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Haemodynamic Studies in High Altitude Pulmonary Oedema

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The clinical and pathological features of acute pulmonary oedema of high altitudes have been the subject of several recent reports (Houston, 1960; Hultgren *et al.*, 1961; Peñaloza, 1962; Arias-Stella and Kruger, 1963; Nayak, Roy, and Narayanan, 1964; Menon, 1965; Singh *et al.*, 1965), but the haemodynamic effects of the illness are not well delineated (Fred *et al.*, 1962; Hultgren *et al.*, 1964). The purpose of this communication is to present data on the circulatory and respiratory parameters observed in (1) 6 subjects with high altitude pulmonary oedema studied at 3658 metres within 24 hours of the onset of the illness, and (2) 3 subjects restudied 5 times after recovery.

Subjects and Methods

Clinical History. Cases 1, 2, and 3 (Table I) are residents of Nepal (altitude 1524–2438 m.). They reached a post at 4267 m. between March and June 1967, and acclimatized successfully. On September 25, they had to move up to 5182 m., and after some army exercises (digging trenches, pitching tents) developed acute pulmonary oedema on September 27. Case 4, a plainsman, climbed to 3658 m. in late September 1967, went on up to 4572 m. within the next 24 hours, and on exertion developed acute pulmonary oedema on September 28. Case 5 is a native of Tibet, born and brought up at altitudes of over 4267 m. He came to India in 1965, where he was stationed at a height of 2103 m. In May 1967, he went to 3658 m. where he developed acute pulmonary oedema and was taken to a lower altitude. He returned to 3658 m. on September 19, when within 48 hours he developed acute pulmonary oedema for the second time. Case 6 is a plainsman who had an attack of high altitude pulmonary oedma at 4267 m. in July 1967, for which he was flown to sea-level. He returned to 3658 m. on September 27, and developed pulmonary oedema on September 30.

All initial studies were performed within 24 hours of the onset of the illness at an army general hospital at 3658 m. Because of their previous history of pulmonary oedema, Cases 5 and 6, on arrival at 3658 m.,

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TABLE

CIRCULATORY PARAMETERS IN HIGH

Case No.	Age (yr.)	Body surface area (m.²)	Heart rate/min.	Cardiac output index (l./min./m.²)	Stroke volume index (ml./beat/m.²)	Blood volume (ml./m.²)		
						Total	Central	Pulmonary
1	22	1·60	125	2·4	19	3900	467	206
2	23	1·72	75	4·5	60	4700	865	410
3	38	1·80	75	3·2	43	3600	880	349
4	28	1·70	96	3·4	35	2580	648	176
5	20	1·58	110	3·0	27	2900	440	155
6	26	1·70	140	3·5	25	4200	518	224

