The BEST study — a prospective study to compare business class versus economy class air travel as a cause of thrombosis

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Background. As many as 10% of airline passengers travelling without prophylaxis for long distances may develop a venous thrombosis. There is, however, no evidence that economy class travellers are at increased risk of thrombosis.

Objectives. A suitably powered prospective study, based on the incidence of deep-vein thrombosis (DVT) reported in previous studies on long-haul flights, was designed to determine the incidence of positive venous duplex scans and D-dimer elevations in low and intermediate-risk passengers, comparing passengers travelling in business and economy class.

Patients/methods. Eight hundred and ninety-nine passengers were recruited (180 travelling business class and 719 travelling economy). D-dimers were measured before and after the flight. A value greater than 500 ng/ml was accepted as abnormal. A thrombophilia screen was conducted which included the factor V Leiden mutation, the prothombin 20210Amutation, protein C and S levels, antithrombin levels, and anticardiolipin antibodies immunoglobulin G (IgG) and immunoglobulin M (IgM). On arrival, lower limb compression ultrasonography of the deep veins was performed. Logistical regression analysis was used to determine the risk factors related to abnormally high D-dimer levels.

Results. Only 434 subjects had a full venous duplex scan performed. None had ultrasonic evidence of venous thrombosis. Nine passengers tested at departure had elevated D-dimer levels and these volunteers were excluded from further study. Seventy-four of the 899 passengers had raised D-dimers on arrival. Twenty-two of 180 business class passengers (12%) developed elevated D-dimers compared with 52 of 719 economy class passengers (7%). There was no significant association between elevation of D-dimers and the class flown (odds ratio (OR) 0.61, $p = 0.109$). The factor V Leiden mutation, factor VIII levels and the use of aspirin were, however, associated with raised D-dimers (OR 3.36, $p = 0.024$; OR 1.01, $p = 0.014$; and OR 2.04, $p = 0.038$, respectively). Five hundred and five passengers were contacted within 6 months and none reported any symptoms of a clinical thrombosis or pulmonary embolus.

Conclusion. The incidence of ultrasonically proven DVT is much lower than previously reported. However, more than 10% of all passengers developed raised D-dimers, which were unrelated to the class flown. A rise in D-dimers is associated with an inherent risk of thrombosis and/or thrombophilia, demonstrates activation of both the coagulation and fibrinolytic systems during long-haul flights, and may indicate the development of small thrombi.

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The association between venous thromboembolism (VTE) and air travel has received considerable attention because of several recent media and scientific reports of fatal pulmonary emboli developing in passengers, either during flights or shortly after disembarking. Although not confined to flying, travel-associated thrombosis is commonly referred to as the 'economy class syndrome'. The term evolved from the premise that the underlying aetiology of VTE is venous stasis secondary to relative immobility; a consequence of being confined to seating with limited legroom. Flight-simulation studies have shown that venous stasis is a consequence of being seated in an aircraft for prolonged periods of time.[1] A number of studies have provided evidence that there is a link between long-haul air travel and VTE,[2-6] although it is accepted that this risk has not been adequately quantified.[7] As yet, no study has demonstrated that passengers travelling in economy class are more predisposed to VTE than those travelling in business class or first class, where there is more legroom and seats recline.

The BEST study (**B**usiness class versus **E**conomy class **S**yndrome as a cause of **T**hrombosis) was designed to be the first large prospective study to compare the incidence of VTE in low- and intermediate-risk[8] economy class and business class passengers. All passengers with any identifiable predisposition to VTE were excluded. The intention was to determine the incidence of thrombosis using a strategy combining D-dimer measurement on departure and arrival, and a full evaluation of all the deep veins by compression ultrasound of all participating passengers on arrival. The study was also designed to evaluate factors such as fluid and alcohol intake, exercise, smoking status and medication.

