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Blood Coagulation Changes at High Altitude

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Abstract. The current concepts of blood coagulation changes in the pathogenesis of acute mountain sickness (AMS), high altitude pulmonary oedema (HAPO), high altitude pulmonary hypertension (HAPH) and chronic mountain sickness (CMS) which afflict the inductees and residents at high altitude have been reviewed. Hypercoagulable state which is more marked during the first few days of exposure is countered by enhanced fibrinolytic activity and accelerated cell mediated immunity. Magnesium levels are increased in normal residents at high altitudes and may be responsible for enhancing fibrinolytic activity and accelerating immune responses. Magnesium levels are significantly reduced in HAPO patients. Judicious use of furosemide in lower dosage is still the mainstay of treatment of HAPO and AMS.

1. Introduction

The interest in high altitude physiology has increased immensely for a variety of reasons which include defence of our country, wealth of mineral reserves, health resorts, instinct for adventure, recreation and natural beauty of mountains. A large number of people therefore live at high altitudes or go to high altitude. Solar radiation, hypoxia, hypobaric pressure, and cold are the primary factors which adversely affect the physiological responses in man at high altitude. Main illnesses which afflict inductees and residents at high altitude are acute mountain sickness (AMS), high altitude pulmonary oedema (HAPO), high altitude pulmonary hypertension (HAPH) and recently discovered chronic mountain sickness (CMS) in the Himalayas. Our experience of these illnesses dates back to the days of the Chinese aggression on our Northern borders in 1962. A large amount of relevant information has been collected, since then on the clinical and pathophysiological aspects of the above disorders[1-9]. Pathogenesis of these disorders is far from clear. The aim of the present communication is to review the current concepts of blood coagulation changes in their pathogenesis.

2. Haemostasis at High Altitude

First few days of recent arrivals at high altitude are very critical. During these days important adaptative changes take place in them, failure of which may initiate adverse pathophysiology resulting in development of acute mountain sickness and high altitude pulmonary oedema. These are fast developing acute illnesses which if left untreated could prove fatal. In fulminating cases, commonly precipitated by exercise, the whole course from the onset to death may be less than 30 minutes. There is a time lag from 6 to 96 hours between arrival at high altitude and onset of both the disorders[1–6]. However, majority of HAPO cases occur within the first 4 days and the chances of its developing become remote after 7 to 14 days.

It is in this context that changes in blood coagulation at high altitude within first few days of arrival become revealing.

On immediate arrival or within 24 hours at high altitude there is a tendency towards hypercoagulation associated with an increase in platelet count, factors X and XII, and thrombotest activity. It is also reflected by shorter prothrombin time, bleeding time, clotting time in glass and in silicone, and stypven time. Clot retraction is impaired. This state of hypercoagulation is countered by a compensatory rise in fibrinolytic activity evident by reduction of clot lysis time, plasma fibrinogen, and factor VIII[3,5].

On day 3, factor V decreases, bleeding time and stypven time are further shortened, and factor VIII shows a rise. On day 7, a progressive rise occurs in factors V, VIII, X and XII, thrombotest activity, platelet count and platelet factor 3 (PF-3). Clotting time in glass and silicone, prothrombin time, and stypven time show further shortening.

On day 14, haematocrit rises and of all the parameters, factors V and X, and clot retraction return to normal. Throughout the fortnight, factor XII remains high, clot lysis time short, thrombin clotting time prolonged, and platelet adhesiveness remains within normal range. PF-3 availability remains high in the later half of the fortnight only. No significant change occurs in calcium time throughout the fortnight[3,5].

A delicate balance seems to exist between the coagulant and fibrinolytic forces. Based on the numerical score, in this study, the state of hypercoagulation, on arrival at high altitude (3692 m), has been expressed as + 11 on day 1, + 9 on day 3, + 28 on day 7, and + 17 on day 14 in recent arrivals. From the above account it is evident that immediately on arrival at high altitude there is a tendency towards a hypercoagulation state, however, it is counteracted by increase of fibrinolytic activity in the normal circumstances[3,4,5,10].

This hypercoagulation state persists throughout the early fortnight after arrival at high altitude and then starts regressing. What seems to be an adaptative compromise during continuous stay at high altitude, there is further regression of the

coagulant state. It is indicated by persistent short clot lysis time accompanied with prolongation of bleeding time, clotting time in silicone, prothrombin time, stypven time, calcium time, and thrombin clotting time. Thrombotest activity is reduced. Platelet adhesiveness, PF-3, factors V, VIII and XII and clot retraction are restored to normal. However, the reduction in hypercoagulation on prolonged stay at high altitude is partly checked by significant increase in plasma fibrinogen[3,4].

Our findings that acute exposure to high altitude brings about a state of hypercoagulability in man are in conformity with those of Genton and his associates in their animal studies[11]. They recorded significant reduction in platelet half life and fibrinogen half life in calves exposed to high altitude (4310 m) for 10 days. Plasminogen showed a rapid decrease in animals but fibrinolytic activity was not found to be altered. Our observations on platelet numbers are at variance with those of Gray *et al*[12] and Chatterji *et al*[13] who recorded fall in platelet counts in their subjects after 2 days exposure to high altitude, however, the latter authors showed a concomitant decrease in platelet aggregation and explained that their results could be affected by the presence of increased fibrinogen degradation products[14,15] due to increased fibrinolytic activity at high altitude and also by increased amount of 2, 3-diphosphoglycerate (2, 3 DPG), a known physiological inhibitor of platelet aggregation[16], which usually increased on exposure to hypoxia[17]. Fall in plasma fibrinogen and factor VIII were observed by Maher and associates[17] on second day of high altitude exposure (simulated altitude 4400 m) but no alterations were found in platelet count, prothrombin time. thrombin time and PF-3, though the partial thromboplastin time was shortened in this study.

