6 High Altitude Induced Thrombosis: Challenges and Recent Advancements in Pathogenesis and Management

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Abstract

Venous thrombosis and pulmonary embolism together form a serious disorder of accelerated and unwanted intravascular blood clot formation which is termed as venous thrombo-embolism (VTE), and can be life threatening. The exposure to high altitude hypoxic environment forms one of the lesser known risk factors for VTE. A number of human and animal studies have provided some mechanistic insights into pathogenesis of high altitude induced thrombo-embolism (HATE). Increasing evidences suggest that the molecular pathogenesis of high altitude induced thrombosis/VTE is distinct from thrombosis occurring at plains. The molecular pathogenesis and clinical management of HATE remains challenging, however, recent advancements provides some insights which are discussed with an attempt to understand molecular pathogenesis and available treatment options for this disorder.

Keywords

High altitude physiology · Thrombosis · Altitude induced thrombosis · Thrombo-embolism

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6.1 Introduction

The pathological formation of blood clot or *thrombosis* is a serious physiological disorder; if not treated immediately, can be life threatening. Although, recognized for centuries, yet the spectrum of treatment remains highly limited and depends mainly on anticoagulant therapy which bears a significant risk of bleeding. Depending on the vessel type, thrombotic disorders can be either arterial or venous in nature, distinguishable predominantly by the sequence of events leading to the thrombosis. In brief, an arterial clot is primarily triggered by the rupture of an artherosclerotic plaque, and is called "white thrombus." On the other hand, thrombi that occur in the veins are rich in fibrin and thus called "red thrombus," largely occurring without damage to the vessel wall. Venous thrombosis (VT) occurs due to changes in the composition of the blood, changes that reduce or abolish blood flow, and/or changes to the endothelium, i.e. the Virchow's Triad. In addition, the genetic and environmental factors can increase the risk of developing venous thrombosis. Although the mechanistic detail of arterial thrombosis has been widely studied (Jackson 2011; Lippi et al. 2011), the more extensive studies are needed for the in-depth understanding of the pathogenesis of venous thrombosis (Reitsma et al. 2012; Lopez and Chen 2009).

Venous thrombosis (VT) which leads to pulmonary embolism (the condition in which blood clot from elsewhere gets stuck in lung vasculature) is known by the name of **Venous Thrombo-embolism or VTE**. VTE has an incidence of approximately 1 per 1000 in adult populations annually (Heit et al. 2016; Heit 2002, 2015), and is more dangerous than VT alone. According to an estimate, 30% of patients diagnosed with VTE die within 30 days (Heit et al. 2016; Heit 2015). The major consequences of venous thrombosis are death, recurrence, post-thrombotic syndrome, and major bleeding due to anticoagulation (Cushman 2007).

6.2 Genetic Risk Factors for VTE

Several Genetic defects leading to the increased propensity of thrombosis, sometimes referred to as "*thrombophillic disorders"* or "*thrombophillia*," have been identified; the major ones are listed in the following.

6.2.1 Factor V Leiden

Coagulation factor V is an important protein for both coagulation and anticoagulant pathways (Dahlback 2016; Lam and Moosavi 2021) . Activated Factor V protein (factor Va) of coagulation pathway acts as a cofactor for factor Xa in prothrombinase complex which converts prothrombin to thrombin. Its inactive form functions as cofactor for Activated Protein C (APC), which mediates anticoagulant pathway by inactivating factor VIIIa. A point mutation in APC cleavage site in Factor V increases the risk of venous thrombosis; individuals heterozygous for this mutation

bear a fivefold increased risk for venous thrombosis while this risk becomes 50-fold in homozygous state (Rosendaal 1999; Emmerich et al. 2001).

6.2.2 Deficiency of Protein C, Protein S and Antithrombin

APC is Vitamin K dependent protein that inhibits coagulation pathway by inactivating Factor VIII a and factor Va, both of which are important for coagulation to proceed (Esmon 1993). Since activated form of Protein C has anticoagulant activity and is important for fibrinolytic pathway, its deficiency can also cause thrombophillic state (De Stefano and Leone 1995). Protein S, another vitamin K dependent protein, functions as a cofactor to APC and is present in free or bound form in plasma; its deficiency also interrupts the activity of APC and hence favors prothrombotic state (Joshi and Jaiswal 2010; Pintao et al. 2013). Antithrombin (AT, previously known as AT III) is a multifunctional protein which inhibits essentially all enzymes of coagulation pathway (Rau et al. 2007).