Although recent media reports have dramatised the 'economy class syndrome', a World Health Organisation (WHO) report[7] suggests that the actual incidence of travel-associated VTE might be much lower than previously estimated. In an attempt to quantify the true incidence accurately we decided to use D-dimers as well as compression ultrasonography (CUS). CUS is an excellent technique to assess venous thrombosis above the knee. Unfortunately, the sensitivity of this technique diminishes markedly below the knee.[9] The D-dimer, a specific degradation product of cross-linked fibrin, is a well-established highly sensitive test for the detection of VTE.[10,11] We therefore decided to use positive D-dimers (≥ 500 ng/ml) as an indicator to identify passengers with travel-induced thrombotic activity.

As the risk of VTE is known to increase with duration of travel,[6] the London-to-Johannesburg route was chosen. It has a flight duration of approximately 11 hours and is therefore a 'high-risk' flight, with the added advantage of not having major time zone changes as a potential confounding variable.

Materials and methods

Recruitment

Passengers booked on two daily non-stop scheduled flights from London's Heathrow Airport to Johannesburg International Airport, between April 2002 and June 2002, were approached for inclusion in the study at the South African Airways check-in desk. An estimate of the number of passengers required to evaluate the increased risk of thrombosis caused by long-haul flight was derived from two other prospective studies[3,5] which reported an incidence of between 3% and 10%. The aim was to enrol approximately 1 000 passengers, as this would give a greater than 90% power to detect a lower incidence of thrombosis than that previously reported. There was an active attempt to recruit equal numbers of economy class and business class passengers. Financial constraints limited the duration of the study, which was terminated before equivalent numbers of business class passengers could be recruited.

Exclusion criteria were a known history of VTE, current warfarin and/or low-molecular-weight heparin usage, pregnancy, surgery within the last 6 weeks and the intention to use medical support stockings in-flight. All passengers who agreed to participate were required to sign a consent form, complete pre- and post-flight questionnaires, and undertake pre- and post-flight blood sampling. Ultrasonography of the lower limbs on disembarking was encouraged but optional. All participants who completed the study were allotted an extra 5 000 South African Airways Voyager Air Miles (frequent flyer) for the flight.

Questionnaire

A questionnaire documenting the class flown, age, gender, height and weight, was given to passengers on departure. They were asked to record their in-flight fluid intake (non-alcoholic and alcoholic) and amount of in-flight exercise performed. Smoking status, use of aspirin, anti-inflammatory agents, sleeping tablets, oral contraceptives (OC) and hormone replacement therapy (HRT) were also documented.

Phlebotomy

Venepunture was performed after check-in and immediately on disembarkation. The phlebotomists were instructed not to make more than two attempts at venepuncture in an attempt to ensure volunteer compliance and not impact negatively on future volunteer recruitment. Blood was taken from each volunteer passenger using a 21-gauge needle and the Becton Dickinson Vacutainer system. Pre- and post-flight blood samples collected included one 5 ml ethylenediamine tetra-acetic acid (EDTA), one 10 ml serum separation table (SST) and two 5 ml sodium citrate standard Becton Dickenson Vacutainer tubes.

Specimen preparation

The blood specimens collected in 0.105M (3.2%) trisodium citrate (9 volumes blood: 1 volume citrate) tubes were centrifuged at 2 500 *g* for 10 minutes. Specimens collected pre-flight at Heathrow Airport were centrifuged, plasma separated, aliquoted into plastic tubes and frozen at –20°C within 30 minutes of collection. The pre-flight specimens were transferred from Heathrow Airport to St Thomas's Hospital, London, each evening for storage at –20°C for 1 month and subsequently at –70°C. On completion of the study all plasma specimens were couriered on dry ice to the National Health Laboratory Service Laboratories at Johannesburg Hospital (South Africa) for testing. The post-flight specimens were transferred from the Johannesburg International Airport to the Johannesburg Hospital Laboratories for processing after the arrival of each flight. The maximum time between blood collection and processing and/or freezing was 3 hours. The buffy coat was separated from the EDTA specimen post platelet count analysis and stored at –70°C until DNAextraction was performed for factor V Leiden and prothrombin 20210Agene mutation analysis.

Specimen analysis

All specimens were analysed by the National Health Laboratory Service. The post-flight EDTA specimens underwent platelet count analysis on a Coulter GENS within 4 hours of collection. The pre-flight trisodium citrate specimens underwent D-dimer testing. Analysis of the post-flight trisodium citrate specimens included assays for D-dimers, fibrinogen, factor VIII (FVIII), protein C (PC), protein S (PS) and antithrombin (AT). Anticardiolipin testing was performed on blood collected in the SST tubes.

