

Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study

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Summary

Background High altitude pulmonary oedema (HAPE) that is severe enough to require urgent medical care is infrequent. We hypothesised that subclinical HAPE is far more frequent than suspected during even modest climbs of average effort.

Methods We assessed 262 consecutive climbers of Monte Rosa (4559 m), before ascent and about 24 h later on the summit 1 h after arriving, by clinical examination, electrocardiography, oximetry, spirometry, carbon monoxide transfer, and closing volume. A chest radiograph was taken at altitude.

Findings Only one climber was evacuated for HAPE, but 40 (15%) of 262 climbers had chest rales or interstitial oedema on radiograph after ascent. Of 37 of these climbers, 34 (92%) showed increased closing volume. Of the 197 climbers without oedema, 146 (74%) had an increase in closing volume at altitude. With no change in vital capacity, forced expiratory volume in 1 s and forced expiratory flow at 25–75% of forced vital capacity increased slightly at altitude, without evidence of oedema. If we assume that an increased closing volume at altitude indicates increased pulmonary extravascular fluid, our data suggest that three of every four healthy, recreational climbers have mild subclinical HAPE shortly after a modest climb.

Interpretation The risk of HAPE might not be confined to a small group of genetically susceptible people, but likely exists for most climbers if the rate of ascent and degree of physical effort are great enough, especially if lung size is normal or low.

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Introduction

High altitude pulmonary oedema (HAPE) is a potentially fatal consequence of rapid altitude ascent, especially when ascent is accompanied by substantial exercise. The incidence of HAPE in the USA is often said to be 2–5%.^{1,2} Although the altitudes of most ski and alpine areas in the USA are only between 8000 and 10 000 feet (2400 to 3000 m), most lowlanders travel quickly to altitude and undertake intense activity. By contrast, much higher ascents of Himalayan or Andean peaks allow acclimatisation by means of gradual ascent. Thus, HAPE tends to be less frequent on well planned ascents to much greater heights, despite the greater degree of hypoxaemia. Consequently, HAPE, although well recognised, is thought to be relatively rare, whether at moderate or very high altitudes.

Consistent with the view that HAPE is uncommon are the constitutional differences between people who develop HAPE and those who do not. People who go on to develop HAPE have higher pulmonary artery pressures,^{3–5} smaller lungs,^{6–9} and higher pulmonary artery wedge pressures during even normoxic sea level exercise than those who do not develop HAPE.^{6,7} Epithelial sodium and water transport could also be compromised in these people.⁴ Thus, there is a general sense that in a small fraction of the population, genetic factors, which produce a symptomless sea level phenotype demonstrable nonetheless by physiological measurements, predispose to HAPE.

Clinically significant HAPE leads to symptoms that cause the patient to seek medical attention. Because some degree of shortness of breath, tachycardia, cough, and arterial oxygen desaturation are frequently experienced at altitude, and because most climbers are keen to pursue the activities for which they came to high altitude areas in the first place, lesser degrees of HAPE might well go unreported. Thus, if all degrees of severity of HAPE are considered, its incidence might be much higher than 2–5%. A suggestion that HAPE could be much more common comes from Operation Everest II, a chamber simulation of a Mount Everest climb. As the participants passed through 6100 m, all but one of the seven developed clinical evidence of HAPE with substantial pulmonary gas exchange defects.¹¹ This effect was not seen at lower altitudes, and, more importantly, was also not seen at higher altitudes, when ascent was purposefully slower.¹⁰ The early data of Singh¹² support this concept as well, with an approximate 15% incidence in soldiers functioning at altitudes above about 3000 metres.

The notion that HAPE results from mechanical disruption of the pulmonary blood:gas barrier due to high pulmonary vascular pressures¹³ suggests that the condition might be more frequent than previously thought, since most healthy people exercising in acute hypoxia develop high mean pulmonary artery pressures (often >4 kPa), and pulmonary wedge pressures (often >2 kPa).¹⁴ Thus, conditions consistent with mechanical failure of pulmonary capillaries might be common during heavy exercise, even at moderate altitudes.

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We therefore postulated that, although the rate of severe, life-threatening HAPE is indeed low, subclinical degrees of pulmonary fluid accumulation might be far more frequent than currently believed in normal climbing circumstances. If subclinical oedema is relatively frequent, the margin of safety for further ascent and exercise at altitude might be small.

