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Original Article

Incidence of high altitude pulmonary edema in low-landers during re-exposure to high altitude after a sojourn in the plains

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ABSTRACT

Background: There is uncertainty whether acclimatized low-landers who return to high altitude after a sojourn at low altitude have a higher incidence of pulmonary edema than during the first exposure to high altitude.

Methods: This was a prospective cohort study consisting of men ascending to 3400 m by road (N = 1003) or by air (N = 4178). The study compared the incidence of high altitude pulmonary edema during first exposure vs the incidence during re-exposure in each of these cohorts.

Results: Pulmonary edema occurred in 13 of the 4178 entries by air (Incidence: 0.31%, 95% CI: 0.18%–0.53%). The incidence during first exposure was 0.18% (0.05%–0.66%) and 0.36% (0.2%–0.64%) during re-exposure (Fisher Exact Test for differences in the incidence (two-tailed) $p = 0.534$). The relative risk for the re-exposure cohort was 1.95 (95% CI, 0.43%–8.80%). Pulmonary edema occurred in 3 of the 1003 road entrants (Incidence: 0.30%, 95% CI: 0.08%–0.95%). All three cases occurred in the re-exposure cohort.

Conclusion: The large overlap of confidence intervals between incidence during first exposure and re-exposure; the nature of the confidence interval of the relative risk; and the result of the Fisher exact test, all suggest that this difference in incidence could have occurred purely by chance. We did not find evidence for a significantly higher incidence of HAPE during re-entry to HA after a sojourn in the plains.

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Introduction

High altitude pulmonary edema (HAPE) affects apparently healthy individuals when acutely exposed to the hypobaric hypoxia of high altitude (HA). There appear to be some geographical variations in its incidence. In the

South American Andes, it is most frequent in those native residents of HA who descend to the plains for a sojourn and return to be re-exposed to hypoxia.¹ On the contrary, the incidence of HAPE is reported to be very low amongst the permanent residents of the Himalayan belt.^{2–4}

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Generally, residents of low altitudes are susceptible to HAPE if acutely exposed to HA. Some suffer from HAPE during the first exposure to HA while others remain unaffected and acclimatize well. The incidence of HAPE amongst such previously unacclimatized subjects has been variously reported to range between about 0.01% and about 5%.^{5,6} Most residents of low altitudes remain healthy on returning to HA after sojourns in the plains, but some suffer from HAPE during the re-exposure to hypoxia.^{1,7}

In the past, prevalence data from hospital records and other cross-sectional studies have shown that, at any given time, most HAPE patients were those who had been re-exposed to HA.^{6,7} These observations formed the basis of the belief that re-exposure to HA, after a sojourn in the plains, carries a higher risk for HAPE.

However, the larger absolute number of HAPE patients with a history of recent re-exposure to HA may have another explanation. Any individual enters HA for the first time only once (the first exposure) but may leave and re-enter on several occasions (re-exposures). In any group of people the total number of instances of re-exposure to HA is therefore necessarily larger than the total number of first exposures. Since the population-at-risk is larger during re-exposure it is expected that a larger number of HAPE patients at any given time will be from this group of individuals.

Most earlier estimates of the incidence of HAPE have suffered from the lack of precise estimates of the population-at-risk.^{6,8–11} There have also been differences in the diagnostic criteria used for HAPE. These deficiencies in the reported incidences have been summarized recently.¹² Thus, it is not clearly known if there really is a higher incidence of HAPE during re-exposure to HA after a sojourn in the plains than during the first exposure.

Research questions

We wished to resolve this issue and designed a study that hoped to answer the following questions:

1. What is the incidence of HAPE in a cohort of healthy previously unacclimatized males during their first exposure to HA?
2. What is the incidence of HAPE in a similar cohort of healthy acclimatized males, re-exposed to HA after a sojourn in the plains?

