ORIGINAL RESEARCH

High-Intensity Intermittent Exercise Increases Pulmonary Interstitial Edema at Altitude But Not at Simulated Altitude

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Objective.—Ascent to high altitude leads to a reduction in ambient pressure and a subsequent fall in available oxygen. The resulting hypoxia can lead to elevated pulmonary artery (PA) pressure, capillary stress, and an increase in interstitial fluid. This fluid can be assessed on lung ultrasound (LUS) by the presence of B-lines. We undertook a chamber and field study to assess the impact of high-intensity exercise in hypoxia on the development of pulmonary interstitial edema in healthy lowlanders.

Methods.—Thirteen volunteers completed a high-intensity intermittent exercise (HIIE) test at sea level, in acute normobaric hypoxia (12% O_2, approximately 4090 m equivalent altitude), and in hypobaric hypoxia during a field study at 4090 m after 6 days of acclimatization. Pulmonary interstitial edema was assessed by the evaluation of LUS B-lines.

Results.—After HIIE, no increase in B-lines was seen in normoxia, and a small increase was seen in acute normobaric hypoxia (2 ± 2; $P < .05$). During the field study at 4090 m, 12 participants (92%) demonstrated 7 ± 4 B-lines at rest, which increased to 17 ± 5 immediately after the exercise test ($P < .001$). An increase was evident in all participants. There was a reciprocal fall in peripheral arterial oxygen saturations (Spo_2) after exercise from $88\% \pm 4\%$ to $80\% \pm 8\%$ ($P < .01$). B-lines and Spo_2 in all participants returned to baseline levels within 4 hours.

Conclusions.—HIIE led to an increase in B-lines at altitude after subacute exposure but not during acute exposure at equivalent simulated altitude. This may indicate pulmonary interstitial edema.

Key words: altitude, exercise, ultrasound, high altitude pulmonary edema

Introduction

Ascent to high altitude leads to a reduction in ambient pressure and a subsequent fall in available oxygen. The vascular response to hypoxemia is vasodilatation, whereas in the human lung, it leads to vasoconstriction and a rise in pulmonary artery pressure.[1,2] This in turn increases microvascular hydrostatic pressure and may lead to the accumulation of a high-permeability type interstitial fluid (a capillary stress failure) in the presence of normal

Disclaimer: The authors have no conflicts of interest to declare.

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cardiac function.[3] In certain individuals, this can lead to a clinical deterioration, further hypoxemia, and the development of high altitude pulmonary edema (HAPE), a potentially life-threatening condition for climbers and trekkers in remote locations.[1,4]

Compared with sea level, completing the same aerobic work (eg, walking) at high altitude will be more strenuous because of the reduction in the maximal rate of oxygen uptake ($\dot{V}o_2$max) experienced at high altitude, meaning they will be working at a higher percentage of it.[5,6] Strenuous exercise has long been proposed as a potential risk factor for the development of HAPE.[7] Even in the absence of HAPE, most climbers and trekkers experience a degree of dyspnea and decreased

performance at altitude, and it has been hypothesized that this may be related to an increase in interstitial lung fluid.[8]

Lung ultrasound (LUS) is a noninvasive technique for the assessment of a range of pulmonary and pleural disease.[9,10] Interstitial edema is characterized on LUS by the presence of B-lines, also known as ultrasound lung comets.[10,11] In hospital practice, B-lines have been correlated with chest x-ray and computed tomography scan assessments of interstitial edema as well as invasive measurements of extravascular lung water (EVLW) using thermodilution.[4,12,13]

The LUS technique has been used as both a clinical and research investigation at high altitudes, and its strength and weakness when used in this environment have been discussed in reviews by Fagenholz et al[14] and Wimalasena et al.[15]

Fagenholz et al[14] first reported the use of LUS as a diagnostic tool for HAPE in a prospective case-control study of patients admitted to the Himalayan Rescue Station in the Khumbu valley (5400 m). In their observational study, patients with a HAPE had a higher number of lung comets than controls, and their presence was negatively correlated with peripheral oxygen saturation.[16]

The use of LUS to describe subclinical pulmonary edema (also described as clinically silent HAPE) was first reported in a study by Pratali et al in 2010.[17] The authors performed LUS on 18 participants during a 2-week trek to Everest Base Camp. Fifteen participants exhibited B-lines at 3440 m, and all participants showed evidence of increased B-lines at 4790 m. In 2012, they followed up this study using LUS to show that patients who had chronic mountain sickness experienced a rapid increase in pulmonary interstitial fluid after exercise at altitude compared with healthy high altitude dwellers.[18]

Exercise-induced pulmonary edema and ventricular function during exercise at sea level have also been evaluated using LUS, with Agricola et al[19] reporting that exercise alone can lead to elevation of pulmonary arterial pressure sufficient to induce pulmonary edema.