6.2.3 Prothrombin Mutation

The mutation in the gene for Prothrombin or factor II (Varga and Moll 2004), another of the coagulation factor genes, does not change the structure of the molecule but elevates the plasma levels of prothrombin increasing the risk of thrombosis for lifetime (Bank et al. 2004; Poort et al. 1996). Nearly 6% of all patients of venous thrombosis bears mutation in prothrombin gene (Poort et al. 1996).

6.3 Acquired Risk Factors for VTE

6.3.1 Surgery/Trauma

The risk of thrombosis varies with the type of surgery and trauma (Agnelli 2004). Hip or knee replacement, fracture (hip or leg), and spinal cord injury are classified as strong risk factors for the development of VTE (Bergqvist et al. 1983; Anderson and Spencer 2003). Geerts et al., 1994 showed in a study that 47% of trauma patients have been found to develop DVT (Geerts et al. 1994).

6.3.2 Advanced Age

Numerous reports have associated advancing age with somewhat increased risk of thrombosis (Rosendaal 1999; Oger 2000). Although the precise cause for such a strong association is not clear, factors like reduced activity, aging of veins and thus vein valves, associated with old age are thought to contribute to the increased risk.

6.3.3 Cancer

Malignancy has been linked to thrombotic events since 1865, when Trousseau observed the tendency of cancer patients to develop thrombosis (Merli and Weitz 2017). Since then, several studies have confirmed the higher rate of venous thrombosis in cancer patients (Hisada et al. 2015; Mahajan et al. 2019; Leiva et al. 2020; Khorana et al. 2007; Timp et al. 2013).

6.3.4 Oral Contraceptives and Hormone Replacement Therapy

Daily dose of a combination of an estrogen and progesterone is the most commonly prescribed form of oral contraceptives. The absolute risk of venous thrombosis in oral contraceptive users is 2 to 3 per 10,000 per year against less than 1 in nonuser women of reproductive age (Jick et al. 2000; Vandenbroucke et al. 1994; Dragoman et al. 2018).

6.3.5 Immobilization

The link between stasis/immobilization and VTE dates back to World War II when Simpson noted pulmonary embolism in people sitting on deck-chairs for prolonged periods, taking refuge in air-raid shelters and also demonstrated that sitting posture confers a greater risk than other positions (Simpson 1940). An early autopsy study found that 15% of patients who were at bed rest for less than a week had venous thrombosis; the rate was 80% with bedrest for longer duration (Gibbs 1957; Pottier et al. 2009). DVT has been shown to occur more frequently in the paralyzed limb of a hemiplegic, rather than the unaffected limb (Warlow et al. 1976)). A recent report establishes the link between immobilization and thrombosis in which prolonged sitting (more than 12 h) in front of computer is found to cause thrombosis which is termed e-thrombosis (Beasley et al. 2003; Sueta et al. 2021). However, while it is known that immobilization among patients does increase the risk of VTE, the specific role of underlying conditions cannot be excluded from consideration.

6.4 Modern Lifestyle Risk Factors for VTE

There are some other acquired risk factors for VTE which are associated with modern lifestyle (Crous-Bou et al. 2016). These include obesity, high circulating lipids, smoking, diabetes mellitus, etc. In addition to these, acute thrombotic episodes have been allegedly associated with some trivial events like sneezing and coughing attacks, sexual intercourse, strenuous physical exercise, migraine, etc.; however, the role of such events as a true trigger in any case of thrombosis is questionable (Lippi et al. 2009).

6.4.1 Virchow's Triad

Rudolph Virchow in the year 1859, first described the occurrence of thrombosis in vein. He concluded that the three factors (popular as Virchow's Triad)—(1) blood flow, (2) vessel wall, and (3) blood composition, determine the tendency of an individual to develop thrombus. "Virchow's triad" has proved to be "seminal" for modern research on thrombosis. According to the current understanding of VTE, the rise in prothrombotic factors (including IIa, tissue factor, VIIa, VIIIa, Va, Xa, platelets) defects in anticoagulant pathways, hyperactivation/dysfunction of endothelium can all stimulate thrombus formation; which may be due to single/multiple, known/unknown, genetic or/and acquired factors.

