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# High-altitude Provoked Thrombotic Complications

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**ABSTRACT**

On rapid ascending to high-altitude particularly very high-altitude or extreme high-altitude, there is a risk of developing high-altitude illness and most people may experience acute mountain sickness which may further lead to potentially life-threatening pathologies like high-altitude pulmonary edema, high-altitude cerebral edema, high-altitude-induced thrombosis etc. if not treated on time. Hypercoagulability state associated with high-altitude which lead to the formation of a clot in the blood vessels, a condition called deep vein thrombosis, which may further complicate and lead to pulmonary embolism. Lack of epidemiological data poses a constraint in evaluating the actual incident rate of thromboembolic disorders at high-altitude. In the present scenario, the most commonly used diagnostic marker for thrombosis is the D-dimer test which has low specificity. Various anticoagulants are also available for anticoagulation therapy but they have their own limitation. Under this review, worldwide reported incidents and management strategies related to thrombotic complications are consolidated and presented. It also summarizes diagnostic and anticoagulation therapy regimes against thrombosis existing at present. Accurate diagnosis and therapeutics are a thrust area of further exploration and there is an urgent need to develop quick and advanced methods to reduce the mortality associated with this disorder especially with respect to high-altitude.

**Keywords:** Hypoxia; High-altitude; Deep vein thrombosis; D-Dimer; Anticoagulants

## 1. INTRODUCTION

High-altitude (HA) receives millions of visitors every year which include pilgrims, adventure seekers, tourists, and soldiers. Most of the visitors are unaware of the illnesses and adverse physiological changes associated with a rapid ascent to high-altitude. According to western literature, HA can be defined as altitude ranging from 1500 m to 3500 m. On the other hand, Indian literature defines HA as altitude ranging from 2438 m to 3658 m, 'very high-altitude' as altitude ranging from 3658 m to 5487 m, and 'extremely high' as altitude of 5500 m and above as shown in Fig. 1[1-4].

Travelling to high-altitude areas lead to various kinds of high-altitude illness and it is becoming a pathological phenomenon about which healthcare management strategies are required. The main cause of high-altitude illness is hypoxia along with other stresses like cold and exertion. All these stresses are cumulatively responsible for the development and progression of various maladies like acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), high-altitude cerebral edema (HACE), high-altitude-induced thromboembolic disorders, etc. Unfortunately, high-altitude maladies are associated with morbidity and mortality significantly; therefore, there is a need for learning and recognizing early symptoms, prompt and timely therapy as well as proper preventive strategies by a medical specialist at high-altitude.

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The information about the susceptibility of the individuals going to HA is one of the prominent check point before finalizing ascent which is depending upon their past history of HA travelling, any pre-existing diseases, recent surgery and others. So, proper counselling of HA travellers is prerequisite by which adverse health conditions could be ignored[5].

This review focuses on thrombotic complications which are provoked at high-altitude and summarises the reported incidents, along with an overview of existing diagnostic and treatment strategies for thrombotic diseases. The present review may give wide scientific awareness for researchers working in the field of high-altitude medicine.

Thrombosis may be defined as a common medical condition that occurs due to the formation and propagation of a blood clot within the vasculature. It can occur either in arteries or veins. A blood clot formed in the deep veins especially in legs (Deep Vein Thrombosis DVT) may break off and travel up the veins through the heart and get lodged in the arteries of the lungs. This condition known as pulmonary embolism (PE) can be fatal when the size of the embolus is large (Fig. 2). People who lead a sedentary lifestyle are at a greater risk of developing DVT. DVT is also seen in people confined to bed for longer periods after surgeries and even travellers who take long-duration flights frequently. Thromboembolic disorders are a major cause of morbidity and mortality worldwide[6]. Several prothrombotic risk factors often work in a league to manifest clinical thrombosis. These include hereditary or acquired thrombophilia, immobility, surgical