Methods

Study design

We designed a 2-week study on Monte Rosa (4559 m on the Swiss-Italian Border). We included all climbers who had ascended from the Italian side at Alagna, successfully reached the summit of the mountain, and had consented to the study. Climbers were examined immediately before commencing the ascent at Alagna, altitude 1200 m. This is the cable car base from which climbers are lifted to 3200 m in 30 min or so, most often in the early afternoon. Climbers then generally hike for 1–2 h to 3600 m and stay overnight in a cabin. Early the next morning, the climb continues. The fastest climbers reach the Rifugio Regina Margherita (a hostel and research laboratory at 4559 m) by 9 am, with the majority arriving 2 to 3 h later. We did a second examination inside the Rifugio Regina Margherita about an hour after each participant's arrival, since most climbers wanted a short rest but then became anxious either to descend or to continue their tour. A minority of climbers remained overnight in the Rifugio Regina Margherita and were re-examined 24 h later. There were two investigative teams, one at Alagna and one on the summit in the Rifugio Regina Margherita. Halfway through the study, the two teams switched locations.

346 people consented to the study and were examined at Alagna. Several failed to reach the summit due to poor weather. A few more turned back because the ascent was too demanding. All those who did not reach the summit were questioned when possible by the Alagna team on descent. In no participant interviewed was failure to reach the summit associated with symptomatic illness. 262 participants (39 women) reached the summit of Rifugio Regina Margherita, and completed most elements of the study at both locations. Data was not available for all participants for all measurements because of equipment failure and time constraints of climbers.

At Alagna, 18 of 346 participants were noted to have clinical abnormalities: hypertension (five); asthma (one); mild chronic obstructive pulmonary disease (one); and restrictive spirometry due to known systemic sclerosis (one). Ten individuals had cardiac murmurs (eight systolic apical ejection murmurs and two pulmonary). Most affected people were aware of their condition and were under medical care. Each participant was informed of these findings and made their own decision on whether to climb or not. Those who chose to climb and reached the summit were included in the study. Only a single participant developed clinically severe HAPE. He was given emergency treatment and evacuated by helicopter. His data were incomplete and are therefore not included in this report.

At Alagna, we obtained written informed consent from the participants and took a brief medical history with a cardiorespiratory focus. Age, sex, bodyweight, height, and pack weight were also determined. At the summit, we took a brief history of the participant's climbing time points and cardiorespiratory symptoms at rest. At both sites we did a cardiorespiratory examination and 12-lead electrocardiography, and recorded the Lake Louise score for symptoms of acute mountain sickness.¹⁵ The Lake Louise system allows points for acute mountain sickness

symptoms and signs, based on severity. Points are summed, with a possible span of 0–28. A score of greater than 3 is accepted as evidence of acute mountain sickness. We used a COSMED (model Quark β , Rome, Italy) spirometer, with identical systems at Alagna and the Rifugio Regina Margherita, to measure vital capacity forced exhalations. The spirometers were calibrated with a 3 L syringe daily. The best of three vital capacity forced exhalations was used for derivation of forced expiratory volume at 1 s (FEV_{1s}), forced vital capacity (FVC), forced expiratory flow at 25–75% of forced vital capacity (FEF_{25-75}), and a flow volume curve. We measured single breath transfer for carbon monoxide (DLco) with the computer-operated portable Sensormedics Vmax system (Model 2900 Fullerton, CA, USA). Identical units were placed at Alagna and the Rifugio Regina Margherita and were calibrated several times daily. Because the Vmax uses infrared analysers, methane rather than helium is used as the insoluble gas for alveolar volume calculations. We also measured pulse oximetry, with similar oximeters (NONIN Medical, Plymouth, MN, USA) in both study locations. Measurements were made at rest with the hands warmed after 30 s of signal stabilisation. Chest radiography was done with a portable radiography machine (Euroastre, Italy), standard radiography film (Dupont, France), and posteroanterior projection at a distance of 1 m, only at Rifugio Regina Margherita. Radiographs were coded and scored independently by three radiologists who were unaware of the results. Lung fields were divided into six zones (upper, middle, and lower for each lung). We assigned a score from 0 to 5 to each zone according to the following criteria: 0=normal; 1=signs of interstitial oedema; 2=alveolar oedema with well distinguished pulmonary vessels; 3=alveolar oedema with poorly distinguished pulmonary vessels; 4=alveolar oedema with no pulmonary vessels distinguished; 5=complete opacification with only the air bronchogram visible. Several normal chest radiographs were inserted for quality control. The coefficient of variability between observers was less than 10%, and their scores were averaged.

