High Altitude Pulmonary Oedema

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Abstract. High Altitude Pulmonary Oedema (HAPO) is the most common serious ailment affecting troops serving at high altitude. The incidence is about 1 in 200 amongst individuals proceeding by air to an altitude of 11,000 feet (3,413.7 m). The manifestations of HAPO are : cough, dyspnoea, haemoptysis, weakness, absence of signs of infection, presence of pulmonary rales and cyanosis and prompt disappearance of symptoms and signs with treatment with bed rest, and therapy with supplemental oxygen. Prompt and adequate treatment yields eminently gratifying results in practically every instance. Oxygen and bed rest remain the sheet anchor of treatment, supplemented on occasion by diuretics and sedatives. The role of digoxin in the therapy of HAPO is debateable and its aetiopathogenesis is still unclear. The paper presents the clinical data of the first series of cases to be reported from India, and compares the findings with those of other and subsequent workers.

1. Introduction

High Altitude Pulmonary Oedema (HAPO) is the most common serious illness affecting Indian troops, serving in mountainous areas[1]. Over the past 20 years more than 2000 cases of this potentially life-threatening disorder have occurred in India. HAPO has also affected mountaineers in various parts of the world, and has aroused therefore considerable interest in mountaineering circles. The disease is precipitated by rapid ascent to altitudes above 8,000 feet (2,400 m) and is seldom seen on slow ascent occurring over several days. The most frequent symptoms are breathlessness at rest, chest pain, cough, and expectoration of frothy and sometimes pink sputum. The common physical findings are cyanosis, tachypnoea, tachycardia, right ventricular heave and accentuated pulmonary second sound. Radiologically fluffy shadows are seen in both lung fields. Many deaths have been reported amongst mountaineers and also amongst troops. Descent to lower altitude or administration of oxygen at high rates of flow, generally results in improvement of the patient.

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Historically, the disease was first described by Mosso in 1898. Hurtado reported the first case in South America while Houston[2] was the first to record a case in English literature. Subsequently a few cases have been reported sporadically from various parts of the world. The disease really burst upon the world of medicine in almost epidemic proportions in 1962. Inder Singh[3] *et al* and Menon[1] have reported a few hundred cases. The study of 101 cases of HAPO reported in the latter series was carried out at a hospital located at 11,200 feet (3,413.7 m). The aim of the present paper is to re-evaluate these observations in the light of subsequent studies by workers in different parts of the world.

2. Earlier Observations

2.1 *Observations by Menon[1]*

During the two-year period 1962-64, 101 cases of high altitude pulmonary oedema were diagnosed and treated at the field hospital at Leh, Ladakh in India. The incidence of the disease amongst troops arriving at high altitude by air was 5.7 per thousand. It was less common amongst arrivals by road. As would be expected, out of 66 patients between June 63 and May 64, 49 patients were admitted during the six-month period December 63–May 64 when the roads were closed, as against only 17 admitted during June–November 1963 when arrival was by both road and air. Symptoms usually developed within 1-3 days of arrival. Although in 10 cases of HAPO, the people had subjected themselves to violent exertion immediately after arrival, the fact that 66 of the 101 patients were employed on sedentary duties, tended to diminish the significance of the stress of exertion on the precipitation of HAPO.

Typically, the sequence of events was as follows : during the first three days of arrival the patient often had insomnia, headache, dizziness, nausea and palpitations; and would develop a dry cough, which was short, sharp and suppressed, and did not inconvenience him very much. As the condition advanced, breathlessness would increase and mucoid sputum would be expectorated. Frothy pink sputum, large in quantity, and thin in consistency would indicate the occurrence of pulmonary oedema in all its severity. Substernal discomfort leading on to a dull ache or pain was often present. An occasional patient was apathetic, or boisterously violent or lapsed insidiously into deep coma.

