative correlation between B-line scores and degree of hypoxemia before and after treatment among 60 patients with severe HAPE. There are advantages to sonographic assessments of B-lines, including portability in high altitude environments. Portable sonography is also a relatively simple diagnostic technique with minimal required training. Studies using lung sonography to detect B-lines have reported interrater agreement to be higher than 90% (Jambrik et al., 2004; Fagenholz et al., 2007; Pingitore et al., 2011).

There are limited studies using lung sonography to detect B-lines as a surrogate for pulmonary edema among healthy trekkers at altitude, and its clinical significance is unclear (Wimalasena et al., 2013). The few existing field studies have demonstrated variable incidence rates of B-lines among asymptomatic trekkers at high altitude, as well as inconsistent correlations between B-line frequency and arterial oxygen saturation (SaO_2) (Pratali et al., 2010; Taylor et al., 2017; Coffman et al., 2019). In this prospective cohort study, we evaluated for the presence of subclinical pulmonary edema with gradual ascent using B-line scores and explored associations with clinical parameters. We hypothesized that healthy trekkers would have an increase in B-lines with increasing ascent, which would be related to the severity of hypoxemia.

2. Methods

2.1. Participant recruitment and ethics

Participants were recruited on a voluntary basis from a group of participants on a research expedition trek to Everest Base Camp in Nepal. Inclusion criteria included adult participants over 18 years of age who planned to trek the entire journey. We excluded participants with any preexisting lung or cardiovascular disease, history of severe mountain sickness, and recent exposure to high altitude (> 3000 m) within the past nine months. This study was approved by the Mount Royal University Human Research Ethics Board (Protocol 100012 and 101012) and the Nepal Health Research Council (Protocol 109-2017). This study abided by the Canadian Government Tri-Council policy on research ethics with human participants (TCPS2) and the Declaration of Helsinki.

2.2. Study protocol and ascent profile

Participants had baseline measurements performed at an altitude of 1400 m (Kathmandu, Nepal). They were then flown to 2800 m (Lukla) before beginning the trek (Fig. 1). During the trek, all measurements were made on rest days (no altitude gain) at the following altitudes: 3440 m (Namche), 3820 m (Debuche), 4240 m (Pheriche), and 5160 m (Gorak Shep). At 5160 m, participants trekked to 5300 m (Everest Base Camp) and back (approximately 5 h of walking) prior to measurements. Participants were not taking acetazolamide (Diamox) prophylactically but reported any use of medication as AMS symptoms arose during ascent. Participants were also blinded to all clinical measurements, aside from self-reported symptom scores.

2.3. Serial lung sonography

The method of lung sonography was a modified version of a technique previously described (Jambrik et al., 2004). Lung sonography was performed using a low-frequency transducer on a portable ultrasound device (1–5 MHz phased array transducer, iViz, FUJIFILM SonoSite, Inc). On the right hemithorax, the second, third, fourth and fifth intercostal spaces in the anterior clavicular, mid-clavicular, anterior axillary and mid-axillary lines were sequentially scanned for the presence of B-lines with the participant in the supine position for a total of 16 sites. A B-line was defined as an echogenic, vertical signal that originated from the pleural line, extended to the bottom of the screen, and moved with pleural sliding (Volpicelli et al., 2012). If any B-lines