were kept in the wards of the hospital under observation, when they developed frank pulmonary oedema. The remaining 4 subjects had to be brought to the hospital by helicopter. The hospital was centrally heated and patients were studied in the *x*-ray room while lying supine on the *x*-ray table. They were acutely ill and had received one or more doses of intravenous morphine (15 mg.) and frusemide (40 mg.) before the study. They were also on continuous oxygen inhalation (BLB mask) which was interrupted only for 10 minutes for the collection of expired gases and blood samples. Right heart catheterization was performed by positioning a No. 7 cardiac catheter in the pulmonary artery just beyond the valve. The left atrium was entered by the percutaneous transseptal method, as practised in this laboratory (Roy, Bhatia, and Guleria, 1963). The right femoral artery was cannulated to obtain arterial blood pressures and dye curves. Consecutive dye dilution curves were obtained directly on a polyviso channel through a continuous recording densitometer (Colson) by injecting indocyanine green dye into the main pulmonary artery and then into the left atrium. The difference in the mean transit times of the two resulting curves was taken as pulmonary transit time. The cardiac output was measured from the dilution curves by the formula of Hamilton *et al.* (1932). The volume of blood between the pulmonary artery and the left atrium was obtained by multiplying the pulmonary mean transit time by the average cardiac output, and this represented the pulmonary blood volume. Similarly, the volume of blood between the pulmonary and the femoral arteries was measured by multiplying the pulmonary artery to femoral artery mean transit time by the average cardiac output, and this gave the central blood volume. Details of the technique have already been reported (Roy, Bhardwaj, and Bhatia, 1965a). The total blood volume was estimated by azovan blue dye (Gibson and Evans, 1937). The intracardiac and femoral arterial pressures were recorded through Statham P23AA strain gauge manometers on a 4-channel single gun photographic system. The baseline for all pressure measurements was taken as half the chest thickness at the second costal cartilage, with the patient supine (Roy, Gadboys, and Dow, 1957). Expired gas was collected for a measured period of 3 minutes in a Haldane bag. Minute ventilation was measured directly from a ventilometer. Arterial blood *p*H, P_{CO_2}, and P_{O_2} were estimated by Beckman electrode, arterial blood gas by the technique of McNeill and Van Slyke, and expired gas by Roughton-Scholander gas analyser. Case 5 was restudied at 3658 m. after a week and again at sea-level 8 weeks later; Case 3 was restudied twice at sea-level 4 and 8 weeks later, while Case 6 was restudied after 4 weeks at sea-level. Except for the difference in the altitude, repeat studies were performed under identical conditions of room temperature, technique, equipment, and observers.

Results

Circulatory Parameters (Table I and Fig. 1). The pulmonary arterial (or right ventricular) systolic pressures were moderately raised (36 to 54 mm. Hg), and the pulmonary arterial wedge and left atrial and filling pressures of both the ventricles were normal. The cardiac output was low normal in 5 patients, and as 3 of them had tachycardia, their stroke volume was much diminished, below 30 ml. per beat per square metre of body surface area. The pulmonary blood volume exceeded 310 ml. in 2 subjects.

Respiratory Parameters (Table II). The minute ventilation was generally raised. There was consistent increment in the arterial blood *p*H values, with concomitant reduction in the P_{CO_2} values. Arterial blood P_{O_2} was significantly decreased, and there was significant alveolar arterial oxygen tension gradient (18 to 30 mm. Hg). Case 5 was also anaemic, with an oxygen capacity of only 13·4 volume per cent (packed cell volume was 30%).

Restudy Data (Table III). The pulmonary arterial systolic pressure of Case 6 remained high after 4 weeks. The pulmonary blood volume decreased in Case 3 and increased in Cases 5 and 6. The stroke volumes increased in these 3, and their arterial blood became fully saturated. The *p*H, P_{CO_2}, and P_{O_2} values approached normal in Cases 3 and 5.

I

ALTITUDE PULMONARY OEDEMA

Pressures (mm. Hg)													
Right ventricle			Pulm. artery			Pulm. art. wedge	Left atrium	Left ventricle			Femoral artery		
Syst.	Diast.	End diast.	Syst.	Diast.	Mean	Mean	Mean	Syst.	Diast.	End diast.	Syst.	Diast.	Mean
50	0	5	48	20	30	2	1	120	0	5	120	76	95
54	0	3	—	—	—	—	5	128	0	5	128	70	92
34	0	5	34	15	22	—	4	110	0	5	110	70	80
40	0	2	37	16	24	9	8	112	0	8	112	60	80
36	0	3	36	15	24	3	2	112	0	3	112	60	80
42	0	3	—	—	—	—	1	115	0	5	115	65	80