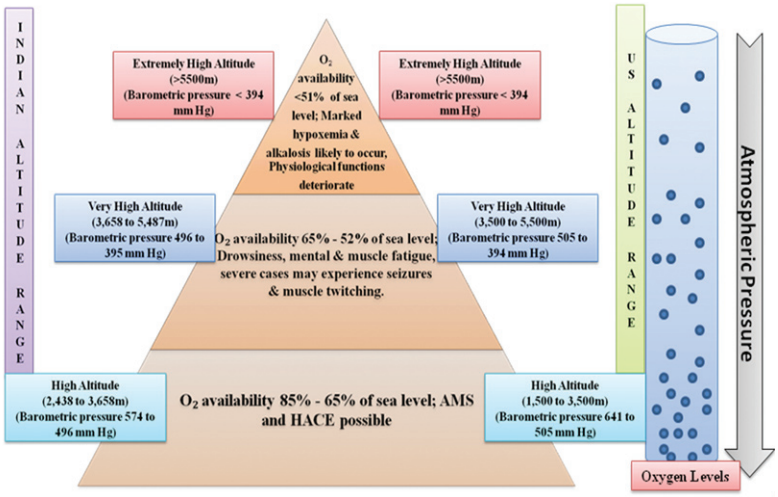


**Figure 1. High-altitude ranges in India and United States (US): Changes in barometric pressure, association of oxygen levels with atmospheric pressure and clinical effects on exposure to high-altitude to extreme high-altitude.**

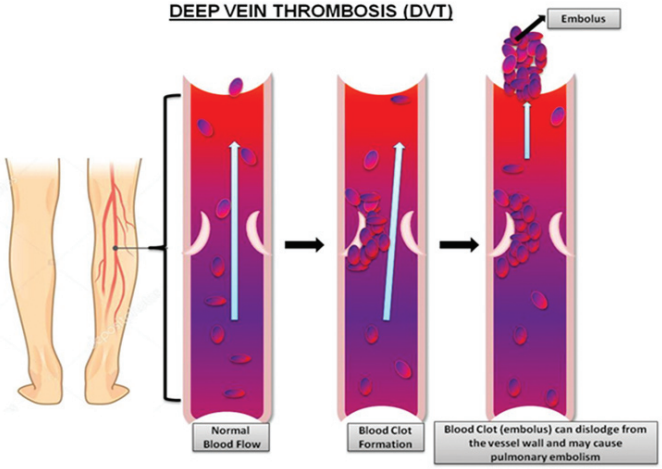


**Figure 2. Illustration of deep vein thrombosis.**

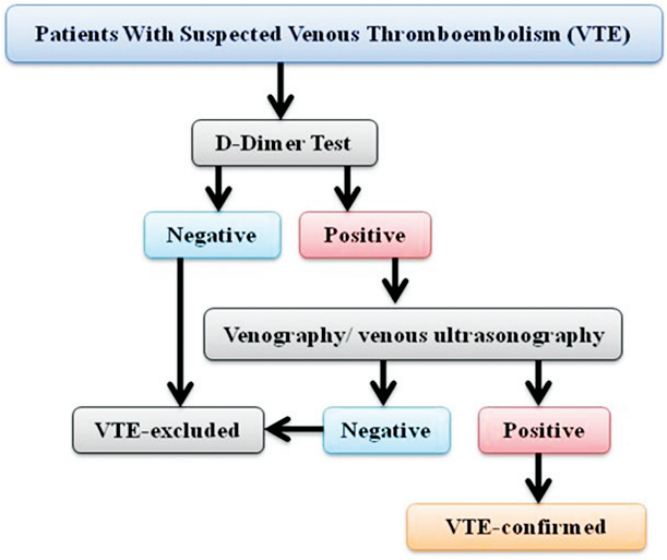


**Figure 3. Diagnosis of venous thromboembolism in suspected patients.**

trauma, inflammation, malignancy, estrogens and high-altitude[2]. HA has been linked to a hypercoagulable state due to cold and hypoxic conditions. Several recent studies have shown an increased risk for cardiovascular diseases and thromboembolic events at HA[7,8].

## 2. INCIDENCE OF THROMBOEMBOLIC DISORDERS (TED) AT HA

Due to the lack of definitive epidemiological data, exact figures for incidences of TED at HA are unavailable. But previous reports do suggest a low incidence of TED in lowlanders at the plain as compared to at HA. Jha[9], *et al.*, observed that the cases of stroke in hospital admissions at HA were 13.7/1000 and that in the plains was 1.05/1000. Kumar[10], *et al.* studied the incidence of DVT in two hospitals serving military personnel (one at HA 3600 m and other at sea level). The relative risk for DVT at HA reported was 24.5 whereas; the lowland hospital received 2 cases/year of DVT in a population of 70,000. In a retrospective study by Smallman[11], *et al.*, United States Air Force cadets stationed at an altitude of 2212 m were observed to have a twofold higher incidence rate of thromboembolic events than military personnel stationed at sea level. Dutta[12], *et al.* described cases of PE among 53 Indian soldiers stationed at HA for up to 4 consecutive months. Only 17 % of those soldiers had a hereditary thrombophilia and most of them had moved to HA from sea level. All available reports summarised in Table 1.