Strenuous exercise at altitude has long been proposed as a potential risk factor for the development of HAPE, with many experienced climbers following the old adage that "slow and steady wins the race."[7] We hypothesized that high-intensity intermittent exercise (HIIE) at altitude would not only increase hypoxemia but also cause surges in pulmonary artery (PA) pressure that may lead to a capillary stress failure. Therefore, the primary objective of this study was to evaluate the hypothesis that strenuous exercise in a hypoxic environment will lead to an increase in B-lines in otherwise healthy individuals. The secondary objective was to compare whether any response would differ between acute normobaric and subacute hypobaric exposures.

Methods

PARTICIPANTS

Thirteen participants (3 women, 10 men; age, 37 ± 10 years [mean ± SD]; height, 179 ± 9 cm; body mass, 79 ± 12 kg) volunteered for the study. None of the participants had been to altitude in the 3 months before undergoing hypoxic testing. All participants were non-smokers with no medical history of chronic lung disease. Participants gave their written informed consent, and ethical approval was granted by the University of Chichester Research Ethics Committee (protocol number 1011_39).

The study involved a HIIE test completed at sea level (Chichester, UK, 29 m) and acute hypoxia in a normobaric chamber (TISS model 201003=1, TIS Services UK, Medstead, UK) simulating an altitude of 4090 m (O_2 12.6%; CO_2 0.04%; N_2 balance) following a crossover design. Participants were subsequently tested in hypobaric hypoxia during the 2012 Birmingham Medical Research Expeditionary Society (BMRES) expedition to Bhutan (Jomulhari Base Camp, Jangothan, Bhutan). The acclimatization period comprised a 6-day ascent to the test altitude of 4090 m following a gentle ascent profile (approximately 400 m/d). The testing took place in a windproof hut, with the participants kept warm using sleeping bags and duvet jackets when required. All participants completed the tests in acute hypoxia and at high altitude, but 2 participants were unavailable for their scheduled sea level session.

HIGH-INTENSITY INTERMITTENT EXERCISE TEST

The HIIE test was developed as a practical means of applying a maximal exercise insult to all participants that required a contribution from both the aerobic and anaerobic energy systems, without the need to set a prescribed resistance related to either a threshold (eg, ventilatory or lactate threshold) or maximal rate of oxygen uptake ($\dot{V}O_2$max). The use of a prescribed resistance would have required participants to complete additional tests in each condition to develop individual power–$\dot{V}O_2$ regressions to estimate a set intensity above $\dot{V}O_2$max. The test was completed on a custom-made supine cycle ergometer (Alticycle, BMRES, Birmingham, UK) the details of which have been described in a previous publication.[20] Briefly, in use the Alticycle requires the individual to lie supine, constrained by a shoulder harness, with feet strapped into the pedals. Multistage

gearing provides high inertia from a 2-kg flywheel, with additional resistance applied via a remotely controlled brake acting on the flywheel. Before testing, all participants rested on the Alticycle for 10 minutes, after which arterial oxygen saturations (SpO_2) and heart rate were recorded (pulse oximeter model MD300C41, Beijing Choice Electronics, Beijing, China). After this, LUS was performed and the B-line score was recorded. For the acute exposure, the participants entered the chamber approximately 5 minutes before the rest period commenced to allow them to be fitted to the Alticycle, giving a total pre-exercise exposure of 15 minutes in hypoxia. Participants then commenced a 5-minute self-paced warm-up, after which they were then asked to complete a best-effort 6000-m time trial cycle against a standard resistance (inertia of the flywheel only, with no brake applied). Participants were instructed not to pace their efforts, but to exercise maximally for as long as possible and then rest and recover before restarting when they felt able. Verbal feedback was given on distance completed only. At the end of the time trial, the total time to complete was recorded along with the heart rate and SpO_2.