The physical findings consisted of central cyanosis (52/101 patients) and a rather low blood pressure. The pulmonary second sound was palpable and the cardiac impulse was of right ventricular pattern. The pulmonary findings were the most significant of all. From a prolongation and harshness of expiration in the right interscapular region as the earliest signs, fine crepitations soon appeared in both interscapular and infrascapular regions. Soon coarse crackling crepitations would appear throughout both lungs and bubbling rates would completely mask heart sounds.

X-ray of HAPO patients indicated woolly opacities in both lungs in the upper and middle zones (Figs. 1 & 2). Starting off as a fuzziness of the vascular shadows in the
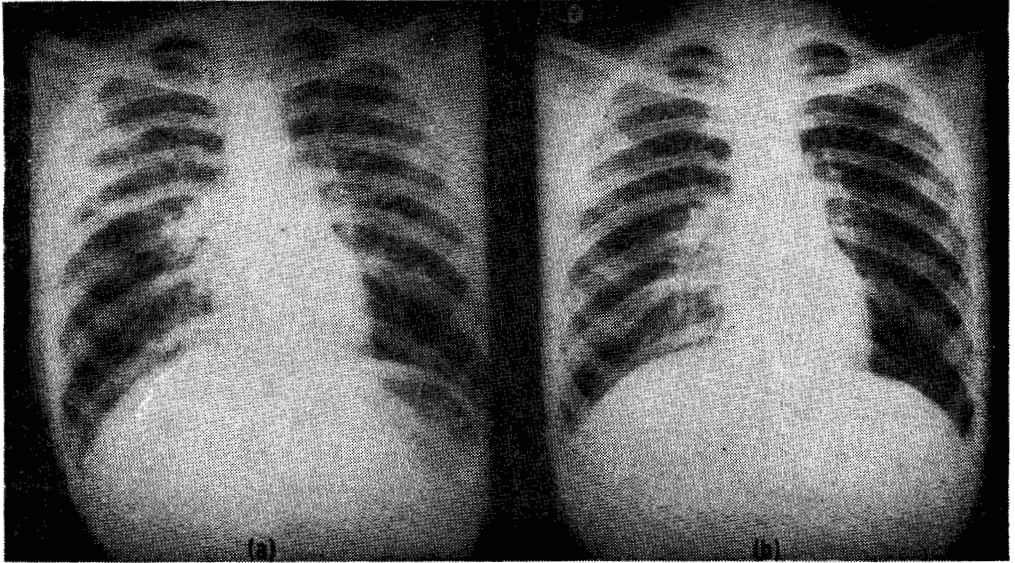

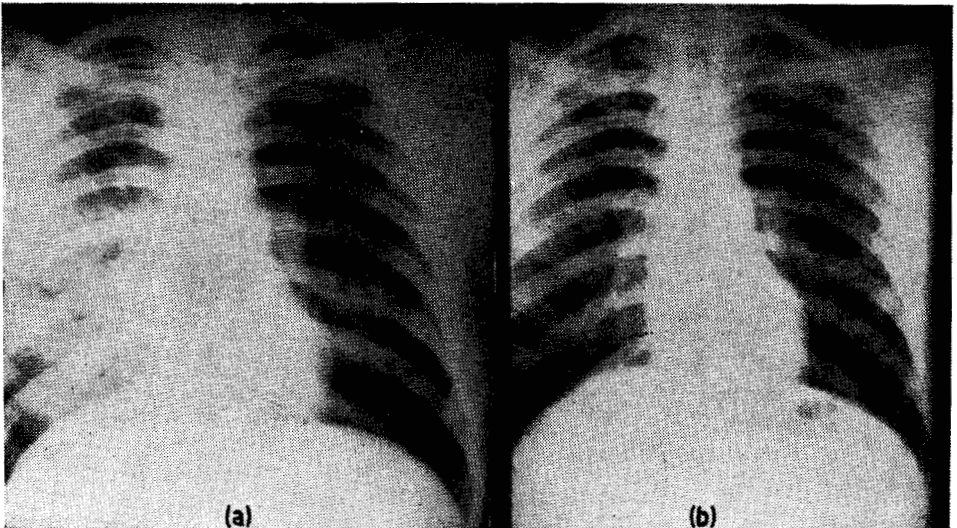**Figure 1.** Lung X-ray of HAPO patient, (a) on admission, (b) four days later.