The rationale for measuring closing volume in the present study is that increased pulmonary extravascular fluid tracks centrally along major pulmonary vessels and airways. Peribronchial fluid accumulating in this way would be expected to compress airways and thus increase the volume at which airways close. Thus closing volume would increase at altitude if there was indeed more pulmonary transvascular fluid leak and peribronchial fluid. This rationale has been used before at altitude.¹⁶ To measure closing volume in the field with portable equipment, we used a method based on Guy's single breath techniques¹⁷ but which does not require foreign inert gases or 100% oxygen. With the above Sensormedics Vmax system, we recorded expired oxygen and carbon dioxide concentrations and expired gas volume during a slow vital capacity exhalation to residual volume, with the participant breathing room air. These data were processed off-line to compute the intrabreath respiratory exchange ratio, R (continuously as a function of exhaled volume), from the standard alveolar gas equation:¹⁸

$$R = \text{PACO}_2 * (1 - \text{FIO}_2) / (\text{PIO}_2 - \text{PAO}_2 - \text{PACO}_2 * \text{FIO}_2)$$

Here, PACO_2 and PAO_2 are instantaneous expired oxygen and carbon dioxide partial pressures, whereas FIO_2 and PIO_2 are inspired oxygen concentration and partial pressure. R was then plotted against expired volume (figure 1). The typical profile shows R, high at total lung capacity, falling progressively with exhaled volume until the point at which airway closure is reached.

Thereafter, R rises again, and the resultant change in slope enables a quantitative identification of airway closure. The terminal rise in R has the same explanation as the terminal rise in nitrogen in the classical single breath oxygen test. This pattern represents cessation of emptying of basal, low ventilation/perfusion ratio (V_A/Q) gas exchange units that have low R, with continued emptying of apical, high $VO_2 A/QO_2$ (high R) gas exchange units.

We determined all 468 closing volume values (values from 234 climbers at Alagna, and their 234 paired values at Rifugio Regina Margherita) in this manner from plots like those of figure 1. Importantly, the analysis of all 468 records was completed (all by one individual) before any knowledge of the clinical and radiological findings in any participant, and all Rifugio Regina Margherita records were analysed before those from Alagna. Although there might be minor uncertainty from interobserver variation in determining closing volume, analysing all records masked permitted a consistent approach to comparing effects of altitude on those who subsequently developed mild HAPE and those who did not.

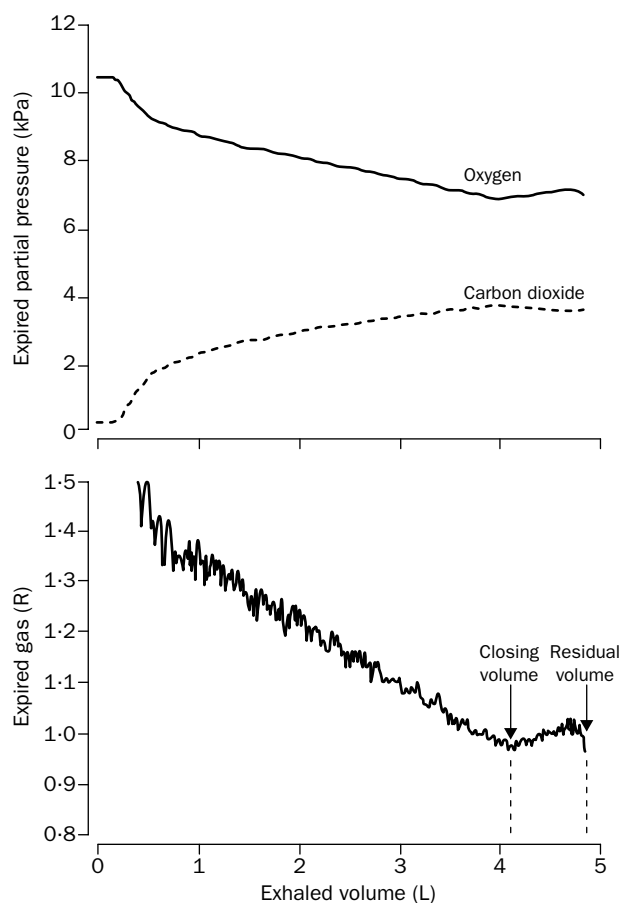


Figure 1: Expired oxygen and carbon dioxide partial pressures

From a single participant at 4559 m during a slow vital capacity exhalation to residual volume, with the participant breathing room air (upper panel). These data were processed to yield (from the alveolar gas equation) the intrabreath respiratory exchange ratio, R, which is plotted against expired volume (lower panel). Data during the first L, reflecting deadspace gas washout, are not useful. The volume at which R ceases to fall and begins to rise marks closing volume (4.09 L below total lung capacity in this case) as explained in the text. Vital capacity, 4.85 L here, measured in this manoeuvre, and the difference, 0.76 L, is the closing volume expressed as L above residual volume.