It can be concluded that a transient state of hypercoagulability is induced on acute exposure to high altitude. Increased amount of coagulation factors and increased platelet adhesiveness/aggregation may lead to sequestration of young and adhesive platelets, from circulation, in the pulmonary vascular bed[12]. But the compensatory rise in fibrinolytic activity is a fortunate sign to counteract this tendency. After a fortnight sojourn at high altitude, the initial state of hypercoagulability is almost overcome as a result of persistent increase of fibrinolytic activity which prevails throughout the rest of stay at high altitude[10]. Women at high altitude are better disposed in this respect since their status of fibrinolytic activity is of a higher magnitude than that of men. In our experience, the adverse changes in blood coagulation induced by exposure to high altitude revert to normal on descent to plains. Platelet adhesiveness, clot lysis time, factor V and VIII, stypven time and thrombin clotting time return to normal within one week. PF-3, fibrinogen, thrombotest activity, prothrombin time and calcium time are restored to normal values within one to three weeks of arrival at sea level[4].

3. Acute Mountain Sickness

Acute mountain sickness is the most common manifestation encountered on arrival at high altitude without acclimatization and is characterized by headache, nausea, vomi-

ting, insomnia and lassitude in milder form. In its severe form it may be presented with some neurological features which may include irritability, drowsiness, hallucinations, ataxia, stupor, fits, coma and paralysis etc or it may form a part of high altitude pulmonary oedema accompanied with progressive dyspnea, tachypnea at rest, blood stained and frothy sputum and moist basal crepitations or widespread rales invariably involving both lungs. The pathogenesis of AMS is largely obscure. Rapid ascent, exercise, and anti-diuresis are the common precipitating factors for both AMS and HAPO. These symptoms occur over a period of 6 hours to 5 days when lowlanders ascend to high altitudes[6,18,19]. The symptom-complex of AMS is readily relieved by diuretic therapy. The general consensus is that there is an initial hypersecretion of adrenal corticosteroids, anti-diuretic hormone and aldosterone with renal retention of water and electrolytes and a marked intracellular shift of fluid[6,20-22]. Recently Rennie has summarised that both severity and incidence of AMS are proportional to speed of ascent and degree of exertion and inversely related to age[23]. In his subjects rapid weight gain, associated with flat neck veins and high urine osmolality, is a reflection of body water retention. The above mechanisms are alleged to operate concomitantly with effects of hypoxia and cause peripheral venous constriction leading to increased pulmonary blood volume, congestion and/or frank pulmonary oedema. This in turn results in oliguria and development of cerebral oedema which causes headache and other neurological disorders. The elevation of CSF pressure results in papilloedema and retinal haemorrhages[24-27]. Meehan and Zavala attribute retinal haemorrhages to the frequent Valsalva manoeuveres, increase in venous pressure and its transmission to dilated capillaries[28]. Alternately, the role of the sympatho-adrenal system and increased secretion of catecholamines persistently in the symptomatic group of AMS has been stressed to result in intracellular shift of fluid[29]. Increased levels of circulating catecholamines have been implicated in affecting platelets adversely resulting in increased platelet adhesion, platelet aggregation and formation of platelet and fibrin thrombi within the pulmonary arteries, venules and capillaries in cases of high altitude pulmonary oedema[5]. More recently Maher and associates[30] have observed multiple coagulation abnormalities in a group of subjects who developed symptoms of AMS when subjected to a simulated altitude (4400 m) exposure from 1 to 48 hours. The symptoms in the exposed group were associated with significantly shortened partial thromboplastin time, and fall in plasma fibrinogen and factor VIII levels after one hour of high altitude exposure. While partial thromboplastin time remained reduced throughout the study, plasma fibrinogen and factor VIII were elevated after 24 and 48 hours of the exposure, more or less returning to pre-exposure levels. Some of the subjects showed also an evidence of transient presence of late fibrinogen degradation products suggesting activation of secondary fibrinolysis, a compensatory phenomenon to counter hypercoagulation state. A concomitant rise in 2, 3-DPG seemed to have masked the abnormal platelet activity in this study[30]. However, some workers have noted increase in platelet adhesiveness in the symptomatic subjects who were air-lifted to an altitude of 3658 m, the increase was maximum on the tenth day of the exposure[31]. The alterations in the haemodynamics on arrival at high altitude do play their part in the development of AMS[6] but the role of blood hyperviscosity and

hypercoagulability, and platelet aggregation is largely unknown. However, the acute mountain sickness, benign or malignant, involving brain and lungs, is the variant of the same diseased process and undoubtedly there is increasing body of evidence that thrombosis at least is an important and possibly the primary event in the pathogenesis of acute high-altitude illnesses/variants[32]. Simultaneous appearance of symptom-complex of AMS and the abnormal blood coagulation changes on acute exposure to high altitude strongly suggests the involvement of coagulopathy in the aetiopathogenesis of this disorder. If these observations are further confirmed, then a rational therapy with anticoagulants and anti-platelet aggregating drugs could be evolved for prophylaxis and treatment of this syndrome. Till then prevention oi acute mountain sickness can be best achieved by gradual ascent and avoidance of strenuous exertion by trekkers at the high altitude.

4. High Altitude Pulmonary Oedema

High altitude pulmonary oedema is a noncardiogenic pulmonary oedema[33] which develops on arrival at high altitude between 6 and 96 hours. Majority of cases occur within first four days and the chances of its developing become remote after 7 to 14 days[1,34].