To achieve these aims we recruited two cohorts of participants entering HA, some for the first time (first exposure, FE) and others for any subsequent exposures (re-exposure, RE). The cohorts were followed prospectively and all occurrences of HAPE amongst them were recorded. We tested the null hypothesis that there is no difference in the incidence of HAPE between the FE cohort and the RE cohort.

Material and methods

This prospective cohort study was conducted at the High Altitude Medical Research Center located at about 3400 m above sea level in the western Himalaya. The ethics committee of the research center approved the study.

All participants were male soldiers who were ascending to HA on duty. Soldiers have to be asymptomatic and free from disease before they are assigned duties at HA. Since acclimatization to HA may reduce the incidence of HA-related illnesses all soldiers follow an altitude-dependent acclimatization schedule on entering HA.⁷ For an altitude of 3400 m this consisted of a two-day period of rest followed by four days of gradually increasing physical activity. On the seventh day at HA all soldiers underwent a medical examination to confirm that they were free from illness. The participants in our study consisted only of these acclimatizing soldiers. Only those soldiers who belonged to one of three military units were recruited as participants. There were two criteria for selecting these units: Firstly, they were located in close proximity to the research center, and secondly, the composition of men in these units was not restricted to any particular region of India, and therefore represented the general Indian population.

For some participants it was the first exposure to HA while for others it was a re-exposure after a sojourn in the plains. Many participants had entered HA on more than one occasion and each instance was recorded as a separate event. Some reached the HA area directly from the plains (200–300 m) after a 45–60 min journey by aircraft. These soldiers usually arrived early in the morning. Others reached after a road journey of 3–4 days. There were two possible road routes both of which involved overnight halts at camps en route. The altitude of these camps ranged between 2700 m and 4500 m. These men usually arrived at the final destination (3400 m) late in the evening of the third or fourth day after beginning their journey from low altitudes.

Data collection occurred in two phases. The first 3-month phase was from 17 April 2000 to 18 July 2000 and the next longer period extended from 10 Aug 2000 to 30 Oct 2004.

All data collection was done in the clinical laboratory where the ambient temperature ranged between 24 °C and 26 °C throughout the period of data collection.

Subjects reached the laboratory before 9:00 am. They were explained and informed about the nature of the study and their consent was obtained. A standard questionnaire was used to collect data regarding date of first exposure to HA and dates of descent, dates of re-ascent after a temporary absence from the HA area, and the mode of ascent during each exposure to HA. The questionnaire also recorded information regarding occurrence of severe AMS or admission for HAPE during any of the previous exposures to HA.

The clinical data gathered included heart rate, respiratory rate, systemic arterial blood pressure, and hemoglobin saturation. Symptoms of acute mountain sickness were elicited and recorded on standardized forms. Details of clinical examination are not given here and neither is that data presented in this paper.

Whenever any study participant fell ill he sought medical advice at the emergency department of the only hospital. All doctors in the hospital used the same criteria for diagnosis of HAPE. The diagnostic criteria included a mandatory history of recent entry to HA; the symptoms of breathlessness at rest and cough with expectoration; with tachycardia and moist breath sounds on auscultation; low saturation of hemoglobin as measured by pulse oximetry, and radiological confirmation

by the presence of mottled opacities in the lung fields. These diagnostic criteria were used uniformly throughout the period of the study.

Since data was collected over several years it was not possible to ensure the same level of consistency in maintaining records. It was necessary therefore to review and validate the data. We identified all those occurrences where important data like entry-mode (road or air) and nature of exposure (FE or RE) was missing. We also verified that all occurrences of HAPE were correctly recorded. For this we compared our data records with the hospital admission records of the only hospital where our participants could have been admitted for HAPE. Our research center is located inside this hospital.

We expected subjects who entered HA by road to experience a more gradual exposure to hypoxia compared to those who traveled by aircraft. We expected the physiological response to hypoxia and the incidence of HAPE to be unequal in these two groups. They were analyzed separately.

