
APEX team with the Huayna Potosí mountain range behind at 19,974ft are Toshiba clinical applications specialist Shane Hanlon and expedition leader Andrew Beck (left and right of the Viamo portable ultrasound system)

Ultrasound for Detection of High Altitude Pulmonary Edema – The APEX 3 study

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Viamo
performance to go

Abstract

Background:
High altitude pulmonary edema (HAPE) is a life-threatening condition of relatively unknown pathophysiology. Increased vascular permeability has been implicated. Ultrasonographic screening for lung comets appears a reliable method to monitor alveolar fluid accumulation. APEX 3, a charitable student-run expedition to the Bolivian Andes (5270 m), studied this phenomenon in normal healthy volunteers.

Materials and Methods:
28 normal healthy volunteers underwent measurements of oxygen saturation, blood pressure and ultrasonography (Toshiba Medical Systems) at sea level a month prior to departure, in La Paz (3650 m), and at days 2, 5 and 7 at the Chacaltaya laboratory (5200 m). Statistical analysis was performed using McNemar chi square text, with $p<0.05$ as statistically significant.

Results:
Lung comets were visualised at sea level in 1/26 subjects, 7/23 by day 2 at 5270 m, and 13/19 by day 7. There was significant association between subject's ascent and the presence of lung comets (sea level vs. day 2 at 5270 m, McNemar $p<0.05$) and their likelihood of developing comets significantly increased during the week they spent at maximum altitude (day 2 at 5270 m vs. day 7 at 5270 m, McNemar $p<0.05$).

Conclusion:
Ultrasonographic detection of lung comets is associated with development of subclinical high altitude pulmonary edema in healthy volunteers.

Introduction

High altitude pulmonary edema (HAPE) is a life-threatening condition defined as noncardiogenic pulmonary edema occurring at altitudes exceeding 3000 m in non-acclimatised individuals.[1] Anyone ascending high enough and without adequate acclimatisation is vulnerable to HAPE[2], although some individuals seem more susceptible than others. At an altitude of 5500 m, 2–15 % of people can be expected to suffer from HAPE, although it has been postulated that a slow ascent of approximately 300–350 m/day is enough to prevent onset.[3] A widely accepted pathological explanation for HAPE has not yet been established[4], but a theory suggests the pathogenesis relates to an increased vascular permeability in hypoxic subjects at altitude. The leakage of intravascular fluorescin dye into the extravascular tissues and the lung fluid has been demonstrated in two studies in rats stressed in a hypoxic environment.[5 6] Based on this observation, Purushothaman et al. hypothesised that altitude illness may occur from the extravasation of fluid into the lungs.[5]

The presence of pulmonary edema and interstitial fluid is usually detected at sea level using chest radiography and (more sensitive) computed tomography; however, neither technique is easily applied at altitude. Thus, an alternative method, ultrasonography, which may be applied as a bedside test or away from a hospital setting, is of interest. The degree of pulmonary vascular leakage and consequent edema can be measured ultrasonographically by the detection of so called "lung comets". Comets are artefacts from the microreflections of the ultrasound beam in the presence of lymphatic fluid from interstitial or alveolar fluid.[7] Ultrasound scanning has been shown accurately to assess for pneumonia, pleural effusion, pulmonary embolism and atelectasis, and as such fills a key diagnostic role in the care of critically ill patients. Based on this experience, ultrasonography for the presence of comets appears to be an accurate method of detecting fluid in the absence of clinical signs of HAPE and, although it may not influence clinical decisions at altitude, has great research potential as a less expensive, more versatile alternative to CT scanning.[8]

APEX is a Scottish charity with a strong history of high altitude experimentation in previous expeditions. This expedition (APEX-3) to the Bolivian Andes in the summer of 2011, aimed to build upon this foundation, and upon the previous research in the field to discover more about the physiology and detection of HAPE. Unique in the fact that it is entirely student run, this project investigated the changes in global vascular permeability as a potential leading cause of the life-threatening physiological responses to altitude. Multiple measurements were performed, but this report is focused on the potential detection of subclinical lung fluid using ultrasonography in subjects at high altitude. The hypotheses tested were that detectable comet numbers would increased as subjects ascended to higher altitudes and that these numbers would stabilise once subjects were acclimatised at high altitude.

Methods

28 healthy research volunteers aged 18–25 were recruited. Exclusion criteria exempted volunteers who:

a) Had previously been admitted to hospital with acute asthma
b) Had significant cardiorespiratory disease
c) Took regular cardiovascular medications
d) Were, or believed they may be, pregnant
e) Smoked

The expedition took one group of 28 people to high altitude at the Laboratorio Fisica Cosmica, Chacaltaya, La Paz, Bolivia (5270 m). The group arrived in La Paz, Bolivia (3600 m) four days prior to travelling to the laboratory. Subjects had baseline measurements taken at sea-level before the expedition in May 2011 and one reading in La Paz.

