HIGH ALTITUDE PULMONARY OEDEMA - RESPONSE TO EXERCISE AND COLD ON SYSTEMIC AND PULMONARY VASCULAR BEDS

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Abstract

Fourteen subjects who were acclimatised to a height of 7000 feet (average duration 3 ± months) were investigated. Five were normal subjects (Group I) and 9 were those who developed high altitude pulmonary oedema (Group 2).

At the National Institute of Heart Diseases, Rawalpindi, clinical examination, chest X-ray, electrocardiogram, haematological tests, thyroid functions, echocardiography and lung function tests were normal. During exercise testing the blood pressure response was exaggerated in Group 2 compared to Group 1 (P <0.01). Cardiac catheterisation revealed no significant difference in the intracardiac pressures in the resting state in the two groups (P = NS). With cold pressor test the pulmonary pressure and aortic pressure rose significantly in Group 2 as compared to Group 1 (P < 0.01).

It is suggested, therefore, that pulmohary and systemic vascular beds are hyper-responsive to cold in the susceptible subjects (Group 2). This phenomenon may be further aggravated by exertion, hypoxia, and other undetermined factors in producing pulmonary oedema (JPMA 38: 211, 1988).

INTRODUCTION

The reason why particular individuals get pulmonary oedema at altitude has exercised the minds of researchers for several decades. In spite of the vast amount of work done no clear cut picture has emerged. It is therefore necessary to explore all aspects. One such aspect is the reactivity of the systemic and or pulmonary vascular bed. With this in mmd it was decided to test the vascular response of normal individuals and those who developed pulmonary oedema at altitude to exercise and cold.

METHODS

Nine subjects, mean age 25±5 years who developed high altitude pulmonary oedema (Group 2) were compared with five subjects, mean age 31±8 years, with similar experience at high altitude without any suggestion of pulmonary oedema (Group 1). Full informed consent was obtained and measurements were made of all medication.

All subjects in both groups were acclimatised to a height of 7000 feet for an average duration of 3 ± 2 months. Prior to ascent each subject was examined in detail at the local hospital and a chest X-ray and 12 lead ECG were obtained. The ascent to a height of 16,000 feet was achieved in an average duration of about two weeks. A medical officer, well conversant with high altitude physiology, either accompanied the subjects or was present at the stated height. In the subjects who developed high altitude pulmonary oedema (Group 2), the medical officer documented the tase. A history was obtained and clinical examination confirmed the diagnosis. These cases were evacuated after first aid by a helicopter to the nearest hospital (at 5000 feet) in 12—48 hours. Here on arrival the subjects were evaluated clinically and chest X—ray, ECG, routine blood and urine analysis were performed -The subjects were then referred to National In- stitute of Heart Diseases, Rawalpindi (at 1500 feet) for

evaluation after 2—3 weeks. A detailed clinical examination was performed in all cases. Chest X-ray and 12 lead ECG were repeated -

Haematological test, including blood complete picture, urea and electrolytes, sugar, lipid profile, cardiac enzymes, thyroid function, blood gases and formal lung function tests, were performed in all the cases. 2D echocardiography was performed using 2.5 MHz transducer positioned in the third or fourth left intercostal space with the subjects in the slight left lateral position.

All subjects underwent a maximum symptom limited exercise test using modified Bruce protocol. Right and left heart catheterisation was performed under pre-medication (Inj. pethidine 75 mg I/M) sedation and local anaesthesia with 1% xylocaine. Catheter insertion was percutaneous by the Seldinger technique via the femoral vessels. Intra-cardiac pressures were recorded through fluid-filled catheters under resting conditions and following cold pressor test. This test was performed by inserting the left hand and lower third of the forearm in crushed ice for two minutes and then measuring the pressures. Left ventricular cineangiography and selective right and left coronary angiography was performed in all the cases.

The results were analysed using a paired 't' test for changes within groups and the unpaired 't' test for samples for differences between Groups 1 and 2. Differences were considered significant when $P < 0.05$. Results are expressed as mean ± SEM.