Statistical analysis

Only climbers who completed both the Alagna and Rifugio Regina Margherita portions of the study were included in the analysis ($n=262$). Since the number of climbers completing a given test component at both Alagna and Rifugio Regina Margherita was different for each test, particularly for the DLco test, there were different numbers of participants for each variable.

We compared the results of each test at Alagna and Rifugio Regina Margherita by a paired t test. Participants were divided into two groups according to the combined physical examination findings (chest rales, tricuspid regurgitant murmur) and radiological findings of interstitial and alveolar oedema, or both. Overall, there were 40 with positive findings in any one or more of these elements, and 222 with no abnormal clinical or chest radiological findings. Changes from Alagna to Rifugio Regina Margherita in each of the above variables were then compared by unpaired t test between the climbers with evidence of increased pulmonary extravascular fluid and those who had no such evidence, with all available pairs of data at the two altitudes. Data are expressed as mean (SD) in the text to indicate participant variance and as mean (SE) in the figures and table to enable group comparisons.

We did multivariate linear regression to determine whether the changes in closing volume from Alagna to the Rifugio Regina Margherita were correlated with any of the independent variables.

Role of funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

For the 262 climbers examined at both locations, mean weight was 72.2 kg (SD 10.6), age was 39.8 years (12.0), and height was 174 cm (14). The mean weight of the backpack was 11.3 kg (4.8) and the time taken for the ascent was 4.3 h (1.3). Mean FVC at Alagna was 4.74 L (0.90; 104.4% predicted [13.3]); FEV₁ was 3.88 L (0.71 103.4% predicted [12.8%]), and FEV₁/FVC was 82.1% (6.5; 102.2% predicted [7.7]). 30 climbers were current smokers and 17 had smoked in the past. 88 had been to altitudes over 2500 m in the 3 months before the study but only three had resided at or above this altitude. 28 had a previous history of mild acute mountain sickness, two of HAPE, and two of high altitude cerebral oedema. 11 had taken non-steroidal anti-inflammatory agents on the day of the ascent and 12 had taken acetazolamide. Two were on throxine replacement therapy and three were on angiotensin converting enzyme inhibitors for hypertension. One asthmatic participant was on inhaled beclomethasone and salmeterol, and another was on

	Alagna, 1200 m		RRM, 4559 m	
	No oedema	Oedema	No oedema	Oedema
FVC (% predicted)	104.0 (0.9)	105.0 (2.2)	104.0 (0.9)	102.0 (2.1)*
FEV ₁ (% predicted)	104.4 (0.9)	103.4 (2.2)	104.9 (0.8)*	102.6 (1.8)
SaO ₂ (%)	96.2 (0.1)	95.6 (0.2)	77.0 (0.4)*	76.7 (1.0)*
Lake Louise score	0	0	2.6 (0.2)*	3.6 (0.4)*†
Closing volume	0.325	0.277	0.493	0.615
(L above residual volume)	(0.018)	(0.034)	(0.021)*	(0.46)*†

Data are mean (SE). RRM=Rifugio Regina Margherita. *Significant effects of altitude; †Significant differences between groups at either altitude.

Physiological variables in climbers with and without clinical evidence of oedema, at low and high altitude

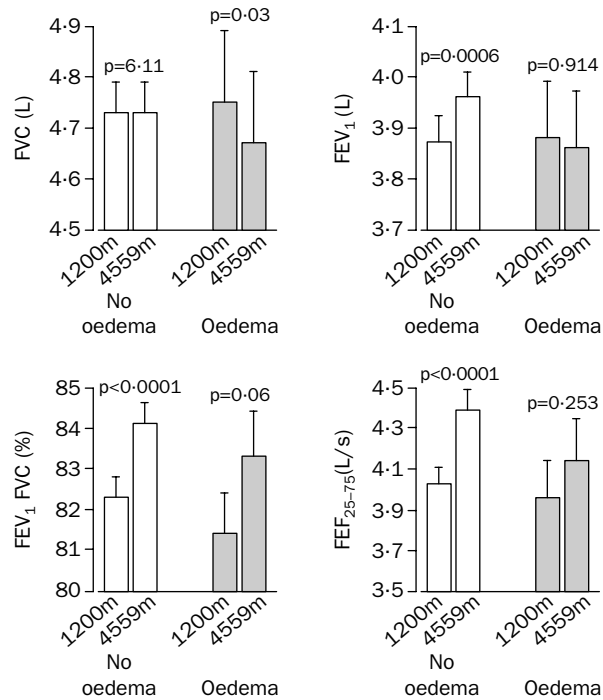


Figure 2: Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) in participants with and without oedema
FVC and FEV₁ (upper panels); FEV₁/FVC and FEF₂₅₋₇₅ (lower panels). Open bars represent the participants without clinical evidence of oedema, and hatched bars the participants with evidence of oedema.

inhaled salbutamol. These numbers are only for those climbers who completed both the Alagna and Rifugio Regina Margherita portions of the study.