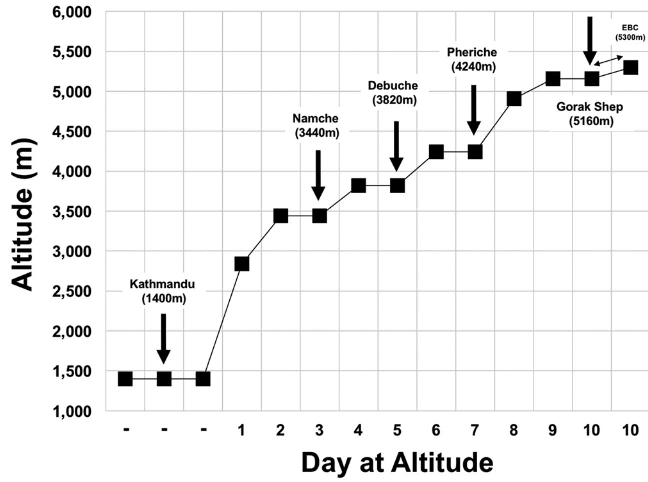

Fig. 1. Participant Ascent Profile. Ascent profile of entire trek with associated measurement days (down arrows). On day 10, participants trekked to Everest Base Camp (5300 m) and back to 5160 m prior to measures taken (bidirectional arrow).

were observed on the right, then the left hemithorax was also scanned, for a total of 28 sites. Otherwise, the left hemithorax was not scanned for the purposes of efficiency. The location and number of B-lines were documented during each examination. The B-line score was defined as the total number of B-lines observed during a complete examination on the right side. Left-sided B line counts were not included in the score. Images were obtained by the primary sonographer (RL) who was trained in the performance of lung ultrasound and remained blinded to the rest of the ancillary measurements during ascent. Images were archived digitally and reviewed approximately two weeks later for quality and assessment of interrater reliability by a second blinded reviewer (IM), who is certified by the American Registry for Diagnostic Medical Sonography.

2.4. Ancillary measurements

On the same day as lung sonography, participants completed two symptom-based tools. First, the Lake Louise Score has scores ranging from zero to 15, with a score greater than 3 suggesting AMS (Roach et al.,1993). Second, participants graded their shortness of breath (SOB) on a scale of zero to four in terms of increasing severity (none, slight, moderate, severe or very severe). Ancillary measurements included pulse oximetry (SpO_2; %), heart rate (HR; min^{-1}), and blood pressure (BP; mmHg). Arterial blood samples were also obtained from the radial artery in a subset of participants (n = 12) by a registered respiratory therapist (HN; Abbott iSTAT, CHEM8 cartridges; Mississauga, Ontario, Canada). These measures included the partial pressure of arterial oxygen (PaO_2), SaO_2, partial pressure of arterial carbon dioxide ($PaCO_2$), pHa, bicarbonate, hematocrit (hct) and hemoglobin concentration ([Hb]). The iSTAT unit calibrates for atmospheric pressure and heats the sample to body temperature (37 °C) for the correction of blood gas and electrolyte measures.

2.5. Statistical analysis

To test the effect of ascent to high altitude on B-line scores and ancillary measures, one-factor repeated-measures analyses of variance (ANOVAs) were used. For data that was non-parametric (e.g., Lake Louise and shortness of breath scores), a Friedman repeated-measures ANOVA on ranks was used. Where significant F-ratios were detected, a Student-Newman-Keuls *post hoc* test was utilized for pair-wise comparisons. In order to assess for possible associations between ancillary measures and B-line scores, we used a Pearson product moment

Table 1
Baseline participant demographics. Values reported as mean ± standard deviation (SD).

Characteristic	n (%) or Mean ± SD
Total participants	20
Male	9 (45)
Female	11 (55)
Mean age (years)	24.7 ± 5.8
Mean weight (kg)	72.6 ± 16.3
Mean Height (cm)	172.5 ± 12.5
Mean body mass index (kg/m^2)	24.2 ± 3.4
Race	
White	14 (70)
Asian	5 (25)
Other	1 (5)

correlation (r), or Spearman Rho (ρ) for non-parametric data (e.g., an abundance of zero data). Statistical significance was assumed at $P < 0.05$. All statistical analysis was performed using Sigmaplot v. 14 (Systat).