RESULTS

Control Subjects (Group 1)

Five control subjects who were posted to high altitude (Group 1), were studied 2—3 weeks after arrival. These individuals underwent detailed evaluation including catheterisation for presumed coronary artery disease, showed no abnormality, and were found to have normal haemodynamics. None of these control subjects had symptoms consistent with high altitude pulmonary oedema. They were amongst a number of normals who were referred for cardiovascular evaluation for T wave changes. These changes were detected on routine medical and ECG check-up. Subjects in Group 1 underwent detailed cardiovascular assessment similar to Group 2 including right and left heart catheterisation and measurement of their response to cold pressor test. Informed consent was obtained in all the cases.

High altitude pulmonary oedema subjects (Group-2) Clinical Features

Symptoms, signs and their frequeiicy are given in Tables I and II.

TABLE-1. Symptoms in 9 Subjects with High Altitude Pulmonary Oedema (Group 2).

Symptoms	No (%)
Persistent Cough	: 9 (100)
Shortness of Breath	: 9 (100)
Chest Pain	: 6 (67)
Palpitations	: 4 (44)
Fainting	: 4 (44)

TABLE – II. Clinical Signs in 9 Subjects with High Altitude Pulmonary Oedema (Group 2).

Signs	No (%)
Cyanosis	: 9 (100)
Hyperpnoea	: 9 (100)
Bilateral Crepitations	: 9 (100)
Tachycardia	: 9 (100)
Low Blood Pressure	: 8 (89)

Radiological Features

Classical features of pulmonary oedema were seen in 8 (89%) cases. In one case (11%) where the clinical picture was classical, radiological picture revealed no evidence of pulmonary oedema. On detailed scrutiny, it was noted that the chest X-ray was performed 5 days after the episode.
Electrocardiographic Features (Table III).

TABLE – III. Electrocardiographic features in 9 Subjects with High Altitude Pulmonary Oedema (Group 2).

Electrocardiographic feature	No (%)
Sinus Tachycardia	: 8 (89)
Right axis deviation	: 7 (79)
R Wave $V_1 - V_2$	
S Wave $V_5 - V_6$	: 3 (33)
LBBB	: 1 (11)
Normal	: 1 (11)

Signs tachycardia in 8 (89%) cases and right axis deviation in 7 (7 8%) cases were the commonest ECG findings. R wave in chest leads V1-V2 and S wave in V5-V6 suggestive of right ventricular overload was recorded in 3 (33%) cases. In one (11%) case ECG picture revealed left bundle branch block while

it was normal in one (11%) subject.
After initial evaluation at the base hospital the subjects were evacuated to National Institute 'of Heart Diseases, Rawalpindi (height 1500 ft) for evaluation. Detailed clinical examination in all the cases was non-contributory. Chest X-ray was normal in all subjects. ECG was normal in 8 (89%) of the nine cases studied (one subject revealed LBBB Pattern). Haematological tests, thyroid function tests, blood gases and formal lung function tests were normal in all the cases. Exercise ECG (Table IV)

TABLE – IV. Blood Pressure (mmHg) and Heart Rate (beats per minute) response (Mean ±SD) in High Altitude Subjects.

	Group – 1 (n=5)		Group – 2 (n=9)	
	At Rest	After Ex	At Rest	After Ex
SBP	114±9	** 165±14	109±11	*** + 201±15
DBP	76±6	* 90±12	79±8	** + 96±12
MBP	85±9	** 112±12	91±8	*** + 133±12
HR	74±7	** 162±18	75±8	** 160±15
RPP	6364±1060	18144±1160	6846±1205	*** + 23104±1250

Difference within group from control– * P<0.05 ** P<0.01 *** P<0.001

Difference between groups – +P <0.01

Key

SBP : Systolic blood pressure (mm Hg) HR : Heart Rate (bpm)
DBP : Diastolic blood pressure (mm Hg) RPP : Rate Pressure Product
MBP : Mean blood pressure (mm Hg)