Arterial oxygen saturation at altitude was lower, as expected (96.1% [1.5%] at Alagna, 77.3% [5.7%] at Rifugio Regina Margherita; range 60–93%, $p=0.001$). Electrocardiogram at altitude showed right axis deviation in 32 (13%) of all climbers, not present in any at Alagna. FVC was similar at low and high altitude (4.72 L [0.90] or 103.8% predicted [13.0] at Rifugio Regina Margherita, $p=0.2$). FEV₁ was increased by 2% at altitude (3.95 L [0.73] or 104.6% predicted [11.6]), so that the FEV₁/FVC ratio was also 2% higher at 84% (6.9%; $p=0.02$). Closing volume was increased overall at altitude (0.316 L [0.252] above residual volume at Alagna, 0.513 L [0.293] above residual volume at Rifugio Regina Margherita). This increase was significant, $p=0.001$ ($n=234$).

40 (15%) of 262 participants (excluding the one with severe HAPE) had radiological or physical diagnostic evidence supportive of increased pulmonary extravascular lung water (rales, or oedema on chest radiograph) but had no HAPE-related symptoms (undue shortness of breath, cough and sputum, cyanosis) in excess of those without such findings. Comparing the two groups, there were no significant differences in age, sex, weight, height, smoking history, intercurrent diseases, pack weight, climbing time, spirometry and DLco at low altitude, or arterial oxygen saturation. Overall Lake Louise score was lower for the 216 individuals without evidence of extravascular fluid than for the 40 participants at Rifugio Regina Margherita ($p=0.04$). Of 201 climbers radiographed at Rifugio Regina Margherita, 14 had evidence of increased pulmonary extravascular water with four having oedema in more than two lung zones. Of the climbers who stayed overnight ($n=50$) only three worsened clinically. In these 50 there were no significant changes in closing volume over time at Rifugio Regina Margherita above residual volume on summit arrival (0.459 L [0.054] vs 0.449 L

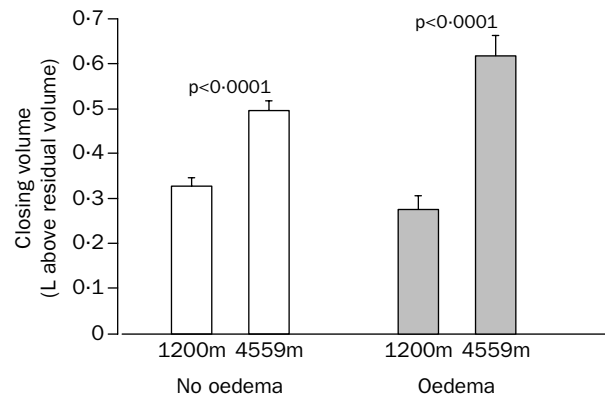


Figure 3: Closing volume in litres above residual volume at Alagna and Rifugio Regina Margherita

In the participants with (hatched bars) and without (open bars) clinical evidence of oedema. Both groups show highly significant increases in closing volume with ascent.

[0.057] 24 h later, $p=0.82$). The table shows the principal variables for both groups at Alagna and Rifugio Regina Margherita. Figure 2 shows the changes in vital capacity, FEV₁, FEV₁/FVC, and forced expiratory flow in the middle half of expiration, FEF₂₅₋₇₅. There was no discernible reduction in FEV₁/FVC ratio at altitude in either group, and, if anything, there was an increase (ascribed to reduced gas density).

Figure 3 shows closing volume at Alagna and Rifugio Regina Margherita for the 37 participants with clinical evidence of increased extravascular lung water at altitude and the 197 without such evidence. Although the increases in closing volume were highly significant in both groups ($p<0.0001$), they were twice as great in those climbers with evidence of increased extravascular water as in those without (figure 4). Figure 5 shows the distribution of closing volume changes with altitude in the two groups. Increases were seen in 34 (92%) of 37 participants with evidence of oedema, a greater percentage than in the remaining 197. A key observation is that 146 (74%) of those 197 climbers without radiological or clinical evidence of even interstitial pulmonary oedema also had an increase in closing volume after ascent to altitude. Vital capacity (at low altitude) in the remaining 51 (26%) climbers without clinical evidence of oedema and who had reduced closing volume with altitude (figure 5) was then compared with vital capacity in the 74% of climbers of the same group but