3. Results

3.1. Participant characteristics

A total of 20 participants were included in the study. Baseline characteristics obtained at 1400 m are reported in Table 1. Males comprised 45% of the cohort. The mean age was 24.7 ± standard deviation (SD) 5.8 years and the mean body mass index was 24.2 ± 3.4. None of the participants reported any preexisting medical conditions. The baseline median Lake Louise score was zero (range 0–2) and none of the participants reported any shortness of breath. Two participants took acetazolamide 250 mg twice daily for symptoms of AMS (headaches) which started at altitudes above 3820 m (day 4). Table 2 reports the sonographic, clinical, and ancillary measures throughout the incremental ascent to 5160 m.

3.2. Lung sonography

All participants underwent complete exams with lung sonography at the five predetermined altitudes, with the exception of two participants at the highest altitude (5160 m) due to fatigue and gastrointestinal illness. Twelve participants had B-lines (Fig. 2). B-lines were most commonly visualized in the inferior intercostal spaces in the mid-axillary region. The lowest number of B-lines were observed in the intercostal spaces of the anterior clavicular line. The number of B-lines per participant ranged from zero (the majority of measures) to six per participant. None of the participants exhibited more than three B-lines in a single intercostal space. Only one participant out of twelve had concurrent left sided B-lines.

One of the participants who began taking acetazolamide for AMS was diagnosed with HAPE on day 10 at an altitude of 5160 m after developing exertional dyspnea, cough, and fatigue. Physical examination revealed a resting HR of 118 bpm^{-1}, RR of 25 min^{-1}, and SpO_2 of 55% on room air. Sonography revealed three B-lines. The participant improved with descent and supplemental oxygen. Given this participant's condition, lung sonography was repeated on the descent and B-lines were not present at an altitude of 1400 m.

All images were deemed adequate in quality based on depth and gain. There was perfect agreement (Kappa = 1.0) between the two independent sonographers (RL, IM). The amount of time required for each participant's lung sonography examination was less than three minutes after participants were appropriately positioned and draped. Sonography was well-tolerated.

3.3. Relationship between altitude, ancillary measures, and B-line scores

B-line scores were significantly higher at 4240 m compared to lower altitudes ($P < 0.03$), but there was no difference between 4240 m and 5160 m (Fig. 2A). There were 12 participants with B-lines with ascent, but no relationship between B-Lines and the development of HAPE (Fig. 2B). There was no significant correlation between B-lines and

Table 2
Mean values of sonographic, clinical, and ancillary measurements at baseline and during incremental ascent to altitude.

Variable/Altitude	1400 m (D0)	3440 m (D3)	3820 m (D5)	4240 m (D7)	5160 m (D10)
Atmospheric Pressure (mm Hg)	648	509	486	461	411
Pressure of Inspired O_2 (mm Hg)	136	107	102	97	86
Sonography (n = 20)					
B-line Scores - Total Count	3	0	1	17	12
B-line Scores - Mean	0.15 ± 0.49	0 ± 0	0.05 ± 0.22	0.85 ± 1.5*,†	0.67 ± 1.14
Arterial Blood Gas/Electrolytes (n = 12)					
PaO_2 (mm Hg)	83.3 ± 8.3	47.6 ± 7.9*	53.4 ± 6.5*,†	47.4 ± 6.1*,†	36.6 ± 5.1*,†
SaO_2 (%)	96.4 ± 1.4	84.3 ± 7.7*	87.9 ± 4.1*	83.8 ± 6.7*	73.6 ± 8.0*,†
$PaCO_2$ (mm Hg)	35.1 ± 4.5	30.8 ± 3.8*	29.9 ± 3.3*	29.2 ± 3.6*	25.7 ± 2.3*,†
pHa	7.43 ± 0.03	7.46 ± 0.03*	7.43 ± 0.02†	7.43 ± 0.03	7.46 ± 0.03
$[HCO_3^-]$ (mmol/L)	23.3 ± 2.2	21.84 ± 2.7*	19.9 ± 1.9*,†	19.4 ± 2.4*	18.1 ± 1.9*
hct (%)	42.8 ± 3.6	42.6 ± 3.6	42.6 ± 3.4	44.2 ± 4.2	44.3 ± 3.4*,†
[Hb] (g/L)	145.4 ± 12.3	144.9 ± 11.9	144.8 ± 11.6	150.3 ± 14.2	150.8 ± 11.4*,†
Ancillary Measures (n = 20)					
SpO_2 (%)	96.1 ± 1.3	90.3 ± 3.1*	90.2 ± 4.1*	86.4 ± 5.8*,†	77.3 ± 7.7*,†
Heart Rate (min^{-1})	80.3 ± 9.5	90.4 ± 12.6*	82.5 ± 9.6†	79.9 ± 12.7	87.2 ± 17.3*,†
Systolic Pressure (mm Hg)	117.4 ± 11.3	118 ± 9.3	119.4 ± 12.8	120.5 ± 13.6	121.3 ± 9.8
Diastolic Pressure (mm Hg)	79.7 ± 8.3	86.4 ± 7.7*	87 ± 8.4*	86.3 ± 8.7*	87.7 ± 8.1*
Mean Arterial Pressure (mm Hg)	92.3 ± 8.6	96.9 ± 7.2*	97.8 ± 8.9*	97.7 ± 9.3*	98.9 ± 7.5*
Symptom Scores (n = 20)					
Lake Louise AMS Score (0–15)	0 (0–2)	1 (0–6)*	0 (0–4)*,†	1 (0–5)*,†	2 (0–5)*,†
Shortness of Breath Score (0–4)	0 (0)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–1)