Each subject underwent maximum symptom-limited (by dyspnoea or chest pain) exercise test and completed stage V of the modified Bruce protocol achieving his maximal target heart rate predicted for his age. In all the cases the ECG was normal. Systolic blood pressure, diastolic blood pressure, and mean blood pressure were not significantly different in the two groups in the control state (pNS). On maximal exercise systolic blood pressure, diastolic blood pressure and mean blood pressure rose in both groups but were significantly higher in Group 2 compared to Group 1 (P< 0.01). The resting heart rates in the two groups were not significantly different (pNS). On maximal exercise the heart rates increased in both groups significantly (P< 0.01) but did not differ from each other (pNS). The double product (rate pressure product) in the control state did not differ significantly in the two groups (p=NS). On maximal exercise the double product rose considerably in both groups but the increase was significantly greater in Group 2 compared to Group 1 (P < 0.01). No cardiac dysrhythmias were detected at any stage, with all subjects remaining in sinus rhythm.
Haemodynamics (Table V)

TABLE – V. Haemodynamic Data (mmHg) in response to Cold Pressor Test in High Altitude Subjects.

	Group – 1 (n = 5)		Group – 2 (n = 9)	
	Rest	Cold Pressor Test	Rest	Cold Pressor Test
RAP	3 ±1	4 ±2	2 ±3	2 ±3
RVSP	20 ±4	22 ±5	16 ±8	*28 ±6
RVEDP	2 ±3	3 ±2	1 ±3	2 ±2 *
PAP	22 ±4	25 ±5	19 ±6	+36 ±3
	10 ±5	15 ±4	9 ±6	*+22 ±3
PCWP	8 ±5	9 ±6	7 ±6	9 ±5
LVSP	110 ±12	*130 ±10	115 ±8	**149 ±12
LVEDP	5 ±3	5 ±4	4 ±4	5 ±3
AP	113 ±15	*140 ±12	115 ±9	**155 ±12
	70 ±18	* 90 ±12	72 ±14	** +97 ±9
MAP	(88 ±11)	*(107 ±12)	(86 ±12)	**+(117 ±11)

Difference within group from control– * $P < 0.05$ ** $P < 0.01$
Difference between groups – + $P < 0.01$

RAP : Right Atrial Pressure (mm Hg)
RVSP : Right Ventricular Systolic Pressure (mm Hg)
RVEDP : Right Ventricular End Diastolic Pressure (mm Hg)
PAP : Pulmonary Artery Pressure (mm Hg)
PCWP: Pulmonary Capillary Wedge Pressure (mm Hg)

LVSP: Left Ventricular Systolic Pressure (mm Hg)
LVEDP: Left Ventricular End Diastolic Pressure (mm Hg)
AP : Aortic Pressure (mm Hg)
MAP : Mean Aortic Pressure (mm Hg)

The control values for right atrial pressure, right ventricular systolic pressure, right ventricular end-diastolic pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, left ventricular systolic pressure, left ventricular end-diastolic pressure and aortic pressure did not differ in the two groups (pNS). With cold pressor test right ventricular systolic pressure showed an increase which was not statistically significant (pNS). Pulmonary artery pressure, left ventricular systolic pressure and aortic pressure showed significantly higher values in Group 2 compared to Group 1 (P < 0.01). There was, however, no significant change in the right atrial pressure, right ventricular end-diastolic pressure, pulmonary capillary wedge pressure and left ventricular end-diastolic pressure respectively (p=NS). Left ventricular cineangiograms and selective right and left coronary angiograms were normal in both the groups.

DISCUSSION

High altitude pulmonary oedema usually begins 24-72 hours after arrival at altitudes greater than 8000 eet[1]. In the Peruvian Andes series the vulnerable altitude began at 12,000 feet[2] while in the Indian series it was 11,000 feet[3]. In our series the vulnerable altitude was 16,000 ± 3000 feet. This difference may possibly be due to the fact that we were only dealing with advanced cases of pulmonary oedema (Group 3 & 4 severity). In evaluating therapy of high altitude pulmonary oedema in Peru, a simple

method of grading severity has been used based on clinical picture, the ECG, and the chest film[2]. General experience indicates that patients with grade IV severity usually die unless prompt therapy is instituted. Our data refers only to obvious and advanced cases of high altitude pulmonary oedema severe enough to require medical attention.