Incidence (calculated as the ratio of number of HAPE events to the numbers-at-risk) is presented as a percentage with its confidence intervals (CI). We looked for significant differences between incidences using the non-parametric Fisher Exact test as the 2×2 tables were unbalanced and did not satisfy all the criteria for a Pearson Chi square test. Statistical analysis used SPSS version 15 for Windows and the online Vassarstats website (www.vassarstats.org). Alpha was set at 0.05.

Results

We recorded 5439 exposures to HA in 2626 participants during the study period that extended for nearly 5 years. Table 1 summarizes the data in terms of exposure-type and entry-mode. The four instances where the exposure-type was not known were excluded and all further analysis is for the remaining 5435 exposures. There were 20 events of HAPE amongst 5435 HA exposures in 19 persons. In only one participant did HAPE develop twice – once during FE and then during RE. The overall incidence of HAPE, irrespective of exposure-type or entry-mode, was 0.37% (95% CI: 0.24%–0.57%).

There were no significant differences in the mean ages between the two cohorts in those who traveled by aircraft (FE vs RE: 31 ± 7 years vs 30 ± 6 years) or in those who traveled by road (FE vs RE: 30 ± 6 years vs 31 ± 7 years).

All cases of HAPE, irrespective of exposure-type, occurred between the first and seventh day at HA (3.0 ± 1.5 days). The mean sojourn in the plains for the RE cohort who developed HAPE was 64.7 ± 20.6 days (range 27–93 days). The mean sojourn in the plains for those who did not develop HAPE was 60.7 ± 43.0 days. The difference was not significant.

Incidence of HAPE amongst the air-entry cohort (Table 2)

There were in all 4178 confirmed air-entry events with 13 events of HAPE (Incidence amongst all air-entry events: 0.31%, 95% CI: 0.18%–0.53%). The confidence intervals of the incidences in FE cohort and RE cohort showed considerable overlap (Fig. 1). The relative risk for HAPE in the RE cohort was

Table 1 – Distribution of 5439 exposures to high altitude (3400 m) based on the exposure-type and entry-mode. The numbers in parentheses indicate the numbers of HAPE cases within each group.

	First exposure	Re exposure	Exposure-type not known	Total
Entry by Air	1095 (2)	3083 (11)	1 (0)	4179 (13)
Entry by Road	352 (0)	651 (3)	0	1003 (3)
Entry-mode not known	48 (0)	206 (4)	3 (2)	257 (6)
Total	1495 (2)	3940 (18)	4 (2)	5439 (22)

1.95 (95% CI, 0.43%–8.80%). Since this confidence interval included unity it indicated the possibility of no difference in risk.

Incidence of HAPE amongst the road-entry cohort (Table 3)

Out of the confirmed 1003 road entrants three developed HAPE (incidence amongst all road-entry events: 0.30%, 95% CI: 0.08%–0.95%). All three cases of HAPE occurred in the RE cohort. Since none of the FE cohort developed HAPE the relative risk was not calculated.

Discussion

The main finding of our study was that there was no statistically significant difference between the incidence of HAPE in the air-entry FE cohort (0.18%, 95% CI: 0.05%–0.66%) and the air-entry RE cohort (0.36%, 95% CI: 0.20%–0.64%) (Table 2, Fig. 1). Though the incidence in the RE cohort was about twice the incidence in the FE cohort but the overlap in their confidence intervals was too large. The difference in the incidences could have arisen purely due to chance. This was corroborated by the large 95% confidence interval of the relative risk encompassing unity, and the result of the Fisher exact test for the air-entry cohorts ($p = 0.537$).

Were there inconsistencies in the criteria used to diagnose HAPE? All army doctors who arrive for duty in the hospital underwent a refresher course on high altitude illnesses at our research center. Instruction included the effects of hypoxia

Table 2 – Comparison of incidence of HAPE in those arriving by air to be exposed to HA (3400 m) for the first time vs those arriving by air but re-exposed after a sojourn in the plains.