After 4 days at 3600 m in La Paz subjects travelled by 4x4 to the Chacaltaya laboratory. Further samples were taken on the day after arrival at 5270 m and on the 5th and 7th day. There were five sample days in total. The intensity of the research was similar to the pervious Apex expeditions and ascent profile had been used safely on two previous expeditions.

Imaging techniques

Tests were conducted by an experienced ultrasonographer utilizing the Toshiba Viamo portable ultrasound system with a 7 MHz linear transducer. The examinations were performed in the supine position Ultrasound scanning of the anterior and lateral chest were obtained on the right and left hemithorax, from the second to the fourth intercostal spaces (on the right side to the fifth), parasagitally from parasternal to the midaxillary line (Fig. 1). The comet-tail sign was defined as an echogenic, coherent, wedge-shaped signal with a narrow origin in the near field of the image with through transmission beyond both the parietal and visceral pleura (Fig. 2). In each intercostal space, the presence of comet-tail signs was recorded at the parasternal, midclavear, anterior axillary and midaxillary sites: zero being defined as a complete absence of comet-tail artefact on the investigated area. Two independent observers assessed the images for quality and any intra- or inter-observer variability in the lung comet scores. Images were scanned using a PLT-704ST linear transducer: preset at 6.2 MHz Pulse Subtraction Tissue Harmonic Imaging defaulted to a depth 4 cm, focus 2 cm.

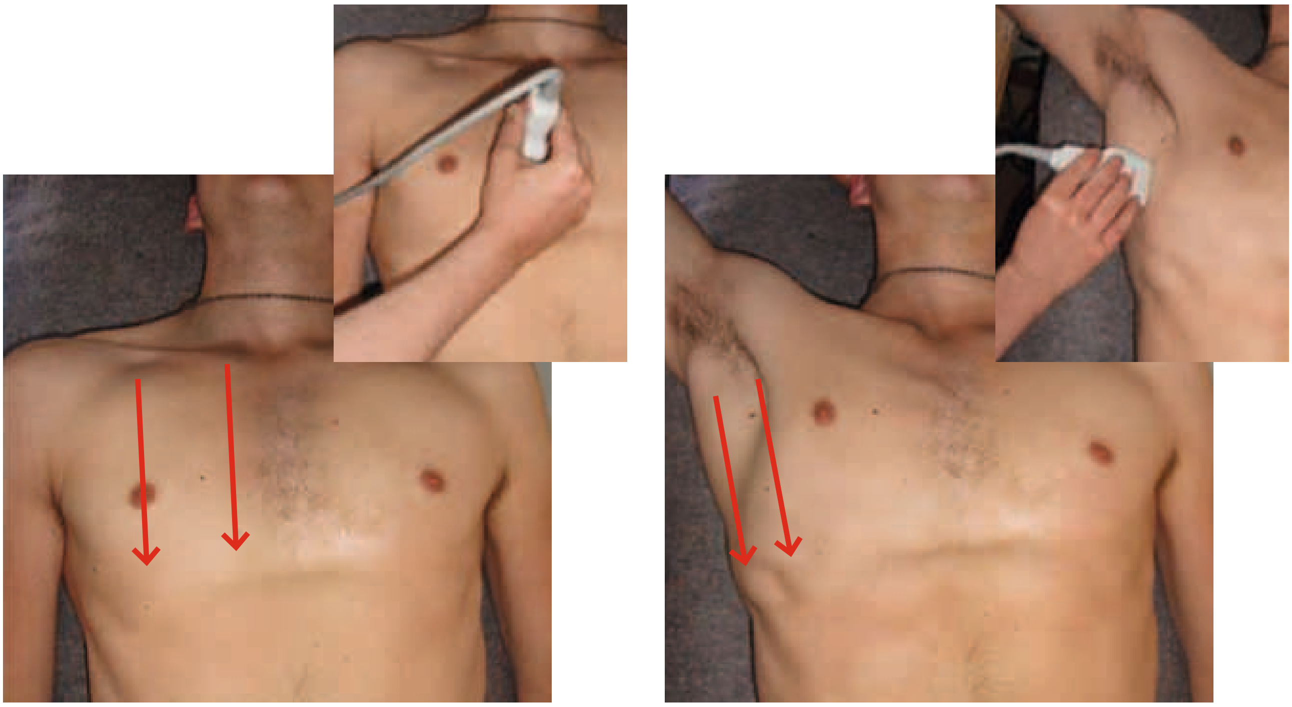

Fig. 1: Scanning planes – Parasternal, mid-clavicular, anterior and mid-axillary lines.

