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"Long Haul" Flight and Deep Vein Thrombosis: a Model to Help Investigate the Benefit of Aspirin and Below-knee Compression Stockings

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Objective: *to develop a model simulating factors of ''long haul'' flight to investigate the relationship with DVT.*
Materials and methods: *volunteers (19 males: 20 females) sat for 6 h in a warm (>25°C), dry environment, limited in movement, consuming alcohol (40 ml of 40% alcohol/hour) and salted foods (300 g). Half of the subjects received 150 mg aspirin and wore especially designed below-knee, compression stockings (Class 1 profile). Changes in full blood counts were recorded, and as an indication of DVT formation, plasma was analysed for D-dimer. Limb swelling was assessed from leg measurements.*
Results: *after 6 h, in controls, there were significant rises in platelet packing (Pct; $p<0.04$), total platelet numbers ($p<0.003$) and total numbers of white blood cells (WBC's; $p<0.001$). With aspirin plus stockings, there were similar significant rises in total platelet numbers ($p<0.002$) and total WBC's ($p<0.001$). In both groups, significant rises were seen in all WBC types (except basophils). Wearing compression stockings prevented calf swelling seen in controls after 6 h ($p<0.002$). No subject developed a DVT, or a change in levels of D-dimer.*
Conclusion: *changes in the cellular components of blood, particularly WBC's, combined with vaso-compression and reduced flow could predispose towards DVT. Aspirin, combined with compression stockings, may provide prophylaxis.*

Key Words: Air travel; Long haul flight; Deep vein thrombosis (DVT).

Introduction

Whether "long haul" airline flight predisposes passengers to the development of a deep vein thrombosis (DVT) remains topical and until recently, controversial. Although certain risk factors predisposing towards DVT such as a previous history of DVT, recent surgery, a known (or occult) malignancy, Factor V Leiden or other coagulopathy[1–7] are known, the recent deaths of seemingly healthy, young individuals following a long haul flight has raised both awareness and questions as to the true basis underlying this problem.[8–10]

The incidence of an airline flight-associated DVT (f-DVT), progressing ultimately to the development of a pulmonary embolus (PE) and potentially death, has been difficult to assess due to both a lack of awareness and also, that the fatal event may occur some time (often days) after the flight when the direct association with recent air travel may not be made. Even, however, if realised, the presentation by PE would underestimate significantly, the true incidence of f-DVT.[11,12]

Probably, the first report of a potential association between airline flight and DVT was in 1954.[13] Since then, reports of f-DVT have been sporadic and limited. In the mid 1990's, an assessment of in-flight deaths, whilst concluding that myocardial infarction was the pre-eminent cause, found that of approximately 1000 deaths per year on US carriers, 13% were from PE (secondary of course, to extensive DVT).[14,15] Similarly, one major hospital in Hawaii reported having seen 44 of 254 patients found to have a DVT, who had developed their symptoms during, or shortly after, a long haul flight[16] and separately, significant fluid retention (>1 l) in the lower limbs was noted in the long haul air travellers (perhaps, promoting venous compression).[6] The current media activity surrounding this problem however, has led to more concentrated efforts to assess more closely, the association between airline flight and DVT development. Recently, various authors have reported an up to four-times increase in DVT seen in those who had recently travelled by air,[17] that up to

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2000 deaths may result per year (in the UK) from f-DVT [personal communication; Khan F, Director of the Institute of Aviation Medicine, United Kingdom], and that the incidence of f-DVT may be between 5% and 10%.[18]

The most recent report (May 2001) assessed prospectively, the incidence of f-DVT on a long haul flight and also, the potential prophylaxis against f-DVT offered by wearing below-knee, Class 1 graduated compression stockings.[18] Here however, the subject population chosen was over 50 years of age, a factor itself known to be associated with a higher risk of developing a DVT. Furthermore, although the study demonstrated the efficacy of (Class 1) compression stockings in preventing f-DVT development, those physiological processes that might initiate its development were not apparent. The pathophysiology underlying f-DVT thus, remains unclear.

Those factors thought to contribute to a potential f-DVT include the hypobaric environment with hypoxia and low humidity, dehydration (linked in part to alcohol intake), and venous compression, from both sitting for long periods in relatively cramped conditions and the retention of fluid known to occur in the lower limbs.[6,19–21] In the hospital setting, prophylaxis against DVT (which in low risk surgery can reduce the risk of DVT from 5–10% towards zero) is offered by anti-coagulants (heparin, Fragmin or warfarin), associated with graduated compression stockings, fluid replacement and early mobilisation.[22,23] These treatment elements do indeed, help to address many of the factors thought to contribute to f-DVT. It is natural therefore, to try and transfer these hospital treatment options to the problem of f-DVT.