Apart from the established risk factors, the exposure to high altitude has been associated with increased incidences of thrombotic disorders, of which the venous type are more prevalent than arterial ones (Anand et al. 2001; Dilly 2021; Whayne Jr. 2014; Gupta and Ashraf 2012). Although, known for decades but as compared to other risk factors, the understanding about the pathogenesis of high altitude induced thrombosis remains highly limited.

6.5 Hypoxia at High Altitude

The barometric pressure in the atmosphere (760 mm of mercury) varies with the height or altitude from sea level. The fall in barometric pressure at altitudes lead to a proportional decrease in the partial pressure of oxygen (PaO_2), present in atmosphere, which determines the availability of oxygen for breathing. For reference, at the Everest base camp (5300 m altitude), the PaO_2 in atmosphere becomes half of that at sea level. This decreased availability of oxygen for breathing leads to oxygen limiting conditions in body, generally referred to as hypoxia. High altitude physiology may be divided into the study of short-term changes that occur with exposure to hypobaric hypoxia (the acute response to hypoxia) and studies of longer-term acclimatization and adaptation. Hypoxic challenge, such as that posed by high altitude exposure, is countered by natural physiological mechanisms of adaptation. The major adaptive changes that occur in the body can be by either increasing the oxygen delivery to tissues (by elevating hemoglobin levels) or reducing oxygen demand. The latter mechanism appears to be preferred by body as the metabolic rate and mitochondrial reactions (that solely depends on oxygen) are observed to be reduced with fall in available oxygen (Hochachka et al. 1996). However, these adaptive mechanisms cannot completely overcome the hypoxic challenge, but do increase the chances of longer survival under hypoxia.

6.6 High Altitude Thrombo-Embolism (HATE)

The term *high altitude* refers to the terrestrial elevations over 1500 m (about 5000 ft). At such elevated altitudes, diminished oxygen partial pressure, decreased temperature, lower humidity and increased UV radiations, dehydration, etc. may result in several complications/maladies. The commonly encountered ones are acute mountain sickness, HAPE (High Altitude Pulmonary Edema) and HACE (High Altitude Cerebral Edema), which form the major high altitude illness (Basnyat and Murdoch 2003). Besides these, higher incidence of thrombotic episodes is reported at high altitude, most of which occurs in veins (Anand et al. 2001; Dilly 2021) and can thus be termed as HATE (High Altitude Thrombo-Embolism). Multiple factors including hypoxic environment, immobilization, dehydration, reduced atmospheric pressure have been suggested to be responsible for HATE by many investigators, although there is no conclusive/concrete evidence to confirm the contribution of these different stressors.

6.7 Pathogenesis of HATE

Several reports have highlighted an increased risk of venous thrombosis following exposure to high altitude environment, although there mechanism behind the pathogenesis of such events is not yet completely elucidated. Apart from low PaO_2 due to reduced atmospheric pressure (hypobaric hypoxia), other factors such as low temperature, reduced mobility (especially for troops at mountains and during air travel), and dehydration also affect the physiological systems in the body and thus may contribute to increased risk of thrombosis at HA.

For decades, studies to evaluate the role of HA in thrombotic episodes and its effect on coagulation system are being done in various settings. These settings can be broadly classified as:

1. Ascent to an elevated region,
2. Long duration air travel,
3. Simulated high altitude.

6.7.1 Ascent to an Elevated Region

Several studies to ascertain the risk of thrombosis due to stay at HA have been conducted till date. Singh and Chohan had observed a tendency of hypercoagulation in Indian troops on immediate arrival at 3600 m with the increase in the platelet count, factor X, factor XII, thrombotest activity and thrombin clotting time, along with a significant increase in plasma fibrinogen and fibrinolytic activity (Singh and Chohan 1972a, b). In 1975, Ward reported deep vein thrombosis followed by pulmonary embolism in mountain climbers and a significant rise in platelet adhesiveness was observed in patients who developed ischemic strokes at HA (Sharma

1980, 1986; Sharma et al. 1977). During a study at Andes (at 3600 m and above) involving an ascending group of 28 young men, a significant increase in platelet count and hematocrit was noted 48 h after their visit as compared to the values in them at low altitude of 600 m (Hudson 1999). There have been conflicting reports about the changes in platelet count upon high altitude induction: increase (Singh and Chohan 1972b; Sharma 1980; Kotwal et al. 2007); decrease (Chatterji et al. 1982; Vij 2009); and no difference (Sharma 1986; Maher et al. 1976; Le Roux et al. 1992). During stay above 6400 m, changes in coagulation with the increase in D-dimer levels have been described, which was suggestively attributed to endothelial cell damage (Le Roux et al. 1992).