TABLE II

RESPIRATORY PARAMETERS IN HIGH ALTITUDE PULMONARY OEDEMA

Case No.	Minute vol. (l./min.) BTPS	Minute vol. (l./min.) STPD	R.Q.	Vent./perf. ratio	Mean alveolar O_2 tension	Arterial blood: pH	P_{CO_2} (mm. Hg)	P_{O_2} (mm. Hg)	O_2 content (vol. %)	O_2 cap. (vol. %)	O_2 satn (%)	HCO_3^- (mEq/l.)	Base excess (mEq/l.)	Mixed venous blood O_2 cont. (vol. %)	Alveolar-arterial O_2 tension gradient (mm. Hg)
1	11·8	6·5	1·16	2·04	70	7·46	24	52	21·9	25·3	87	16·6	−4	17·1	18
2	8·7	4·9	1·11	1·04	64	7·45	29	42	18·6	23·8	78	19·6	−2·5	15·5	22
3	13·8	7·1	0·93	1·08	65	7·49	26	40	18·4	23·8	78	19·2	−1	14·9	25
4	12·1	6·6	1·75	0·99	69	7·45	34	49	17·9	21·1	85	22·5	0	15·7	20
5	14·1	7·2	1·03	0·81	56	7·43	35	27	7·2	13·4	54	21·9	−1	4·1	29
6	15·6	7·9	0·83	0·86	60	7·52	27	30	14·7	22·2	66	21·0	0	11·5	30

Discussion

To evaluate the present findings, the major haemodynamic parameters of the 5 subjects studied by Fred *et al.* (1962) and Hultgren *et al.* (1964) are grouped with our observations, and shown in Table IV and Fig. 2. The partial oxygen tension of the arterial blood was not estimated in the previous studies, but the arterial oxygen saturations of 64 to 76 per cent recorded in 3 of their patients are within the range of our observation of 54 to 86 per cent. The heart rate of the 4 subjects studied by Hultgren *et al.* exceeded 105 beats a minute, 81 in Fred *et al.*'s patient, whereas the rate in 3 of our patients was below 100, and in 1 the rate reached as high as 140 a minute. Cardiac output index data, available only in 3 subjects, were between 2·5 and 3·0 l./min./m.^{2}, similar to the output index observed in 3 of our subjects. However, in the remaining 3, the value was within our normal range of 3·5 to 4·5 l./min./m.^{2} Because of tachycardia, the stroke volume index of the 3 subjects was low, similar to the values obtained by Hultgren *et al.*; the remaining 3 had normal values. Hultgren and coworkers (1964) had emphasized the occurrence of severe pulmonary arterial hypertension in high altitude pulmonary oedema, but in their own subjects, only one patient had severe increase in the pulmonary arterial pressure, and in the remaining 3 the pressure was only moderately raised. The subject studied by Fred *et al.* had a pulmonary arterial systolic pressure of 68 mm. Hg. In the present series all the patients had moderate increases in pulmonary arterial pressure ranging from 34 to 48 mm. Hg systolic. It thus appears that an increase in the pulmonary arterial pressure in high altitude pulmonary oedema

TABLE

RESTUDY OF PHYSIO-

Case No.	Date in 1967	Altitude (metres)	Heart rate/min.	Cardiac output index (l./min./m.^{2})	Stroke volume index (ml./beat/m.^{2})	Blood volume (ml./m.^{2}): Total	Central	Pulmonary
3	28 Sept.	3658	75	3·2	43	3600	880	349
	28 Oct.	198	65	3·2	49	4900	—	—
	20 Nov.	198	60	3·4	57	3400	646	233
5	22 Sept.	3658	110	3·0	27	2900	440	155
	30 Sept.	3658	80	4·7	59	2500	714	—
	20 Nov.	198	75	4·3	57	3600	925	423
6	30 Sept.	3658	140	3·5	25	4200	518	224
	27 Oct.	198	120	4·5	38	3800	685	325
Normal average		198	85	4·1	49	3000	960	210