Adolescents and children, unmindful of exerting unnecessarily, are more prone to develop HAPO and reinductees including high altitude natives who reascend after a short stay, even one day in some cases, at lower altitude are at greater risk[35-38]. In haemodynamic studies of patients of HAPO, the pulmonary blood volume is found to be increased and remains so from 3 to 24 weeks after evacuation to sea level[34]. There is no evidence of left ventricular failure. The left atrial and the pulmonary venous pressures are normal. Electrocardiac findings reveal right atrial strain or right ventricular overload[39] and a normal heart size[40]. Radiologically patchy densities noted in high altitude pulmonary oedema are identical in distribution and intensity to the increased areas of blood flow[9,34]. Necropsy studies reveal widespread pulmonary oedema, severe capillary congestion, and enormous distension of the pulmonary blood vessels upto capillaries, extensive plugging of alveolar capillaries with sludged red blood cells, fibrinous and protein-rich exudate in the alveoli and hyaline membrane lining these, features similar to those seen in patients with respiratory distress syndrome. Also multiple fibrin thrombi were observed not only in pulmonary capillary bed but in the kidney, plugging the glomerular and peritubular arteries, and also in the sinusoids in liver[34]. Such dilatation of preterminal arterioles and vascular obstruction by thrombi containing platelet aggregates, white and red blood cells, and fibrin strands in lung fields have been described by a number of workers[41-44]. Besides the above lesions, infection and atelectasis in lung and haemorrhages in the brain have also been reported in mountaineers who suffered from acute mountain illness[45-47].

Some degree of pulmonary hypertension appears to be inevitable at high altitudes and it exists invariably as a part of high altitude pulmonary oedema. The persistence

of pulmonary hypertension for weeks after the pulmonary oedema has subsided is an indication that the changes induced in the pulmonary circulation are not entirely functional. The sludging of cells and the fibrin thrombi in the alveolar capillaries and venules add an organic element to the picture. These findings suggest that exposure to hypoxic stress causes a breakdown of the fibrinolytic enzyme system, and the equilibrium between fibrin formation and dissolution is upset[48]. These observations prompted us to study the blood coagulation parameters in the acute stage of illness in HAPO patients on the spot (3692 m). As described earlier, within first few days at high altitude, a state of hypercoagulability in recent arrivals runs parallel with the incidence of occurrence of HAPO[3,5,49,50]. Blood coagulation studies carried out in patients of HAPO and compared with suitable controls reveal a causal relationship between changes in fibrinolytic activity, blood coagulation factors, platelet functions, and formation of thrombi in the pulmonary circulation. The following changes have been observed at the very outset of the illness. Fibrinolytic activity is reduced. Plasma fibrinogen and factor VIII are increased. Factor XII is decreased. Platelet adhesiveness and PF-3 are significantly increased and are associated with fall in platelets. Clot retraction is markedly impaired. Less significant changes are noted in factor V, factor X, and the haematocrit which are increased; thrombin clotting times are reduced[3,5,49]. Electrophoretic mobility of platelets is reduced[3,51]. Both arterial and venous adenosine-diphosphate (ADP) levels are significantly low compared to controls and there is evidence of sequestration of ADP and platelets in the pulmonary bed in patients[3,5]. In light microscopy of peripheral blood smears of HAPO patients, larger and young adhesive platelets are found in aggregates in greater numbers[5,52]. The electronmicroscopic studies of platelets of HAPO patients reveal that the integrity of plasma membrane, capacity for pseudopodia formation, and the ability of degranulation are intact, showing thereby that platelets from the patients are active both structually and functionally (Fig. 1)[3,5,52]. It is evident that in patients of high altitude pulmonary oedema platelet factor 3 and the substrate for thrombin generation and fibrin formation are provided abundantly. PF-3 provides an active catalytic surface for the interaction of plasma coagulation factors leading to thrombin generation. The resulting consolidation of platelets leads to their degranulation with the release of more PF-3 and ADP and further fibrin formation. Increased platelet factor 3 and platelet adhesiveness in the patients promote the above chain of events resulting in formation of platelet and fibrin thrombi in lungs at the capillary and venular level. This impedes the pulmonary blood flow and results in overperfusion and exudation of protein rich fluid and even cells. This process results in patchy oedema formation in lungs. Such scattered thrombotic occlusions in cerebral microvasculature might be expected to result in cerebral oedema with consequent compression and symptom-complex of AMS. Papilloedema and retinal haemorrhages can also be, perhaps, accounted for by such thrombotic process in retinal vessels.

No alteration in fibrinolytic activity has been reported so far in patients of AMS but a state of hypercoagulability and evidence of coagulopathy have been the early feature in this sickness. In HAPO, however, higher plasma fibrinogen levels associ-