Altitude and day (D) of ascent indicated. All values are reported as mean ± standard deviation, with the exception of Lake Louise Scores and SOB scores, where median and range are reported due to ordinal data. PaO_2, arterial partial pressure of oxygen; SaO_2, arterial oxygen saturation; $PaCO_2$, arterial partial pressure of carbon dioxide; pHa, arterial pH; $[HCO_3^-]$a, arterial bicarbonate concentration; hct, hematocrit; [Hb], hemoglobin concentration; SpO_2, peripheral oxygen saturation.

* Significantly different than 1400 m ($P < 0.05$).

† Significantly different than prior alitiude ($P < 0.05$).

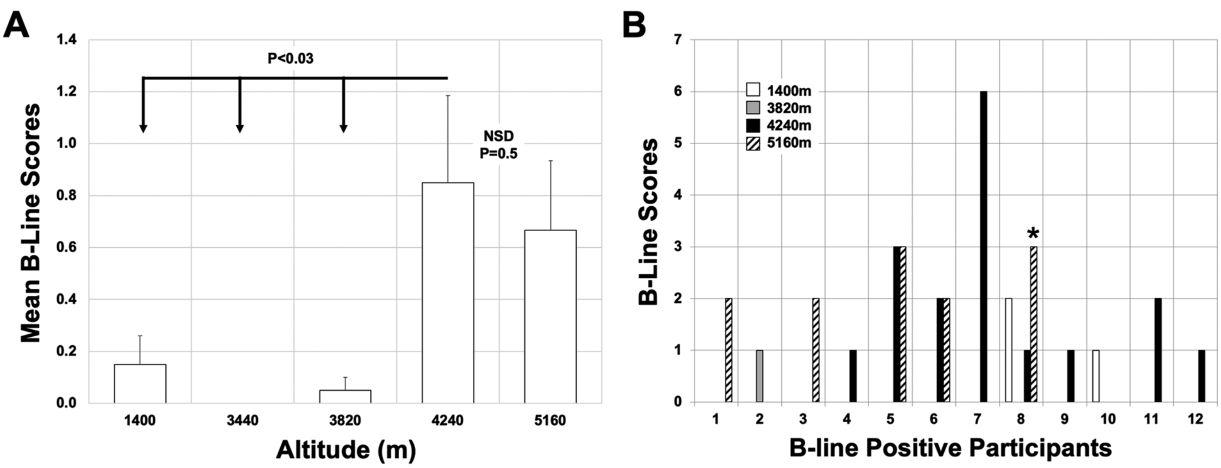

Fig. 2. B-line Scores with Ascent. A. Mean B-line scores of participant group at each altitude. B-line scores were significantly higher at 4240 m compared to 1400 m, 3440 m, and 3820 m ($P < 0.03$). B-line scores were not different statistically between 4240 m and 5160 m ($P = 0.5$). B. Individual B-line scores at each altitude for twelve participants who exhibited B-lines during study. Altitude of measurement is indicated in the legend. * Participant 8 was diagnosed with HAPE at 5160 m.