	First exposure to HA	Re-exposure to HA	Total
Number of events with HAPE	2	11	13
Numbers of events without HAPE	1093	3072	4165
Total	1095	3083	4178
Incidence (95% CI) ^a	0.18% (0.05%–0.66%)	0.36% (0.2%–0.64%)	

^a Fisher Exact Test (two-tailed) $p = 0.534$.

Fig. 1 – Incidence of HAPE in air-entry FE cohort (unshaded bars) and in the air-entry RE cohort (shaded bars). Vertical lines indicate confidence intervals. The pair of bars on the right pertains to incidences calculated after assuming events with missing entry-mode to be air-entry events (also see Table 4).

and the diagnosis and management of high altitude illnesses. This practice was begun in 1992 and was continuing while this study was in progress. Hence the criteria used for HAPE diagnosis would have been consistent throughout the duration of this study.

In healthy unacclimatized plains-dwellers who ascend to HA for the first time, or on subsequent occasions, the chances of developing HAPE are determined by the rate of ascent, altitude achieved, physical exertion immediately on arrival at HA, pre-existing disease and individual susceptibility.¹³

All our participants came to HA by aircraft or by one of two possible road routes. However, there were differences in the altitudes of night-halt camps between the two road routes. When we began the study the majority traveled by the route with lower night-halt camps. Later the proportions traveling by the second route increased. We did not identify these

details during the study and hence cannot comment if this influenced the incidence of HAPE amongst road-entry cohorts. But it is important that on the second road route the camps were located at much higher altitudes (up to 4500 m) than the final destination (3400 m) and the participants who traveled along this road were subject to greater hypoxia. This may have contributed to the slightly higher incidence in road-entry RE cohort (0.46%, Table 3). It is also likely that participants undertook physical exertion at these camps during disembarkation and embarkation. Some subjects may also have had disturbed or inadequate sleep and an uncertain hydration status during the journey. These factors could also have influenced the incidence of HAPE amongst the road-entry cohort.

The final altitude achieved for all participants was 3400 m. After arriving at this altitude, all participants underwent a period of acclimatization. Individual perceptions on the likelihood of suffering HAPE and administrative effectiveness would have determined the faithfulness of adherence to acclimatization guidelines. It is likely that some participants, who do not suffer HAPE during their first exposure, may harbor a false sense of immunity from HAPE and indulge in reckless physical activity. This may have contributed to a higher incidence of HAPE during re-exposure. Our study was not designed to examine this aspect and this may be its limitation. We believe that failure to follow the acclimatization schedule in a disciplined army unit would be an exception rather than the rule and we do not expect this to have had a large influence on the study.

How did we handle missing data? Four entry events were excluded for analysis as already explained earlier. Yet there were 254 other events (48 FE events with no HAPE and 206 RE events with 4 HAPE) where the entry-mode was not known. Considering that the overall numbers of HAPE cases were not many these 4 cases amongst 206 RE events could influence the calculated incidence. One approach to deal with this missing entry-mode data was to assume that in these 254 events the entry-mode would be approximately in the same ratio as in the entry events where full data was available. Another approach was to once assume that all 254 events were air-entry and then to assume all were road-entry. This would produce the most variation in the calculated incidences and provide two extreme results. We opted for the latter approach as this would result in the maximum possible difference between the incidences in FE cohort and RE cohort. While this may appear to be an attempt to adjust data but the resultant exaggeration of the difference between the incidences in the two cohorts would go against our null hypothesis and thus makes our analysis more stringent. The results of these assumptions are shown in Table 4.