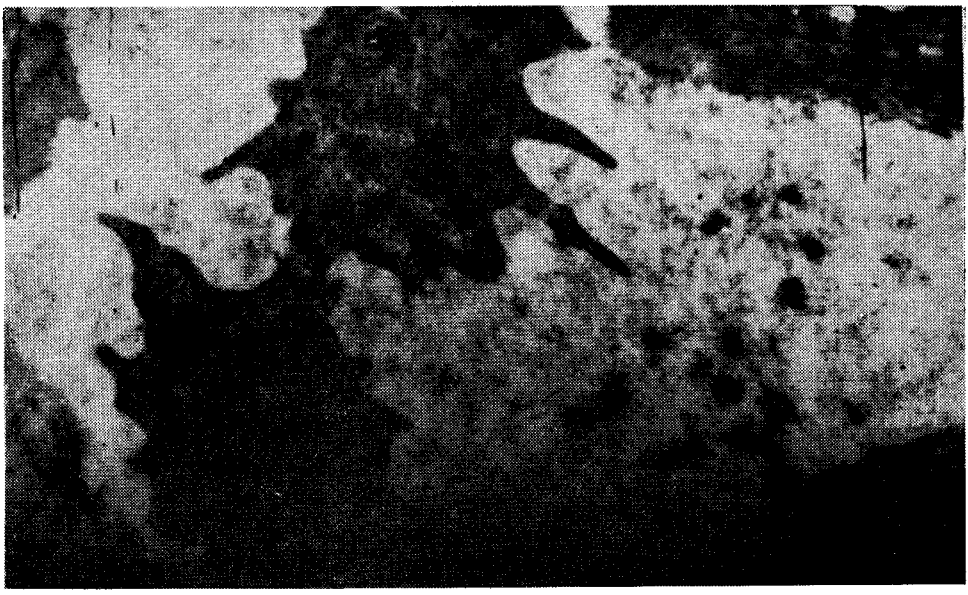

Figure 1. Electronmicrograph of platelets from patients of high altitude pulmonary oedema, stained with uranyl acetate and lead citrate, X 20,000. Pseudopodia, dense granules and glycogen particles are seen.

ated with reduced fibrinolytic activity appear to be characteristic[49]. In the event of breakdown of the fibrinolytic system in this disease the pendulum swings to coagulation acceleration and proves fatal unless treated energetically with appropriate measures and drugs to clear pulmonary congestion and remove impediments to blood flow in the microcirculation in lungs and other affected organs[1,50,53,54].

An important feature, in HAPO patients, is the markedr ise in immunoglobulins IgG, IgA and IgM[3,5,52,55,56]. IgG and IgM get adsorbed on the surface of platelets, alter their mobility, increase their aggregation, and enhance the release of ADP which in turn promotes the availability of PF-3, the latter amplifies further the coagulation process. Recently we have found that a diachotomy of immune responses exists in patients of HAPO[57,58]. Immunoglobulins are increased on one hand and on the other, the cell mediated immunity (CMI) is impaired. This derangement of CMI helps to promote persistence of immune complexes, activated clotting factors, and end products of blood coagulation and thereby accentuates intravascular coagulation in this disorder. Impairement of CMI in HAPO coincides with diminished fibrinolytic activity, when fibrinolytic activity improves the CMI is also restored[60,59]. Our most recent and interesting observation is that both erythrocyte and leucocyte magnesium contents are significantly higher in normal and healthy residents at high altitude but are reduced significantly in patients of high altitude pulmonary oedema[60,61] (Fig. 2). The role of magnesium on immune response and blood

coagulation is well documented. Magnesium deficiency is associated with decreased synthesis of immunoglobulins[62,63] and depressed CMI[64]. Magnesium exerts a favourable effect on blood coagulation which it reduces by its vasodilatory action, its stabilisation of fibrinogen and platelets, and by its stimulation of fibrinolysis[65,66]. Therefore, low magnesium levels in patients of HAPO have a relevance since these are related to diminished fibrinolytic activity and impaired CMI in them.

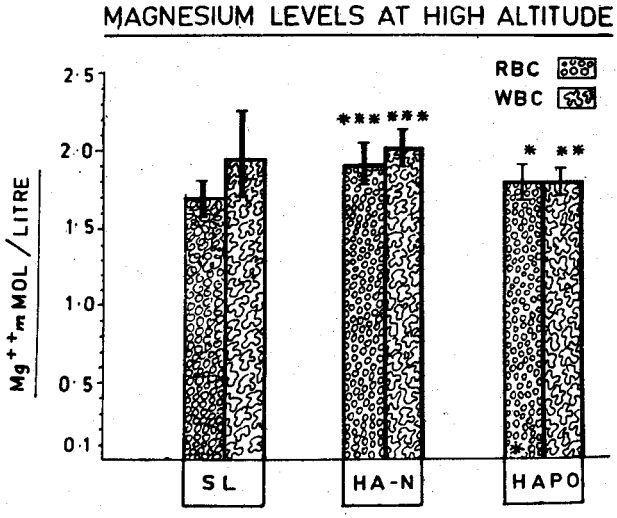

Figure 2. Erythrocyte and leucocyte magnesium levels in mMol/L in sea level residents (SL), high altitude residents (HA-N), and patients of high altitude pulmonary oedema (HAPO).

High altitude provides both enhanced fibrinolytic activity and accelerated immune responses. Possibly it is because of this higher fibrinolytic and immune-potential that malignancy is scarce at high altitude. Studies of populations in the Andes, the Himalayas and the United States have shown a low or less common incidence of myocardial infarction, ischaemic heart disease, and arteriosclerotic heart disease mortality[67,68].

The inter-relationship between the abnormalities in fibrinolysis, blood coagulation factors and platelet functions described above in the pathogenesis of high altitude pulmonary oedema is depicted in Fig. 3.