The international normalised ratio (INR), activated partial thromboplastin time (aPTT) and D-dimer analyses were performed on an Automated Coagulation Laboratory (ACL) Futura (Instrumentation Laboratories, Milan) using Thromborel R (Dade Behring — ISI 1.01), ILaPTT SPliquid reagent (Instrumentation Laboratories) and ILD-dimer kit (Instrumentation Laboratories) reagents respectively. The latter kit has been validated in our laboratory against the Gold D-dimer enzyme-linked immunosorbent (ELISA) assay. Any value ≥ 500 ng/ml was considered positive.

The FVIII, fibrinogen, PC and AT were analysed on an ACL 9000 (Instrumentation Laboratories). The FVIII was assayed using FVIII-deficient plasma from Dade Behring and ILaPTT SP reagent. The control plasma used was standard human plasma (SHP) from Dade Behring. The fibrinogen, PC and AT tests were all performed using standard Instrumentation Laboratories reagents. The PS testing was performed on an ACL3000 using the Instrumentation Laboratories Functional Protein S kit. The anticardiolipins were assayed with the QACAimmunoglobulin G (IgG) and immunoglobulin M (IgM) ELISAkits from Cheshire Diagnostics Limited.

Factor V Leiden and prothrombin mutations were analysed using a multiplex assay and real-time PCR. Genomic DNAwas extracted from peripheral blood anticoagulated with EDTA using the method previously described.[12] The multiplex PCR used contained two unlabelled primer sets and two pairs of fluorescent labelled probes. A 306-bp fragment of the Factor V gene was amplified using unlabelled primers and labelled probes previously reported.[13] A 291-bp fragment of the prothrombin gene was also amplified using unlabelled primers and labelled probes previously described.[14] PCR reactions were performed using the LightCycler. Fluorescence was measured continuously during the melting curve analysis.

Lower limb CUS

After venepuncture had been carried out at Johannesburg International Airport, passengers were asked to stay for CUS of the deep venous system of both legs. The paired venae commitantes of the calf, the soleal, popliteal and the femoral veins were all insonated. This was done by five experienced ultrasound technicians (employees of Tecmed South Africa under Toshiba Japan) using Toshiba Nemio 20 ultrasound machines with 7211 MHz probes.

Passengers without connecting flights who were unwilling to wait were asked to attend the Milpark Hospital for an ultrasound assessment within 1 week of disembarkation. A single senior ultrasonographer performed these delayed ultrasounds using a Hewlett Packard instrument with a 7210 MHz probe.

A second senior ultrasonographer and a vascular surgeon randomly checked all ultrasound examinations. The same vascular surgeon reviewed all the ultrasound films of those passengers who were shown to have positive D-dimers.

Follow-up

Attempts were made to contact all passengers who supplied telephone contact details 6 months after this study flight in order to ascertain whether there were any clinical sequelae suggestive of VTE because of the flight studied.

Statistical analysis

A logistical regression analysis was performed using Stata version 7 statistical software to assess risk factors that contributed to a positive D-dimer result (≥ 500 ng/ml). Only subjects with complete datasets were included in the analysis. In the logistical regression analysis D-dimer positivity was initially regressed against all the characteristics in Tables Iand II, after which those characteristics with high *p*-values and odds ratios (ORs) close to 1 were removed. In the final analysis class travelled, presence of factor V Leiden mutation, FVIII levels, aspirin use, age, sex, height in 10 cm units, weight in 10

kg units and smoking status were regressed against D-dimer positivity for 778 passengers who had complete data.

Ethics approval

The study was approved by the Ethics Committees for Human Research from both the University of the Witwatersrand and St Thomas's Hospital College.

Results

Passenger demographics

These are summarised in Tables I and III. Business class and first class passengers were analysed together as the majority of passengers who flew in business class had a flat bed. There was a 4:1 ratio of economy class to business class passengers recruited despite an attempt to obtain equivalent numbers. There was a similar number of men and women in the economy class group but a 2:1 ratio of men to women in business class. While the height, weight and fluid intake were similar in both classes, the mean alcohol intake was 66% higher in business class. Only 6% of all passengers in both classes exercised during the flight.

