Original article

Features and incidence of thromboembolic disease: A comparative study between high and low altitude dwellers in Saudi Arabia

Farjah H. Algahtani a,⇑, Fatmah S. AlQahtany b, Abdulrahman Al-Shehri c, Abdelgalil M. Abdelgader d

a Department of Medicine, Division of Oncology/Hematology, College of Medicine, King Saud University, King Saud University Medical City, Riyadh, Saudi Arabia
b Department of Pathology, Hematopathology Unit, College of Medicine, King Saud University, King Saud University, Medical City, Riyadh, Saudi Arabia
c Hematology-Oncology Department, Aar Central Hospital, Saudi Arabia
d Physiology Department, College of Medicine, King Saud University, King Saud University, Medical City, Riyadh, Saudi Arabia

 ARTICLE INFO

Article history:
Received 12 January 2020
Revised 3 March 2020
Accepted 4 March 2020
Available online 12 March 2020

Keywords:
Venous thromboembolism
Deep vein thrombosis
Pulmonary embolism
High altitude

ABSTRACT

To estimate and compare the incidence of thromboembolic disease among patients who are clinically suspected for VTE among high and low altitude dwellers in Saudi Arabia. A prospective study conducted over two years (2011–2013) conducted in two different geographical areas in Saudi Arabia; Abha City and Riyadh City. Patients clinically suspected with deep vein thrombosis and pulmonary embolism was recruited to the study. A detailed social, medical and laboratory investigations were taken from all patients including lifestyle, occupation and smoking. A total of 234 patients participated in the study. There were 146 (62.4%) females and 88 (37.6%) males. Mean age was 51.7 years. A 56.8% incidence of DVT was seen among high altitude dwellers compared to 13.0% among low altitude dwellers. Also, a 12.6% incidence of PE was documented among high altitude dwellers, compared to 4.1% of the low altitude dwellers. VTE was significantly more among high altitude dwellers (81.9%) compared to low altitude dwellers (21.9%). Mean WBC count was significantly higher among the high altitude dwellers (10.8 ± 9.7 vs. 8.2 ± 3.4, p = 0.043). Mean platelet count was significantly higher among the high altitude dwellers compared to the low altitude dwellers (327.4 ± 162.4 vs. 212.0 ± 158.9, p = 0.005). The likelihood of developing VTE is greater among people who resided at moderate to high altitude for prolonged periods of time. The changes in the factors for coagulation including platelet counts may not reflect the true status of hypercoagulability especially if patients have stayed longer in high altitudes because of physiological adaptation to the environment.

1. Introduction

Venous thromboembolism (VTE) may manifest as pulmonary embolism (PE) and/or deep vein thrombosis (DVT) (Saha et al., 2011). Several previous studies suggested a cascade of events that is related to the enhancement of the coagulation process by increased platelet adhesiveness, red cell anisocytosis, polythermia and progressive initiation of the coagulation cascades in relation to exposure to high altitude (Saha et al., 2011; Gupta and Ashraf, 2012). However, the exact underlying mechanism is still poorly understood (Gupta and Ashraf, 2012).

The risk for VTE is increased on exposure to high altitude because of increased hypercoagulability predisposing the patient into a series of thromboembolic events (Gupta and Ashraf, 2012; Schrijver et al., 2005). Hypoxia that occurs at high altitude promotes VTE by coagulation activation with an increase in systemic inflammation (Brill and Suidan, 2013; Van Veen and Makris, 2008; Sabit et al., 2010). Patients who have inherited thrombophilia are at greater risk for thrombotic events with exposure to high altitude (Margaglione et al., 2000; Shrestha et al., 2012). Several studies also reported that lowlanders who stay at high altitude even for a small period of time develop different types of VTE, both venous and arterial thrombosis (Gupta et al., 2011; Al-Shraim et al., 2012; Khan and Katramados, 2010; Cheng et al., 2009; Nair et al., 2008; Lopez de Guimaraes, 2009; Indermuehle et al., 2010). A 30 times higher risk of spontaneous thrombosis and stroke have been reported on long-term stay (at least one year).
at high and extreme altitude (>3000 m above sea level) (Anand et al., 2005; Anand et al., 2001; Jha et al., 2002).

