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Short Communication

Sub-clinical High Altitude Pulmonary Edema in Lowlanders at 3600 m : An Observational Study

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Abstract

High altitude pulmonary edema (HAPE) is a potentially fatal disease requiring emergency evacuation from high altitude areas. We planned this study in order to identify subjects, who developed sub-clinical HAPE in healthy lowlander males (n=109) over 7 days of study period. The subjects, who were asymptomatic for high altitude related illnesses on day 3 of their stay at 3600 m, were subjected to X-ray chest. Those with positive radiological findings for HAPE (Vock's score >2 in one lung quadrant) were labelled to have sub-clinical HAPE. Incidence of sub-clinical HAPE was found to be 6.42% (7 out of 109) as per our suggested definition in male lowlanders after 3 days of stay at 3600 m.

Introduction

Clinically overt high altitude pulmonary edema (HAPE) is responsible for a patient to seek medical help on an emergency basis but early stages of this disease might be missed by the clinicians because some level of symptoms like breathlessness, cough, tachycardia and fall in arterial oxygen saturation are seen at high altitude (HA) even in normal individuals after acute ascent. All lowlanders, irrespective of their genetic susceptibility, are vulnerable to HAPE especially if they ascend too fast or indulge in excessive physical activity at HA (1). Some of these asymptomatic lowlanders after ascent may have radiological findings suggestive of HAPE. Earlier studies have identified this sub-clinical form of HAPE (sub-clinical HAPE) using modalities based on clinical, radiological, sonographic, bio-chemical and pulmonary function assessments and have hypothesized its occurrence by eliciting impaired diffusing capacity, altered pulmonary mechanics and broncho-alveolar lavage fluid studies (1-4). Out of these modalities available for diagnosis of HAPE, X-ray chest (CXR) is an investigation, which is routinely

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carried out in developing countries for this purpose in spite of the inherent limitations like exposure to ionizing radiation, requirement of expertise and size of equipment etc associated with it (4, 5). With this background, we planned our study to identify sub-clinical HAPE in lowlander healthy males at HA in a resource limited settings.

Materials and Methods

Selection of subjects

A total of 161 healthy Indian male lowlanders, with no past history of HA exposure, underwent a resting cardio-pulmonary screening at Chandigarh before getting enrolled for the study. They ascended from Chandigarh (350 m) to Leh (3600 m) in a pressurized aircraft in 55 min. Any participant with persistent tachycardia or hypertension despite adequate rest before examination, suggesting undue high sympathetic drive or with past history of any cardiovascular/respiratory/metabolic illnesses at Chandigarh, was excluded. Subjects with HA related illnesses like acute mountain sickness (AMS), high altitude cerebral edema or HAPE at Leh were also excluded. All subjects were fully informed about the study protocol and a written consent was obtained to participate in this study. The protocol was approved by the institutional ethical review committee as per declaration of Helsinki.

Experimental protocol

All subjects were examined three times at HA viz. within first 24 hr of arrival (D1) to rule out AMS, thereafter at 72 hr (D3) and finally on seventh day of arrival (D7). On D3, CXR of all subjects was carried out employing standard techniques of postero-anterior radiography. Two radiologists, with four and five years of work experience respectively, were blinded for the clinical status of the subjects and they reported the CXR independently based on Vock's score (VS) (4).

We considered a subject to have sub-clinical HAPE if he was asymptomatic for HAPE with VS >2 in at least one of the quadrants of CXR on D3. Any CXR with inter-observer difference in VS of more than 1 was not considered as sub-clinical HAPE. Age matched subjects from the study group, who did not have clinical and radiological findings of HAPE on D3, were randomly selected using random number tables to form the control group. All subjects carried out their normal daily routine activities under medical supervision without indulging in excessive physical exertion during the study period. In order to elucidate the presence of interstitial edema, possibly leading to decline in gas exchange across alveolar membrane, measurement of arterial PO_2 (PaO_2) and PCO_2 ($PaCO_2$) levels in sub-clinical HAPE cases and controls were carried out using ABL 300 of Radiometer Copenhagen on radial artery blood sample collected under strict anaerobic conditions in heparinised syringe (Heparin dose = 10 µL/ml of blood) on D3. CXR along with PaO_2 and $PaCO_2$ measurements were carried out in the both sub-clinical cases and controls again on D7.

Statistical analysis

All data were expressed as mean±SD and Student's unpaired test was applied for statistical comparison ($p<0.05$) for all the tests using IBM SPSS Statistics for Windows, Version 22.0 software.

Results

Out of a total of 161 enrolled subjects, 35 were lost to follow up and 17 subjects with AMS on D1 were excluded from the study. Remaining 109 subjects (mean age 21.5±7.22 years) fulfilled all the inclusion and exclusion criteria of the study protocol. Their mean height (in cm) was 171±4.67 and mean weight (in kg) was 55±10.21. Only 6.42% (7/109) subjects were found to have sub-clinical HAPE with mean VS of 4.29±1.25. Mean VS of control group (n=7) was 1±1.15 on D3. VS determined by the two radiologists had an agreement of 94% and hence no sub-clinical HAPE cases were excluded from the analysis. CXR of all sub-clinical HAPE cases got cleared of edema by D7. The physiological profiles of sub-clinical HAPE case and control groups are shown in Table I.