Figure 2. Lung X-ray of HAPO patient, (a) on admission, (b) four days later·

right middle zone, woolly shadows would spread throughout both lungs. The pulmonary conus was prominent in some patients. Barium swallow examination in six patients taken during the acute phase and repeated after recovery showed some easing of the pressure on the barium filled oesophagus with recovery. The electrocardiogram was normal in most patients, but an occasional finding was raising of ST segment in praecordial leads, symmetrical T-Wave inversion and clock-wise rotation of the heart. An abnormal Q-Wave was never present.

The disease in most patients responded very well to bed rest and oxygen therapy by intra-nasal catheter/BLB mask at rates of flow of 6-8 litres/min at the hospital, located at 11,200 feet (3413.7 m). 34 of 101 patients (i.e. 34 per cent) recovered completely on oxygen alone. Improvement was apparent within 30 min to 120 min. Digoxin was administered to 66 patients in a dosage of 0.5 to 1.5 mg I.V. Response to treatment was invariably good. In 24 of these patients digoxin was administered only after two hours of oxygen had not improved the condition of the patient. In the remaining 42, digoxin was injected at the start of treatment. A small trial dose of digoxin 1.5–2 mg I.V. without supportive oxygen in six patients yielded equally good results. Diuretics (mersalyl or hydrochlorothiazide) was given to 48 patients on admission, but this practice was discontinued in the latter part of the study, as no useful purpose seemed to be served. Morphia invariably improved the depth of respiration and decreased dyspnoea.

There were four deaths altogether, all in the initial stages of the study (i.e. between cases 1 and 16) and no death occurred subsequently.

On the basis of this study of 101 cases it was suggested that myocardial failure secondary to hypoxia appeared to be a fundamental causative factor in the production of HAPO.

2.2 *Observations by Other Workers*

The clinical observations mentioned above have not been added to substantially during the two decades that have passed since they were described, despite several reports of HAPO by authors around the world. However, views have been expressed regarding the usefulness of various therapeutic measures and also on the funda-

Table 1. Incidence of high altitude pulmonary oedema

Author	Region		Incidence
Menon[1]	Ladakh	Himalayas	0.57%
Singh and Roy[4]	Ladakh	Himalayas	2.3–15.5%
Hultgren[5]		Peru	0.4%
Houston[6]		Kenya	0.44%

mental cause of HAPO. The following paragraphs discuss some of the observations made by other workers with a view to re-evaluate the earlier findings[1] in the light of newer knowledge.

2.2.1 *Incidence of HAPO*

The incidence of HAPO as reported by various workers is shown in Table 1.

The discrepency between the findings of Singh & Roy[4] and the remaining authors is difficult to explain, but there is no doubt that the incidence is much lower than 15 per cent and is definitely less than 1 per cent. Recently Adya (personal communication, 1984) reporting from the Ladakh Himalayas has given the figure of 0.24 per cent amongst all inductees by air, and 0.13 per cent amongst fresh inductees by air, and 0.3 per cent amongst re-inductees during the year 1983.

2.2.2 *Therapy of HAPO*

Evacuation to lower altitude and administration of *oxygen* have been accepted as the most important aspects of therapy. As far as troops at high altitude are concerned, evacuation to an altitude below 11,200 feet (3,413.7 m) (the location of the hospital) has not been found necessary as all patients of HAPO recovered at this altitude with adequate therapy. Besides, since the aim of deploying troops for long periods at high altitude is to defend the outposts, evacuation of the individual after recovery to the plains is likely to affect morale. Mountaineers on the other hand have laid stress upon evacuation to a lower altitude as oxygen alone is reportedly ineffective. This is obviously because of the greater heights at which mountaineering parties operate. At 11,200 feet (3,413.7 m) there is no doubt about the efficacy of oxygen alone in 34 per cent of patients.