We aimed in this study to develop a model to mimic as many of the effects of long haul flight as possible (without flying) and within the hospital setting. Then, using this model, we aimed to assess (i) any changes in blood components that may initiate the development of f-DVT, and (ii) the potential benefits of prophylaxis from giving a single aspirin tablet (150 mg) orally, in combination with wearing specifically designed, below-knee, Class 1 compression stockings.

Methods

This study was performed with the approval of the joint University College London and University College London Hospitals NHS Trust Committees on the Ethics of Human Research.

Volunteer subjects

Thirty-nine healthy volunteers (19 males and 20 females) were recruited (median age 25 years; range 23–32 years). Volunteers were excluded if they had any co-existing morbidity, or were on any form of medication. Following informed consent, each subject was randomised to one of two groups; Group 1 – "control", or Group 2 – "aspirin + stockings". One hour before the trial commenced, all subjects had (baseline) leg measurements taken, as the circumference (in centimetres) at 5 cm, 15 cm and 25 cm above the medial malleolus of the ankle. At this time also, subjects in the aspirin + stockings group were given 150 mg aspirin, orally. At time zero (0 h), both groups had (baseline) blood samples taken from an ante-cubital fossa vein, collected into 5 ml EDTA tubes, for assessment of full blood count, and into 5 ml citrated tubes for analysis of D-dimer by ELISA. The aspirin + stockings group were given a pair of below-knee, light compression stockings of Class 1 profile giving ~18–20 mmHg "squeeze" at the ankle and which were worn until completion of the trial.

Trial protocol

To mimic as many of the conditions imposed by a long haul flight as possible, without flying and within the constraints of a hospital setting, subjects were seated in a (Victorian) lecture theatre, on hard wood benches, with minimal knee room, huddled together, for a period of 6 h. The room was maintained warm (>25 °C) and stuffy (all possible ventilation closed). Subjects were (partially) dehydrated by receiving 40 ml of 40% alcohol ("double" vodka) with 30 ml orange juice hourly, for each of the 6 h and by eating a total of 200 g salted peanuts and 100 g salted crisps. No additional fluid or food intake was permitted. Free movement was limited to visits to the toilet only.

At the end of the 6 h period, all subjects had ante-cubital fossa venous blood samples taken as before, together with repeat leg circumference measurements (as described above).

Analysis of blood samples

All blood samples were processed simultaneously, by the Department of Haematology at University College Hospital, London. Full blood counts were performed as per routine using an automated Coulter Counter®.

Analysis of D-dimer was made using the commercially available Dimertest® GOLD EIA (Quadratech, Surrey, U.K.) assay kit. [This kit has a specificity for D-dimer of >95% with a lower limit of detection of 32 ng/ml; the accepted index for DVT is >500 ng/ml].[24]

Assessment of an enhanced potential to develop a DVT was gauged from a rise in haematocrit and cellular blood constituents. The formation of a DVT was determined by systemic levels of D-dimer of at least >500 ng/ml.[24] Confirmation of any suspected DVT would be made by Duplex ultrasound scan.

Statistics

All experimentally obtained results for full blood counts, systemic levels of D-dimer and leg measurements were distributed normally as determined by a one-sample Kolmogorov–Smirnov test for normality. Accordingly, results have been presented as mean values with S.E.M. Comparisons between, or within, experimental groups were made using the Student's *t*-test for paired or unpaired results as appropriate; all tests two-tailed.

Results

Following randomisation, the control group consisted of 19 subjects – 10 females and 9 males, median age 22 years (range 21–35 years), and the aspirin + stockings group of 20 subjects – 10 females and 10 males, median age 22 years (range 20–26 years). [Age; $p>0.1$, Mann–Whitney *U*-test.]

At the start of the trial (0 h), as expected, there were no significant differences between the control and aspirin + stockings groups in; (i) leg measurements (ankle, calf and leg; all $p>0.1$), or (ii) systemic levels of D-dimer [30/39 subjects recorded a D-dimer level below the level of detection (32 ng/ml)[24] and the remaining 9/39 subjects recorded D-dimer levels <90 ng/ml]. All components of the full blood count were comparable, with the exception however, of total numbers of platelets. Here, in the aspirin + stockings group, by receiving 150 mg aspirin orally, one hour before blood samples were taken, this appeared to reduce significantly the platelet count; a total platelet count of $253 \pm 13 \times 109$/l, as compared to $293 \pm 14 \times 109$/l for the control group ($p<0.04$; Student's unpaired *t*-test; Fig. 1).