The interest in such studies was further fueled by several reports in the recent years. Bartsch et al. observed no increase in fibrin or thrombin levels in resting mountaineers who had ascended to 4559 m on foot (Bartsch et al. 2001). However, another group reported a significant rise in fibrinogen levels along with the rise in platelet activation factors in volunteers after long-term stay above 3500 m and concluded that prolonged stay at HA leads to a hypercoagulable state (Kotwal et al. 2007). Anand et al. in 2001 reported thrombosis as a complication of long-term stay at HA with a 30% higher risk (Anand et al. 2001). In addition to this, stroke cases with rate of 13.7/1000 hospital admissions were reported from HA area as compared to 1.05/1000 from plains (Jha et al. 2002).

A big question arises in HATE pathogenesis that if the hypercoagulable state and platelet activation are also associated with VTE at plains, then whether the HA associated VTE is any different in pathogenesis. In a recently published human cross sectional study, Prabhakar et al. studied the cohort of patients who developed VTE at HA, and compared this with patient cohort who developed VTE at plains (Prabhakar et al. 2019). The changes in several blood markers including coagulation, platelet activation, inflammatory response, and others were analyzed to establish HA associated pathophysiological factors in VTE. Platelet counts were found significantly elevated in HA patients (>35% patients vs. <10% of patients at plains). Besides markers of coagulation/thrombosis such as vWF and D-dimer, they also observed elevated levels of soluble platelet activation markers (P-sel, CD40L, PF4) and inflammatory markers—IL1b, IL6, and IL10 HA patients. The hypoxia associated markers—HIF-1α and the chaperoneHSP-70 were also elevated in HA cohort. The study thus highlights that the involvement of platelet activation, endothelial activation, and inflammatory molecules becomes more pronounced in HA associated VTE as compared to VTE at plains. The role of hypoxia response pathway genes was also emphasized in genome-wide expression analysis of HA-VTE patients (Jha et al. 2018).

6.7.2 Long Haul Air Travel

Numerous studies including cohort and randomized controlled trials have been performed to evaluate the risk of thrombotic complications due to long duration (>6 h) air travel. The risk of VTE associated with air travel has been found to be

more than that with "weak" risk factors (like bed rest for more than 3 days, laparoscopic surgery, obesity, increasing age) and similar to "moderate" risk factors (e.g. congestive heart failure, hormone replacement therapy, deficiency of protein C and protein S) (Philbrick et al. 2007). Philbrick and coauthors observed some interesting trends about air travel related VTE reports by reviewing 24 publications from 1999 to 2005 (Philbrick et al. 2007). Case control studies, cohort studies, and randomized controlled trials (RCTs), providing information about incidence of VTE after travel, were collectively analyzed, and further define long haul air travel as a critical risk factor for development of venous thrombosis.

In a crossover study of 71 volunteers, markers of coagulation activation and fibrinolysis (thrombin-antithrombin or TAT complex, prothrombin fragment 1 + 2 or F1 + 2, D-dimers) were measured before, during, and after 8 h flight (Schreijer et al. 2006). The study also included some volunteers with already present risk factors, i.e. factor V leiden and oral contraceptive use. Activation of coagulation and fibrinolysis was evident in some of the volunteers (especially those with respective risk factors) after flight as compared to only immobilized state and daily life. This study supported the role of hypobaric hypoxia in activating coagulation system during air travel (Schreijer et al. 2006).

Concurrently, Manucci noted an increase in thrombin formation and fibrinolysis in volunteers taken to 1200 m and then to 5060 m, by air (Mannucci et al. 2002). Air travel has been proposed to amplify the risk of venous thrombosis in individuals with an already present risk factor. The supporting evidence comes from a study on 210 patients who were found to have 16% higher risk after air travel as well as 14% higher risk in women who were previously taking oral contraceptives (Martinelli et al. 2003).

6.7.3 Simulated Hypobaric Hypoxia

In an elegant single-blind, crossover study performed in a hypobaric chamber, the effect of an 8-h seated exposure to hypobaric hypoxia on hemostasis was studied on 73 healthy volunteers (Toff et al. 2006). Individuals were exposed alternately to hypobaric hypoxia, like the conditions of reduced cabin pressure during commercial air travel (equivalent to atmospheric pressure at an altitude of 2438 m), and normobaric normoxia (control condition; equivalent to atmospheric conditions at ground level). Blood was drawn before and after exposure to assess activation of hemostasis and markers of coagulation activation, fibrinolysis, platelet activation, and endothelial cell activation were evaluated. Changes were observed in some hemostatic markers during the normobaric exposure, attributed to prolonged sitting and circadian variation (Toff et al. 2006). However, there were no significant difference in any marker after hypobaric hypoxia as compared with the normobaric normoxia exposure.