LUNG ULTRASOUND

The LUS was performed using a MicroMaxx portable ultrasound machine (Sonosite, Bothell, WA) and an 8-MHz linear array transducer. Participants were scanned in the supine position using insonnation points on each hemithorax (anterior intercostal rib spaces 2 and 3, in the midclavicular line, and lateral intercostal spaces 5 and 6, in the midaxillary line), giving a total of 8 examination zones.[15] To reduce bias, the LUS scans were carried out by the same operator for each session who was observed by a minimum of 1 other trained operator who recorded their count independently, with the mean of the 2 taken as the count for each site. The mean B-line count at each site was recorded, and the sum total was used in the statistical analysis.

Postexercise LUS scans were performed immediately after the HIIE test, and in the field study, subsequent scans were performed at 1 and 2 hours after exercise. Participants whose B-line score had not returned to their baseline after 2 hours also had a 4-hour post-exercise scan. Alongside the LUS, participants were asked to indicate the development of a cough. During the field study, participants completed a Lake Louise Acute Mountain Sickness questionnaire daily.[21]

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences version 20.0 (IBM UK Ltd,

Portsmouth, UK). The normality of the data was tested with the Shapiro-Wilk test. Paired data were then analyzed using Student's *t* tests, and differences between serial measurements were compared using analysis of variance with sphericity tested with Mauchly's test, and when necessary Huynh-Feldt Epsilon correction factors were applied. Post hoc comparisons were made using *t* tests with a Bonferroni correction applied. Relationships between data were assessed using Pearson product moment correlations. An alpha level of $\leq .05$ was used for all statistics, and all data are presented as mean $\pm$ SD.

Results

The HIIE test distance (Table) took longer to complete in both hypoxic conditions compared with sea level, with the increase being significantly greater for the acute exposure ($P < .01$), but not for the subacute exposure ($P = .08$). However, compared with the acute exposure, the time to complete the HIIE test was reduced after subacute exposure by approximately 19% ($P = .018$).

No B-lines were evident before exercise (baseline) at either sea level or on acute exposure to normobaric hypoxia. After exercise at sea level, no B-lines were detected; however, after acute exposure to hypoxia B-lines were present in 7 of the participants, giving an increase in the mean count compared with baseline ($P < .01$; Table). During the field study at 4090 m, 12 of the 13 participants (92%) demonstrated B-lines at rest (Table), with the mean count increasing vs baseline immediately after strenuous exercise ($P < .001$), and they were evident in all participants (Figure). B-lines continued to be universally present at 1 (mean count vs baseline, $P = .08$) and 2 hours after exercise, with the counts for 5 participants remaining above their baseline value. Those 5 participants with elevated B-lines were scanned again at 4 hours, when all had returned to their baseline values (Figure). There was no statistical difference in the distribution of B-lines (anterior vs posterior) before (4 ± 3 vs 3 ± 2) or after (9 ± 3 vs 9 ± 3) exercise.

Baseline SpO_2 (Table) values were lower during both acute and subacute exposure compared with baseline ($P < .001$). After exercise there was no change in SpO_2 at sea level, but a comparable fall in both the acute and subacute exposure occurred ($P < .001$), with the latter returning to baseline values at subsequent time points. There was no correlation evident between SpO_2 and the number of B-lines. Baseline heart rates in both the acute and subacute exposure were greater than those at sea level at rest ($P < .01$; Table), but not different during exercise. A cough was reported by 11 of the 13

Table. Time to complete high-intensity intermittent exercise test, ultrasound B-line count (sum of 8 sites), peripheral arterial oxygen saturation, and heart rate for each exposure

	HIIE test time (s)	B-line (count)[a]					Peripheral arterial oxygen saturation (%)					Heart rate (beats/min)	
		Baseline	0	1	2	4 (n = 5)	Baseline	0	1	2	4 (n = 5)	Baseline	0
Sea level (n = 11)	656 ± 151	0	0	—	—	—	99 ± 1	97 ± 1	—	—	—	62 ± 12	170 ± 22
Acute (n = 13)	1090 ± 298	0	2 ± 2[b]	—	—	—	90 ± 4	83 ± 6[bc]	—	—	—	81 ± 16[c]	155 ± 21[c]
Subacute (n = 13)	884 ± 243	7 ± 4	17 ± 5[b]	12 ± 5	9 ± 6	5 ± 4	88 ± 4	80 ± 8[bc]	86 ± 6	85 ± 5	88 ± 8	87 ± 14[c]	159 ± 14[c]

HIIE, high-intensity intermittent exercise.