Upon initial exposure to hypoxia (such as ascension and climbing to higher altitudes), platelet count, platelet aggregability and bleeding time may remain normal (Schobesberger et al., 2005), however with prolonged stay and exposure at high altitude (>1 year), consequently has an effect on the platelet function and fibrinogen levels, either increased or decreased levels (Vij, 2009; Ashraf et al., 2006).

In one study, platelet count was reported to decline to as much as 31% with increased altitude (Vij, 2009). However, in another study, a rise of platelet count was observed within a week on exposure to high altitude (Hudson et al., 1999). Plasma fibrinogen concentration also was reported to increase by as much as 61% when exposed to high altitude for one year (Vij, 2009). Despite these contents, there were reports however, that mild to moderate exposure to high altitude may not trigger venous thrombosis especially during long-hour flights and, even long hours of immobilization during air travel (Toff et al., 2006; Hodkinson et al., 2003; Schreijer et al., 2006; Saudi Arabia, xxxx).

Patients with chronic thrombus had a significantly higher occurrence of raised right ventricular systolic pressure noticed by echocardiography and an advanced occurrence of following events due to residual PE (Chang et al., 2020). Venous thromboembolism (VTE) complicates several anticancer regimens including chemotherapy and antiangiogenic agents (Gervaso et al., 2020). Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a major health problem in the world and the third most frequent Cardiovascular disease in Western countries (Yamashita et al., 2020).

To our knowledge, very few studies have been conducted in Saudi Arabia that looked into the effect of high altitude on hemostasis and the risk for venous thrombosis. This study was conducted to estimate and compare the incidence of thromboembolic disease among patients who are clinically suspected for VTE in two different geographical areas of Saudi Arabia.

2. Methods

This is a prospective study conducted over two years (2011–2013) conducted in two different geographical areas in Saudi Arabia; Abha City and Riyadh City. Abha City is the capital of Assir province in Saudi Arabia. It is moderately highly elevated at 2200 m above sea level in the abundant mountains of south-western Saudi Arabia. On the other hand, Riyadh, Saudi Arabia's capital and largest city is situated in the center of the Arabian Peninsula on a large plateau, and is approximately 600 m above sea level (Toff et al., 2006).

Patients clinically suspected with deep vein thrombosis and pulmonary embolism was recruited to the study. All patients lived in the specified geographical area for at least one year prior to the conduct of the study. Written and informed consent were taken from all patients. Patients who are temporarily stayed in both geographical areas, or travelled very frequently (at least every 3 months) in and out of the area, and those who were on anticoagulation within the last 6 months of the study were excluded from the study.

A detailed social history was taken from all patients including lifestyle, occupation and smoking. Medical history taking included BMI, history of trauma, history of surgery, immobilization for long hours, history of fracture, malignancy, sickle cell disease and plasma disorders. For female patients, history of contraceptive use and hormonal replacement therapy were also noted. Physical examination of all patients included signs and symptoms of plethora and organomegaly, neurological assessment and leg examination. Laboratory assessment included complete blood count, thrombophilia work up, and D-dimer level.

Data were examined for completeness and accuracy prior to exporting into a Predictive Analysis Software version 18.1 (PASW, SPSS Inc., IBM, Chicago, Illinois, USA). The mean, standard deviation and percentages were used to express demographic characteristics. Independent t-test was used to compare two different population means. Correlations between parameters were done using the Pearson correlation test. Statistical significance was considered when p values are <0.05.

Ethical approval for the conduct of the study was provided by the Institutional Review Board of the College of Medicine, King Saud University, Riyadh, Saudi Arabia.

3. Results

A total of 234 patients participated in the study. There were 146 (62.4%) females and 88 (37.6%) males. There were 111 patients (47.4%) from Abha City and 123 patients (52.6%) from Riyadh City. Mean age of all patients was 51.7 ± 20.9 years (range: 6 years to 100 years).