Another group studied changes coagulation of arm and leg veins by measuring various parameters and by thromboelastography pre- and post-10 h exposure to simulated normobaric hypoxia (equivalent to 2400 m) (Schobersberger et al. 2007).;

however no significant activation of coagulation system was observed. In a study by Crosby et al. 2003, eight healthy volunteers were exposed to simulated hypoxic conditions for 8 h at differing altitudes to unacclimatized (3600 m) and fully acclimatized volunteers. Again, no changes were observed in markers of coagulation activation like F1 + 2, TAT, factor VIIa following hypoxic exposure. Contrary to these reports, Bendz (2000) in his study on 12 volunteers, reported activation of coagulation after sudden exposure to simulated HA (2400 m) for 2 h (Bendz et al. 2000, 2001). This study, however, lacked an adequate control group and faced immediate criticism by another group (Bartsch et al. 2001).

A case report of a 19-year-old female who developed sinus vein thrombosis after high altitude training in a hypoxic chamber (Torgovicky et al. 2005), supports the view that HA conditions predisposes an individual to thrombotic events regardless of age as a predominant risk factor. The patient in the study was working as a training instructor in a high altitude simulation chamber 2 months prior to the event and participated in six training sessions. During training she complained of dyspnea and within few days after last hypoxic exposure she developed severe frontal headaches. The CT and MRI procedures confirmed sinus vein thrombosis which was later controlled by anticoagulant drugs (Torgovicky et al. 2005).

6.8 Evidence from Pre-Clinical Studies

Studies on humans are highly limited at the interventional front, primarily due to the limited ability to control the associated variables, and animal studies are thus required to test the hypotheses generated by human cohort studies.

In a first of its kind study, Tyagi et al. found that the simulated HA (cold surrounding plus hypoxia) exposure of 6 h was able to induce prothrombotic phenotype in rats which was marked by increased platelet adhesion and aggregation and reduced bleeding time (Tyagi et al. 2014). Observed in absence of any induced vascular injury, the results emphasize the role of systemic activation of platelets in hypoxic environment. Hypoxia, but not cold climate, was found to be primarily responsible for increased platelet activation. The platelet proteome was also found to be distinctly altered in the exposed animals and the platelet calpain regulatory subunit was shown to regulate thrombogenesis through platelet activation. Besides calpain, other prothrombotic factors such as Tissue factor and fibrinogen were also upregulated in HA exposed platelets in vivo (Tyagi et al. 2014). Interestingly, the most striking platelet aggregation changes were observed in response to ADP and not thrombin, suggesting the increased sensitivity of platelets to ADP under hypoxic conditions in vivo. This finding was also supported by an expedition study wherein platelet aggregation in 22 human subjects was measured before and after ascent to HA (5300 m); platelet aggregation was observed to be higher in response to only ADP at HA as compared to the levels at plains in the same individual (Rocke et al. 2018).

Another study demonstrated, using the rat model of VTE, that exposure to simulated HA hypoxia led to NLRP3 inflammasome induction through HIF-1α

pathway (Gupta et al. 2017). The pharmacological targeting of HIF-1α through si-RNA approach was shown to limit VTE in animals. Hypoxia induced signaling was also involved in VTE pathogenesis in non (hypoxia) exposed animals, suggesting the role of stasis induced local hypoxic microenvironment in VTE pathogenesis (Gupta et al. 2017)**.** The HIF-1α has also been implicated in thrombus recanalization in mice model of DVT (Evans et al. 2010) Moreover, platelets are proposed to activate NLRP3 inflammasome in innate immune cells including neutrophils and monocytes, thereby increasing plasma IL-1β (Rolfes et al. 2020). Importantly, it has been shown that platelets themselves can assemble NLRP3 inflammasome in sepsis and can produce and release IL-1β.