Table I. Passenger demographic data

Characteristics	Business class	Economy class
Number	180	719
Age		
Median (years)	47	43
Range (years)	28 - 78	18 - 81
Sex		
Male	119	368
Female	61	351
Median height (cm)	176	173
Range (cm)	130 - 201	120 - 210
Median weight (kg)	82	76
Range (kg)	49 - 126	44 - 168
Median fluid intake (l)	1.0	1.0
Range (l)	0 - 3.25	0- 5.00
Mean alcohol intake (l)	0.250	0.175
Range (l)	0 - 2.38	0 - 1.5
Exercise (yes / no)	10 / 170	41 / 678
Percentage (yes)	6	6
Smokers (yes / no)	25 / 155	121 / 598
Percentage (yes)	14	17
Passengers (*N* (%))		
Using aspirin	22 (12.2)	89 (12.4)
Using anti-inflammatories	4 (2.2)	26 (3.6)
Using sleeping tablets	24 (13.3)	94 (13.1)
Using OCs	9 (5)	72 (10)
Using HRT	12 (6.7)	71 (9.9)
Ultrasound (*N* %))		
Immediate	77 (42.8)	310 (43.1)
Within 7 days	9 (5)	38 (5.3)

OCs = oral contraceptives; HRT = hormone replacement therapy.

Table II. Thrombotic screen results

Test	Total number tested	Total number positive / deficient	Percentage abnormal results
Factor V Leiden	844	31	3.7
Prothrombin 20210A	844	22	2.6
Protein C (IU / dl) (normal range 70 - 160)	873	18	2
Antithrombin (IU / dl) (normal range 76 - 125)	873	5	0.6
Protein S (IU / dl) (normal range 60 - 140)	871	79	9
ACLAIgG GPLU / ml (normal range < 16)	817	9	1.1
ACLAIgM MPLU / ml (Normal range < 14)	817	12	1.5
Test	**Number of tests**	**Mean**	**Range**
Factor VIII (%) (normal range 50 - 150)	899	107.5	33 - 293
Fibrinogen (g / l) (normal range 2 - 4)	873	2.94	0.66 - 6.58
Platelet count (x 10^9 / l) (normal range 140 - 400)	702	271	127 - 497

D-dimers

Nine of the 491 samples taken at departure from Heathrow had D-dimer levels higher than 500 ng / ml, 1% from business class and 2% from economy class (Table III). These 9 passengers were excluded from further analysis. Seventy-four of 899 samples taken on arrival had elevated D-dimers (Table III). Twenty-two of 180 business class passengers had elevated levels compared with 52 / 719 in economy class (7%). This difference was not significant (OR 0.61, $p = 0.109$).

Logistical regression analysis on 784 passengers with complete datasets produced significant positive correlations between elevated D-dimers and the presence of the factor V Leiden mutation (OR 3.36, $p = 0.024$), FVIII levels (OR 1.01, $p = 0.014$) and the use of aspirin (OR 2.04, $p = 0.038$) (Table IV).

A separate logistical regression analysis on D-dimers was performed on the subset of female passengers who were taking

Table III. D-dimer results per class

	Business class passengers	Economy class passengers
D-dimers > 500 ng / ml on disembarking (*N* (%))	22 / 180 (12)	52 / 719 (7)
D-dimers > 500 ng / ml on embarking (*N* (%))	1 / 104 (1)	8 / 387 (2)

Table IV. Regression analysis of factors that have a statistically significant association with positive D-dimers in both sexes

	Odds ratio	*P*-value	95% confidence interval
Factor V Leiden	3.36	0.024	1.17 - 9.63
Factor VIII	1.01	0.014	1.00 - 1.01
Aspirin	2.04	0.038	1.04 - 3.99

Table V. Regression analysis of potential hormonal factors contributing to the development of positive D-dimers in females

	Odds ratio	*P*-value	95% confidence interval
Hormone replacement therapy	2.15	0.083	0.91 - 5.10
Oral contraceptive	1.23	0.707	0.42 - 3.62

HRT or OCs (Table V). There were 382 female passengers with complete datasets available for this assessment. The OR of 2.15 for HRT might be clinically significant even though the *p*-value is 0.083.