5. High Altitude Pulmonary Hypertension

High altitude pulmonary hypertension either forms a part of high altitude pulmonary oedema[1] and is acute at the onset, or occurs after a long stay at high altitude in temporary residents[2] and permanent dwellers[69–72] as a protracted course. In the

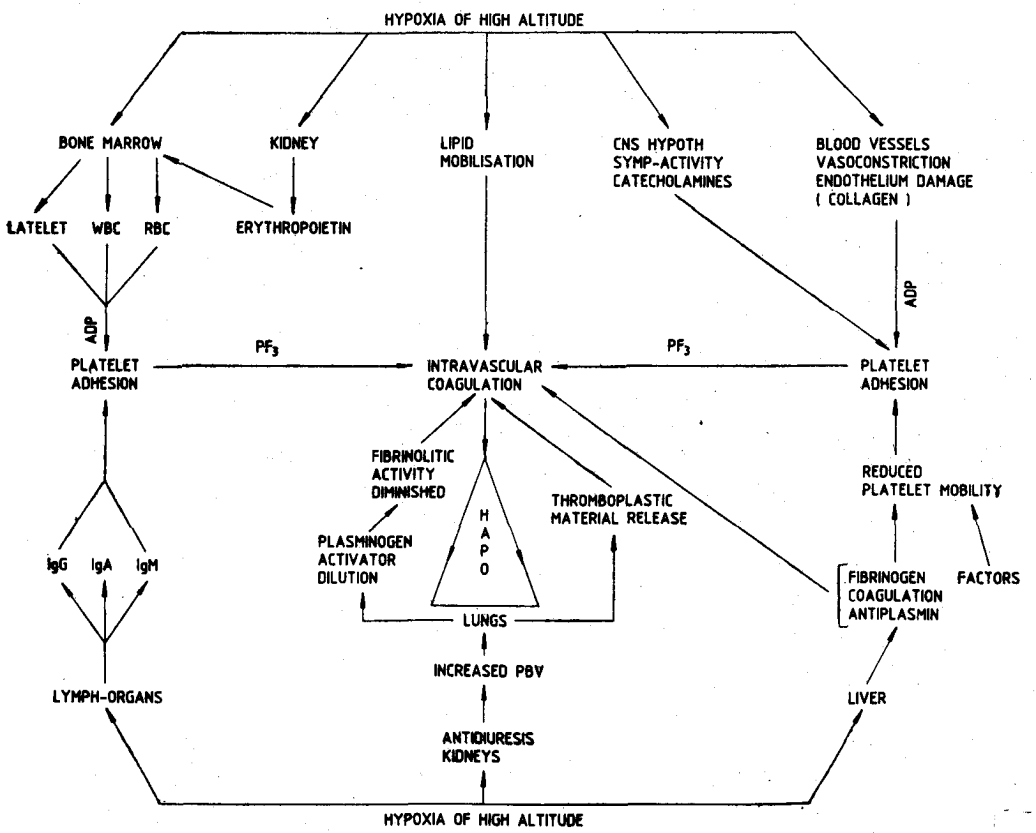

Figure 3. Interrelationship of mechanisms in the origin of adverse changes in fibrinolytic activity, blood coagulation factors, platelet functions, and immune responses predisposing to intravascular coagulation in high altitude pulmonary oedema.

latter situation 5 to 42 months elapse before it makes its appearance. The hypertension either continues to persist on arrival at sea level or, if it subsides, it reappears within 2 to 3 weeks of individual's return to high altitude[73]. The hall-mark of clinical pathology is characterised by dyspnea on effort, chest pain, accentuated or split second pulmonary sound, clockwise rotation, and prominent pulmonary artery on X-ray examination. When right ventricular failure supervenes, the juglar venous pressure is raised, liver becomes tender and palpable, and ascites, oedema and cyanosis follow. All these consequences, of pulmonary hypertension and right ventricular hypertrophy, appear to result from progressively increasing pulmonary vasoconstriction and muscularisation of pulmonary arterial bed resulting in increased pulmonary vascular resistance[71,74] in subjects exposed to hypoxia of high altitude, the hypoxia may be intermittent or continuous.

Only partial reversibility of pulmonary hypertension, as a result of oxygen inhalation and evacuation to sea level, and its rapid return on ascent to high altitude

prompt us to believe that it may have an organic basis. Association of adverse coagulation changes and necropsy evidence of widespread fibrin thrombi in the alveolar capillaries and branches of the pulmonary arteries and other organs in patients of high altitude pulmonary hypertension confirms our doubts[2–4,7,75]. Our suitably control-matched study reveals that those who do not develop pulmonary hypertension at high altitude only exhibit higher plasma fibrinogen levels and fibrinolytic activity, but those who develop HAPH show lower plasma fibrinogen concentration despite high fibrinolytic activity, indicating that this may not be adequate to counter the intensity of the coagulation forces in patients in whom fibrinogen is being constantly depleted by deposition in the pulmonary vascular bed. The coagulation process in the affected subjects is facilitated by a significant increase in platelet adhesiveness, platelet factor 3, factors V and VIII. Factor XII is not generally increased in patients and it is recovered only on return to sea level, thereby indicating that the Hageman factor-dependent pathway of fibrinolysis remains insufficiently responsive in them. Lowering of both venous and arterial levels of ADP in patients of HAPH is a further proof of excessive utilisation of ADP resulting in platelet sequestration and fibrin deposition in pulmonary vasculature[3,4,76].

Electrophoretic mobility of platelets is also reduced in HAPH, like in HAPO, and is related to high plasma fibrinogen and clotting factors in these disorders, and increased immunoglobulins in HAPO[3–5,51,52].

Electronmicroscopic studies of platelets from high altitude pulmonary hypertension patients do not reveal any gross abnormalities. The membranous and cytoplasmic constituents are abundant and capacity of pseudopodia formation and degranulation is adequate (Fig. 4).

In both high altitude pulmonary oedema and high altitude pulmonary hypertension, the abnormal state of blood coagulation is attended with increased platelet adhesiveness, platelet factor 3, factors V, VIII and X, and the haematocrit values. The outstanding difference between the two is in the fibrinolytic activity which is reduced in the former but remains persistently increased in the latter[3].