Recently, in hypoxia exposed mice, the platelet depletion prevented hypoxia driven increase in pro-inflammatory cytokines CXCL4 and CCL5 in lungs (Delaney et al. 2021)**.**This study further strengthens the central role of platelet activation which can influence inflammatory milieu in hypoxic conditions, leading eventually to immunothrombosis. The concept of immunothrombosis has recently gained interest in the view of COVID-19 pathology, which also involves hypoxemia, platelet activation, and hyperinflammatory status. VTE episodes have been shown to occur predominantly in COVID-19 patients (Di Minno et al. 2020; Middeldorp et al. 2020). In COVID-19, the acute respiratory distress syndrome (ARDS) and/or thrombosis form major cause of patient mortality (Middeldorp et al. 2020; Althaus et al. 2021; Magro et al. 2020; Ackermann et al. 2020). The platelet-neutrophil aggregates are believed to be involved in ARDS and thus role of hypoxemia induced platelet driven inflammation cannot be ruled out (Althaus et al. 2021; Viecca et al. 2020; Martinod and Deppermann 2021; Middleton et al. 2020; Le Joncour et al. 2020). The platelets interact by P-selectin present on platelet surface which binds with PSGL-1 on neutrophils and platelet-neutrophil interaction has been demonstrated to trigger NETosis. The activated platelets have upregulated surface P-selectin and thus can cause increased formation of platelet-neutrophil aggregates. Platelet activation with increased platelet-leukocyte aggregates and altered platelet transcriptome has been demonstrated in critically ill COVID-19 patients (Manne et al. 2020).

6.9 Clinical Management of HATE

As the HA has not reached a well-recognized risk factor status for thrombo-embolism globally, the clinical guidelines are still not clear and detailed. The thrombotic risk patients, traveling via long haul flights are generally advised to not take any additional medication unless any symptoms are present. However, as evident from prior studies, HA travel and HA stay for months or even days can pose a greater risk than a long-haul flight (Gupta and Ashraf 2012). This warrants formation of a standard clinical guideline for HATE prophylaxis and/or treatment, separate from long haul travel. Before travel to HA, a clinical assessment of thrombotic risk is advisable. A history of thrombotic episodes or presence of one or more VTE risk factors, any planned provoking activity which involves strenuous

Table 6.1 The Well's scoring system for Deep Vein Thrombosis

Clinical feature	Assigned score
Malignancy (active cancer or palliative treatment within last 6 month)	1
Paralysis, paresis or plaster immobilized lower limb	1
Recent bedridden state for 3 or more days or surgery with 12 weeks requiring anesthesia	1
Localized tenderness along the deep venous system	1
Swelling of entire leg	1
Calf swelling (minimum 3 cm larger than that on the asymptomatic side)	1
Pitting edema of the symptomatic leg	1
Collateral non varicose superficial veins	1
Documented history of deep vein thrombosis	1
Alternative diagnosis as likely as or more than deep vein thrombosis	**−2**

(Adapted from Wells et al. 2003)
Total Score of 2 or more = Deep vein thrombosis likely
Total Score of less than 2 = Deep vein thrombosis less likely

Table 6.2 The Well's scoring system for Pulmonary Embolism

Clinical feature	Assigned score
Clinical signs and symptoms of DVT (leg swelling, pain, palpation of leg veins)	3
An alternative diagnosis less likely than pulmonary embolism	3
Heart rate of more than 100 beats/min	1.5
More than 3 days of immobilization or surgery in previous 4 weeks	1.5
History of DVT or pulmonary embolism	1.5
Hemoptysis	1
Malignancy (within last 6 months or palliative)	1

(Adapted from Wells et al. 2000)
Total Score of more than 4 = Pulmonary embolism likely
Total Score of less than or equals 4 = Pulmonary embolism less likely

activity or long term immobilization—all of this need to be considered carefully as part of the risk assessment. Trained physician need to be able to assess and guide patients about the risk; preventive non-pharmacological or pharmacological measures can then be taken as appropriate for the individual depending upon the risk assessment outcome (Trunk et al. 2019).

The symptoms of DVT or PE can be assessed by Well's scoring system (Tables 6.1 and 6.2). Presently, after onset of any thrombosis like symptoms, immediate descent to low altitude region, if possible, is done to limit the symptoms and perform diagnostic tests. In case of a positive D-dimer test, a confirmatory scan (CT scan or MRI for PE or CVT; Doppler ultrasonography for DVT) is generally advised for diagnosis of thrombotic event. This practice is similar to that used for any VTE episode at plains. The travelers who have prior risk factors for VTE can be advised prophylactic oral anticoagulants—which include Factor X inhibitors

(apixaban, edoxaban, or rivaroxaban) as discussed previously . Oral anticoagulant therapy is a currently accepted line of treatment, and can be started following clinical suspicion even before radiological confirmation, if there is no known bleeding risk to the patient. After excluding the surgery requirement, the oral anticoagulant therapy is continued for 6 months at the minimum with strict INR monitoring.