PaO_2 at 5160 m ($\rho = -0.49$, $P = 0.13$, $n = 11$) and a strong and significant negative correlation between B-lines and SaO_2 ($\rho = -0.75$, $P = 0.008$, $n = 11$). No other relationships between B-lines and ancillary measures were found.

4. Discussion

4.1. Main findings

We found the incidence of B-lines was increased among healthy trekkers during an incremental trek to Everest Base Camp (5300 m). These findings are consistent with the results from previous studies which found an increase in B-line scores among participants gradually exposed to high altitude (Pratali et al., 2010; Taylor et al., 2017; Coffman et al., 2019). However, our study found a lower incidence and number of B-lines among trekkers than previous studies. These findings may reflect the younger age of our participants. Also, the current study uses a different technique for lung sonography and was performed primarily during rest days. It is possible that our B-line scores would have been higher if examined immediately after exertion. However, we found the number of B-lines at an altitude of 5160 m was not higher compared to 4240 m despite trekking to and from Everest Base Camp (5300 m) on the same day. In addition, we found a significant negative correlation between arterial oxygen saturation and B-line incidence at the highest altitude (5160 m), similar to Pratali et al. (2010).

However, in our study, there was a lack of a clear relationship between the B-line score and HAPE occurring in one participant. He developed clinical signs of HAPE at 5160 m and required treatment with descent, supplemental oxygen, and nifedipine. Interestingly, the sonographic examination found only three B-lines, which is considered within the normal range. While this represented an increase from prior examinations in this participant (see Fig. 2), the change was minimal. Other participants with more B-lines did not develop clinical HAPE. These findings suggest limited discriminant power of B-line score for illness severity. In contrast, Ma et al. (2017) found significant correlations between B-line scores and both indices of oxygenation and disease severity scores among 60 Chinese patients with HAPE. Our study supports the concept of subclinical pulmonary edema developing at high altitude in healthy trekkers but is too small to make conclusions about the relationship to the incidence of HAPE.

Previous studies have attempted to assess EVLW at altitude using other measures, namely pulmonary function measurements. The largest study by Cremona et al. (2002) showed increased airway closing pressures among climbers with radiographic edema compared to those without. They proposed that closing pressures rise due to small airway compression on expiration by edematous tissue. Similarly, lung diffusion has also been shown to decrease at altitude due to reductions in membrane diffusing capacity (Agostoni et al., 2013). Vital capacity and forced vital capacity have also been measured at altitude, although they are subject to multiple influences, including respiratory muscle weakness, cold air-induced airway hyperreactivity, and exertion. The findings by Dehnert et al. (2010) showed that pulmonary function testing is not a valid indicator for detecting early interstitial fluid accumulation among mountaineers at high altitude. Based on evidence demonstrating B-lines as a reliable surrogate marker for cardiogenic pulmonary edema, B-lines may also be a reliable indicator of EVLW resulting from high altitude hypoxia (Jambrik et al., 2004; Picano et al., 2006; Cogo and Miserocchi, 2011; Al Deeb et al., 2014; Pivetta et al., 2015). B-lines have shown good correlation to radiographic edema and lung density on computed tomography, as well as elevated brain natriuretic peptide levels in heart failure (Agricola et al., 2005; Volpicelli et al., 2008; Manson et al., 2011; Baldi et al., 2013).