6. Chronic Mountain Sickness

Individuals suffering from chronic mountain sickness or Monge's disease have been found to have a much higher degree of pulmonary hypertension. Chronic mountain sickness—Phobrang type—has a recent history, in the Western Himalayas at vulnerable altitude of approximately 14,000 feet (4267 m)[77,78]. The corresponding altitude for CMS to develop is 9,840 feet (3000 m) in the Peruvian Andes[79]. Most patients are young between 24 and 53 years of age. It runs a protracted course and takes 8 to 25 months to appear in its florid plethora of the syndrome of alveolar hypoventilation accompanied with symptoms of pulmonary hypertension, right ventricular hypertrophy, and consequences of chronic hypoxaemia. Besides the higher

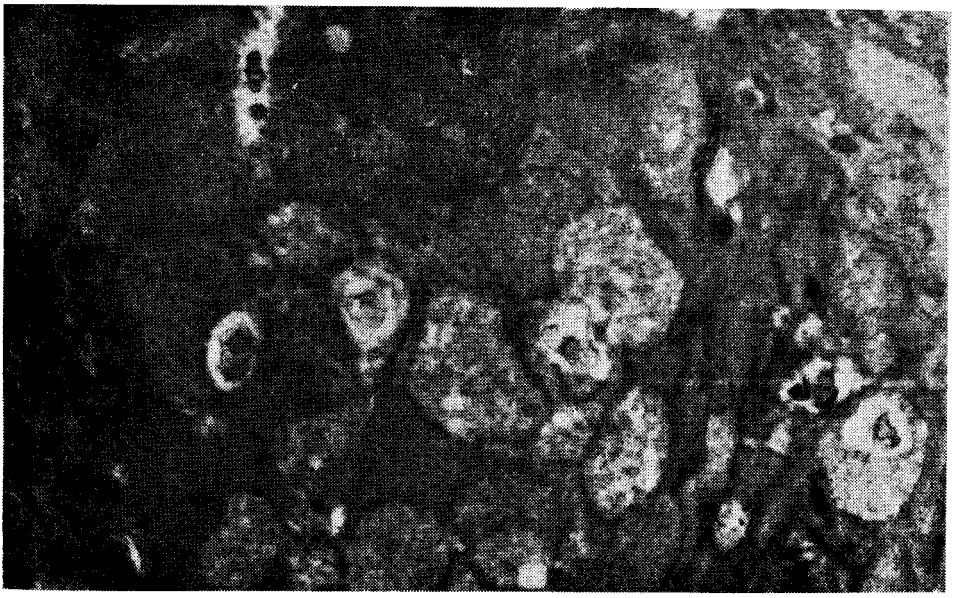

Figure 4. Electronmicrograph of platelets from patients of high altitude pulmonary hypertension, stained with uranyl acetate and lead citrate, X 10,000. Platelet plasma membrane is intact. Some platelets show degranulation, close clumping of platelets does not permit visualisation of pseudopodia.

haemoglobin and haematocrit, the CMS of 'Phobrang type' has an added element of renal protein loss[7,8]. Unique clinical features drawing immediate attention consist of: intensely suffused conjunctivae with swelling of eyelids, cyanosed and congested buccal mucosa, magenta coloured and cyanosed tongue with or without sublingual haemorrhages, red palms and soles with cyanosed tips of fingers and toes, clubbing and breaking of finger nails with or without splinter haemorrhages, cyanosed earlobes and pinnae, petechial haemorrhages over legs, pedal oedema, and engorged neck veins. X-Ray chest shows prominent pulmonary conus, increased hilar vascular markings and diminished aeration of lung fields and evidence of right ventricular enlargement. Electrocardiography shows all the signs of right ventricular strain and overload and an accentuated degree of right AQRS deviation which could be of the order of + 152° to + 158°. Systemic hypertension may also be exaggerated in these patients. We carried out some blood coagulation parameters in six patients presented to us at an altitude of 3692 m in their florid state. Compared to suitable high altitude controls, patients have significantly increased plasma fibrinogen (400.1 ± 37.1 mg/dl), haematocrit (74.3 ± 3.1%), and haemoglobin (23.1 ± 2.6 g/dl); significant decrease in activated partial thromboplastin time (27.1 ± 5.2 sec, compared to normal 35 to 50 sec) and platelet numbers (177.8 ± 10.9 thousand per cmm, compared to normal 197.4 ± 19.3); and significantly reduced euglobulin lysis time (ELT 165 ± 75 min, compared to normal 399 ± 48) Erythrocyte sedimentation rate is reduced to

3-5 mm. There is no change in the total and differential leucocyte counts. Alterations in fibrinogen, activated partial thromboplastin time, platelets, haematocrit, haemoglobin and ESR indicate a trend towards hypercoagulable state in patients of chronic mountain sickness. However, increase in fibrinolytic activity in them, indicated by short euglobulin lysis time, tends to counteract this trend. A very characteristic feature of CMS patients in the presentation of their peripheral blood smear. The hyperchromatic and large RBCs form a mosaic pattern with little plasmatic matrix and seem to strangulate the WBCs which appear distorted in shape, some are tailed but there are no other abnormalities. Large and young platelets lie scattered singly or in batches and seem to be strangulated in the mosaic. Rouleaux formation by RBCs is also common.

Another redeeming feature in patients of CMS is presence of accentuated cell mediated immunity (CMI) indicated by 'spontaneous flare' and 4 + DNCB—reaction in them[81], unlike patients of high altitude pulmonary oedema who exhibit impaired CMI in the acute stage of illness[57–61]. Accentuated CMI and fibrinolytic activity, perhaps, account for the protracted course of CMS.

