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

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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 cascadedo 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; Schreijier 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)

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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 (Schobersberger 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 contentions, 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; Schreijier 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 Sofware 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 qas 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 $\times$ 10^5/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 bedbound, 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 ye ars 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

Table 1
Demographic characteristics of all patients (n = 234).

Variables	n (%)
Signs and symptoms	
Lower leg swelling	84 (35.9)
Lower leg pain	77 (32.9)
Chest pain	22 (9.4)
Shortness of breath	36 (15.4)
Hemoptysis	5 (2.1)
Headache	10 (4.3)
Blurred vision	1 (0.4)

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

significantly higher incidence of both DVT and PE among high altitude dwellers compared to low altitude dwellers (12.6% vs. 4.9%, p < 0.001). DVT was predominantly of the left side and is more distal than proximal. PE was predominantly segmental in 9.4% of patients. There were significantly more high altitude dwellers who had VTE compared to patients who dwelled at low altitude (81.9% vs. 21.9%, p < 0.001). DVT alone was seen in 56.8% of high altitude dwellers compared to 13.0% among the low altitude dwellers (p < 0.001). PE alone was also seen in 12.6% of high altitude dwellers compared to 4.1% 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).

Table 5 shows the comparison between high and low altitude dwellers on the incidence of VTE, signs and symptoms of VTE and presence of medical and surgical factors related to VTE. History of immobilization, pregnancy and use of oral contraceptives were also significantly greater among the high altitude dwellers than the low altitude dwellers p < 0.05). However, the incidence of post-thrombotic stroke was significantly greater among the low altitude dwellers compared to 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 = 2.2% 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).

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

Table 4
Incidence and anatomical location of DVT and PE between high and low altitude dwellers.

Variables	All patients	High altitude dwellers N = 111	Low altitude dwellers N = 123	*p* values
With VTE	118	91 (81.9%)	27 (21.9%)	<0.001
DVT alone	79	63 (56.8%)	16 (13.0%)	<0.001
PE alone	19	14 (12.6%)	5 (4.1%)	<0.001
Both DVT and PE	20	14 (12.6%)	6 (4.9%)	<0.001
Anatomical location of DVT (with or without PE)				
Left	87	65 (58.6%)	22 (17.9%)	<0.001
distal	69	48 (43.2%)	21 (17.1%)	<0.001
proximal	18	17 (15.3%)	1 (0.8%)	<0.001
Right	11	11 (9.9%)	0	<0.001
Anatomical location of PE				
Bilateral	11	8 (7.2%)	3 (2.4%)	0.043
Right pulmonary artery	3	3 (2.7%)	0	
Segmental	22	15 (13.5%)	7 (5.7%)	
Subsegmental	2	2 (1.8%)	0	

Table 5
Comparison of signs and symptoms and history of VTE between high and low altitude dwellers.

Variables	High altitude dwellers N = 111	Low altitude dwellers N = 123	*p* values
Signs and symptoms			
Lower limb swelling	82 (73.9%)	2 (1.6%)	<0.001
Lower limb pain	77 (69.4%)	0	<0.001
Shortness of breath	26 (23.4%)	10 (8.1%)	0.001
Hemoptysis	4 (3.6%)	1 (0.8%)	0.140
Headache	2 (1.8%)	8 (6.5%)	0.076
Blurring of vision	1 (0.9%)	0	0.291
History			
Smoking	0	6 (4.9%)	0.018
Trauma	5 (4.5%)	6 (4.9%)	0.893
Fracture	5 (4.5%)	1 (0.8%)	0.074
Immobilization	12 (10.8%)	1 (0.8%)	0.001
Sickle Cell Anemia	3 (2.7%)	1 (0.8%)	0.265
Malignancy	3 (2.7%)	3 (2.4%)	0.899
Pregnancy	13 (11.7%)	0	<0.001
Surgery	13 (11.7%)	5 (4.1%)	0.028
Oral contraceptive use	11 (9.9%)	0	<0.001
Hormone replacement tx	1 (0.9%)	0	0.291
Diabetes	16 (14.4%)	19 (15.4%)	0.825
Hypertension	12 (10.8%)	21 (17.1%)	0.169
Heart failure	3 (2.7%)	0	0.066
Lung disease	4 (3.6%)	4 (3.3%)	0.883
Post-thrombotic stroke	8 (7.2%)	59 (47.9%)	<0.001

the risk for VTE as reported by Gupta in 2012 (Gupta and Ashraf, 2012) and Schreijier in 2005 (Schreijier 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 ($p = 0.005$). 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 (Schreijier et al., 2006). However, we found more cases of distal DVT than proximal DVT (60.3% vs. 16.1%); contrary to Chan's report (Schreijier 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.

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