Singh[7] has advocated the use of the quick-acting diuretic furosemide, 40-80 mg intravenously in the management of HAPO. Recently doubts have been expressed regarding the usefulness of diuretics. Hultgren[8] is of the opinion that there is insufficient evidence from appropriately conducted clinical studies that furosemide is indicated and warned that in severe cases of HAPO (with a low cardiac output, haemoconcentration, and shock) furosemide is more likely to aggravate hypotension.

Marticorena & Hultgren[9] evaluated their therapeutic measures and compared the treatment of 20 controls on conventional therapy (including bed rest, and continuous administration of oxygen) with 16 patients on bed rest alone (without oxygen or other therapy). No treatment failures occurred in either group. They concluded that HAPO of mild to moderate severity can be treated successfully with bed rest alone, *without the administration of oxygen, and without moving the patient to a lower altitude.* Oxygen therapy was considered slightly more effective as relief of symptoms was rapid. It is of interest to note that all the patients in the study were children between three years and 19 years (mean age 9.8 years) and were almost all permanent residents of high altitude who had gone to the plains for a short sojourn and developed

HAPO on coming back to high altitude. The situation in India is rather different both as regards age and residence at high altitude and it would be illogical to apply Marticorena & Hultgren's findings to our situation.

The clinical details of the 101 cases of HAPO reported by the author[2] have been re-examined in the light of the observations of Marticorena & Hultgren[9]. The treatment afforded to the 100 cases who reached hospital alive are given in Table 2. It was found that all the four deaths occurred early in the series before experience had been gained; there was no death amongst 94 consecutively treated cases—all treatment schedules being successful. The clinical data of 41 consecutive patients treated during the latter part of the study were reviewed and grading of severity of pulmonary oedema done as described by Marticorena & Hultgren i.e., based upon clinical symptoms, signs, radiological findings, and heart and respiratory rates, (see Appendix for criteria used). The grading and results of therapy in these 41 patients are given in Table 3.

23 of the 41 patients (56 per cent) improved on bed rest with oxygen therapy alone, irrespective of the severity of pulmonary oedema. Even amongst patients with severe pulmonary oedema 12 out of 20 patients (60 per cent) needed no other therapy apart from oxygen. Lung signs cleared up in 2.9 days. Addition of morphine, digoxin or diuretics (Inj mersalyl/chlorotheazide) did not appreciably shorten the duration of persistence of lung signs. Diuretics were given to only 5 patients (12 per cent). Lung clearance took 4-5 days in severe cases. Although it cannot be inferred from this that diuretic therapy delayed recovery, there is no doubt that it did not hasten it in these particular patients. Certain unpublished observations by Dutta are pertinent in this connection. In 1972 Dutta (at Ladakh), treated 25 consecutive

Table 2.   Treatment regimes of 101 patients of HAPO

Bed rest	Oxygen	Digoxin	Morphia	Diuretics	Antibiotics	No. of patients	Deaths
+	+	—	—	—	—	30	—
+	+	—	—	—	+	3	2
+	+	+	—	—	—	8	—
±	+	+	—	—	+	3	—
+	+	+	+	—	—	6	—
+	+	+	+	—	+	2	—
+	+	+	+	+	—	1	—
+	+	+	+	+	+	23	1
+	+	—	—	+	+	1	—
+	+	+	—	+	—	5	—
+	+	+	—	+	+	18	—
—	—	—	—	—	—	1	1
					Total :	101	4

No. of patients treated with diuretics   :   48
No. of patients treated withoutdiuretics :   52

Table 3.   Response to therapy of various grades of HAPO

	Treatment	Grade 1 (Mild)	Severity of HAPO Grade 2 (Moderate)	Grade 3 (Serious)	Grade 4 (Severe)	No of patients
(a)	Oxygen only	—	3 (2)	8 (2.6)	12 (2.9)	23
(b)	Oxygen + Digoxin	—	1 (3)	4 (2.9)	3 (3.7)	8
(c)	Oxygen + Digoxin + Morphine	—	2 (2)	—	3 (2.7)	5
(d)	Oxygen + Digoxin + Morphine + Diuretics	—	1 (3)	2 (4)	2 (4.5)	5
	Total		7	14	20	41

