Travelling to High Altitudes Could be Thrombogenetic!

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.

Review Article

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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]. Burtscher [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, FiO2 = 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, polycythemia, 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 hypoxic 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-clearing protease (ADAMTS13). 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. 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. The negative predictive value (NPV) of D-dimer is excellent as a fibrin degradation product (FDP), 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.

**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 a fibrin degradation product (FDP), 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.
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. Rath 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. Rath 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 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.

References


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