ALTERATION IN THROMBOGENIC PARAMETERS AS A POTENTIAL RAMIFICATION OF HIGH ALTITUDE INFLUENCE ON INDIVIDUALS

Abstract: The peculiarity of alteration in platelet indices among other physiological changes on adaptation to high altitude is controversial. This review has revealed insufficient information about how changes in platelet indices can be attributed as a consequence of high-altitude terrain. Further clinical trials are necessary to understand the potential relation between high altitude and changes in thrombocytes and their activity.

Keywords: Thrombosis, thrombocytes, hypothermia, hypoxia, altitude.

Introduction

80 million people in Asia and 35 million people in the Andean mountains are considered to be living at high altitudes >2500 m above sea level. The most challenging issues of high altitude are low temperatures and hypobaric hypoxia. Due to massive erythropoiesis, we see an increase in blood viscosity, disruption of microcirculation, and increasing the risk of numerous ischemic disorders such as stroke, myocardial infarction, and other thrombotic events, as a consequence of hypercoagulable state.[1,2] Recently, thrombotic events have been highlighted as contributing to the severity of SARS-CoV2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection.[3] Cellular hypoxia is a typical ultimate stage of brain injury that happens not only after suffocation but also when cerebral perfusion is disrupted directly in case of embolic stroke.[4] Thus, the observation that thrombosis seen in various systemic manifestations is a recognised complication of exposure to
high altitude has triggered interest in the effects of the latter on hemostasis in humans. During adaption to high altitude increase in hematocrit and erythrocytosis is a well-established fact but the changes in thrombocytes and the mechanism involved remain controversial fact.

As a result, our research question was about the alteration in thrombogenic parameters as a potential outcome of high-altitude terrain on humans. We conducted a systematic search for relevant studies from the literature including data from 2002 till April 2022 with the help of databases like Google Scholar and PubMed.

Main part

A study conducted by Pandey et al identified discrepancy, 8 out of 303 patients diagnosed with high altitude pulmonary edema (HAPE) had pulmonary embolism. When the extensive investigation was done, it was concluded that with regard to thrombotic risk, pulmonary embolism can show clinical features similar to HAPE and should be considered in patients presenting with shortness of breath from high altitude.[5] A two-year prospective study (2011–2013) was conducted in two different geographical areas of Saudi Arabia, the study enrolled patients who were clinically suspected of having pulmonary embolism or deep vein thrombosis. Chances of the latter at high altitude dwellers were 56.8% compared to 13.0% of low altitude dwellers.[6]

Hypothermia is part of the “lethal triad” in cases of a traumatic patient. Platelet count (PLT) shows declines in case of hypothermia.[7,8] Evidence suggests that anesthetise-induced hypothermia reduces platelet function by inhibiting aggregation and impairs coagulation cascade enzymes.[9,10] This enables us to dwell upon the evidence regarding environmentally induced hypothermia and hypoxia effect on platelet indices and function.

Niu et al observed the Chinese Tibetan population which is long exposed to very high altitude and a hypoxic environment on the Qinghai-Tibet Plateau. Tibetans had significantly lower mean platelet volume (MPV), indicating the low prevalence of vascular disease in the Tibetan population. Platelet large cell ratio (P-LCR) accounts for the percentage of platelets circulating in the blood. Platelet distribution width (PDW) is a measure of anisocytosis shown by thrombocytes. Chinese
Tibetans had lower P-LCR and PDW, which correlated with the change in MPV, according to the findings when comparing them with the Han population in the plains. Tibetans had higher PLT irrespective of low MPV. However, PDW does not show a significant difference.[11] Juntendo University conducted an observational study on 2882 patients. MPV was observed before and after the elective percutaneous coronary intervention of participants. It was reported patients with low MPV have a higher chance of major adverse cardiac events including myocardial infarction.[12] Contradictory to this a previous study in Italy with 1411 participants who underwent coronary angiography reported no association between MPV and coronary artery diseases.[13] On further investigation, it was noted MPV can be used as a prognostic factor for cardiovascular diseases as an indicator of platelet size. Moreover, various cohort studies like He et al, Sun et al, and Jiang et al proved that low MPV shows a lower prevalence of cardiac death. [14,15,16] Large-sized platelets will contain more alpha and dense granules aiding in the production of more pro-thrombotic factors leading to the formation of thrombophilia condition.[17] Interleukin 3 in conjunction with the granulocyte-macrophage colony-stimulating factor, promotes the formation of large thrombocytes capable of thrombotic activity.[18] Additionally, Chinese Tibetan populations have high PLT due to their gut microbial communities consisting of *Alistipes* and *Parabacteroides*.[19] Hence, the increase in PLT is not obviously related to long-term hypobaric hypoxia or hypothermia. The issue of how high altitude affects MPV is still open to discussion.