The prior case reports suggest that thrombogenic effect of HA exposure can go beyond the stay at HA. A report recently detailed the case of a healthy 42-year-old mountain guide who experienced shortness of breath and left calf swelling while working and skiing at 3500 m HA. Following the descent to low altitude region, he again felt shortness of breath and developed severe thoracic pain, hemoptysis, and arm cramps. The thoracic CT scan confirmed the PE in left and right lung lobes with infarction pneumonia and was put on anticoagulant therapy (Hull et al. 2016).

Due to the bleeding risk associated with anticoagulant use, there has been a need to develop a safer anti-thrombotic therapy. To address this, a highly ambitious trial of vitamin supplement was conducted for a long term of 2 years on 6000 Indian soldiers posted at HA (3500 m) (Kotwal et al. 2015). This randomized field trial was aimed at lowering the plasma homocysteine (Hcy) levels by Vitamin B12, B6, and folate and thereby reducing the thrombotic risk at HA. The supplementation was found to be protective against thrombotic episode with relative risk value of 0.29. There were total five events in the intervention group as compared to 17 events in control arm. The pro-coagulant factors—PAI-1 and fibrinogen were reduced in the intervention group (Kotwal et al. 2015). However, the exact mechanism of this effect, however, could not be established.

As hypoxemia is one of the common etiological factors in both HATE and COVID-19, and these both involve platelet activation and thrombo-inflammation, the antiplatelet therapy in COVID-19 can offer some possible insight for HATE management as well. A recent meta-analysis revealed that antiplatelet therapy against COVID-19 has not produced any significant effect on patient mortality (Hu and Song 2021), likely due to the use of aspirin as antiplatelet agent in most of those studies. The use of other antiplatelet drugs or a combination of such drugs may prove to be more beneficial. In recent times, a clinical trial was conducted, wherein an antiplatelet cocktail therapy, including GpIIb/IIIa inhibitor Tirofiban, followed by Aspirin (Cox inhibitor) and Clopidogrel (P2Y12 inhibitor) was administered to hypoxic COVID-19 patients (Viecca et al. 2020). The D-dimer and CRP levels were reduced in treated patients, indicating the anti-thrombotic and anti-inflammatory outcome of this antiplatelet regimen. Moreover, all the treated patients consistently experienced a progressive reduction in A-a O_2 gradient during the study period which indicated improved respiratory function. Although done in a few samples ($n = 5$), there was a consistent and significant improvement in the prothrombotic, inflammatory, and respiratory parameters in hypoxic COVID-19 patients. This clinical evidence supports the consideration of antiplatelet drugs and particularly that of GpIIb/IIIa and/or Clopidogrel inhibitor for HA associated thrombotic risk patients with careful monitoring of coagulation profile.

Platelet activation, however, should not only be seen as a negative prognostic factor or in simple words—a troublemaker. Platelets primarily are responsible for

hemostasis and thus the inhibition of platelet activity, where the activated platelets are important for physiological events such as hemostasis, can lead to clinical mismanagement in the form of either bleeding propensity or heightened inflammation. This is because platelets do carry a pool of inflammatory and anti-inflammatory molecules, angiogenic factors, chemokines, and vasoconstrictors such as serotonin (Koupenova et al. 2018). In sepsis, for example, the platelets can serve to limit the pro-inflammatory response (Derive et al. 2012). Therefore, the efforts should be aimed at limiting the hyperactivation of platelets after confirming the platelet hyperactivity and HATE risk assessment.

6.10 Conclusion

High altitude environment is a lesser known but proven risk factor for life threatening thrombo-embolic disorders. Over the last few decades, a growing number of molecular and clinical studies have contributed to the progress in understanding the HATE pathogenesis. The underlying mechanism of HATE appears to be overlapping but still distinct from thrombosis at plains. Furthermore, in-depth studies are required to understand the biomarkers and mechanistic intricacies of this disorder. Moreover, there is a definite need for the formulation of comprehensive clinical guidelines at the global level for the prophylaxis and treatment of HATE.

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