For all patients, mean systolic BP was 121.8 ± 21.4 mmHg, mean diastolic BP was 72.0 ± 11.7 mmHg, mean respiratory rate was 20.2 ± 3.1, mean heart rate was 88.4 ± 17.3 bpm, mean spO2 was 94.3 ± 5.7, mean weight was 75.5 ± 16.2 kg., mean height was 158.4 ± 10.7 cm., mean protein S was 56.7 ± 24.7, mean WBC count was 8.8 ± 5.1 × 10^9/L, mean Hemoglobin was 11.6 ± 2.5, mean hematocrit was 36.4 ± 9.5, mean platelet was 286.0 ± 159.9, mean ESR was 44.1 ± 37.6 and mean magnesium level was 1.9 ± 0.3. D-dimer was elevated in 40 (17.1%) patients. Duplex ultrasound was positive for VTE in 70 (29.9%) patients. Venography was positive in 5 (2.1%) patients and spiral CT of the chest showed signs of PE in 27 (11.5%) patients. Seventeen patients (7.3%) were bed-bound, 12 (5.1%) were oxygen dependent, and 8 patients (3.4%) died within the study period. Demographic characteristics of patients are shown in Table 1. Risk factors, medical and pertinent history findings form all patients are shown in Table 2.

Table 3 shows the clinical and laboratory variables between high and low altitude dwellers. High altitude dwellers were significantly younger compared to low altitude dwellers (44.8 ± 21.9 years vs. 57.9 ± 17.9 years, p = 0.030). Furthermore, high altitude dwellers had significantly higher body temperature (p = 0.007), heart rate (p = 0.032) and hemoglobin level (p = 0.013) compared to low altitude dwellers. On the other hand, low altitude dwellers had significantly higher systolic BP (p < 0.001), spO2 (p < 0.001), WBC count (p = 0.001) and ESR level (p = 0.011).

Table 4 shows a significant difference in the incidence of VTE between high and low altitude dwellers. High altitude dwellers have a higher incidence of DVT alone compared to low altitude dwellers (56.8% vs. 13.0%, p < 0.001). Furthermore, high altitude dwellers have a significantly higher incidence of PE compared to low altitude dwellers (12.6% vs. 4.1%, P < 0.001). There was also a
Incidence and anatomical location of DVT and PE between high and low altitude dwellers.

Comparison of clinical and laboratory variables between high and low altitude dwellers (p < 0.001). PE alone was also seen in 12.6% of high altitude dwellers compared to 4.9% of low altitude dwellers (p < 0.001). Signs and symptoms such as lower limb swelling and pain were significantly seen more among the high altitude dwellers (p < 0.001).

Of the 118 patients who had VTE was done and showed significant differences in the frequencies between high altitude and low altitude dwellers such as; there were more cases of malignancy among low altitude dwellers (high altitude = 22.2% and low altitude = 22.2%, p < 0.001), lower limb swelling (high altitude = 86.8% and low altitude = 3.7%, p < 0.001), lower leg pain (high altitude = 82.4% and low altitude = none, p < 0.001), with positive family history of VTE (high altitude = 1.1% and low altitude = 14.8%, p = 0.002), pregnancy (high altitude = 13.2% and low altitude = none, p = 0.046), hypertension (high altitude = 13.2% and low altitude = 40.7%, p = 0.002). Mean WBC count was significantly higher among the high altitude dwellers (10.8 ± 9.7 vs. 8.2 ± 3.4, p = 0.043). Mean platelet count was significantly higher among the high altitude dwellers compared to the low altitude dwellers (327.4 ± 162.4 vs. 212.0 ± 158.9, p = 0.005).