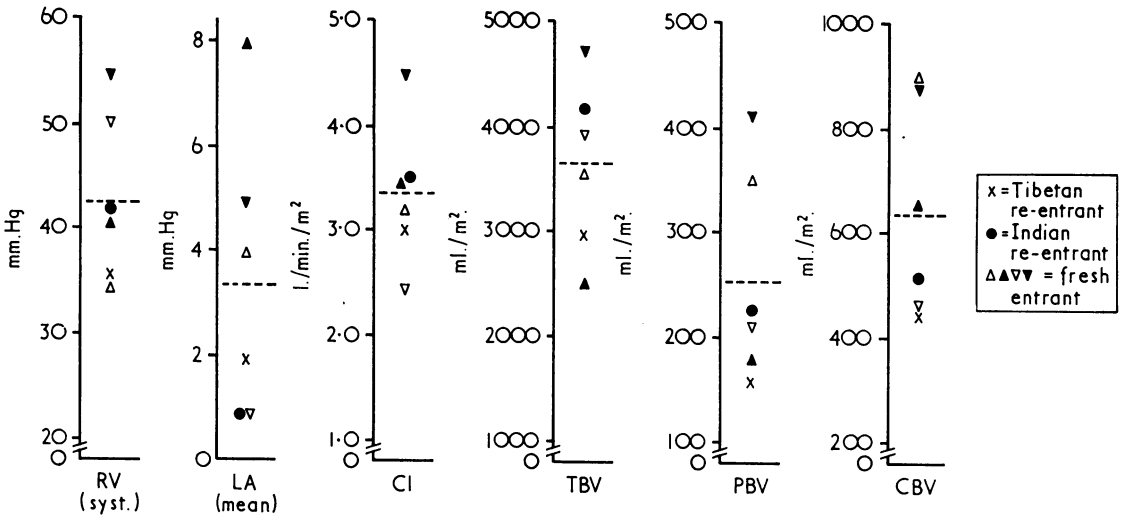

FIG. 1.—Circulatory parameters in 6 subjects with high altitude pulmonary oedema. The Tibetan re-entrant is Case 5, the Indian re-entrant is Case 6. ▽ = Case 1; ▼ = Case 2; Δ = Case 3; ▲ = Case 4. RV = right ventricular; LA = left atrial; CI = cardiac index; TBV, PBV, and CBV are total, pulmonary, and central blood volume, respectively. The horizontal broken line in each panel represents the average of the six observed values.

is a constant observation, but a severe degree of hypertension is not a common finding.

Fred *et al.* could not obtain a pulmonary artery wedge pressure but recorded a normal left atrial pressure in the single patient they studied, whereas Hultgren *et al.* did not catheterize the left heart and obtained normal to low pulmonary arterial wedge pressures in their 4 patients. So far simultaneous pulmonary arterial wedge and left atrial pressures have not been measured in patients with high altitude pulmonary oedema. This was done in 3 subjects in the present study, and both mean pressures were found to be the same. The left atrial mean pressure in the 6 subjects was between 1 to 8 mm. Hg, which is within our normal range of 2 to 11 mm. Hg (average 4 mm. Hg) obtained by

III

LOGICAL PARAMETERS

Pressures (mm. Hg)					Min. vol. (l./min.) STPD	R.Q.	Vent./ perf. ratio	Mean alveolar O_2 tension	Arterial blood			
Right ventricle			Left atrium	Femoral artery								
Syst.	Diast.	End-diast.	Mean	Syst. diast. mean					*p*H	P_{CO_2} (mm. Hg)	P_{O_2} (mm. Hg)	O_2 satn (%)
34	0	5	4	110/70 (80)	7·1	0·93	1·08	65	7·49	26	40	78
27	0	6	6	130/70 (88)	7·7	0·74	0·71	96	7·44	37	57	89
25	2	5	7	130/72 (88)	8·1	0·74	0·67	94	7·42	39	70	93
36	0	3	2	112/60 (80)	7·2	1·03	0·81	56	7·43	35	27	54
40	0	4	4	118/60 (80)	8·4	1·02	1·09	66	7·44	26	56	89
33	0	5	8	130/68 (90)	—	1·18	1·10	107	7·38	39	90	97
42	0	3	1	115/65 (80)	7·9	0·83	0·86	60	7·52	27	30	66
42	0	3	8	138/68 (90)	6·3	0·87	0·58	106	7·48	34	70	94
21	0	3·5	4	120/70 (85)	5·4	0·79	0·67	95	7·41	39	87	96