The pathophysiology of CMS emanates from restricted ventilatory response to hypoxaemia and/or hypercapnoea resulting in diminished arterial oxygen saturation so that polycythaemia and cyanosis develop in this syndrome[80–84]. Functional arteriolar constriction at the precapillary level in the pulmonary vascular bed leading to sustained rise of pulmonary arterial pressure and its subsequent consequences is reversible on descent to sea level[85]. The role of prostaglandins in development of pulmonary hypertension is largely controversial as acetylsalicylic acid fails to prevent adverse changes in blood coagulation parameters[86] and pulmonary hypertension in the cattle exposed to simulated altitude of 4,500 m. Sleep hypoxaemia, during sleep at high altitude, has also been suggested as the physiological basis of Monge's disease[87]. Few necropsy reports are described illustrating the pathological features of this disease[80,88,89]. These studies compiled by Heath and Williams[90] emphasize, the thickening of peripheral pulmonary arteries and muscularization of pulmonary arterioles, the whole basis of development of pulmonary hypertension resulting from alveolar hypoxia at the high altitude[90]. Arias-Stella and colleagues have also reported presence of fresh and partially organized thrombi in the pulmonary arteries and arterioles in their material together with occurrence of colloid goitre and hyperplasia of the zona glomerulosa of the adrenal cortex[80]. Our above study, reporting alteration in blood coagulation parameters in CMS (Phobrang type), may be relevant in this context. The degree of fibrinolytic activity observed in CMS may not be adequate to deal with fibrin deposition in the pulmonary microcirculation and this process may gradually lead to occlusion of the alveolar capillaries, reduction of oxygen exchanging capacity, and production of hypoxaemia. This, however, is only a postulation which needs confirmation.

Oxygen administration has no place in the therapy of CMS. Other forms of therapy recommended are : evacuation to lower levels, phlebotomy, steroids, and a

ventilatory stimulant—medroxyprogesterone acetate (MPA)[79,90,91]. A combined therapy consisting of lowering altitude, acetylsalicylic acid, acetazolamide, and deep—breathing yogic exercise was used in the treatment of CMS in the Himalayas in a recent study with satisfying results[77,78]. It may be of passing interest that recently yoga has been shown to induce a state of hypocoagulability in man[92]. Yoga promotes fibrinolytic activity with a concomitant fall in plasma fibrinogen; prolongs activated partial thromboplastin time and platelet aggregation time; and spares platelet consumption. Learning and practice of yoga may be prescribed as a part of training, advantageously, for the mountain trekkers and soldiers before their induction to the high altitudes.

7. Discussion

There is an increasing body of evidence that the above disorders of high altitude, occurring in mountain climbers and dwellers, are the variants of the same primary event resulting from the lack of acclimatization and adaptation to these environments. There is a good reason to believe that hypercoagulation and thrombotic process play an important and possibly a primary role in their development and progression from a mild state to a severe one. Admittedly, there is a clear need for their early recognition and prevention and appropriate treatment to check avoidable mishap[93–95]. Acute mountain sickness of mild intensity, benign AMS, is a self limiting illness and the early phase of severe symptoms subside within 2 to 5 days but complete recovery takes few weeks to months. Those who have cerebral and pulmonary elements need energetic treatment. Those who fail to adapt within 6 months have to be evacuated to plains[6]. In contrast to symptoms of hyperventilation and tachycardia which occur on immediate arrival and respond to oxygen inhalation, the symptom-complex of AMS is not readily relieved by oxygen therapy. Though oxygen is essential to relieve dyspnoea during the acute stage of HAPO, induced diuresis is the mainstay of treatment of both AMS and HAPO. Diuretics, furosemide in particular, have been effectively used to reverse the fluid retention[6,20]. Furosemide has been used in the dosage of 40-80 mg every 12 hours for 2 days and with this regimen, symptoms and signs of AMS are relieved within 6 to 48 hours. In severe cases of AMS especially with pulmonary and cerebral elements, morphine 15 mg added with the first dose of furosemide has been found very effective as it brings about more effective diuresis, reduces pulmonary blood volume, alleviates anxiety and induces mild sleep, all these factors promote rapid recovery. In more severe cases with neurological involvement betamethasone combined with furosemide has proved life saving[6]. Recently, dexamethasone, a potent synthetic glucocorticoid with negligible mineralocorticoid activity, which has been effective in the management of cerebral oedema of diverse origin[96], has been used with significant success in reduction of AMS symptom score in subjects exposed to simulated altitude of 4570 m[97]. Furosemide, though found effective as a prophylactic measure against development of AMS, however, used in large dosage of 80 to 200 mg given orally may result in copious diuresis with massive potassium loss

and hence lead to overdehydration, cramps, and non-relief of headache in an already dehydrated individual in the high altitude environments where water is not readily available to replace the loss. Under the above circumstances furosemide administered in large doses may prove inconvenient and hazardous, hence it has not found favour with some authors and rightly so[46,90]. We have recently started using a lower dosage regimen of 20 mg furosemide every 12 hours to treat HAPO with no less success and without any side effects[50,98] and with other good reasons described below.

Acetazolamide, a less potent diuretic, is the only other drug which has been advocated as a prophylactic against AMS[18,19,99–102]. However, it has been partly effective[28,32,97,102]. The exact mechanism by which the acetazolamide is efficacious is unknown but it is known to enhance excretion of bicarbonate, increase ventilation, and thereby reduce arterial desaturation[103]. Acetazolamide no doubt counters respiratory alkalosis but produces acidosis which could be a disadvantage as acidosis predisposes to coagulation. Acetazolamide, in 250 mg oral doses, may be prescribed four times daily for two days before ascent and for four days after. Some climbers have reported marked acute mountain sickness on discontinuation of the drug during ascent[104].