[a] Numbers (0, 1, 2, 4) indicate the hours after exercise when the measurement was made. The B-line count represents the sum of the mean for 2 operators at each of the 8 sites examined. Sample size equals the number of participants for that condition unless otherwise indicated.

[b] Greater than baseline, $P < .01$.

[c] Significantly different from sea level, $P < .01$.
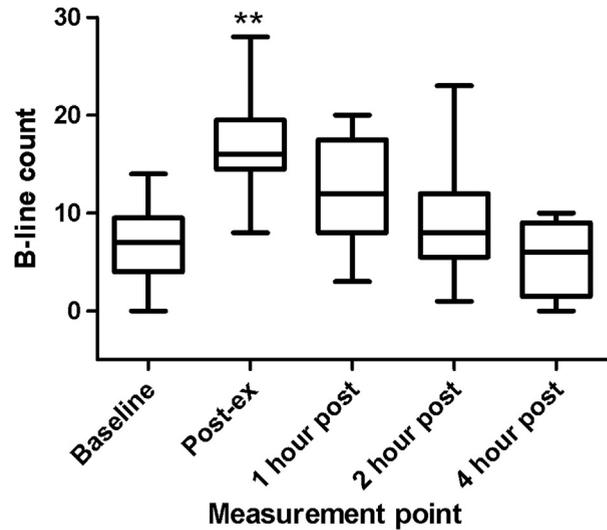
Figure. Lung ultrasound B-line count before (baseline) and after exercise (post-ex, 1 hour post, 2 hours post, 4 hours post) at 4090 m. **Greater than baseline, $P < .01$.

participants (84%) after the HIIE test at altitude. Two participants had Lake Louise Scores indicating the presence of mild acute mountain sickness the morning of their test (both had a score of 3 and included a headache).

Discussion

The principal finding of this study was that HIIE in hypoxia induced an increase in pulmonary interstitial fluid, as measured by the presence of LUS B-lines. This increase, compared with resting values, was greater when participants were exposed to hypobaric hypoxia for 6 days, compared with that observed after acute normobaric hypoxic exposure. In subacute hypoxia, B-lines were elevated in all participants up to 2 hours and in some up to 4 hours after exercise.

After a 6-day trek in the field, the majority of our participants had a modest number of B-lines at rest, suggesting that, as observed in the study by Pratali et al,[17] our participants may have had a degree of underlying interstitial edema before the HIIE test.

The HIIE test at altitude caused increased hypoxemia by factors such as diffusion limitation and increased oxygen extraction as previously observed and described during Operation Everest II (OEII).[2] In addition to hypoxemia, the intermittent intense exercise may have caused large surges in PA pressure as participants alternated between maximal effort and rest. Subsequent uneven hypoxic pulmonary vasoconstriction may have led to areas of capillary stress failure and a high-permeability type edema.

The increase in B-lines observed after subacute exposure, but not during acute hypoxic exposure, can be explained by the difference in pulmonary pressures resulting from the length of exposure and exercise. Groves et al[1] reported higher resting PA pressures at simulated altitude during OEII, which increased further after 3 to 5 minutes of strenuous exercise. It is therefore likely that our participants, when exposed to hypoxia for longer during the field study, had higher resting PA pressure after some acclimatization than with the acute exposure to normobaric hypoxia in the chamber. Given the severity of our exercise test, it is also likely that our participants had similar increases in cardiac output as those reported by Groves et al,[1] and plausible that the PA pressure would have been high enough to cause further interstitial edema to form. Evidently this cannot be proven without direct measurement of PA pressure during HIIE.

The effect of atmospheric pressure on the development of pulmonary interstitial fluid must also be considered in respect of these results. Several authors during the past 2 decades have investigated the possibility of differing physiological responses between normobaric hypoxia and hypobaric hypoxia but physiologists remain divided over opinions.[22,23] The only work of direct relevance to our study is that of Otto et al[24] in 2009, who pioneered the use of ultrasound to detect B-lines at high altitude. During their pilot study, they exposed 2 participants to an acute hypobaric altitude equivalent of 8230 m with 100% O_2 under positive pressure. Both participants exhibited a number of B-lines within 5 minutes despite normal arterial oxygen saturations and the absence of hypoxic symptoms.[24] The results of Otto et al[24] suggest that it may be possible to induce B-lines with hypobaria alone, but the small study size and severity of the hypobaria used limit its interpretation. Additionally, this study compared the effects of acute exposure to the varying hypoxic conditions with no mention of the effects of chronic hypobaria and did not involve exercise as we did. The consensus statement on working in hypoxic conditions by Kupper et al[25] in 2011 concludes that the differences between hypobaric and normobaric hypoxia are too small to have any clinical relevance, and thus these conditions can be used equivalently. In summary, from the studies discussed it seems evident that a minor variance in the physiological response to normobaric hypoxia and hypobaric hypoxia exists; however, the clinical relevance of such a difference is questionable and thus its influence over the main results of our study is unlikely to be significant. It is more likely that B-lines take anywhere from hours to days to evolve and that exercise at high altitudes will exacerbate this, once

