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Review Article

Travelling to High Altitudes Could be Thrombogenic!

Abstract

People ascending to high altitude regions are at risk for a variety of health problems, commonly including acute mountain sickness (AMS), high-altitude cerebral oedema (HACE) and high-altitude pulmonary oedema (HAPE) etc. Increasing travel to mountainous terrains has brought light to several other medical problems as well. It has been well recognized that a hypercoagulable state exists when a person is exposed to high altitude environment. This may manifest as early thromboembolic episodes, which may result in deep vein thrombosis (DVT) or acute pulmonary embolism (PE), which is a potentially fatal condition. The various effects of thrombosis include pulmonary thrombo-embolism (PTE), cerebral venous thrombosis, portal/splenic vein thrombosis, and deep vein thrombosis (DVT). Out of all these conditions, PTE is an extremely common and highly lethal condition that is a leading cause of death in all age groups. Exposure to high altitude (HA), either during air travels, ascension of mountains, or while engaging in sports activities results in hyper coagulability thus predisposing to thromboembolic events. Climbers staying at high altitudes for weeks also possess several risk factors for thromboembolism. A large number of environmental variables suggest that a single cause of HA-induced thromboembolic disorders (TED) may not exist, so that this peculiar phenomenon could be seen as a complex or multifactorial trait. In view of the greatly increased risk of getting deep venous thrombosis and pulmonary embolism at high altitude, it would be interesting to review the studies done so far for defining its cause and treatment. Thus the present review examines the risk of thrombosis at increasing elevations along with the possible underlying mechanisms, the diagnosis and treatment strategies.

Abbreviations

AMS: Acute Mountain Sickness; HAPE: High Altitude Pulmonary Edema; HACE: High Altitude Cerebral Edema; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; HA: High Altitude; TED: Thrombo-Embolic Disorders; VTE: Venous Thromboembolism; aPTT: Activated Partial Thromboplastin Time; PT: Prothrombin Time; VKA: Vitamin K Antagonist; vWF: von Willebrand Factor; PPV: Positive Predictive Value; NPV: Negative Predictive Value; INR: International Normalized Ratio;

Background

For thousands of years, several populations across the worlds have inhabited the high-altitude plateaus in the Andes in South America and the Himalayas in Tibet. These populations have developed mechanisms to respond to the stressful environment of the high-altitude including the oxygen scarcity, referred to as high altitude hypoxia. High altitude (HA) is defined as heights/elevations above 2,700 m (9,000 feet) whereas extremely high altitude is defined as elevations above 5,500-5,800 m (18,000-19000 feet). High Altitude, with its hypobaric hypoxia, direct UV radiations, high wind velocities and cold and chilly conditions, results in various physiological and biochemical stresses to the human body. To overcome these adverse effects of the environment, body undergoes certain physiological changes which often successfully, lead to acclimatization of the individual for the stressful environment. However on the other hand, body may not be able to cope up with the changed environment which leads to the various maladies of high altitude. Ascending to a high altitude greater than 8000 feet, is commonly associated with

acute mountain sickness (AMS) which may later lead to more severe medical conditions such as high altitude cerebral oedema (HACE) and high altitude pulmonary oedema (HAPE), both of which are potentially fatal. AMS itself is characterised by headache, anorexia, nausea, insomnia and malaise [1,2]. The prevalence of AMS depends on the rate of ascent, the altitude reached and individual susceptibility [3]. The exact pathophysiological mechanisms of AMS, HAPE and HACE are not known till date. However, several studies have revealed that hypobaric hypoxia causes over perfusion of microvascular beds, elevated pulmonary capillary pressure and capillary leakage [4,5], leading to HAPE. There has been several studies showing much interest in the role of genetic factors in the prevalence of various high-altitude diseases, but research has not yet reached a conclusive state.

In some way all these reactions to hypobaric hypoxia indicate a critical change of interactions within the vascular system. An important effect of high altitude is on the coagulation cascade in the body. Climbers staying at high altitudes for weeks have several risk factors for thrombosis. On induction to HA, there is an initial hypercoagulable state, which persists for a few weeks but then slowly regresses with time as the patient acclimatizes. This is due to a transient increase in clotting factors and platelet dysfunction [6-9]. This is manifested clinically by Acute Pulmonary Thrombosis in lowlanders who rapidly ascend to high altitudes such as Army jawans, mountaineers and trekkers [10,11]. This abnormality in clotting factors automatically regresses after a few weeks. However, on prolonged stay at high altitude (>5 months), there develops a hyper-fibrinogenic state [7,10] which persists as long as the patient stays at high altitude. There have very few studies demonstrating DVT of

leg veins in persons staying at high altitude for a prolonged period of time (>5 months) [12,13]. When the Indian Army personnel were inducted at heights over 5000 m above MSL, its men faced the ultimate test of survival in adverse environmental conditions, which gave an opportunity to researchers to observe some problems hitherto unknown in the medical literature. Previous reports have shown that pulmonary hypertension of high altitude is also related to intravascular activation of the coagulation process [7,8].