How do our findings compare with earlier reports? There have been two earlier published studies based on Indian soldiers at the same location (both authors have used a slightly different altitude for the same location—ours is based on altimeter readings taken at our research center after calibration with a known benchmarked location at the local airfield during the years 2000–2002). Menon (1965) reported an incidence of 0.57% amongst Indian soldiers during 1962–64. However there is no mention of the exact denominator used for calculation of the risk and hence the validity of

Table 3 – Comparison of incidence of HAPE in those arriving by road to be exposed to HA (3400 m) for the first time vs those arriving by road but re-exposed after a sojourn in the plains.

	First exposure to HA	Re-exposure to HA	Total
Number of events with HAPE	0	3	3
Numbers of events without HAPE	352	648	1000
Total	352	651	1003
Incidence (95% CI)	Indeterminate	0.46% (0.16%–1.34%)	

Table 4 – Incidence of HAPE after including events with missing details.

		First exposure to HA	Re-exposure to HA	Total
Air-entry data after inclusion of events with unknown entry-mode	Number of events with HAPE actual + assumed	2 + 0 = 2	11 + 4 = 15	17
	Numbers of events without HAPE actual + assumed	1093 + 48 = 1141	3072 + 202 = 3274	4415
	Total	1143	3289	4432
	Estimated incidence (95% CI)	0.18% (0.05%–0.63%)	0.46% (0.28%–0.76%)	
Road-entry data after inclusion of events with unknown entry-mode	Number of events with HAPE actual + assumed	0 + 0	3 + 4 = 7	7
	Numbers of events without HAPE actual + assumed	352 + 48 = 400	648 + 202 = 850	1250
	Total	400	857	1257
	Estimated incidence (95% CI)	Indeterminate	0.82% (0.4%–1.68%)	

the calculation can never be confirmed. Nevertheless, it is apparent that our estimate and Menon's estimate do not differ substantially. Singh et al (1965) estimated the incidence to be much higher at 15.5% during first exposure and 13% during re-exposure. Here again no reliable denominators were counted or reported and the validity of this very large incidence is unclear. Both these studies were essentially retrospective clinical studies that did not intend to critically study incidence. Recently Ren et al reported a large questionnaire-based study amongst Chinese Han soldiers exposed to HA for the first time.¹⁴ They reported seven cases of HAPE amongst 3605 soldiers; which is an incidence of 0.19% (and not 1.9% as stated in the paper itself – we presume this to be a typographical error). Their subjects also traveled by air from the plains. We are not sure whether all their subjects reached the same final destination. Altitudes achieved are mentioned to be '>3600 m' and it is likely that the hypoxic exposure may have been non-uniform. There is also no mention whether the soldiers underwent a staged physical activity schedule at HA to allow for successful early acclimatization.

Other studies in the past have examined the incidence amongst mountaineering enthusiasts, pilgrims at HA, and skiers and other sports-enthusiasts at HA.^{5,8,10,11,15–17} These studies involved far smaller numbers, varying altitudes, and some may have used other criteria for diagnosis of HAPE and are therefore not strictly comparable with our study. Table 5 presents a summary of these earlier studies. Fig. 2 graphs the various reported incidences and the corresponding altitude. The numbers of points charted are few but a definite pattern appears to emerge. The trend-line shows that there is an exponential relationship between the incidence of HAPE and the altitude. This may be related to the non-linear decrease in hemoglobin saturation with increasing hypoxia of altitude. We have not charted the incidence reported by Singh et al⁹ because of its extreme-outlier nature.

Limitations of this study

Some limitations have already been mentioned in the preceding paragraphs. One of the challenges of the study was that

Table 5 – Summary of some earlier studies where an incidence of HAPE has been calculated.