physiological adaptation has taken place. However, given the number of confounding factors present during a field study at high altitude (exercise to walk to altitude, length of exposure, acclimatization status, illness, temperature, etc), the isolated effect of barometric pressure on the presence of B-lines cannot be determined definitively. This question might be answered by a study comparing B-line formation in acute normobaric vs hypobaric hypoxia carried out in a chamber setting.

Although the presence of B-lines is an ultrasound finding, the majority of our participants also had reduced peripheral saturations and exhibited a cough after exercise at altitude. It could therefore be argued that they might represent a mild form of inducible pulmonary edema in otherwise healthy climbers although not enough to fulfill the clinical criteria of HAPE.[5] Cough at altitude is common, and although traditionally thought to be a result of breathing cold and dry air, subclinical pulmonary edema has been postulated as a contributory factor.[26] The observation that the cough experienced by our participants rapidly resolved as the interstitial fluid reduced and peripheral saturation improved does suggest it as a contributory factor, but it is not possible to separate this from the impact of exercise and airway irritation.

One must be cautious in recommending the use of LUS to define a diagnosis of HAPE. Although patients who were diagnosed by Fagenholz[16] with HAPE did have significantly more B-lines compared with other participants at the same altitude, the clinical relevance of observing small numbers of B-lines on LUS has yet to be established.

It is important to recognize that the total numbers of B-lines recorded on our study were small. This was probably related to the choice to use an 8-zone examination rather than the 28-zone examination advocated by Fagenholz et al.[14] The 8-zone examination has been shown to be equally sensitive and specific at identifying the presence of interstitial fluid, but the total B-line score will inevitably be smaller. In our participants, there were no differences in the number of B-lines in each zone scanned.[15] This suggests that in the presence of interstitial lung fluid, the more lung zones scanned, the more B-lines would be found. However, further work is needed to examine the correlation between the number of intercostal spaces scanned, the LUS B-line score, and the quantity of edema.

LIMITATIONS

The multiple B-lines observed in this study were typical of those seen in pulmonary interstitial edema, but the differential diagnosis for this sign does include

interstitial pneumonia or pneumonitis. However, all participants had a degree of acclimatization at the time of the subacute testing, and despite 3 subjects reporting acute mountain sickness symptoms, none reported symptoms of productive cough or fever before the test. The rapid resolution of the B-lines during a 2- to 4-hour period after the test makes this differential very unlikely, but the absence of other investigations in the field means it could not conclusively be excluded. A further limitation was our inability to perform Doppler echocardiography during this study. However, although it would have been desirable to have an estimate of PA pressure before and after HIIE, it would have been extremely difficult to perform repeated tricuspid valve Doppler measurements during the multiple short rest periods that characterized this exercise test. Therefore, although echocardiography is a reliable estimate of PA pressure and does correlate albeit weakly with B-lines, the only accurate way to demonstrate our hypothesis would be through direct measurement.[27,28]

Ideally a blinded independent operator would have confirmed the quantification of B-lines. However, blinded confirmation was not possible owing to equipment limitations in the recording of images; therefore, steps were taken to reduce the impact of this limitation by using 2 or more independent observers at the time of the LUS.

As is often lamented in wilderness medicine research, the sample size of 13 participants may have been a further limitation as a larger cohort may have provided stronger statistical and clinical significance.

Conclusions

This study provides the first model for exercise-induced interstitial lung edema in otherwise healthy, non–HAPE-susceptible individuals at altitude. Performing severe intermittent strenuous exercise led to a fall in peripheral oxygen saturation and an increase in interstitial edema as demonstrated by an increase in B-lines. Subclinical pulmonary edema may contribute to the dyspnea and reduced performance, often experienced at altitude, and may be a precursor to HAPE in susceptible individuals. The reliability of HIIE at inducing LUS B-lines makes it a useful model in evaluating pulmonary edema formation at altitude.

Acknowledgments

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