Table 2 Risk factors, history and medical conditions of patients clinically suspected for VTE.

| Variables                        | N (%) |
|----------------------------------|-------|
| Family history of DVT            | 6 (2.6) |
| Smoking                          | 6 (2.6) |
| Trauma                           | 11 (4.7) |
| Fracture                         | 6 (2.6) |
| Long hours of immobilization     | 13 (5.6) |
| Sickle cell anemia               | 4 (1.7) |
| Malignancy                       | 6 (2.6) |
| Pregnancy                        | 13 (5.6) |
| Surgery                          | 18 (7.7) |
| Plasma cell disorders            | 1 (0.4) |
| Oral contraceptives              | 11 (4.7) |
| Hormone replacement tx           | 1 (0.4) |
| Diabetes                         | 35 (15.0) |
| Hypertension                     | 33 (14.1) |
| Congestive heart failure         | 3 (1.3) |
| Lung disease                     | 8 (3.4) |
| Post-thrombotic stroke           | 69 (29.5) |

Table 3 Comparison of clinical and laboratory variables between high and low altitude dwellers.

| Variables                          | High altitude dwellers | Low altitude dwellers | p values |
|------------------------------------|------------------------|-----------------------|----------|
| Age, in years                      | 44.8 ± 21.9            | 57.9 ± 17.9           | 0.030    |
| Systolic BP, in mmHg               | 115.7 ± 17.4           | 130.3 ± 23.6          | <0.001   |
| Diastolic BP, in mmHg              | 70.6 ± 9.7             | 73.9 ± 13.7           | 0.076    |
| SpO2, in %                         | 92.4 ± 6.1             | 97.8 ± 2.1            | <0.001   |
| Weight, in kg                      | 76.0 ± 17.4            | 74.9 ± 14.8           | 0.758    |
| Height, in cm                      | 160.2 ± 10.9           | 155.3 ± 9.7           | 0.112    |
| WBC count                          | 8.2 ± 3.4              | 10.3 ± 7.3            | 0.001    |
| Hemoglobin                         | 11.9 ± 3.1             | 11.5 ± 2.1            | 0.013    |
| Hematocrit                         | 37.0 ± 10.5            | 35.1 ± 7.2            | 0.487    |
| Platelets                          | 318.5 ± 158.4          | 217.0 ± 141.8         | 0.659    |
| ESR                                | 37.2 ± 32.0            | 56.6 ± 44.4           | 0.011    |

4. Discussion

Exposure to high altitude either during mountain climbing, air travel or sports activities has been shown to result in hypercoagulable state which is a predisposition to VTE (Gupta and Ashraf, 2012; Schreijier et al., 2005; Van Veen and Makris, 2008; Anand et al., 2001; Vij, 2009; Hudson et al., 1999; Schreijier et al., 2006). Over the past few years, there have been a lot of literatures that tackled issues on the causes, risk factors and other determinants on the incidence of VTE that led us to a better and broader understanding of the underlying concepts of the disease. In this study however, we wanted to show if there was any significant differences in any of the clinical and laboratory variables of patients suspected for VTE.

Our study showed a high incidence of VTE (both DVT and PE) among our high altitude dwellers (91 of 111 or 81.9% of high altitude dwellers), in contrast to 21.9% incidence with low altitude dwellers. This suggests the association between high altitude and
the risk for VTE as reported by Gupta in 2012 (Gupta and Ashraf, 2012) and Schreijer in 2005 (Schreijer et al., 2005). However, there was no significant difference in the platelet counts between high altitude and low altitude dwellers (Table 3). There should be a consistent hypercoagulable state from amongst our high altitude patients that is showed by a rise in platelet count, high levels of factor X and XII and shortened prothrombin time. Unfortunately, our data failed to show levels of factor X and XII, thus we cannot deduce enough conclusion on the aspect of hypercoagulability based on these variables. One explanation for the insignificant difference in the platelet levels between our high and low altitude dwellers is that, platelet count may have decreased because of adaptability to the high altitude condition with continuous exposure to increased altitude as presented by Vij in 2009 (Jha et al., 2002). It was revealed that platelet counts increases only within the first week of exposure to high altitude (Vij, 2009). The wide disparity in our patients’ exposure and stay at high altitude, thus allowing our patients to adapt to high altitude condition may have caused the insignificant difference in the platelet count between the two groups. We thought that this issue can be better addressed if all participants were exposed to high altitude in an almost the same time, to negate the effects of length of exposure on the changes in the platelet counts, as shown by Hudson in 1999 (Vij, 2009), or there was a measurement of the platelet count before and after exposure to high altitude. More so, high altitude dwellers were significantly younger than our low altitude dwellers. The incidence and likelihood of developing VTE among the younger population is lesser since younger people exercise more, mobilize more compared to their older counterparts, who are more likely to have stasis in their peripheral veins.