Lower limb CUS

Three hundred and eighty-seven passengers had CUS on arrival and 47 passengers had it performed 1 week after arrival. None of the 434 passengers who were assessed had evidence of venous thrombosis of the lower limbs. Two passengers had equivocal scans on arrival. Their femoral veins were compressible but appeared to have diminished flow. Both of these passengers had repeat examinations within 2 days, which were normal, and both had D-dimers within the normal range.

Follow-up

Telephonic contact details were available for 627 of the 899 passengers, of whom we were able to contact 505 (81%) within 6 months of the study flight. Sixty-four of 74 passengers with positive post-flight D-dimers were contacted. None of the passengers contacted reported any signs or symptoms of a delayed thrombotic event pertaining to the study flight. One passenger reported that he developed a clinical deep-vein thrombosis (DVT) after a long flight that he had made six flights after the study flight.

Discussion

There is considerable anecdotal evidence that DVT can follow prolonged airline flight and other forms of travel. This has been reinforced by more recent trials and surveys.[2-6,15] Two studies have suggested a high prevalence of the condition in high-risk passengers,[3,5] although cockpit crew do not appear to be affected.[16] There is, however, no evidence that the economy class syndrome exists, although it is now part of popular mythology.

Our study specifically excluded passengers with a history of VTE, recent surgery, and current pregnancy. No passenger used compression stockings. The study therefore focused on passengers at low or intermediate risk of developing thrombosis. This is the first study that has specifically examined the association between markers of thrombosis (D-dimer) and class of travel.

In contrast to what we expected, there was no statistical relationship between flight class and the development of elevated D-dimers. We had hoped for a more even distribution between the number of business and economy class passengers, but volunteers in economy class outnumbered those in business class. This discrepancy was probably caused by a limited number of business class seats per flight and the fact that many of the business class passengers either checked in late or did not wish to be delayed on disembarking. The similarity in the percentage of passengers with raised D-dimers in both classes might have been the result of immobility rather than the cramped seating as only 6% of passengers reported exercising during the flight.

Although fewer pre-flight D-dimer assays were performed compared with post-flight specimens due to an entire batch of specimens becoming activated during transportation and being discarded, over 7% of our passengers developed raised D-dimers post-flight. This contrasts with the study by Scurr *et al.*[3] where no D-dimer elevation was found, perhaps because blood collection was delayed. The NZATT study[17] has also recently reported elevated D-dimers in passengers following long-haul flights.

In contrast to previous reports none of the passengers in this study who agreed to be examined had ultrasonic evidence of lower limb thrombosis.[3,5,17] Unfortunately many of the passengers declined CUS examination at the end of their long flight. Only 47% of business class and 48% of the economy class passengers agreed to be examined and only 51% of the passengers who had positive D-dimers had ultrasound scans performed. Although the overall percentage of passengers who underwent lower limb CUS was low, there was no bias between the positive and negative D-dimer subgroups. The majority of the ultrasound scans were performed on arrival and this may have resulted in developing thrombi being missed. However, none of the 47 late ultrasounds showed evidence of thrombi. Furthermore, approximately 90% of passengers with elevated D-dimers were contacted at 6 months and none reported any symptoms suggestive of VTE.

The sensitivity of CUS for the detection of thrombi in the lower limb is excellent above the knee, but its utility in the

detection of calf vein thrombi is far less impressive.[9] In contrast, D-dimer measurement is a highly sensitive test but lacks specificity.[18] The clinical significance of elevated D-dimers is difficult to assess. Studies have shown that the D-dimer test is a useful first-step investigation in patients with clinical signs and symptoms suggestive of DVT or pulmonary embolism.[10,18,19] The very high negative predictive value has led to the adoption of this strategy in clinical practice, principally to minimise unnecessary patient exposure to radiological investigations, which are both costly and not without morbidity. It is particularly useful in assessing non-surgical patients as positive D-dimers are almost always observed postoperatively.