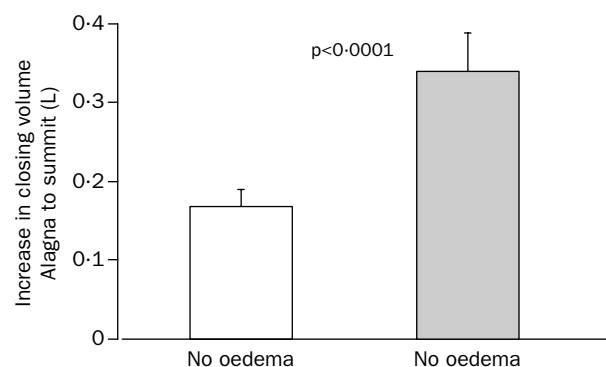


Figure 4: Significant increases in closing volume from Alagna to Rifugio Regina Margherita

Both in participants with (hatched bar) and without (open bar) clinical evidence of oedema. Climbers with evidence of oedema developed on average twice the increase in closing volume after ascent as did those without.

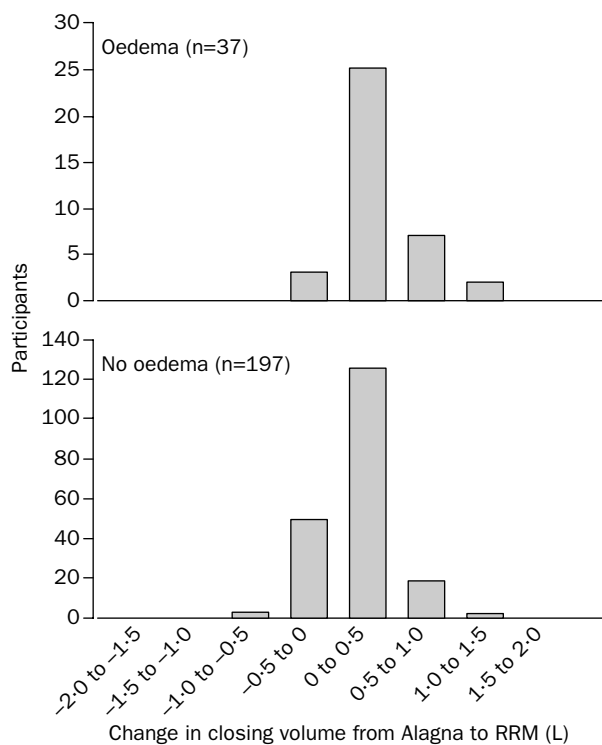


Figure 5: **Distribution of closing volume changes between 1200 m and 4559 m in the 37 subjects with (upper panel) and the 197 without (lower panel) evidence of oedema**

Almost all (92%) of the former (34/37) increased closing volume on ascent while 74% (146/197) of the latter group also increased closing volume after the climb. RRM=Rifugio Regina Margherita.

whose closing volume increased with altitude. This was done on the hypothesis that relatively large lungs were protective against HAPE as suggested previously.⁶⁻⁹ We noted that vital capacity (at low altitude) was indeed greater (108.4% predicted [1.6]) in the 26% with reduced closing volume than in the 74% with increased closing volume (103.5% predicted [1.1], $p=0.013$). We regard these findings as suggesting that subclinical interstitial oedema occurred in a majority (77%, 180 of 234) of recreational climbers to modest altitude when strenuous exercise was required for the ascent.

Multiple linear regression analysis correlating in all 234 climbers the altitude-induced change in closing volume (delta closing volume) with age, weight, height, pack weight, climbing time, FVC, FEV₁/FVC, DLco and DLco/lung volume (DLco/VA), revealed that only DLco/VA was related: delta closing volume = $0.651 - 0.00537 * \text{DLco/VA}$, with $r = -0.26$, $p = 0.02$.

Discussion

Our data do not dispute the low incidence of full-blown HAPE requiring emergency care and evacuation, which was seen in just one of our participants. However, we suggest that subclinical interstitial oedema arises in most recreational climbers to modest altitude.

Features of our study that enhance its power and strengthen conclusions include: the large number of participants; the paired study design comparing each participant with identical methods at low and high altitude; the field nature of the project; the relative uniformity of climbing profile; the wide range of reported physical attributes (age, weight, pulmonary function) of the climbers; and the sequential enrolment of every willing climber.

Potentially, and beyond our control, bias might have occurred after selection insofar as any climbers who failed to reach the summit could not be examined at altitude. However, such exclusions would produce a bias toward reducing the frequency of oedema we report, if failure to reach the summit was due to mountain sickness of any kind, including HAPE. To that extent, our frequency figures would underestimate the frequency of occurrence of increased extravascular lung water. The reasons climbers gave for not reaching the summit were mostly bad weather rather than fatigue or ill health. This explanation is supported by our own observations of the weather and the fact that failures were indeed clustered in those days when the weather deteriorated. Thus, it is not likely that the present results are significantly skewed by those who failed to reach the summit.