High altitude pulmonary oedema occurs more frequently in younger individuals, but probably no age is exempt. In our series the mean age in Group 1 was 33 ± 8 years and in Group 2 was 25 ± 5 years. The Indian subjects were between 18 and 53 years of age[4]. Pulmonary oedema in Peru was most frequently observed in children. In persons of all ages travelling between the Peruvian highlands and the sea coast, the incidence of high altitude pulmonary oedema was 13 times higher in the age group from 1 to 20 years compared to the age group 20 years. It is rare before 2 years[5].

The initial symptoms of high altitude pulmonary oedema begin 24 to 96 hours after arrival at high altitude and are commonly preceded by heavy physical exertion such as climbing, skiing, or carrying heavy loads[6]. In the Indian series 208 out of 332 cases occurred within three days of arrival at high altitude, 84 cases four to ten days after arrival, and the remaining 40 cases eleven to two hundred and forty days after arrival. In the Peruvian Andes series all cases of pulmonary oedema occurred nine to thirty six hours after arrival[7]. In our series the initial symptoms began 12-24 hours after arrival and was preceded by physical work, i.e., climbing. Persistent cough, dyspnoea and chest pain were the commonest symptoms. In the Indian series too, progressive cough and dyspnoea, persistent non-productive cough, marked weakness and fatigue were the most common early symptoms[6]. As the severity of pulmonary oedema increased, usually during the night, dyspnoea at rest became severe and cough became productive. The patient became apprehensive, feared death and might become incoherent. Coma might follow and precede death by 1 to 6 hours if oxygen was not administered or the patient was not carried to a lower altitude[8]. Severe palpitations, incoherence, and fainting were uncommon symptoms in our series.

Signs: The clinical signs in our series included cyanosis, rapid breathing, bilateral crepitations and tachycardia in all the cases. Blood pressure was low in 8 (89%) of the 9 cases studied. In the Indian series cyanosis appeared on the face and extremeties, crepitant rales were heard in the chest. There was no symmetry about 'the rales; they appeared on one or both sides in the intersaapuiar area and spread usually to the upper zones. In fulminant cases the patient felt chocked and wheezes could be heard all over. The patient became rapidly moribund[4]. In 21 patients observed in Peru the mean arterial blood pressure was 106/69 mm Hg. Tachycardia due to severe hypoxia was present in our cases with heart rates upto l60/min in severe episodes. The respiratory rate increased and a mean value of 32/min was observed in Peruvian studies[1].

Radiological Features

Classical features of pulmonary oedema were seen radiologically in 8 (89%). In the remaining one case the chest x-ray was taken late after clearance of pulmonary oedema. In our cases the exudate nearly filled both lung fields. The oedema was more severe and common in the right mid lung field as reported by the other workers[2,3,9] In addition there was fullness of the hilar blood vessels and the pulmonary artery was enlarged. The heart size was not increased. Repeat chest films after recovery revealed clearance of exudates and decrease in prominence of pulmonary arteries but no change in heart size.

Electrocardiographic Features

Sinus tachycardia in 8 (89%) and right axis deviation in 7 (78%) were[4] the commonest ECG findings in our cases. There was evidence of overload in 3 (33%) cases. These changes probably reflect some degree of pulmonary arterial hypertension concomitantly present with pulmonary oedema.