Hartman et al conducted an observational module on 16 consenting healthy and sportive subjects (F: n=9; M: n=7). Thrombopoietin (TPO) (P=0.0006), platelets (P=0.031), and erythropoietin (P=0.003) levels risen dramatically. Haemoglobin, hematocrit, and platelet indices remained unchanged. There was substantial evidence to find the correlation between TPO and platelets (r=0.52, P=0.043), but not between erythropoietin and platelets (r=0.26, P=0.32). This means thrombocytes and erythropoietin do not show direct proportionality. MPV as a single variable can be used for screening purposes for bleeding disorders and bone marrow diseases.[20,21,22] The difference between pre- and post-exposure values for mean platelet component (25.85±2.65 g/dl vs. 26.17±1.8 g/dl; P=0.66) or mean platelet
The study concluded with regards to such observations that TPO does not act as a mediator of increased PLT at altitude.[23] Data in this study, in order to understand the relation between low PLT and high altitude, was also not conclusive.

Ladakh is a region in India. It falls from an altitude of 5753 m above sea level at its source at Indira Col on the China border down to 3620 m at its snout. It is inhabited by people of Indo-Aryan heritage who are said to be markedly different from Tibetans. Yanamandra et al wanted to look at haematological parameters in native highlanders aged 4–19 years. Residents and visitors to high altitude have sought that such individuals have a greater incidence of thrombotic events. It was found, that PLT was $378.4\pm152.8 \times 10^{3}/mL$, with the highest PLT of $429.3\pm112.4 \times 10^{3}/mL$ in the 5–8 years age group and gradually decreasing to $292.1\pm88.9 \times 10^{3}/mL$ in the 15 years age group. PLT decrement with age was found to be of statistically significant. On the contrary, PLT increased in the Tibetan highlanders but decreased in the Ladakh population with a decline in age.[24]

It is well known that primary haemostasis occurs in the body as the first step of platelet plug formation. It has the following steps vasoconstriction, platelet adhesion, degranulation, and platelet aggregation. During platelets degranulation in the inflammation foci, thromboxane A2 (TXA2) is formed after the chain of enzyme-linked reactions.[25,26] However, despite the pathophysiology of TXA2 with platelets, the study conducted by Juan et al states there is no correlation between increased level of TXA2 and platelet-derived growth factor with platelet indices in chronic mountain sickness.[27] In a recent study by Paterson et al the discovery of increased platelet reactivity on exposure to acute hypobaric hypoxic elicited by high altitude terrains. It was demonstrated that hypoxia upregulates basal levels of vasodilator-stimulated phosphorylation protein (VASP) phosphorylation in a P2Y12 signalling pathway. VASP is mediated by cyclic adenosine monophosphate. An increase in VASP results in an increase in cyclic adenosine monophosphate, which reduces platelet aggregation. The clinical relevance of isolated and increased P2Y1 activity is unclear as the overall ADP sensitivity was not changed. It is speculated that other pathways are involved.[28,29]
A clinical trial by Zhang et al reported variability in hemoglobin and hematocrit at high altitude has no role in changes in PLT. Platelet functions like aggregation and adhesion might be explained by the physiological changes that occur at high altitude adaptation but its influence on PLT can not be explained.[30,31,32] On blood flow-cytometric assay by Kicken et al participants showed an increase in thrombin generation and a decrease in platelet aggregation at high altitudes. This mechanism can be described as raised adenosine levels activating the RBC A2B adenosine receptor. Adenosine monophosphate-activated protein kinase provokes diphosphoglycerate mutase, which generates 2,3 diphosphoglycerate and decreases the activation of the A2B adenosine receptor (2,3-DPG). 2,3-DPG acts as an inhibiting factor for platelet aggregation.[33,34,35]