Because closing volume revealed changes in a much greater proportion of our participants than clinical examination or radiography did, it is reasonable to ask how specific and sensitive is closing volume as a marker of interstitial oedema? In general, there is agreement that interstitial oedema of any cause can lead to increased closing volume from airway compression by peribronchial cuffs of fluid.^{19,20} Indeed, this is standard teaching in medical school.²¹ Other processes might be considered potentially responsible for increased closing volume in our study. In particular, bronchoconstriction could be postulated as a candidate. Heavy exercise in cold dry air certainly provides known stimuli for smooth muscle contraction and perhaps also for acute airway inflammation.²² However, there was no discernible reduction in FEV₁/FVC ratio at altitude in either group. Bronchoconstriction generally reduces FEV₁/FVC, and thus this cause does not explain the present results.

With respect to sensitivity, it should be recalled that the closing volume measurements were all completed before knowledge of which climbers had radiological or clinical evidence of interstitial oedema. Our finding that some climbers who showed independent evidence of mild oedema did show an increase in closing volume with altitude suggests sensitivity. Moreover, the average increase was twice as great as in those climbers with no other evidence of oedema. We presume that random measurement error and other sources of variability account for the 8% of participants whose closing volume did not increase despite other evidence of oedema. We therefore agree with previous workers^{16,19,20} who have used closing volume as a marker of interstitial pulmonary oedema and found it to be a satisfactory technique in circumstances where direct determination of extravascular lung water cannot be accomplished. Note also that the Lake Louise score for acute mountain sickness showed differences between the groups, diagnostically positive (>3) in those with evidence of oedema and negative (<3) in those without.

We are not surprised at finding evidence for a high (77%) frequency of increased interstitial fluid. It is well known that even sea level exercise is associated with increased pulmonary arterial pressures and transvascular fluid flux.²³⁻²⁵ It is also well known that hypoxia independently increases pulmonary arterial pressures,^{14,26} and the combination is synergistic. Exercise can also lead to high pulmonary artery wedge pressures.^{6,26} HAPE is classically associated with increased pulmonary artery pressures (and even at sea level, HAPE survivors are reported to have higher than average pulmonary artery pressures).^{3,6} High pulmonary vascular pressures facilitate transvascular fluid movement in the lung, and could lead to mechanical failure of the capillaries,²⁷ which would also

favour accumulation of extravascular fluid. We interpret the data to suggest that even at modest altitudes and rates of ascent, such as in the present case (4559 m in about 24 total hours encompassing about 4 h of climbing), and with heavy but not extreme physical effort, the healthy human lung is on the edge of failure in terms of fluid balance.

The specific amount and rate of altitude gain in our study is not extreme in the world of recreational climbing. As long as the weather holds, there is little time pressure. There is a well-equipped overnight summit cabin should conditions deteriorate. The very fact that every day more than 30 individuals, many in their sixth or later decades, reach the summit during the climbing season is testament to its attainability by most well prepared healthy people. Thus, we would argue that our results apply broadly to many moderate climbs around the world.

Our findings are consistent with those of Operation Everest II, in which at 6100 m a rapid rate of chamber ascent led to clinically evident HAPE in almost all of the seven participants.^{10,11} This result was not seen again despite greater hypoxia as further altitude was gained, presumably because ascent was consciously decelerated. The lesson from this event is similar to that proposed herein: HAPE is not confined to a few genetically susceptible individuals. They might well be the first to become ill, but essentially all healthy people are vulnerable, and there may not be a large margin of safety when standard climbing paradigms are undertaken. The work of Singh¹² further supports this conclusion in Indian soldiers at high altitude, where the incidence was much higher (15%) than the 2–5% referred to earlier. Participants in Singh's study probably underwent rapid ascent, were required to exercise vigorously, and carried heavy packs as soldiers on duty.

Three separate groups of investigators, studying participants from three different ethnic groups (Indians,⁹ Europeans,⁸ and North Americans^{6,7}) have reported that HAPE survivors seem to have smaller lungs than those who do not develop HAPE. Viswanathan⁹ showed large differences in absolute vital capacity in a substantial number of people (more than 50 in each of two groups), but this finding cannot be interpreted without reference to body size. When Viswanathan did the study, no statistical interpretation was given. Thus it is not clear if the lungs were really different in size between groups when body size was taken into account. So too, Steinacker's⁸ results are equivocal, with *p* values that were no smaller than 0.13 for FVC when body size was taken into account. The data of Eldridge⁶ and Podolsky⁷ were significant, but the number of participants was only seven in the HAPE-resistant group and nine in the HAPE-survivor group. Despite these limitations in the three studies, all produced data suggesting that HAPE-resistant people have lungs whose size is larger than predicted, while HAPE-survivors have essentially normal lung volumes. Our findings also lend support to the idea that climbers whose closing volume increases with ascent have a lower average vital capacity than those in whom closing volume falls with ascent.