## 3. DIAGNOSIS OF VENOUS THROMBOSIS

Mortality and morbidity increase in venous thromboembolism due to the missed diagnosis in early phase[13]. Many conditions show similar signs and symptoms as VTE therefore early and accurate diagnosis of VTE is very important[14]. Despite non-specific symptoms, history and physical examination of patients are considered for the diagnostic process as they may provide an alternative cause for the symptoms which might be helpful in classifying patients for venous thrombosis[15]. Many tests have been evaluated over the years for diagnosing venous thrombosis[16]. D-dimer is one of them which denotes production of protein fragments when a blood clot gets dissolved in the body[17]. Usually it is not detectable at a very low level and it goes away with time but in case of a major clot D-Dimer level increases[18]. A D-dimer test is used to rule out the presence of a serious blood clot inside the body[19]. A negative D-dimer test means that the patient probably does not have a blood clot[20]. The D-dimer test often gives false-positive results in the case of malignancy, surgery or trauma, and pregnancy[21].

Another test for diagnosing VTE is venography in which uses a special type of radiographic material (dye) which is injected into the large vein in the foot so that the deep veins can be seen clearly[22]. The contrast dye mixes with the blood and flows proximally so that the complete deep venous system of the leg, comprising the external iliac along with common iliac veins, can be imaged [23]. It is considered as most accurate

**Table 1. Clinical cases of thromboembolic cases reported over the years**

| Publication year | Description/ Title | Ref. # |
|---|---|---|
| 1983 | Altitude-related deaths in seven trekkers in the Himalayas. | [35] |
| 1986 | Cerebral venous thrombosis due to high-altitude polycythemia. | [36] |
| 1990 | Chronic thrombosis of major pulmonary arteries. | [37] |
| 1999 | Venous thromboembolism at high-altitude. | [38] |
| 2000 | Portal system thrombosis: a new dimension of high-altitude illnesses. | [39] |
| 2002 | Deep vein thrombosis at high-altitude. | [40] |
| 2002 | Stroke at high-altitude: Indian experience. | [9] |
| 2003 | A case of cerebral sinus thrombosis developed during a high-altitude expedition to Gasherbrum I. | [41] |
| 2005 | Sinus vein thrombosis following exposure to simulated high-altitude. | [42] |
| 2006 | High-altitude-induced deep venous thrombosis: a case study of 28 cases. | [10] |
| 2009 | Cerebral venous infarction during a high-altitude expedition. | [43] |
| 2011 | Quantification of the 5-year incidence of thromboembolic events in U.S. Air Force Academy cadets in comparison to the U.S. Naval and Military Academies. | [11] |
| 2018 | Profile of pulmonary embolism in service personnel posted at high-altitude area. | [12] |
| 2019 | Cerebral Venous Thrombosis at High-altitude: A Retrospective Cohort of Twenty-one Consecutive Patients | [44] |
| 2019 | Cerebral Venous Thrombosis at High-altitude: Analysis of 28 Cases. | [45] |

test for diagnosing blood clots but it is invasive in nature[24]. Thus, it has been replaced by venous ultrasonography, which is readily available, painless, and can be performed easily without any painful procedure[25,26]. Venous ultrasonography uses sound waves to produce the images of veins in the body[27]. It is a standard imaging test as it can detect blockages in the deep veins[28,29].

## 4. TREATMENT STRATEGIES: ANTICOAGULATION THERAPY

Once VTE is diagnosed, treatment should be initiated, which either includes the usage of anticoagulants such as heparin, low molecular weight heparin or oral vitamin K antagonists to avoid additional clot enlargement[30]. Anticoagulants can be of two types like injectables and tablets such as heparin or low molecular weight heparin and warfarin, dabigatran, apixaban, rivaroxaban, edoxaban, respectively[31]. In certain cases, interventional procedures (like thrombectomy or the usage of inferior vena cava filters) and thrombolytic therapy may be used to breakdown the clot or may also be employed depending on the severity of the complication[32].