However, the separate comparative analysis done among the 118 patients who had VTE, we found a significant difference in the platelet count. High altitude dwellers had significantly higher platelet counts compared to the low altitude dwellers (p < 0.001). The reason for these significant differences is because those high altitude patients who did not have DVT have lesser incidences of lower limb swelling, lower limb pain and use of oral contraceptives and lower levels of systolic and diastolic BP, hemoglobin, hematocrit, ESR, and higher levels of platelet counts.

Our study also showed that 89% of DVT cases affected the left leg, similar to the findings of Chan (Schreijer et al., 2006). However, we found more cases of distal DVT than proximal DVT (60.3% vs. 16.1%); contrary to Chan’s report (Schreijer et al., 2006).

Despite these conflicting findings, it is certain that the incidence of VTE is magnified with increased altitude. The disparities in the anatomical location, frequencies in the symptomatologies and even in the laboratory values may have to be explained by other independent factors such as race, length of stay and exposure to high altitude and individual’s physiological capability to adapt to changes in altitude.

5. Conclusion

The likelihood of developing VTE is greater among people who stayed at moderate to high altitude for prolonged periods of time. The changes in the factors for coagulation including platelet counts may not reflect the true status of hypercoagulability especially if patients have stayed longer in high altitudes because of physiological adaptation to the environment. A follow-up study is warranted to determine the effect of migration from low to high altitude or vice-versa with special attention to duration of exposure and length of stay.

Acknowledgements

This work was supported by the College of Medicine Research Center, Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia.

References

Al-Shraim, M.M., Zafer, M.H., Rahman, G.A., 2012. Acute occlusive mesenteric ischemia in high altitude of southwestern regions of Saudi Arabia. Ann. Afr. Med. 11, 5–10.
Anand, A.C., Jha, S.K., Saha, A., Sharma, V., Adya, C.M., 2001. Thrombosis as a complication of extended stay at high altitude. Natl. Med. J. India 14, 197–201.
Anand, A.C., Saha, A., Seth, A.K., Chopra, G.S., Nair, V., Sharma, V., 2005. Symptomatic portal system thrombosis in soldiers due to extended stay at extreme altitude. J. Gastroenterol. Hepatol. 20, 777–783.
Ashraf, H.M., Jayed, A., Ashraf, S., 2006. Pulmonary embolism at high altitude and hyperhomocysteinemia. J. Coll. Phys. Surg. Pak 16, 71–73.
Brill, A., Suidan, G.L., Wagner, D.D.Z., 2013. Hypoxia, such as encountered at high altitude, promotes deep vein thrombosis in mice. J. Thromb. Haemost. 11, 1773–1775.
Chang, H.-Y., Chang, W.-T., Chen, P.-W., Lin, C.-C., Hsu, C.-H., 2020. EXPRESS: Pulmonary thromboembolism with computed tomography defined chronic thrombus is associated with higher mortality 20458940209055515. Pulmonary Circolat. https://doi.org/10.1177/20458940209055515.
Cheng, S., Ching, S.M., Singh, R., 2009. Cerebral venous infarction during a high altitude expedition. Singapore Med. J. 50, e306–e308.
Gervaso, L., Montero, A.J., Jha, X., Khorana, A.A., 2020. Venous thromboembolism in breast cancer patients receiving cyclin-dependent kinase inhibitors. J. Thromb. Haemost. 18 (1), 162–168. https://doi.org/10.1111/jth.14630.
Gupta, N., Ashraf, M.Z., 2012. Exposure to high altitude: a risk factor for venous thromboembolism. Semin. Thromb. Haemost. 38, 156–163.
Gupta, A., Singh, S., Abulwafa, T.S., Khanna, A., 2011. Retinal vein occlusion in high altitude. High Alt. Med. Biol. 12, 393–397.
Hodkinson, P.D., Hunt, B.J., Paramar, K., Ernsting, J., 2003. Is mild normobaric hypoxia a risk factor for venous thromboembolism?. J. Thromb. Haemost. 1, 2131–2133.
Hudson, J.G., Bowen, A.L., Navia, P., Ros-Dalenz, J., Pollard, A.J., Williams, D., Heath, D., 1999. The effect of high altitude on platelet counts, thrombopoietin and erythropoietin levels in young Bolivian airmen visiting the Andes. Int. J. Biometeorol. 43, 85–90.
Indermuehle, A., Cook, S., Marty, H., 2010. A young mountaineer surviving sudden cardiac arrest at high altitude pi: bcrt0720092130 BMJ Case Rep. https://doi.org/10.1136/bcr07.2009.2130.
Jha, S.K., Anand, A.C., Sharma, V., Kumar, N., Adhya, C.M., 2002. Stroke at high altitude: Indian experience. High Alt. Med. Biol. 3, 21–27.
Khan, M., Katramados, A.M., 2010. Deep cerebral sinusovenous thrombosis precipitated by high-altitude exposure. Can. J. Neurol. Sci. 37, 700–702.
Lopez de Guimaraes, D., Menacho Lopez, J., Villanueva Palacios, J., Mosquera Vasquez, V., 2009. Splenic infarction at high altitude, Huaraz-Peru (3,100 masl). Rev. Gastroenterol. Peru 29, 179–184.