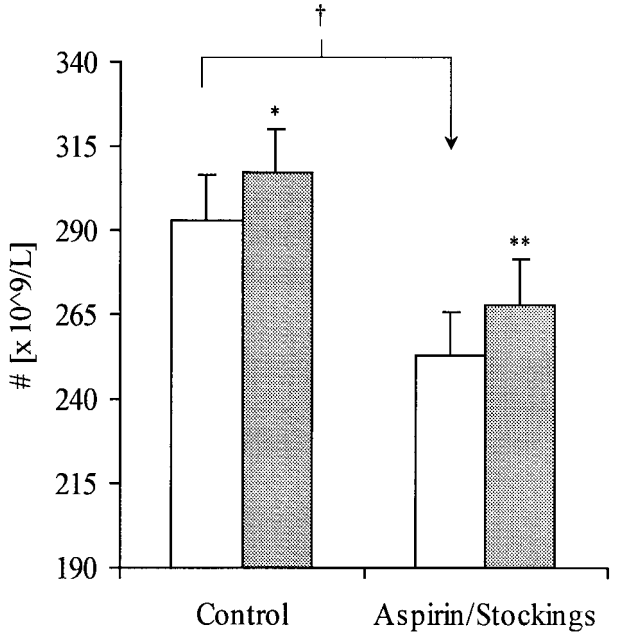

Fig. 1. Total numbers of platelets. Total number of platelets in the peripheral blood samples taken from subjects in the control and aspirin + stockings experimental groups at the start of the trial (0 h; open bars), and after the six hour experimental period (6 hours; shaded bars). Bars represent the mean value + the S.E.M. Levels of significance comparing 0 h versus 6 h; *<0.003, **$p<0.002$, [both, Student's' paired *t*-test]; †$p<0.04$ for control versus aspirin + stockings at 0 h. (Student's unpaired *t*-test.)

During the trial, no subject developed calf pain (suggesting clinically, the possibility of DVT formation). Furthermore, although a rise in the systemic levels of D-dimer would be expected by six hours if a DVT were present, there was no significant change seen in either the control or aspirin + stockings groups. In similar fashion to the levels recorded at the start of the trial period, 34/39 subjects had systemic levels of D-dimer below the level of detection (32 ng/ml)[24] and the remaining 5/39 subjects recorded levels <90 ng/ml.

After the 6 h trial period in the control group, there was a trend for an increase in haemoglobin ($p<0.07$) and a slight trend for increased haematocrit ($p<0.1$), indicating perhaps, partial success at dehydrating our subjects. There was a significant rise in platelet packing (Pct; $p<0.04$) and a $5.1 \pm 1.4\%$ increase in the total number of platelets ($p<0.003$; Fig. 1). The total white blood cell count increased by $19 \pm 3\%$ ($p<0.001$; Fig. 2), which was reflective of an increase in the total numbers of; (i) lymphocytes – $32 \pm 5\%$ ($p<0.001$), (ii) monocytes – $18 \pm 6\%$ ($p<0.006$), (iii) eosinophils – $53 \pm 14\%$ ($p<0.001$), and (iv) neutrophils – $14 \pm 5\%$ ($p<0.02$); Table 1. (All, Student's paired *t*-test.)

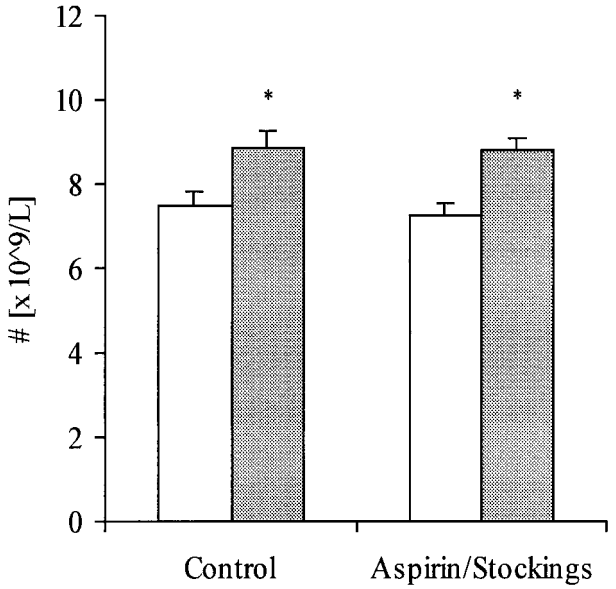

Fig. 2. Total numbers of white blood cells. Total number of white blood cells in the peripheral blood samples taken from subjects in the control and aspirin + stockings experimental groups at the start of the trial (0 h; open bars), and after the six hour experimental period (6 h; shaded bars). Bars represent the mean value + the S.E.M. Levels of significance comparing 0 h versus 6 h; *$p<0.001$. (Student's paired *t*-test.)