The D-dimer is an end product of plasmin digestion of cross-linked fibrin, which in turn is generated by thrombin.[20] The D-dimer is therefore a marker of thrombin generation signifying that the coagulation cascade must have been triggered. The level of elevation of D-dimers is dependent on the mass and age of the thrombus and hence D-dimers may be raised without radiological evidence of thrombosis at the time of testing in patients presenting with symptoms suggestive of thrombosis.[18,21] Bernardi *et al.*[21] confirmed this concept in their study in which 6% of subjects with positive D-dimers at presentation subsequently developed DVTs despite an initial normal ultrasound study.

It must be accepted that the D-dimer is at best a surrogate marker of thrombosis and may be elevated in the absence of thrombus. It is interesting, however, that factor V Leiden (the major inherited risk factor for venous thrombosis) was identified as an independent risk factor in passengers with elevated D-dimers. The incidence of 3.7% heterozygous individuals in this study is comparable with general population studies in the Western world.[22] The question of whether pre-flight knowledge of factor V Leiden genotype would influence the implementation of in-flight prophylaxis requires a prospective study.

The prothrombin gene 20210Amutation was identified in 2.6% of passengers but surprisingly was not a predictor of positive D-dimers. The other routine tests of hereditary thrombophilic states, i.e. protein C, protein S and antithrombin deficiencies, likewise did not prove to contribute to positive D-dimers. The number of passengers with low protein S levels was surprisingly high and did not correlate with the use of oestrogen products. The presence of anticardiolipin antibodies was not related to positive D-dimers. Although statistically significant, it is difficult to draw any definite conclusion from the finding of the correlation between elevated factor VIII levels and positive D-dimers in the absence of an elevated odds ratio (OR 1.01). The very tight 95% confidence interval (1.00 - 1.01) is, however, intriguing. Factor VIII becomes elevated during stress and the stress of flying possibly contributes to an underlying thrombophilic state. However, an elevated factor VIII level consequent to subclinical thrombosis as suggested by positive D-dimers cannot be excluded.

There was a relationship between HRT and elevated D-dimers. This observation, although not statistically significant, suggests that women using this medication should be particularly cautious when travelling long distances. Positive D-dimers were, however, not correlated with OC usage. In light of the well-documented association between OC usage and VTE, this observation cannot be explained.[23,24] In particular there was no association with age.

Smoking status was not related to the development of positive D-dimers. Smoking is a potent cause of arterial thrombosis but there is not much evidence linking it to venous thrombosis. Although one might have expected that passengers who were taller or heavier than the norm, and therefore subject to greater in-flight space restriction, would have a higher incidence of elevated D-dimers, this was not borne out by the statistical analysis.

An assessment of advice previously offered to passengers, viz. to increase fluid intake, limit alcohol intake and actively perform the exercises recommended in the in-flight magazine, revealed that none of them could be supported by the results of our study. The use of sleeping tablets was expected to be a potential factor contributing to the tendency to thrombosis by decreasing in-flight movement. No association was noted.

Aspirin, but not other anti-inflammatory agent usage, was statistically significantly associated with positive D-dimers. Aspirin has been well documented to prevent arterial thrombosis but the evidence for its preventing venous thrombosis is far less convincing.[25,26] It is unlikely that it causes thrombosis. A more plausible theory is either that it caused gastritis, which falsely elevated the D-dimers, or that the passengers who used aspirin comprised a group of high-risk individuals. The NZATT study[17] has now reported that aspirin does not prevent travel-associated venous thromboses.

In conclusion, in the largest prospective study to date, we have shown that the incidence of clinical and/or CUS-documented lower limb venous thrombosis is much lower than has been previously reported as it occuured in none of the passengers studied. No passenger reported symptoms of DVT or pulmonary embolism within 6 months of the study flight. This may in part be explained by differences in passenger demographics as high-risk passengers were excluded from this study. We have also demonstrated that a significant number of passengers developed elevated D-dimer levels during flight. This was unrelated to flight class. The large prospective study proposed by the WHO may shed further light on the true risk of air travel-associated thrombosis.

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