16 healthy test subjects flew to La Paz, Bolivia, where one’s plasma vWF increased significantly after altitude exposure prior to low altitude values. P-selectin and PLT were not correlated at sea level or during altitude-induced hypoxia in an experiment by Turton et al.[36] Platelet P-selectin forms platelet-leukocyte aggregates when it interacts with P-selectin glycoprotein ligand-1 on leukocytes. Furthermore, P-selectin-PSGL-1 interaction increases tissue factors, which together play a role in creating a prothrombotic state. During platelet-platelet interactions, or platelet aggregation contributed by P-selectin.[37,38,32] Even in cases of HAPE patients, high-altitude exposure shows reduced PLT and shortened platelet function analyzer closure time by about 20%, indicating increased platelet aggregation. It also increases P-selectin levels by about 250% but did not affect on plasma coagulation. There were no differences in PLT, platelet aggregation, or sP-selectin values between placebo-treated HAPE patients and controls.[32]

Jha et al proposed that hypoxia at high altitude causes changes in the expression of genes related to blood coagulation and haemostasis, which in turn results in platelet dysfunction and enhanced vulnerability to venous thrombosis. Hypoxia was found to increase the expression of ANG, EGR1, lamin A (LMNA), MMP14, neurofibromin 1 (NF1), PDZ and LIM domain 1 (PDLIM1), PLOD1, solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLCA4), solute carrier family 9 (sodium/hydrogen exchanger), member 1 (SLC9A1), and TEK.[39]
Among Iranian mountain climbers, 29 deaths in total were recorded between March 2006 and June 2010.[40] In emergency medicine, managing patients in mountain and remote areas is a significant challenge. An observation study conducted at the Severe Hypothermia Treatment Centre by Anna Jarosz and her colleagues dealt with cases of 152 hypothermia over a period of 2 years. They saw a decline in erythrocyte count and PLT. The international normalized ratio was as high as 10.5. The possible reason was thought to be chronic illnesses such as liver failure and splenomegaly, poor nutritional status resulting in chronic anemia and thrombocytopenia or clotting factor deficiency.[41] Horioka et al study indicated that platelets are activated and form aggregates in hypothermic spleens. Thrombocytopaenia seen usually triggered by sequestration in the liver and spleen. Prostacyclin’s effect on platelet aggregation and endothelial synthesis may be impaired by hypothermia, leading to increased platelet activation and thrombosis.[42,43]

According to de Vrij et al, thrombocytopenia during hibernation is primarily caused by body temperature. Mice in vitro research shows that the spontaneous production of P-selectin and the active conformation of GPIIb-IIIa are not significantly altered by incubation at temperatures of 34°C and 31°C. A slight increase in platelet activation but a significant increase in agonist-induced responsiveness are the effects of moderate hypothermia reported by Lindenblatt et al.[44,45,40] Although there is experimental evidence for mice to infer any hypothesis regarding the consequence of hypothermia on thrombocytes there is a need to have robust trials on humans.

Conclusion

High altitude terrain effects on platelet indices and platelet function are extremely under-investigated area. The link between how hypobaric hypoxia directly manipulates platelet indices is scares, its effect on the platelet aggregation and reactivity needs further investigation to formulate a universally accepted hypothesis. There is a substantial lack of evidence to analyse the relation between altitude-induced hypothermia and thrombocytes level. Consequently, to fulfil this research gap further clinical trials and randomized controlled trials are obligatory.
References:


