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*TH*rombosis A*ET*iology of *A*viation-Related Travel: The THETA θ study

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Background. Long-haul flights have been associated with a two- to four-fold increased risk of aviation-related thrombosis (ART). Several studies have investigated the extent to which hypoxic hypobaric exposure, dehydration and prolonged immobilisation during air travel induce changes in haemostasis.
Objective. To investigate the role of high altitude as a risk factor for ART.
Methods. Healthy volunteers aged ≥18 years (N=40), without risk factors for venous thromboembolism, were exposed to an exacerbated altitude of 18 000 feet (5 486 m) for 1 hour. During the flight, the oxygen (O_2) levels of the participants, who received supplemental O_2, were measured by pulse oximetry and maintained at >92%. Venous blood and urine samples were collected prior to departure and immediately after flying in an unpressurised twin-engine airplane. D-dimer levels, thromboelastography (TEG) parameters, von Willebrand factor (VWF) activity and urine osmolality were measured.
Results. The participants were 19 men and 21 women, with a mean (standard deviation) age of 46 (14) years. A significant difference in D-dimer levels, VWF activity, urine osmolality and TEG parameters (reaction (R) time, kinetic (K) time and maximum amplitude (MA)) before and after the 1-hour flight was observed (p<0.001). Urine osmolality correlated positively with VWF activity levels (r=0.469; p<0.002).
Conclusion. Air travel at high altitude induced a hypercoagulable state in healthy volunteers. Future research should focus on whether thromboprophylaxis can significantly obviate the activation of coagulation in response to high altitude.
Keywords. Flying, aetiology, thrombosis, aviation.

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The first case of venous thromboembolism (VTE) related to air travel was reported by Homans[1] in a 54-year-old medical doctor who developed a deep-vein thrombosis (DVT) after a 14-hour flight from Boston to Venezuela in 1946. Following increasing case reports of VTE related to air travel, the term 'economy class syndrome' was coined by Symington and Stack[2] in the 1970s. Prolonged flights of >6 hours are associated with a two- to four-fold increased risk of aviation-related thrombosis (ART).[3,4] This relationship has since been extended to any mode of prolonged travel. Several studies have investigated both passenger-related risk factors such as recent surgery, previous VTE and thrombophilias, as well as travel-related risk factors for developing ART related to the aircraft cabin.[3,4] In particular, stasis and hypercoagulability, two components of Virchow's triad, have been explored as travel-related risk factors. Nonetheless, the data to date are inconclusive.

The concept of stasis of the venous circulation during prolonged sitting in a cramped space is well described.[5] In 1940, Simpson[6] reported that autopsies revealed a six-fold increase in deaths from pulmonary embolism as a result of sheltering in confined spaces during air raids in London. In the BEST (Business class versus Economy class Syndrome as a cause of Thrombosis) study, however, we observed no difference in the risk of ART between immobilised business class and economy class passengers.[7] In this study of 899 low- and intermediate-risk participants, D-dimer levels were measured before and after an 11-hour flight from London to Johannesburg. We reported an increase in D-dimer levels after the flight in 74 participants (8.2%), with no significant difference in D-dimer levels between business class (n=22; 12%) and economy class passengers (n=52; 7%), suggesting that there are additional mechanisms apart from immobility that result in hypercoagulability during flights. In this study, increased D-dimer levels (>500 ng/mL) correlated significantly with the presence of the factor V Leiden mutation (odds ratio 3.36; p=0.024). Similarly, other long-distance flight studies have demonstrated an increased risk among participants with one or more personal risk factors for VTE.[8-10] According to the LONFLIT thrombosis study, the incidence of DVT in 355 low-risk travellers was 0% for a 10 - 15-hour flight, compared with 5% in 389 high-risk travellers.[11] It has also been proposed that exposure to the low-humidity and high-altitude hypoxic environment of the airplane (referred to as hypobaric hypoxia) may induce a hypercoagulable state predisposing at-risk passengers to ART. In a study of 960 acclimatised soldiers who ascended to altitudes above 15 000 feet (4 572 m), high altitude was associated with 15 thrombotic events and significant activation of coagulation.[12] Nonetheless, studies on haemostasis of healthy volunteers in hypobaric chambers, similar to the conditions of reduced cabin pressure during commercial air travel, did not show changes in markers of coagulation activation, fibrinolysis, platelet activation or endothelial cell activation before and after exposure.[13,14]

In order to improve our understanding of the mechanisms of high-altitude-induced thrombosis associated with air travel, we performed a prospective study in 40 volunteers in an unpressurised aircraft at an altitude of 18 000 feet (5 486 m) for 1 hour. This study investigated D-dimer levels, thromboelastography (TEG) parameters, von Willebrand factor (VWF) activity and urine osmolality as markers of a hypercoagulable state.

Methods

Study design and population

This study was performed in Johannesburg, South Africa, between 2016 and 2020. Healthy volunteers aged ≥18 years without risk factors for VTE, living in Johannesburg and not subordinate to the study investigators, were invited to participate in the study. The following exclusion criteria were applied: body mass index >25 kg/m^2, extremes of height (<165 cm or >185 cm), smokers, personal history of VTE or chronic venous insufficiency, recent surgery, current pregnancy or use of oestrogen-containing therapy, antiplatelet therapy and/or anticoagulant therapy.

Study protocol

Venous blood and urine samples were collected prior to departure and immediately after flying in an unpressurised twin-engine airplane. Venous blood was collected by atraumatic venepuncture. The flight was 1 hour at an altitude of 18 000 feet (5 486 m), with two passengers flying at a time. A medical practitioner monitored all participants' O_2 saturation with pulse oximetry during the flight to ensure adequate oxygenation. Supplemental O_2 was administered by titration via nasal cannula to all participants to maintain O_2 saturation levels >92%. However, the O_2 requirements were not documented. The flight conditions were standardised with regard to flight route, duration and environmental conditions. Fluid intake was controlled in all participants on the day of the study. Participants were contacted telephonically after 2 months to ask about symptoms of VTE, using a standardised questionnaire. Written informed consent to collect and use anonymous data was obtained. The study protocol was approved by the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M10722).

Data collection

Demographic data were collected from participant interviews.

Laboratory investigations

Venous blood was collected in 3.2% sodium citrate (Becton-Dickinson, UK) for D-dimer levels and VWF activity. The samples were centrifuged at 3 500 *g* for 15 minutes, within 30 minutes of collection. The platelet-poor plasma was separated and frozen at –20°C until analysis, which took place within 24 hours of collection. Sample analyses were performed at the accredited National Health Laboratory Service coagulation laboratory at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg. D-dimer levels were measured with the STA-Liatest immuno-turbidimetric assay (Diagnostica Stago, France) on the STA-R Max automated coagulation analyser (Diagnostica Stago, France). The intra- and inter-assay coefficients of variation (CVs) for D-dimers were 4.6% and 3.3%, respectively. VWF activity was measured with the Siemens Innovance immuno-turbidimetric assay (Siemens Healthineers, Germany) on the STA-R Max analyser. The intra-assay CV for VWF activity was 2.8%. Urine osmolality was measured on the Cobas chemistry analyser (Roche Diagnostics, Switzerland). The TEG analyses were performed on site using the TEG 5000 analyser (Haemonetics Hospital Solutions, China). Daily quality control was performed prior to sample analysis on all analysers.

Data analysis

Data were analysed using Statistica 13.2 software (StatSoft, USA). Normally distributed continuous data are presented as means with standard deviations (SDs). Categorical data are presented as frequencies and percentages. Comparisons for continuous measurements were performed using a parametric paired *t*-test. Correlations were performed by Pearson's method as a measure of linear association between two variables. Statistical significance was set at $p<0.05$.

Results

During the study period, 48 volunteers were screened, of whom 40 were included in the final analysis. The baseline characteristics are summarised in Table 1. The participants were predominantly of white ethnicity (90%); 19 were men and 21 were women; and the mean (SD) age was 46 (14) years.

The laboratory test results were in the normal range (Table 2). Significant differences in plasma levels of D-dimers and in TEG parameters (reaction (R) time, kinetic (K) time and maximum amplitude (MA)) measured pre and post the 1-hour flight (Fig. 1A - D) were observed. Significant increases in VWF activity and urine osmolality measured pre and post the flight were also observed (Fig. 1E - F). Age correlated positively with pre-flight ($r=0.647$; $p<0.001$) and post-flight D-dimer levels ($r=0.655$; $p<0.001$) (Supplementary Fig. 1, available online at https://www.samedical.org/file/2263). No significant correlation between age and the mean D-dimer difference (pre to post) was observed. Urine osmolality correlated positively with VWF activity levels ($r=0.469$; $p<0.002$).

On follow-up at 2 months, none of the participants had developed symptoms suggestive of VTE.

A significant difference between pre- and post-flight D-dimer levels, VWF activity, urine osmolality and TEG parameters was observed ($p<0.001$).

Discussion

It is estimated that over two billion passengers travel by air each year.[15] There is a large body of conflicting data on changes in haemostasis induced by hypoxic hypobaric exposure, dehydration and prolonged immobilisation during air travel. In the present study, in order to investigate the role of high altitude as a risk factor for ART we exposed 40 volunteers to an exacerbated altitude of 18 000 feet (5 486 m) for 1 hour in an unpressurised airplane. During the flight, the O_2 levels of the participants, who received supplemental O_2, were measured. O_2 levels were maintained at >92% by pulse oximetry to prevent a hypercoagulable state secondary to hypoxia.[16] Normally, the air pressure inside the cabins of commercial airplanes is pressurised to 8 000 feet, which is essential to prevent hypoxia.

We assessed D-dimers and TEG parameters as markers of a hypercoagulable state, before and after flight exposure. Earlier studies that investigated global coagulation tests as well as testing thrombin generation in healthy volunteers in hypobaric chambers did not show changes in haemostasis.[13,14] Viscoelastic testing methods such as TEG examine the real-time formation of a clot in a whole-blood sample. In the present study, the TEG individual parameters, viz. R time, which is a measure of clot initiation, K time, which is a measure of the speed of clot formation, and MA, which is a measure of the clot strength, changed significantly after 1 hour. Although the parameters were within normal reference

Table 1. Demographics of the study population (*N*=40)

Characteristic	*n* (%)*
Age at study entry (years), mean (SD)	46 (14)
Gender	
Male	19 (47.5)
Female	21 (52.5)
Ethnicity	
White	36 (90.0)
Indian	3 (7.5)
Coloured	1 (2.5)

SD = standard deviation.
*Except where otherwise indicated.

intervals, these changes support a hypercoagulable state at high altitude. These findings are in contrast to a small cohort of healthy volunteers who ascended to 17 000 feet (5 300 m) climbing Mount Everest. TEG measurements (R and K time) increased significantly compared with sea level, while the MA did not change.[17] However, these volunteers were exposed to numerous variables, including hypothermia, which is a known cause of a hypocoagulable state. D-dimers, a degradation product of cross-linked fibrin, also increased significantly, which is indicative of fibrinolysis post exposure to high altitude. As expected, D-dimers and age correlated positively, reflecting the normal physiological response to ageing. Previous studies have suggested that passenger-related factors such as age contribute to the development of ART.[18] However, we did not observe a statistical correlation in the mean difference of pre- and post-flight D-dimer levels as a function of age. Additionally, it is interesting to note that a difference in D-dimer levels was not observed in a previous study of 27 short-haul cockpit crew members.[19] While these flights were in pressurised airplanes, in contrast to the current study, it has been proposed that tolerance to the effect of altitude develops, similar to that in Sherpas who accompany climbers on high-altitude climbs. However, there was no control group of non-frequent flyers in this study.

The humidity of the air inside the cabin on commercial flights is maintained at 10 - 20% by removing moisture from the cabin air. During the flight, insensible water loss is increased, which promotes lower limb oedema and induces changes in blood viscosity. Conflicting results have been reported as to whether dehydration on long-haul flights may indeed lead to hypercoagulability during air travel.[20]

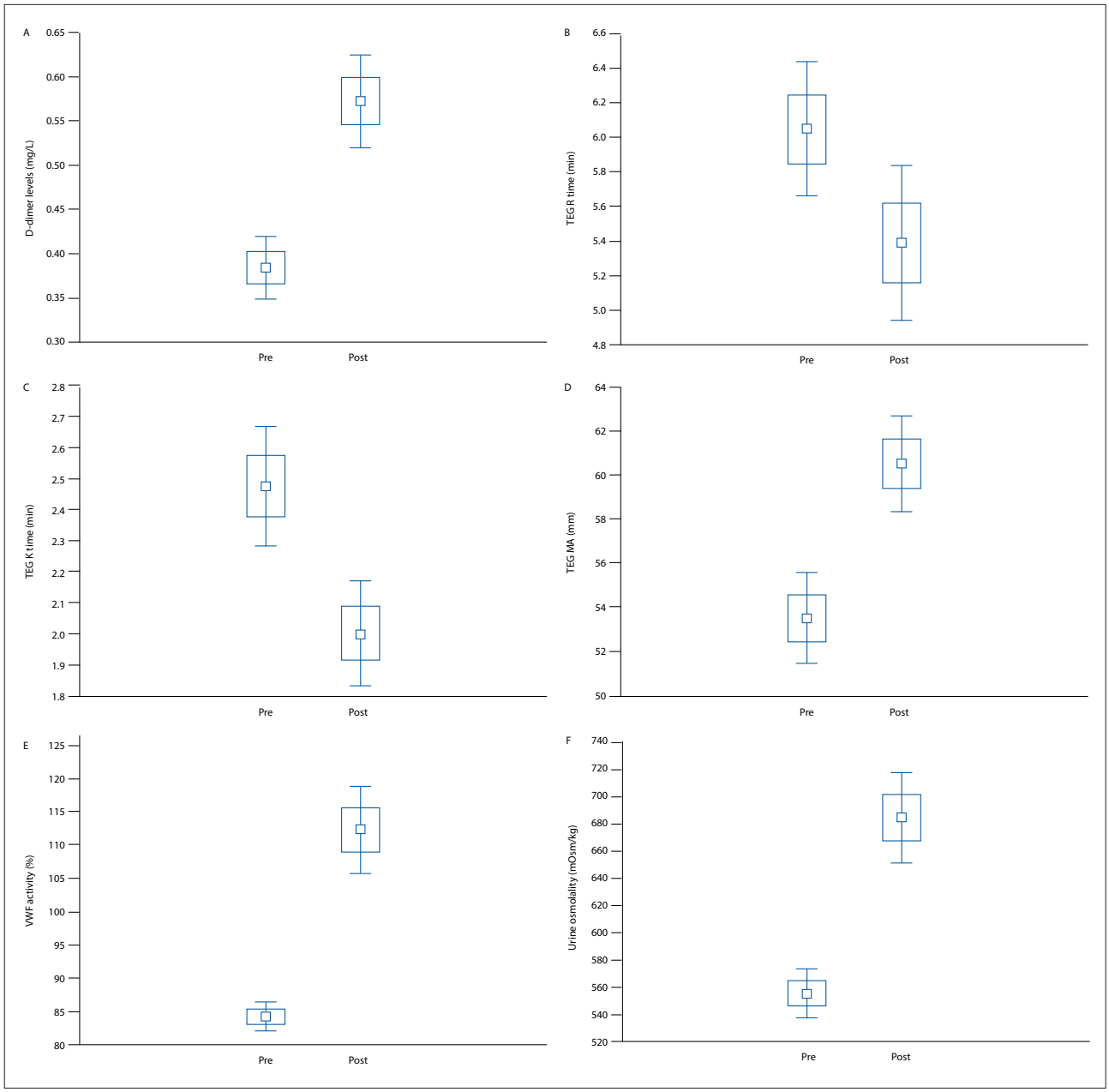


Fig 1. Box-and-whisker plots of pre- and post-flight laboratory parameters. The small box represents the mean, the larger box represents ± 1 times the standard error, and the whiskers represent a 95% confidence interval defined as the variable mean ± 1.96 times the variable standard error. (A) D-dimer levels; (B) TEG parameters, R time; (C) TEG parameters, K time; (D) TEG parameters, MA; (E) VWF activity; (F) urine osmolality. (TEG = thromboelastography; R time = reaction time; K time = kinetic time; MA = maximum amplitude; VWF = von Willebrand factor.)

Table 2. Pre- and post-flight laboratory results

Laboratory test	Pre	Post	*p*-value
D-dimer level (mg/L), mean (SD) (ref. <0.5)	0.38 (0.11)	0.57 (0.17)	0.001
TEG R time (min), mean (SD) (ref. 5 - 10)	6.05 (1.25)	5.39 (1.44)	0.001
TEG K time (min), mean (SD) (ref. 1 - 5)	2.47 (0.62)	2.00 (0.54)	0.001
TEG MA (mm), mean (SD) (ref. 50 - 75)	53.51 (6.65)	60.50 (7.00)	0.001
VWF activity (%), mean (SD) (ref. 50 - 150)	84.28 (7.03)	112.33 (21.07)	0.001
Urine osmolality (mOsm/kg), mean (SD) (ref. 50 - 1 200)	555.60 (58.41)	684.43 (106.74)	0.001

SD = standard deviation; ref. = normal reference interval; TEG = thromboelastography; R time = reaction time; K time = kinetic time; MA = maximum amplitude; VWF = von Willebrand factor.

In order to determine whether exposure to high altitude is associated with the release of antidiuretic hormone (ADH), the present study assessed urine osmolality as a surrogate marker. ADH is difficult to measure because it circulates at low concentrations (<5.4 pmol/L), with a short half-life of 15 - 20 minutes. ADH increases plasma levels of coagulation factor VIII and VWF. In this study, significant differences in the plasma VWF activity and urine osmolality measured pre and post the 1-hour flight were observed. We observed a significant correlation between urine osmolality and VWF activity levels after 1 hour of flying, in the absence of hypoxia. These findings suggest that the release of ADH on exposure to high altitude also contributes to the development of a hypercoagulable state.

Conducting studies at an exacerbated high altitude is costly and logistically challenging. Our results must be interpreted in light of certain limitations. Firstly, the study was not statistically powered to draw conclusions regarding the direct relationship between plasma assays of coagulation activation and the risk of VTE. Owing to the low incidence of ART, a large number of participants would be required. No cases of ART were recorded in this low-risk population during the study period. Secondly, these results cannot be generalised to participants with VTE risk factors such as obesity, use of oestrogen-containing therapy and thrombophilia, who were not included in the study population. Although we describe 'healthy volunteers' prior to inclusion, participants were not examined by compression ultrasound to exclude DVT or tested for asymptomatic thrombophilias. Lastly, plasma and urine assays were not performed in a non-flying control population.

Conclusion

This study illustrates a significant difference in plasma markers of coagulation activation as well as urine osmolality measured pre and post a 1-hour flight at high altitude. The findings suggest that flying at high altitude induces a hypercoagulable state in healthy volunteers. Future research should focus on whether thromboprophylaxis can significantly obviate the activation of coagulation in response to high altitude.

Data availability. AUTHOR: please complete The data sets generated and analysed during the present study are available from the corresponding author (ES) on reasonable request.

Declaration. None.

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Author contributions. All authors performed the research. Study design and concept: BFJ; data collection: BFJ, SL, FL; laboratory analysis: BFJ, FL; statistical analysis: ES; writing: ES, SL, BFJ.

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Conflicts of interest. None.

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