Note :   (Figures in brackets indicate average number of days for clinical clearance of lungs)

patients of HAPO with bed rest, oxygen inhalations and morphia, withoutadministration of furosemide. He compared the results with 25 cases of 'similar' severity treated on 'accepted' lines with bed rest, morphia, atropine, furosemide. betamethasone and aminophylline. He observed that there was no difference in the outcome— all patients recovered. These observations cast serious doubts about the need for even quick-acting furosemide in the treatment of HAPO (personal communication).

This retrospective analysis of the clinical findings in the 1962-1964 series of 101 cases of HAPO, if anything, confirms the impression that it would be incorrect to lay down a standard method of treatment for all cases. There are no satisfactory criteria for grading the severity of pulmonary oedema in a manner to assist prognostication of eventual result. Although Marticorena & Hultgren's method is useful, as it is based upon several clinical and radiological criteria, it does not still provide an adequate background against which to plan the treatment of the individual patient. As indicated in Table 3 a patient with grade 4 (severe) pulmonary oedema may respond to oxygen inhalations alone, whereas another with only grade 2 (moderate) pulmonary oedema may not.

Marticorena & Hultgren's cases from Peru were almost all, residents of high altitude, whereas in India the population affected belong to the plains and undertake 1-2 year spells of duty at high altitude and then return to the plains. This basic difference in permanent residence may explain the occasional need for supplemental drug therapy amongst Indians suffering from HAPO.

2.2.3   *Pathophysiology of HAPO*

On the basis of the study of 101 cases it has been suggested that myocardial failure is an important factor in the production of HAPO. This has been postulated because of certain observations elaborated in the original article[1] that tend to support this view. Briefly, these consist of history of nocturnal dyspnoea in 59/100 patients,

considerable elevation of pulse rate preceding rise in respiratory rate, a distinct rise in B.P. with recovery, barium swallow studies in six patients suggesting pressure on the oesophagus during the acute phase, and response to rapid I.V. digitalization in patients not recovering with oxygen therapy alone (and even in the absence of oxygen therapy).

As against this there have been studies doubting the role of myocardial dysfunction in the production of HAPO. Fred et al.[10], Hultgren et al[8,11,12], and Roy et al[13] have produced evidence to suggest this is not so. They have recorded normal wedge and left atrial pressures. Increased pulmonary artery pressures have been recorded by Vogel et al[14] and Kronenberg el al[15]. All these studies have been performed on a handful of subjects and no large scale study has been done perhaps because invasive studies, especially at high altitude, have inherent risks.

The prevailing opinion amongst most authorities is that the myocardium is basically sound, and the cause of HAPO has to be searched elsewhere. However, authorities are not unanimous on the subject. Alexander et al[16] felt that a decrease in myocardial contractility at altitude could result from impairment of myocardial oxygenation secondary to failure of oxygen transport or a decrement in coronary arterial tension or both. Balasubramanian and co-workers[17,18] demonstrated left ventricular dysfunction at high altitude by serial estimation of systolic time intervals in a pilot study of 20 volunteers inducted by air. Hoon[19] in his B C Roy Memorial Oration reporting on his findings in 329 subjects taken by air to high altitude demonstrated by non-invasive methods 'positive evidence of left ventricular dysfunction—the stroke volume was decreased, cardiac output decreased despite tachycardia, and all parameters of myocardial contractility levels. The evidence in respect of these conclusions is considered unequivocal'.   ·

Subsequently, Das[20] working on volunteers in the Himalayas has reported evidence of improvement in all myocardial function parameters by non-invasive techniques following the administration of digoxin.

These observations would tend to suggest that the role of left ventricular dysfunction in the production of high altitude pulmonary oedema cannot be lightly brushed aside, and further studies would have to be done on patients of HAPO during the acute phase and again on recovery before LV failure can categorically be excluded.