## 5. LIMITATIONS OF CURRENT DIAGNOSTICS AND TREATMENT MODALITIES

Current diagnostics available for VTE have serious limitations, especially when considered with respect to availability at high-altitude. For example, plasma D-dimer levels can increase in many physiological and pathological conditions as in pregnancy, trauma, cancer, inflammation and several other clinical conditions; on the other hand, impaired fibrinolytic activity and use of oral anticoagulants prevent the increase in plasma D-dimer levels. D-dimer testing is also negative in case of onset of symptoms more than two weeks before blood sampling. High sensitivity and low specificity in the diagnosis of acute VTE is a significant clinical problem[46].

Venography, as mentioned above, is the most accurate technique for diagnosing VTE but is an invasive procedure and venous ultrasonography, though non-invasive, is not as reliable for calf vein DVT, which has a significant risk of extending to PE. Also, both venography and venous ultrasonography are not readily available at HA, which can lead to further delay in accurately diagnosing VTE and thus delay in proper management and treatment, which in severe cases can lead to the death of the individual[47].

Treatment followed by anticoagulant therapy (Table 2) is to be given such that the benefits outweigh the potential risks such as bleeding[48]. Unfractionated heparin poses an 8-10-fold higher risk for heparin-induced thrombocytopenia (HIT) than low molecular weight heparin. Although, fondaparinux has the specific benefit as it shows an extremely low incidence of HIT but it has numerous boundaries as an anticoagulant comprising its extended half-life (17–21 h with regular renal function) and absence of an antidote[49] . Thus, the decisions regarding the choice of anticoagulant, its dosage and duration of the treatment are to be customised according to an individual's needs with periodic monitoring and follow-ups.

## 6. FUTURE PERSPECTIVES

In this review, an effort has been made to understand maladies associated with ascent to high-altitude when proper acclimatisation process is not followed. Limitations in available diagnostic and treatment regime obligate to continue research in altitude-related illness to reveal the exact underlying pathophysiology and the mechanism which will pave the way for developing specific and reliable diagnostic markers and therapeutics with a long-term perspective to improve the health and performance of every individual.

**Table 2. FDA approved anticoagulants and their mechanism of action[33,34]**

| Medicine | Dosage | Half-life | Mode of dose | Mechanism of action |
|---|---|---|---|---|
| Apixaban | 10 mg twice daily for 7 days followed by 5 mg twice daily | 12 h | Orally | Direct factor Xa inhibitor |
| Edoxaban | Adults <60 kg: 30 mg once daily, Adults >60 kg: 60mg once daily for 21 days | 10-14 h | Orally | Direct factor Xa inhibitor |
| Rivaroxaban | 15 mg twice daily for 21 days, | 5-9 h | Orally | Direct factor Xa inhibitor |
| Dabigatran | 150 mg orally twice daily for 5- 10 days with a parenteral anticoagulant | 12-17 h | Orally | Direct thrombin inhibitor |
| Betribaxan | 160 mg on day 1, followed by 80 mg once daily for 35-42 days | 19-27 h | Orally | Factor Xa inhibitor |
| Fondaparinux | Adults < 50 kg: 5 mg once daily, Adults 50 to 100 kg: 7.5 mg once daily | 17-21 h | Subcutaneously | Indirect factor Xa inhibitor |
| Dalteparin | 100 units per kg every 12 hours | 3-5 h | Subcutaneously | Low-molecular-weight heparin |
| Enoxaparin | 1 mg per kg every 12 hours | 5-7 h | Subcutaneously | Low-molecular-weight heparin |
| Alteplase | 100-mg over 2 hours | 30-45 min | Intravenous | Fibrinolytics |
| Unfractionated heparin | 8,000 to 10,000 units every 8 hours | 1-5 h | Subcutaneously | Unfractionated heparin |
| Warfarin (Coumadin) | 10 mg for the first 2 days with warfarin followed by 5mg for more than a week | 21-89 h | Orally | Vitamin K antagonist |

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Contribution in the current study: Monitoring and editing.

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Contribution in the current study: overall monitoring and guidance during manuscript preparation.

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Contribution in the current study: Designing and conceptualisation of manuscript, overall monitoring and editing.