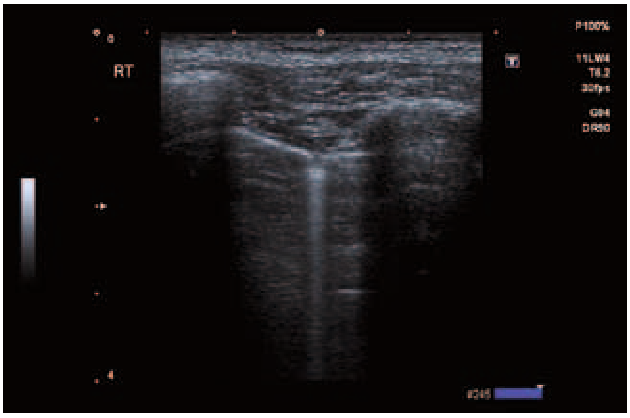

Fig. 2: An example of a lung comet.

The data were split into two sets to answer the two hypotheses: the first hypothesis was addressed by comparing the data from sea level, La Paz and Day 2 at the lab; the second hypothesis by comparing the data from days 2, 5 and 7 from the subject's stay at 5270 m. For the purposes of statistical analysis, the data were categorised as 0 = no comets, and 1 = comets detected on ultrasound. The results were statistically analysed with Cochran's Q test to establish initial significance of associations, then if general significance was present, the McNemar test was used to conduct paired analysis on the data. The data were further analysed in graphical format to compare the presence of no comets, unilateral comets and bilateral comets.

Results

Of the 28 volunteers recruited, two were excluded from the study before the La Paz testing stage for personal reasons, three experienced symptoms of acute mountain sickness (AMS) and withdrew before the second test day at 5270 m, and four withdrew before day 5's tests were complete due to AMS. Subjects experiencing symptoms of AMS were either started on Diamox, or were immediately taken down to a lower altitude in La Paz. These subjects eventuality resulted in exclusion from the study, and all clinical decisions were taken by the expedition doctor. For the purposes of the analysis, the two excluded subjects have been removed from the study and their sea level readings ignored.

Ascending altitude and its relationship to lung comet presencet

	Exact sig (1 sided)	Bonferroni corrected p value	n
Sea Level & La Paz	0.188	0.564	26
La Paz & 5270 m (day 2)	0.145	0.435	23
Sea Level & 5270 m (day 2)	0.035	0.105	23

Table 1: Tabulated results of McNemar test with Bonferroni corrected p values comparing presence and absence of lung comets in subjects at sea level, La Paz and at the second day spent at 5270 m.

Cochran's Q test: p value (exact sig) 1 sided = 0.0385, demonstrating a significant association between an increase in altitude and the presence of lung comets in subjects ($p<0.05$). On further exploration of these relationships, it was discovered that there was no association between lung comets and ascent from sea level to La Paz (exact sig 1 sided = 0.188) or from La Paz to 5270 m (exact sig 1 sided 0.145), although the overall ascent profile was significantly associated with the development of comets (exact sig 1 sided = 0.035). When Bonferroni's correction was applied to the p values they increased beyond our level of significance (Table 1).

Based on the odds ratio for this data set, the odds of subjects developing lung comets were 10.94 times higher at 5270 m than at sea level (1/26 subjects had comets at sea level, compared with 7/23 at day 2 at 5270 m).

Time spent at 5270 m and its relation to lung comet development

	Exact sig (2 sided)	Bonferroni corrected p value	n
Day 2 & Day 5	0.07	0.21	19
Day 5 & Day 7	0.625	1.875	19
Day 2 & Day 7	0.008	0.024	19

Table 2: Tabulated results of McNemar test with Bonferroni corrected p values comparing presence and absence of lung comets in subjects at day 2, 5 and 7 of their stay at 5270 m.

There was a significant association between the amount of time spent at altitude, and the presence of lung comets on ultrasound ($p<0.05$): Cochran's Q test exact sig = 0.004. On completion of paired analysis, this association was strongly observed between days 2 and 7 (exact sig 2 sided = 0.008), and remained significant when Bonferroni's correction was applied ($p<0.05$). However, there was no significant increase in subjects developing lung comets between days 2 and 5, and between days 5 and 7 (Table 2).

Based on the odds ratio for this data set, the odds of subjects developing lung comets were 4.95 times higher on day 7 of testing at 5270 m than on day 2 (7/23 subjects had comets on day 2 at 5270 m, compared with 13/19).