Exercise Testing

Systolic, diastolic and mean blood pressures were similar in the groups at rest. With maximal symptom

limited exercise, systolic and mean blood pressures rose in the subjects who had developed pulmonary oedema (Group 2) compared to the control subjects (Group 1). The heart rates did not differ significantly in the two groups both at rest and on maximal exercise. The double product, however, showed significantly higher values for Group 2 compared to Group 1 on maximal exercise because of exaggerated blood pressure rise in Group 2. This data suggests that the subjects who developed high altitude pulmonary oedema exhibited a hyperresponsive systemic arterial vasoreactivity. Similar observations have not been made by anyone else as far as review of available literature showed. Exercise clearly increases the possibility of developing high altitude pulmonary oedema. Indirect evidence of the importance of exercise has been obtained at the Chulee General Hospital in Peru where 11 patients have been successfully treated at high altitude by bed rest alone. Neither oxygen nor drugs were employed at any time during their hospital stay[7].

Haemodynamics

The results of our study show that subjects who experienced high altitude pulmonary oedema (Group 2) had increased pulmonary and systemic arterial vasoreactivity to cold pressor test compared with subjects who reside at similar altitude but have not developed high altitude pulmonary oedema (Group 1). Some individuals appear to be susceptible to high altitude pulmonary oedema. Thus, cold pressor test caused a large but variable increase in the pulmonary and systemic arterial pressure in the susceptible subjects (Group 2) but only a small change in control subjects (group 1). One minor drawback of our study was that the control subjects (Group 1) tended to be older than those with history of high altitude pulmonary oedema (Group 2). This difficulty arose because catheterisation and cold pressor challenge of normal adults is not a routine or ethical practice.

Physiological studies have indicated that subjects with a previous history of high altitude pulmonary oedema show an abnormal rise in pulmonary arterial resistance and an impaired pulmonary oxygen exchange during acute altitude exposure that is not observed in normal subjects. Susceptible individuals also show a more marked rise in pulmonary artery pressure and arterial resistance than normal subjects during low oxygen breathing[9,10,11]. No studies are available (amongst subjects who had developed high altitude pul monary oedema) on the effect of cold pressor test. We believe that the effect of cold in addition to hypoxia and other factors is an important contributory factor to the development of pulmonary oedema among the susceptible subjects (Group 2).

Data from 5 patients studied by Hultgren and 6 subjects studied by Roy[5] are consistent with our fmdings of an elevated pulmonary artery pressure and a normal pulmonary capillary wedge pressure. These workers further observed the effect of 3 intervention upon the circulation in patients with history of high altitude pulmonary oedema:

1) 100% oxygen breathing is accompanied by prompt fall in pulmonary artery pressure.
2) Supine exercise is accompanied by a rise in pulmonary artery pressure without a change in pulmonary capillary wedge pressure.
3) Acute hypoxia results in a rise in pulmonary capillary wedge pressure.

Although as a group susceptible patients (Group 2) showed an excessive rise in pulmonary artery pressure during cold pressor test, two patients in this group did not show such a response. This finding is reminiscent of that by Hultgren and Grover, who also showed that some adults with a history of high altitude pulmonary oedema did not show an increased pulmonary pressor response to hypoxia when tested at low altitude, indicating that pulmonary vasoreactivity may not in itself cause high altitude pulmonary oedema[10]. Although our findings indicate a relationship between susceptibility to high altitude pulmonary oedema and increased pulmonary vasoreactivity to cold pressor test, some other factor or factors must be involved. We have shown an exaggerated vasoreactivity of the systemic arterial vasculature amongst the susceptible individuals (Group 2) to cold pressor test. This response in some unknown way, (by redistribution of body fluids) may contribute to the development of high altitude pulmonary oedema. Available literature provides insufficient data or information on the

subject.

Several subjects have been reported to have developed pulmonary oedema during an upper respiratory ifiness while residing at high altitude. A possible explanation for the association of upper respiratory illness and pulmonary oedema at high altitude is that nasal obstruction further intensifies the hypoxia of altitude and increases the duration and frequency of apnoetc spells durtng sleep[11,12]. This factor was absent in our cases. Another possibility is that viral respiratory infection could increase permeability in the pulmonary vascular bed or alter the alveolar epithelial barrier[12].

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