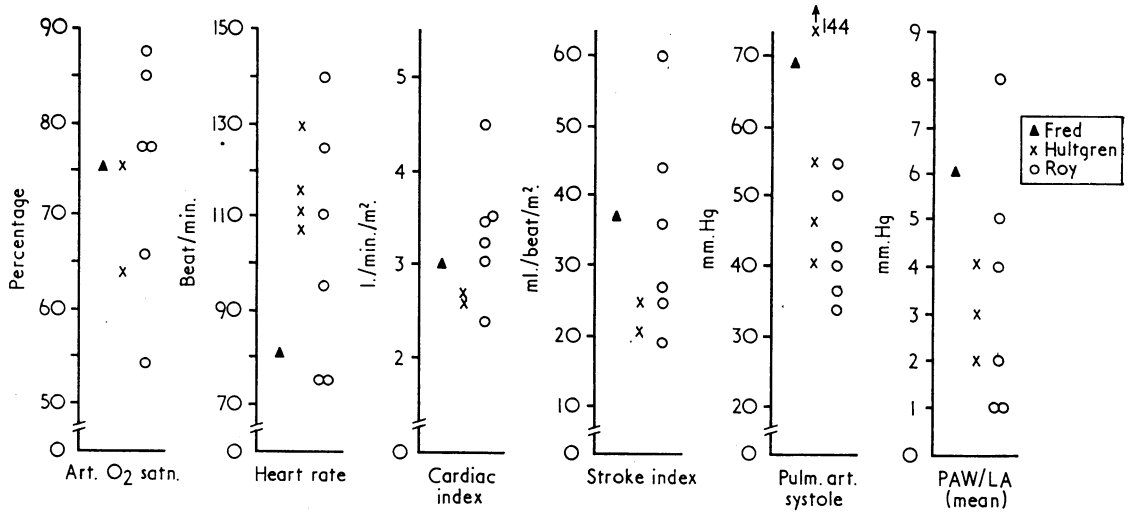

FIG. 2.—Comparison of the main haemodynamic data in 6 subjects with high altitude pulmonary oedema, with the findings in 5 subjects studied by Fred *et al.* (1962) and Hultgren *et al.* (1964). Pulmonary arterial pressures were obtained in only 4 subjects, hence right ventricular systolic pressures have been substituted for comparison.

TABLE IV

COMPARISON OF HAEMODYNAMIC DATA IN 11 SUBJECTS WITH ACUTE PULMONARY OEDEMA OF HIGH ALTITUDE

Parameters	Fred *et al.* (1962) (1 subject)	Hultgren *et al.* (1964) (4 subjects)	Roy *et al.* (present paper) (6 subjects)
Arterial O_2 saturation (%)	76	76; 64; ?	87; 78; 78; 85; 54; 66
Heart rate/min.	81	129; 107; 115; 110	125; 75; 75; 96; 110; 140
Cardiac output index (l./min./m.²)	3·0	2·6; 2·7	2·4; 4·5; 3·2; 3·4; 3·0; 3·5
Stroke volume index (ml./beat/m.²)	37	20; 25	19; 60; 43; 35; 27; 25
Pulmonary artery (systolic) (mm. Hg)	68	144; 55; 47; 41	48; 54*; 34; 37; 36; 42*
Pulmonary artery wedge or left atrium (mean) (mm. Hg)	6	4; 2; 5; 3	1; 5; 4; 8; 2; 1

* Right ventricular systolic.

studying 25 healthy soldiers (Roy *et al.*, 1967). The restudy left atrial pressure values showed consistent increase (4–7, 2–8, and 1–8 mm. Hg) in the 3 subjects. Hultgren *et al.* (1964) also noted a similar rise in the pulmonary arterial wedge pressures when restudied subsequently. The present observations confirm those of Fred *et al.* and Hultgren *et al.* that pulmonary oedema of high altitude is not due to an increase in the pulmonary capillary or left atrial pressures.