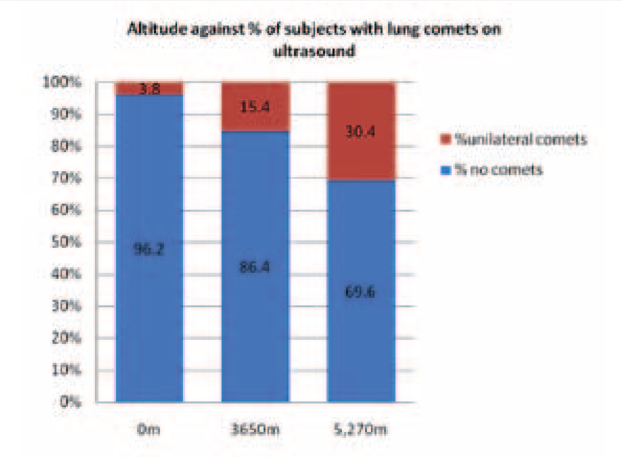

Fig.3: Stacked bar chart showing the % of subjects with no comets, and with unilateral comets at each measured altitude.

The proportion of subjects with unilateral comets increased as altitude increased (Fig. 3) from 3.8 % at sea level to 15.4 % at La Paz (3650 m) and 30.4 % at 5270 m. There were no subjects experiencing bilateral comets during the ascent stages.

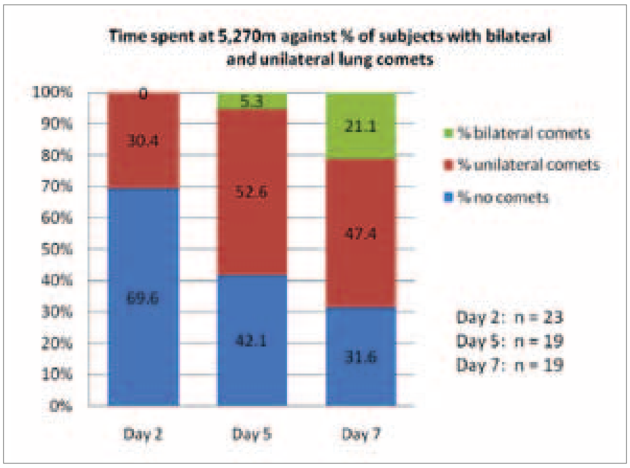

Fig. 4: Stacked bar chart showing the % of subjects experiencing no comets, unilateral and bilateral comets and each test day at 5270 m.

The proportion of subjects with no detectable comets fell from day 2 to day 7 (Fig. 4) from 69.6 % at day 2, to 42.1 % on day 5 and 31.6 % on day 7. Subjects began to demonstrate bilateral comets on day 5 and the number of these cases increased from 5.3 % on day 5 to 21.1 % on day 7. No bilateral comets were found on day 2.

Discussion

The main findings are that the number of lung comets and likelihood of developing subclinical effusions increases with altitude, and increases with time spent at altitude (up to 7 days).

These results dovetail with a 2007 study performed in the Himalayas, suggesting that patients with clinically evident pulmonary edema have higher comet tail scores than asymptomatic controls at the same altitude. Fagenholz et al. elucidated that the comet tail score is predictive of decreasing oxygen saturation (using regression analysis: 1 point increase in CTS corresponded to a 0.67 % in O_2 sats. n= 11, controls= 7) thus reinforcing the power of ultrasound for clinical diagnosis. A similar study in Nepal in 2010 showed the presence of clinically silent comets in 100 % of subjects at 4790 m (n=18) and an accompanying rise in systolic artery pressure. The comets were absent at baseline, and numbers increased during ascent.[10]

This study followed a similar structure to its predecessors, but has reinforced these findings by ascending to a higher final altitude, and using the high quality portable Toshiba Viamo ultrasound system for increased accuracy in comet detection. The ever-increasing portability and durability of portable ultrasound machines is transforming imaging into a crucial diagnostic tool at altitude[11], and so increasing our understanding of edematous imaging changes is becoming increasingly vital to wilderness medicine.

A significant limitation of this study was the time spent at 5270 m. The subjects only had 7 days at peak altitude, so although we can conclude that the number of lung comets increases with time spent at altitude, we cannot extrapolate this conclusion to individuals with longer acclimatisation periods. It would be interesting to see if the number of lung comets falls with prolonged altitude exposure.

It is also important to recognise the limitations of the ultrasound scan as a means of assessing for comets. Ultrasound cannot view the pleural surface under bony structures, and as such 30 % of the pleural surface is hidden from view[12], for example the subscapular, paravertebral or retrosternal pleura.

In the process of elucidating a cause of HAPE and related effects of altitude, the global picture has to be taken into account. By contrasting this picture of lung comet presentation with other examples of vascular leakage, we can begin to build a more complete picture of the human body at altitude.

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