We postulate that the most likely reason why large lungs (relative to body size) are protective against HAPE is that they possess a larger cross-sectional area of the pulmonary circulation, limiting the rise in pulmonary artery pressures (during exercise at altitude) due to intrinsically lower vascular resistance. This theory is compatible with the already-discussed findings of higher pulmonary artery pressures in people susceptible to HAPE. It also fits with the negative correlation recorded

between the increase in closing volume with altitude and DLco/VA, because the latter is known to indicate the size of the pulmonary microcirculation. Although the relation between lung volume and HAPE seems to be firmly established, it is of course not claimed to be the only factor contributing to HAPE susceptibility, as the sodium transport findings of Scherrer,⁴ for example, suggest.

The combination of exercise and altitude gain makes climbers particularly vulnerable to HAPE. How much of the present findings are due to exercise, and how much to hypoxia? Two findings suggest that in our study, hypoxia was the more important factor. First, the whole examination was done on average 60 min after the climb. Thus, 60 min of rest preceded our data collection. Schaffartzik and colleagues²⁸ reported that ventilation/perfusion mismatch, which occurred during hypoxic exercise in healthy people, returned to normal resting levels 20 min after exercise, suggesting that by the time we assessed our participants, exercise-induced effects should have subsided. However, his participants exercised for only a few minutes, whereas the Monte Rosa climb takes many hours, and thus any exercise-related effects might have taken longer to subside. The second finding in favour of hypoxia as the main cause of oedema in our study comes from the 50 participants who chose to stay overnight on the summit. There was no difference in closing volume between the initial summit measurements and those done a day later. Thus, the abnormality persisted at altitude in the absence of any exercise for 24 h.

Previous work has shown that ventilation/perfusion inequality increases at altitude compared with sea level, especially during exercise,^{14,29} in about 50% of healthy participants. The present data are compatible with these findings insofar as mild interstitial oedema could easily explain the greater ventilation/perfusion heterogeneity through maldistribution of ventilation and blood flow, or both. This poor distribution could happen as airways and blood vessels become compressed by accumulated peribronchial or perivascular fluid, and possibly also through reduced alveolar compliance in those regions with increased alveolar interstitial fluid. The high frequency of mild oedema according to closing volume data in the present study is concordant with the high rate of increased ventilation/perfusion mismatching under similar conditions.

We see no conflict between the low incidence of clinically severe HAPE,^{1,2} the associated constitutional abnormalities in HAPE survivors,^{3,4,7} and our suggestion of a high frequency of subclinical interstitial oedema. It seems reasonable that although all healthy people are potentially vulnerable, there is a broad distribution of interstitial fluid accumulation in response to exertion at altitude in the general population. Those most at risk might be the small proportion of people with genetic predisposition through higher pulmonary vascular pressures or altered epithelial sodium and water transport. In these people, ascent might well lead to HAPE. The majority, who do not have these defects, remain at risk according to the present findings of increased closing volume, but require greater hypoxic/exercise stimulus than the Monte Rosa ascent for clinically significant HAPE. The remainder seem resistant insofar as closing volume (as the most sensitive marker of oedema in our study) was not increased. Whether a more challenging combination of ascent and effort would produce HAPE in such people, and what the physiological mechanisms of their resistance to oedema might be, lung volume differences notwithstanding, remain to be determined.

Contributors

George Cremona and Peter D Wagner planned and organised the study, collected and analysed data, wrote the manuscript, and provided some financial support. Carmelo Cavallaro planned the radiological part of the study, provided the equipment, and analysed the radiographs along with Roberto Asnaghi and Alessandro Brunetto. Roberto Donis and Stefano Panzetta did the radiographs on Monte Rosa. Tom Brutsaert, Liliana Perini, Andrew Luks, and Annalisa Cogo helped with the planning and collected data. Paola Lanfranchi helped plan the study, collected and analysed data, and provided some financial support. Nadia Novello, Marci Putnam, and Harrieth Wagner collected and analysed data. Paola Baderna, Timothy M Clark, and Liliana Spagnolatti helped with data collection and physical examination.

Conflict of interest statement

None declared.

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