While we found an increase in the incidence of B-lines at 4240 m, there was no further increase at 5160 m. A possible but unproven explanation is acclimatization following initial exposure to high altitude, stemming from a reduction in interstitial lung fluid. Taylor and colleagues (2017) recently found an increase in lung diffusion capacity by day five at Everest Base Camp (5300 m) compared to sea-level values, possibly related to a reduction in interstitial fluid. Interestingly, they found a trend towards reduced B-lines on day 1 at Everest Base Camp compared to sea-level. Given that our expedition conservatively took ten days to ascend, this may have offered sufficient time to acclimatize before reaching 5160 m, and further reductions in B-lines may have been observed with a more prolonged stay at altitude. Other studies have also shown a reduction in lung fluid compared to sea-level values following sustained periods at high altitude (Agostoni et al., 2011; de Bisschop et al., 2012). There have been new insights into the mechanisms of fluid clearance in edema, such as upregulation of membrane channels and pumps to facilitate ion and fluid transport out of the alveoli (Matthay, 2014). Fluid clearance is increased by cyclic AMP, which is facilitated by endogenous and exogenous stimulation of β-adrenergic receptors (Matthay et al., 2002; Matthay, 2014). Inhaled β_2-adrenergic agonist (salmeterol) has been shown to prevent HAPE (Sartori et al., 2002) and can reduce lung water in established pulmonary edema (Licker et al., 2008). Thus, alveolar fluid clearance at altitude may be boosted by sympathetic drive stimulated by altitude-related hypoxia, although this has not been directly studied.

The clinical significance of B-lines among asymptomatic trekkers at altitude is not known. Theoretically, the presence of EVLW may herald impending symptoms of HAPE with continued ascent without adequate acclimatization in susceptible persons. Cogo and Miserocchi (2011) propose an alternative explanation, that subclinical pulmonary edema at high altitude represents a protective physiologic response against severe edema (i.e. alveolar flooding). The lung is normally able to resist the development of edema, through mechanisms such as increased lymphatic drainage and the mechanical barrier of the basement membrane. When extravascular water volume increases, the interstitial pressure is able to increase by up to 10–15 mmHg, countering further microvascular fluid ultrafiltration (Taylor et al., 1986; Miserocchi et al., 2001; Scallan et al., 2010), which is thought to be an important protective mechanism against severe edema. Degradation of matrix proteoglycans within the extracellular matrix of the interstitium can overwhelm this protective phenomenon, leading to significant edema (Negrini et al., 2008). Numerous studies, including the current study, demonstrate that subclinical pulmonary edema occurs at high altitude, but the vast majority do not develop alveolar flooding and HAPE. The significance of this phenomenon remains to be determined, as well as its role in identifying HAPE-susceptible individuals.

4.2. Study limitations

Due to the fieldwork nature of the study, a limitation is the small sample size (n = 20). Only 16-sites were scanned on the right side to facilitate faster screening of participants on rest days, whereas previous studies obtained more screening windows (Pratali et al., 2010; Taylor et al., 2017; Coffman et al., 2019). Those participants with isolated left-sided B-lines would not have been detected during this study, although both sides were scanned if B-lines were found in the right lung. While this may have reduced sensitivity, prior studies have found that participants develop EVLW more frequently on the right side (Jambrik et al., 2004; Volpicelli et al., 2012).

4.3. Conclusions

We used portable lung sonography to assess B-lines and demonstrated an increased incidence of B-lines among healthy trekkers during ascent to high altitude. B-lines were inversely related to SaO_2 at 5160 m; no other associations were found. Finally, a case of clinically diagnosed HAPE occurred during the study, yet the participant had minimal B-lines suggesting that B-line scores may not be a strong indicator of HAPE. This study contributes further evidence that subclinical pulmonary edema occurs among healthy trekkers with gradual exposure to high altitude, but that it may not predate the occurrence of HAPE in our case. Both the drivers and clinical relevance of this phenomenon remains to be explored.

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Declarations of competing interest

None.

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