Margaglione, M., Brancaccio, V., De Lucia, D., Martinelli, L., Ciampa, A., Grandone, E., Di Minno, G., 2000. Inherited thrombophilic risk factors and venous thromboembolism: distinct role in peripheral deep venous thrombosis and pulmonary embolism. Chest 118, 1405–1411.

Nair, V., Mohapatro, A.K., Sreedhar, M., Indrajeet, I.K., Tewari, A.K., Ananad, A.C., Matthew, O.P., 2008. A case of hereditary protein S deficiency presenting with cerebral sinus venous thrombosis and deep vein thrombosis at high altitude. Acta Haematol. 119, 158–161.

Sabit, R., Thomas, P., Shale, D.J., Collins, P., Linnane, S.J., 2010. The effects of hypoxia on markers of coagulation and systemic inflammation in patients with COPD. Chest 138, 47–51.

Saha, P., Humphries, J., Modarai, B., et al., 2011. Leucocytes and the natural history of deep vein thrombosis: current therapies and future directions. Arterioscler. Thromb. Vasc. Biol. 31, 506–512.

Saudi Arabia: largest cities and towns and statistics of their population". World Gazetteer.

Schreijer, A.J., Cannegieter, S.C., Rosendaal, F.R., Helmerhorst, F.M., 2005. A case of thrombosis at high altitude. Thromb. Haemost. 94, 1104–1105.

Schreijer, A.J., Cannegieter, S.C., Miejers, J.C., Middledorp, S., Buller, H.R., Rosendaal, F.R., 2006. Activation of coagulation system during air travel: a crossover study. Lancet 367, 792–794.

Shrestha, P., Basnyat, B., Kupper, T., Van der Giet, S., 2012. Cerebral venous sinus thrombosis at high altitude. High Alt. Med. Biol. 13, 60–62.

Tof, W.D., Jones, C.I., Ford, I., Pearse, R.J., Watson, H.G., Watt, S.J., et al., 2006. Effect of hyperbaric hypoxia, simulating conditions during long-haul air travel on coagulation, fibrinolysis, platelet function and endothelial activation. JAMA 295, 2297–2299.

Van Veen, J.J., Makris, M., 2008. Altitude and coagulation activation: does going high provoke thrombosis?. Acta Haematol. 119, 156–157.

Vij, A.G., 2009. Effect of prolonged stay at high altitude on platelet aggregation and fibrinogen levels. Platelets 20, 421–427.

Yamashita, Y., Morimoto, T., Yoshikawa, Y., Yaku, H., Sumita, Y., Nakai, M., Kimura, T., 2020. Temporal trends in the practice pattern for venous thromboembolism in Japan: insight from JROAD-DPC. J. Am. Heart Assoc. 9, (2). https://doi.org/10.1161/JAHA.119.014582 e014582.