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and its life threatening complication, pulmonary embolism (PE), are among the most frequent causes of morbidity and mortality in developed countries. In the United States alone, the number of deaths due to VTE are estimated to be as high as 300,000 annually [14]. Blood flow restriction or stasis is considered a major factor driving DVT [15].

Several of the case reports of venous thromboembolism (VTE) in high altitude mountaineers has triggered scientific interest on studying the role of coagulation in high altitude illness [16]. The condition of DVT is itself is not fatal, but the complication of PE can, of course, be life threatening. It has long been understood that DVT can be associated with the following:

- i. Reduction in blood flow;
- ii. Changes in blood viscosity; and
- iii. Damage or abnormality in the vessel wall.

This is described as Virchow's triad [17].

Anand and co-workers reported a 30 times higher risk of spontaneous vascular thrombosis on long-term stay at high altitude in Indian soldiers. Veins are common sites for such thrombotic events [12]. Other Indian studies of Jha et al reported the clinical profile of 30 cases of stroke at high altitude and reported that long-term stay at HA results in hypercoagulable state which is associated with higher risk of stroke [18]. Apart from few segregated case reports [19,20], vascular complications occurring at high altitude have never been systematically studied. This review aims to consolidate the reports of high incidence of deep venous thrombosis of leg veins and deaths caused due to pulmonary embolism at high altitude, as compared to lowlands and define these disease entities as high altitude induced deep venous thrombosis (HA-DVT) and high altitude induced pulmonary embolism (HA-PE). It emphasises on the increased episodes of venous thrombo-embolism at HA, its causes and diagnostic tools which would be helpful in increasing awareness towards this life threatening complication.

Haemostatic imbalance at high altitude

Our body attempts to maintain a state of homeostasis or balance to ensure the optimal operating environment for its complex biological systems. Any change from this state is a change away from the optimal operating environment and body requires certain physiological and biochemical changes to adjust to such change. As discussed, one such imbalance is the effect of increasing altitude on the body's ability to provide adequate oxygen for cellular respiration. With an increase in elevation, the body is forced to respond in various ways to the

changes in external environment. If the adaptive responses to this stressor are inadequate the performance of body systems may decline dramatically and severe medical conditions can arise. If prolonged and not treated appropriately, the results can be serious or even fatal. First few days of recent arrivals at high altitude are very critical. During these days important adaptive changes take place in the body, failure of which may initiate adverse pathophysiology. Ascent to HA causes hypobaric hypoxia and is known to cause physiologic changes in humans such as decreases in tissue oxygenation and other sympathetic compensatory changes such as elevated systemic blood pressure; arrhythmias and vasoconstriction [21]. Bartscher [22], showed the risk of sudden cardiac death of hikers at HA, increased significantly with history of prior myocardial infarction, diabetes, known coronary artery disease and hypercholesterolemia. In addition to these conditions, some individuals also suffer from clotting disorders; history of deep venous thrombosis (DVT) or pulmonary embolus, atrial fibrillation (AF), valvular stenosis, and history of stroke or transient ischemic attack (TIA), have a pacemaker or have an artificial heart valve. These conditions usually require chronic, long-term or lifelong anticoagulant therapy to prevent either an initial or recurring thromboembolic event.

Many research projects have been taken up to study the relationship between hypoxia and hemostasis. It is suggested that a prolonged sojourn at high altitudes could lead to activation of the coagulation system as a result of an increase of hematocrit and blood viscosity. Maher and co-workers [8], investigated several parameters of coagulation and platelet aggregation during simulated high altitude exposure and found some parameters to be changed indicative for a coagulopathy. Also hemostatic changes after acute exposure to hypobaric and normobaric hypoxia (inspired fraction of oxygen, $FiO_2 = 0.11$), showing shortening of activated partial thromboplastin time (aPTT) and an increase in procoagulant plasma factor VIII: C-like activity was reported [23]. In one of the contrasting studies, Bartsch and co-workers [24], could not demonstrate any changes in fibrin or thrombin formation during a 22-hour ascent from 3,200 m to 4,559 m.

At high and extreme altitudes, people are exposed to a variety of changed environmental factors which could influence the hemostatic system (e.g., cold, dehydration, polyglobulia, immobility during periods of bad weather, and exhaustive physical exercise). Since decades, increased thrombotic and thromboembolic events have been described in climbers [16,25-28]. However, reports were mostly either case reports or retrospective observations; therefore, the prevalence of high altitude associated thromboembolism and its underlying mechanism remains unclear. In addition, several mountaineers suffering from thrombosis have individual acquired and genetic risk factors (e.g., oral contraceptives, recent surgery, genetic mutations such as factor V Leiden mutation, and prothrombin polymorphism). Therefore, the impact of hypoxia itself as an independent risk factor for thrombosis at high altitude is still a matter of debate [12,29].

Coagulatory changes at high altitude

Deep vein (or venous) thrombosis is a condition in which a small blood clot (thrombus) or clots (thrombi) develop(s) in the deep veins, usually of the leg. A delicate balance seems to exist between the

coagulant and fibrinolytic forces. Many studies have shown evidence of pro-coagulatory activity under hypobaric hypoxia [30,31]. Red blood cell counts and haemoglobin concentrations increase to maintain oxygen transport in the hypobaric environment of HA. In addition to these, Singh and Chauhan found increased plasma fibrinogen, platelet adhesiveness, platelet factor 3, factor V, factor VIII in individuals who developed high altitude pulmonary hypertension [32]. Some studies also believe that pulmonary hypertension at high altitude is also related to intravascular activation of the coagulation process [7,8]. Earlier studies on Indian soldiers at high altitude indicated a significant increase of plasma fibrinogen levels [7]. Other studies have described changes in the coagulation factors suggesting an activation of the coagulation cascade and associated endothelial cell damage [33]. In a landmark study by Kotwal and co-workers carried out a prospective cohort study at a height of 3,500 m above sea level and concluded that the combination of erythrocytosis, increased platelet count, platelet activation and raised fibrinogen level combined with hypoxia and dehydration at high altitude cause a thrombotic milieu to occur, leading to thrombosis in normal individuals or in asymptomatic cases with inherited/acquired thrombophilia [34]. Bärtsch and co-workers has previously demonstrated that increased fibrinolytic activity did not proceed to HAPE, even though they found an association with pro-coagulant activity [35]. Hyper viscous blood from hypobaric hypoxic altitude induced polycythemia could lead to a thrombotic state [36]. Hefti and co-workers [37], showed an increase in pro-coagulatory state with increased altitude. The increase in pro-coagulants has been seen without an equal counter response of fibrinolysis, thus creating a hypercoagulable state at high altitudes. However the exact mechanism about coagulation changes during ascent to high altitudes is unclear the changes in the coagulation system could be associated with severity of acute mountain sickness. It might be possible that high altitude expedition confers a pro-coagulatory state that could pose an additional risk for venous thromboembolism in people with pre-existing thrombophilic disorders.

High altitude hypoxia and vWF

Some interesting studies have aimed to define the role of the coagulation system, von Willebrand Factor (vWF)-System and the vWF-cleaving protease (ADAMTS13) in acclimatization to high altitude as these factors have been shown to be involved in microthrombus formation and vessel wall alterations [38,39]. VWF is synthesized exclusively by endothelial cells and megakaryocytes. It has further been shown that increased concentrations of vWF occur in different vascular diseases such as cerebrovascular diseases, peripheral and pulmonary vascular diseases [40]. ADAMTS13, a member of the ADAMTS family of metalloproteases, is known to be involved in microvascular diseases. VWF is cleaved under shear stress by ADAMTS13 [41]. Shear stress is also seen as a possible factor leading to vessel alteration with consequent capillary leakage and oedema. Hefti and co-workers [37], identified a pro-coagulatory state with increasing altitude, as reflected with increasing D-Dimer concentrations and APC-resistance (indicated by a decreased APC-R test result). Both increasing D-Dimer concentrations and APC-Resistance have been shown to increase the risk for venous thromboembolism [42]. Hefti et al. [37], also suggested that that

newer markers of the coagulation system such as ADAMTS-13 or APCR are involved in high altitude pathophysiology.

Clotting tests and treatment

Recognizing that a potential illness may exist associated with a blood clot is the first step in getting treatment. Since many of these illnesses are life-threatening (heart attack, stroke, pulmonary embolus), accessing emergency care may be the most important step in treatment. DVT usually requires anticoagulation to prevent the clot from growing and causing a pulmonary embolus. Treatment tends to occur in an outpatient setting using medications that anticoagulate or “thin” the blood. Warfarin, a vitamin K antagonist (VKA), has been successfully used for anticoagulant therapy for over forty years and is the most commonly prescribed VKA for long term anticoagulation [43]. Warfarin use has seen a threefold increase in the past two decades [44]. It is a vitamin K inhibitor and affects Factors II, VII, IX and X of the clotting cascade. The coagulation cascade is dependent on coagulation factors produced in the liver and dependent on vitamin K formation. VKAs such as warfarin, delay the formation of vitamin K which prolong the Prothrombin time (PT). Prothrombin time measures the clotting mechanism of the extrinsic coagulation system. Prothrombin time is a blood test that measures how long it takes blood to clot. A prothrombin time test can be used to check for bleeding problems. PT is also used to check whether medicine to prevent blood clots is working. Warfarin, although effective, is at times difficult to manage due to the narrow therapeutic range. This range is defined by the International Normalized Ratio (INR). The typical therapeutic range for INR in patients being treated to prevent thrombosis is 2.0-3.0. The INR is a calculation that uses the PT blood test. Significant changes in the INR (3.0) can increase morbidity and mortality. Hylek and co-workers [45], found a 1.9 fold increased risk of stroke in AF patients with an INR of 1.9.

In addition to INR, clotting can be tested by measuring D-dimer, activated partial thromboplastin time (aPTT), activated protein C resistance (APC-R) and von Willebrand factor activity in blood. D-dimer is produced by the action of plasmin on cross-linked fibrin. D-dimer production is inhibited when plasmin acts on fibrinogen not involved in clot formation. Thus, the presence of D-dimer confirms the activation of fibrinolysis, secondary to thrombin generation.

Clot degradation can also be tested. One method is by measuring plasminogen activator inhibitor 1 (PAI-1), which decreases fibrinolysis. An increase in PAI-1 shows a decrease in breakdown of clot material leading to an imbalance in hemostasis. The intrinsic coagulation system can be tested with aPTT. Increases in APC-R show increased resistance to activated protein C which inactivates eight pro-coagulant factors.

D-dimer test for diagnosis of suspected pulmonary thrombo-embolism

The plasma level of D-dimer, a fibrin degradation product (FDP), is nearly always increased in the presence of acute pulmonary embolism. Unfortunately, the diagnosis of PE is often missed, because PTE often causes only vague and non-specific symptoms. D-dimer test, being quite sensitive, is of immense value in the diagnosis of PTE [46]. The negative predictive value (NPV) of D-dimer is excellent as

it can easily rule out PTE [47]. However the major problem is the high frequency of false positives with D-dimer. Consequently, it is important that a patient with a positive D-dimer (above the cut-off) is always followed with a confirmatory investigation that typically includes objective techniques such as imaging studies. However, in high altitude areas where PTE relatively is more common, the positive predictive value (PPV) of D-dimer is quite high. Rathi and co-workers [48], concluded that clinical assessment in combination with D-dimer assay can be used for timely differentiation of PTE from other conditions such as HAPE, especially at isolated HA areas. Since D-dimer assay is highly sensitive but less specific, it is an excellent screening test for PTE, with sensitivity of almost 100% and NPV of 100%. So, a negative D-dimer test can easily rule out possibility of PTE completely, thereby it identifies patients to whom anticoagulant therapy should not be given or patients who should not be subjected to invasive imaging tests. Rathi and co-workers [48], further stated that a positive D-dimer test is also equally important, especially in high altitude areas where majority posts are located in inaccessible remote areas and radiological facilities are not available or feasible, because it gives a sense of urgency of patient evacuation to a specialised centre for definite management by fastest means available [48].

Conclusions

This systematic review consolidates studies that show an increased risk of hypercoagulability at high altitudes that could lead to DVT or PE. Incidences of fatal PE are reportedly very high in tourists travelling to HA compare to lowlanders. Future studies should be performed considering this clinical dilemma. In the current scenario, studies in this regard are very segregated. Larger subject groups along with a greater number of INR measurements will yield better and conclusive results. A range in altitude could be examined to provide more precise changes in coagulation parameters. Newer and more reliable early diagnostic methods and prevention strategies needs to be formulated to avoid loss of life. Use of other interventions besides warfarin may become important. Further investigation is needed to understand the increased risk of TED at HA as well as the possible underlying mechanisms.

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