Aspirin has also been used to relieve headache, a component of AMS symptom-complex[6,105]. Recently spironolactone, an antialdosterone, has been used as a successful prophylactic against AMS[105–108], although subjects with acute mountain sickness have lower aldosterone levels than subjects less affected[107]. It remains to be seen as to what extent aldosterone is responsible to cause AMS. Other studies have demonstrated that treatment with digitalis and isoproterenol have not been beneficial[39].

8. Why Furosemide and Allied Drugs ?

Furosemide, apart from inducing rapid diuresis and reducing pulmonary blood volume, enhances plasma fibrinolytic activity; decreases factors V, VIII and X, and thrombotest activity; increases factor XII; reduces platelet factor 3 and platelet adhesiveness; and improves clot retraction in patients of high altitude pulmonary oedema[50,54]. Thus by virtue of its ability of reversing adverse changes in fibrinolytic activity, blood coagulation factors, and platelet function furosemide removes impediments and improves pulmonary blood flow at the capillary and venular level. These beneficial effects of furosemide become manifest within 30 minutes and lead to an uneventful recovery. Furosemide also exerts an inhibitory effect on primary platelet aggregation induced by ADP, both *in vitro* and *in vivo*, an inhibitory effect on platelet secretion has also been demonstrated by its influence on secretion of ^{14}C-serotonin and platelet factor—4 (PF-4) with small concentration of 50 μM[109]. Since furosemide increases the electrophoretic mobility of platelets (our unpublished data), the restoration of the Hageman factor following furosemide administration[54] is responsible for this effect. Hageman factor is a sialoglycoprotein which is easily adsorbed on the

platelet surface and increases its negative electric charge. The above effects of furosemide depend on its vasodilatory activity, cyclic-AMP phosphodiesterase inhibitory and adenyl cyclase stimulatory capacity, and its activation of the Hageman factor—mediated fibrinolytic system as long as the integrity of the renal parenchyma is intact and the diuresis is manifest[54,110,111]. The net effect of the above mentioned mechanisms is increase in cyclic-AMP. The natriuretic effect of furosemide is well known to be mediated by prostaglandin E (PGE) induced cyclic-AMP. Cyclic-AMP has been demonstrated to inhibit synthesis of prostaglandin endoperoxides (PGG_2) which is the immediate precursor of thromboxane A_2 that effects platelet aggregation and secretion of human platetets[112]. Platelet aggregation induced by PGG_2 has been shown to be inhibited by furosemide[113], and also the formotion of malondialdehyde, an indicator of platelet prostaglandin synthesis, is inhibited by furosemide[114]. Evidently furosemide inhibits the synthesis and antagonises the action of prostaglandin G_2 but selectively promotes the action of PGE and synthesis of cyclic-AMP, the latter promotes in turn inhibition of platelet aggregation and release reaction. Aspirin inhibits indiscriminately the synthesis of all prostaglandin endoperoxides by interfering with the action of cyclo-oxygenase enzyme. Furosemide has thus the unique property of inhibiting platelet activity and promoting the fibrinolytic system. Acetazolamide, aspirin, and spironolactone have not so far been shown to induce fibrinolytic effect. Therefore, furosemide has the supremacy over all these drugs to combat the propensity of intravascular coagulation in the management of AMS and HAPO, preferably in smaller doses to retain the benefical effect on blood coagulation and the attenuated diuretic action[50,98]. Similar results can be achieved by using a new synthetic fibrinolytic and anti-platelet agent, piretanide 6 mg administered orally, which is similar in structure and function[115] to furosemide. Bumetanide is another high-ceiling diuretic, similar in structure and function to furosemide, which can be advantageously used in the management of HAPO[117–119]. It is equipotent with furosemide at a fortieth the molar dose. The effective dose is 1 mg intravenously and 2 mg orally daily. It has been used effectively in climbers in the Hindu Kush range of Afghanistan (7450 m)[120]. It induces a peak diuresis 1-2 hours after an oral dose and its action is complete within 4-6 hours. At the moment, bumetanide is slightly cheaper than furosemide and it may prove an effective alternative on the rare occasion when furosemide fails. Houston & Dickinson[121] advocate the use of furosemide to combat the cerebral oedema of AMS and also reinforce the treatment with rapid injection of hyperosmolar solutions of urea, 50 per cent saline, mannitol or 50 per cent sucrose.

Furosemide, like bumetanide, is known to be bound to plasma proteins[122] and it may be slowly released from its stores in liver and kidneys[123] to maintain its continuous effect on platelet and fibrinolytic system. The protective effects of furosemide to prevent development of acute renal tubular necrosis and acute renal failure by nephrotoxic drugs in animals[124] and to prevent crisis of eclampsia in clinical condition of toxaemia in pregnancy[125] can be attributed to beneficial properties of this drug. The improvement of blood flow in transplanted kidneys by using a furosemide-perfusate has been achieved[126] by influencing platelet thrombi and fibrinolytic activity which are

adversely affected and involved in rejection crisis. More recently, with the use of 20 mg furosemide (I V), an efficient excretion fraction and glomerular filtration have been obtained in the allotransplanted kidney patients[127]. Lately, Sniderman and colleagues[128] have treated 28 preterm infants with chronic lung disease due to bronchopulmonary dysplasia/chronic pulmonary insufficiency with 1-2 mg/kg furosemide Qid. Of these 20 infants improved significantly and 12 exhibited deterioration on discontinuation of furosemide. These beneficial effects of furosemide may be presumed by improving the microcirculation of the organs as a result of enhancement of fibrinolytic system and prevention of adverse platelet activation. Furosemide and allied drugs seem to have a rightful place in the treatment of diseases where intravascular coagulation is involved.

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