Recently, Milledge[21] has mentioned the various possible pathophysiological changes in HAPO. He says 'The clinical picture is of left ventricular failure but although it is hard to rule out entirely, the evidence of catheter studies is that pulmonary wedge pressure[18,22] and (on the basis of one patient with a patent foramen ovale) left atrial pressure are normal (Fred et al[10]). In all cases however the pulmonary artery pressure is greatly increased. The various mechanisms suggested are not mutually exclusive and include an increase in capillary permeability as a direct result of hypoxia, or via mediators whose concentrations are increased by hypoxia; a non-

uniform vasoconstriction resulting in torrential flow in less constricted areas, leading to oedema in these areas[23,24] and fluid leakage through the arterial walls proximal to the resistance vessels. There is some suggestive evidence for all these possibilities. The association of proteinuria with acute mountain sickness supports the idea of increased permeability of blood vessels. The other two mechanisms would explain the highly non-uniform appearance of this form of pulmonary oedema as seen on chest radiographs and at necropsy, where some areas of the lungs are found to be perfectly normal some oedematous and some frankly haemorrhagic. In both lung and brain a primary derangement of the clotting mechanism must be considered as a possible underlying mechanism'.

From the above observations by Milledge[21] it would seem that left ventricular failure is a possible, though very unlikely, cause of HAPO. This may perhaps be the correct scientific view. However in the same issue of Thorax, Dickinson presents an interesting paper entitled 'Altitude related deaths in 7 trekkers in the Himalayas'. These are undoubtedly selected cases—all severely ill or dead on arrival at the hospital at Khatmandu. All these patients had pulmonary oedema on necropsy. A note-worthy feature of the therapy given to these patients was the exhibition of penicillin/ampicillin, betamethasone, furosemide, mannitol and diamox to almost all the patients. Morphia given to one patient reportedly produced temporary relief from dyspnoea. Digoxin was administered intramuscularly to an individual, the dose not being specified. To a proponent of digoxin therapy for severe and unresponsive cases of HAPO and to one who has repeatedly observed the efficacy of both digoxin and morphia (like the present author), Dickinson's unfortunate series seems to vindicate the role of digoxin. One cannot help wondering if adequate digitalization would not have reversed the downhill progress as it has done in other equally ill patients in the author's series of 101 cases. This is downright speculation, but one based on close clinical observation. Perhaps, after all, left ventricular failure does play a role in the pathophysiology of HAPO. Until this is disproved, it may be prudent to administer digoxin to all seriously ill patients of HAPO not responding to oxygen inhalations and morphia.

3. Conclusion

This re-appraisal of a report of 101 cases of HAPO originally published in 1965 suggests that the clinical pattern of the disease remains the same over the past two decades; the benefits of diuretic therapy in HAPO are doubtful; and the pathophysiology of the disease is still unclear despite intensive study by workers all over the world. It is felt that the role of digoxin and morphia in the treatment of HAPO needs re-appraisal, and LV function in HAPO also needs to be studied.

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Severity Classification of HAPO
(Modified from Marticorena & Hultgren[9])

Grade	(a) Clinical symptoms and signs	(b) Heart rate	Resp rate	(c) X-ray findings
I (Mild)	Minor symptoms dyspnoea on mild exertion	110	20	Minimal opacities, less than 1/4 of 1 lung
II (Moderate)	Weakness, fatigue, headache, cough, dyspnoea at rest	110–120	20–30	Opacities 1/2 of 1 lung
III (Serious)	Severe dyspnoea, headache, weakness, nausea, cough, wheezing cyanosis	121–140	31–40	Opacities involving at least 1/2 of each lung or unilateral involving all of 1 lung
IV (Severe)	Clouded consciousness, stupor, coma, unable to stand, weakness bubbling rales, copious sputum, usually bloody severe respiratory distress	140	40	Opacities involving lungs extensively

Note : Overall grading is done by addition of grades of (a) and (c) with the average grading of heart rate and respiratory rate (b).