	Entry- and exposure-type	Age (years)	At-risk events	Incidence of HAPE	Altitude	Remarks
Basnyat (2000)	Trek from 2000 m to 4300 m. FE	33 ± 14	228 pilgrims (73% men)	5.00	4300	Stay at HA < 24 h. None had clinically significant edema.
Hackett (1976)	Air + Trek. FE	Not known	278	3.96	4200	Hikers, flew to 2800 m and then trekked to 4200 m.
Ren (2010)	Aircraft. FE	18.6	3605	0.19	3600	Reported as 1.9%. Exact altitude of exposure not known.
Menon (1965)	FE	20–39	Not known (Male soldiers)	0.57	3400	No data about at-risk population.
Singh (1965)	FE	Not known	Not known (Male soldiers)	15.5	3400	No data about at-risk population. Many details not stated.
Sophocles (1986)	Road (few hours). FE	35.6	268,872	0.01	2500	How many actually entered HA and for how long?
Hultgren (1978)	Road (few hours). RE	>21	686 (50% men)	2.62	3750	Only the comparable age-group is shown.
Singh (1965)	? RE	Not known	Not known (Male soldiers)	13	3400	No data about at-risk population. Many details not stated.
Scoggin (1977)	Road. RE	12	Not known	0.05	3100	No accurate count of at-risk population.
Cremona (2002)	Cable car from 1200 m. Climb from 3200 m	40 ± 12	262	0.38	4560	Study designed to examine pre-clinical HAPE.

(FE = First exposure, RE = re-exposure)

Fig. 2 – Incidence of HAPE reported by various studies in the past and in the present study. Solid triangles denote incidence for first exposure and solid circles for re-exposure. There appears to be an exponential relationship between the incidence and the altitude as shown by the trend-line. The incidence reported by Singh et al⁹ has not been included because of its extreme-outlier nature.

data collection was spread across a long period. Supervision of the process passed through several hands. The fact that supervision was not the same at all times is evident from the absence of certain types of data in different periods of the study. However, the basic nature of data to be collected was simple and did not present any academic challenges. Due to this reason we believe that the study did not suffer. However, there were several missing data but these were a very small percentage of the total. We missed only 257 (<5%) instances of entry-mode data and only 4 instances of exposure-type data (<0.1%). Even so, these 257 events included 6 cases of HAPE that made up 27% of all HAPE cases that we recorded. Hence the actual incidence could have been larger in any of our main groups than we calculated. However the overall incidence (0.4%) included all data and all HAPE cases and is not influenced by the missing data.

Unintentional biases could have resulted from two possible sources of error. The first is the failure to include all cases of HAPE that occurred in the cohort thus leading to underestimation of the incidence. This could have happened if one of the participating subjects developed HAPE and this was not included in the HAPE count. However, all patients, who suffered from HAPE, were admitted to a single hospital and we verified the hospital admission records during the period of the study to prevent this error. There was only a very remote possibility that a subject may have suffered from HAPE and simultaneously moved to different location. Hence we are confident that little error exists in the accounting for HAPE cases.

The second possible source of error was including HAPE events from non-participants. This would have falsely inflated the numbers of HAPE cases and led to a higher calculated incidence. But we did not include any occurrence of HAPE in a person not previously included in the study. Hence this error was eliminated.

Another limitation of this study is that we did not collect data about the period of sojourn from all participants. One of the reasons for this was there would have been a in-built bias in this regard as soldiers were sent on leave usually for a periods of 3–4 weeks or for 6–8 weeks for administrative reasons. Thus it would have been difficult to draw useful conclusions about the role of the period of sojourn and the incidence of HAPE. It is also pertinent to remember that the duration of stay at HA before descending for a sojourn could be another confounder in this analysis.

Conclusion

Our study was based on a fairly rigorous count of the important denominator (the population-at-risk). In the cohort that traveled to 3400 m by aircraft for the first exposure the incidence of HAPE was 0.18% (CI, 0.05%–0.66%). The incidence in the re-exposure cohort traveling by aircraft to the same altitude was 0.36% (CI, 0.20%–0.64%). This difference in incidence could have occurred purely by chance. We did not find evidence for a significantly higher incidence of HAPE during re-entry to HA after a sojourn in the plains.

Conflicts of interest

All authors have none to declare.

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