TABLE I: Physiological profile of Sub-clinical HAPE (n=7) and Control (n=7) analysed by using Students Unpaired 't' tests at df = 12.

Parameter	*D3*		*D7*	
	Sub-clinical HAPE	*Control*	*Sub-clinical HAPE*	*Control*
SaO_2 (%)	87.57±4.47	89.71±2.87	91.29±3.03	90.29±1.70
HR (bpm)	96±20.75	77.29±10.44*	96.29±15.43	78.86±8.82*
SBP (mmHg)	128. 71±18.12	109±7.26*	122.71±13.71	111.57±5
DBP (mmHg)	72.43±12.46	64.86±5.64	74.57±12.40	66±7.94
MAP (mmHg)	91.19±13.73	79.57±5.84	90.62±11.97	81.19±6.79
PaO_2 (mmHg)	47.57±2.91	52.31±2.51†	50.34±2.42	53.5±2.9*
$PaCO_2$ (mmHg)	30.6±3.41	28.2±3.68	27.91±3.78	28.21±3.27

* $p<0.05$ † $p<0.01$

Discussion

Sub-clinical HAPE has neither been objectively defined earlier nor is its exact incidence known. We found out that 6.42% of our subjects had sub-clinical HAPE using CXR as per our suggested criteria on D3. Earlier studies carried out at different altitudes with varying ascent rates and physical exertion, have indicated much higher incidence of sub-clinical HAPE using various modalities of investigation. Page et al have reported an incidence of 92.9% of sub-clinical HAPE at 4730m using ultrasonography of chest (6). Cremona et al showed presence of sub-clinical HAPE in 77% of recreational climbers at 4559 m using closing volume measurement (1). Mason et al showed presence of extra-vascular lung water/interstitial edema, as a prelude to sub-clinical edema in the normal individuals, after measuring respiratory epithelial ion transport by trans-epithelial nasal potential difference and forced vital capacity at 3800 m (7). In spite of the differences among these studies and the present study, the evidence points towards occurrence of similar patho-physiological processes, which are active in both sub-clinical and clinical HAPE cases (1-7).

Analysis of PaO_2 and $PaCO_2$ of sub-clinical HAPE cases in the present study indicates presence of pulmonary interstitial edema. Significant lower PaO_2 levels in sub-clinical HAPE cases on D3 and D7 could have been due to a possible impediment to diffusion caused by collection of extra-vascular / interstitial fluid. Higher $PaCO_2$ levels (although insignificant) in sub-clinical HAPE cases on D3 could have been possibly be due to blunting of hypoxic ventilator response, a mechanism that has also been reported in HAPE susceptible individuals earlier (8). Sub-clinical HAPE cases represent a category placed in the middle of a scale whose one end is represented by normal individuals and other end of the scale being clinical HAPE patients.

A rise of 5.82% in PaO_2 and a fall of 8.79% in $PaCO_2$ levels on D7 from D3 levels without any medical intervention can possibly be due to a rise in ventilation in sub-clinical HAPE cases, a compensatory mechanism occurring during initial days of ascent (9). Our sub-clinical HAPE cases developed enough interstitial edema earlier than controls to have radiological HAPE on D3 but the edema was insufficient to cause clinical HAPE. The absorption of accumulated interstitial fluid during the 7 days of stay at 3600 m without further ascent lead to disappearance of radiological opacities. These individuals could have otherwise developed HAPE if they had ascended further or had indulged in unaccustomed physical exercise (1, 3). Resting HR and SBP of sub-clinical HAPE cases were significantly higher than that of the controls on D3. This cardiovascular response could have been due to possibly a relatively higher sympathetic activation in them so as to compensate for their lower PaO_2 (10). In spite of radiological clearance of interstitial edema in these individuals by D7, their relatively higher sympathetic activity persisted probably due to continuous exposure to hypoxia, which resulted in significant higher resting HR on D7.

The main strengths of our study are: uniform ascent rate, first time exposure of subjects to HA and monitored physical activity during the study period.

As most of the cases of HAPE report by 72 hours after ascent, we planned CXR and arterial blood gas pressure measurements on D3 and D7 of their arrival at HA in order to minimise exposure of our subjects to ionising radiations. This makes it a limitation of this study as radiological/blood gas analysis carried out during first 2 days of stay at HA could have possibly identified more sub-clinical HAPE cases. The present study had another limitation in the form of a small sample size as only 7/109 subjects were finally evaluated for cardiopulmonary parameters on D3 and D7. Also, reporting of their resting cardiopulmonary parameters recorded at Chandigarh would have given a physiological baseline for better comparison. Notwithstanding the fact that PaO_2 and $PaCO_2$ levels were measured on D3 and D7, simultaneous recording of respiratory rate on these two occasions would have given a better ventilatory profile of sub-clinical HAPE cases.

Thus, it seems reasonable to conclude that there exists a possibility that lowlanders suffer from sub-clinical HAPE at HA but remain asymptomatic in spite of the presence of radiological pulmonary edema. This edema resolves spontaneously when sub-clinical HAPE cases do not ascend further or indulge in undue physical exertion. In the resource poor settings, CXR could prove to be a useful tool for identification of sub-clinical HAPE cases in order to plan their further ascent to still higher altitudes.

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