Because the pulmonary blood volume estimated in convalescents from high altitude pulmonary oedema was found to be higher than in those convalescing from high altitude pulmonary hypertension (Roy *et al.*, 1965b), and because there was an 80 per cent increase in the pulmonary blood volume in healthy soldiers when air-lifted from sea-level to 3658 m. within 48 to 72 hours of their arrival, a vulnerable period for high altitude pulmonary oedema (Roy *et al.*, 1968), it was surmised that the pulmonary blood volume grossly increased during high altitude pulmonary oedema (Roy, 1966). The present findings did not support this assumption, for the pulmonary blood volume exceeded the upper limit of our normal value of 310 ml./m.² (Roy *et al.*, 1967) in only 2 subjects (Cases 2 and 3). There are two possible explanations for this. (1) The technique employed in the present study to measure the pulmonary blood volume estimates only the intravascular blood volume, and fluid which has already oozed out into the alveolar spaces is not accounted for. (2) The patients were acutely ill and had

received one or more doses of intravenous morphine and frusemide, and it has been shown previously that morphine reduces the pulmonary blood volume (Roy *et al.*, 1965c). This is supported indirectly by the restudy data of Cases 5 and 6 in which the pulmonary blood volume increased considerably 4 to 8 weeks after the episode of oedema.

The total blood volume in 4 subjects exceeded the average normal values, but on restudy variable changes were seen. However, there was evidence of peripheral venous constriction. The average value of the forearm venous distensibility measured plethysmographically (Wood and Eckstein, 1958) in the pulmonary oedema subjects was only 2·8 ml./100 ml. forearm tissue, as against 4·4 ml./100 ml. in healthy subjects. Similar peripheral venous constriction and shift of the blood volume to the pulmonary circuit, with no change in the total blood volume, were also observed in healthy persons in the first 48 to 72 hours after their arrival by air at an altitude of 3658 m. (Roy *et al.*, 1968). The minute ventilation at BTPS was greatly increased, and even when converted to STPD it was still higher than average normal values, indicating hyperventilation. Added to this, was evidence of respiratory alkalosis (high *p*H and low P_{CO_2}). It is difficult to outline the sequence of events leading to high altitude pulmonary oedema. A possible mechanism may be the sudden accentuation of hypoxia due to a change in altitude, and/or exercise causing hyperventilation and respiratory alkalosis, raised pulmonary arterial pressure, and a shift of the blood volume from the periphery to the pulmonary circuit. It is also possible that hypoxia causes pulmonary capillary endothelial damage which, together with the increased pulmonary arterial pressure and blood volume, leads to pulmonary oedema of high altitude.

Summary

Data on the circulatory and respiratory parameters of 6 subjects with high altitude pulmonary oedema studied at 3658 m. within 24 hours of the onset of the illness and of 3 subjects restudied after recovery are given. The pulmonary arterial pressure was raised in all subjects, but the pulmonary capillary, left atrial, and filling pressures of both the ventricles were normal. The cardiac output was reduced or normal despite tachycardia in 3 subjects. The pulmonary blood volume exceeded the upper limit of normal values in only 2 subjects, and the probable explanations for the discrepancy are outlined. It is postulated that the rapid accentuation of hypoxia causing a rise in pulmonary arterial pressure, marked peripheral vasoconstriction shifting the blood volume to the pulmonary circuit, and damaged pulmonary capillary endothelial lining, may be a possible mechanism of acute pulmonary oedema of high altitude.

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