In the aspirin + stockings group, after six hours, there was no significant increase in the haematocrit, but a significant increase in haemoglobin ($p<0.02$). Similar to the control group, there was a $6 \pm 2\%$ increase in the total number of platelets ($p<0.002$; Fig. 1), although platelet packing remained largely unchanged. Similarly, there was a $23 \pm 4\%$ increase in the total white blood cell count ($p<0.001$; Fig. 2), this being reflective of an increase in the total numbers of; (i) lymphocytes – $37 \pm 3\%$ ($p<0.001$), (ii) monocytes – $17 \pm 4\%$ ($p<0.002$), (iii) eosinophils – $61 \pm 12\%$ ($p<0.001$), and (iv) neutrophils – $19 \pm 6\%$ ($p<0.02$); Table 1. (All, Student's paired *t*-test.)

When comparing between the control and aspirin + stockings groups, after the six hour trial period, all facets of the full blood counts were similar except for the total numbers of platelets; $307 \pm 13 \times 109/l$ versus $268 \pm 13 \times 109/l$ for control and aspirin + stockings groups respectively ($p<0.04$; Student's unpaired *t*-test; Fig. 1).

Wearing the below-knee, Class 1 compression stockings did prevent limb swelling during the trial period. There was little or no change in any of the leg measurements (ankle, calf or leg) in those subjects wearing stockings, whereas in the control group of subjects who were not wearing stockings, there was an increase (swelling) in the calf circumference ($p<0.002$; Student's paired *t*-test; Table 2), together with a trend for slightly more swollen ankles ($p<0.09$; Student's paired *t*-test; Table 2). Between the control and aspirin + stockings groups, although the ankle and leg dimensions were similar after six hours, there was a significant increase in calf measurement in the control group ($p<0.01$; Student's unpaired *t*-test; Table 2).

Discussion

Do passengers suffering a f-DVT develop their thrombosis via the same processes as those patients in hospital, for example, following surgery? If so, why should some young, healthy individuals die from a f-DVT whilst other individuals, perhaps with conditions/factors theoretically placing them at a higher risk, be unaffected? The actual patho-physiological mechanisms underlying the development of a f-DVT remain obscure and only recently, have become a focus for intensive investigation. Furthermore, attempts to examine this "phenomenon" have undoubtedly been limited by significant financial considerations and hesitancy on the part of the airline industry. Our aim was to develop a simple, reproducible and cost effective model to simulate, within the hospital setting, many

Table 1. White blood cell types. Total numbers of white blood cell types obtained from the control and aspirin + stockings groups at the start (0 h) and the end of the 6 h experimental period.

	Control		Aspirin + Stockings	
WBC [$\times 10^9$/l]	0 h	6 h	0 h	6 h
LY #	2.17 (0.14)	2.83 (0.19)†	2.04 (0.09)	2.79 (0.14)[a]
MO #	0.52 (0.03)	0.60 (0.03)‡	0.51 (0.02)	0.60 (0.03)[b]
NE #	4.60 (0.33)	5.14 (0.35)§	4.38 (0.30)	5.00 (0.26)[c]
EO #	0.16 (0.04)	0.23 (0.05)†	0.23 (0.05)	0.33 (0.07)[a]
BA #	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)

Mean values are presented with S.E.M. in parentheses. WBC, white blood cell type; #, number; LY – lymphocytes, MO – monocytes, NE – neutrophils, EO – eosinophils, BA – basophils. Levels of significance for 0 h versus 6 h; control group – †$p<0.001$, ‡$p<0.006$, §$p<0.02$; aspirin + stockings – [a]$p<0.001$, [b]$p<0.002$, [c]$p<0.02$. (All, Student's paired *t*-test.)

Table 2. Leg measurements. Measurements of the legs of subjects at the start (0 h) and the end of the 6 h experimental period.

	Control		Aspirin + Stockings	
Measurement	0 h	6 h	0 h	6 h
Ankle (cm)	22.3 (0.3)	22.9 (0.3)	21.8 (0.3)	22.7 (0.4)
Calf (cm)	29.7 (0.4)	30.8 (0.4)†,§	28.7 (0.4)	29.3 (0.4)
Leg (cm)	36.5 (0.4)	37.2 (0.4)	35.5 (0.4)	36.1 (0.6)

Values presented are means with S.E.M. in parenthesis. Levels of significance; †$p<0.002$ versus 0 h [Student's unpaired *t*-test]; §$p<0.01$ for control versus aspirin + stockings at 6 h. (Student's paired *t*-test.)

aspects of a long haul flight, to enable the investigation of its relationship with DVT.

The results demonstrate that the model can indeed prompt features such as dehydration and lower limb swelling, as experienced by passengers undertaking a long haul flight. Considering each in turn: the alcohol load, in combination with the restriction of other oral fluids and consumption of salted foods, produced some degree of dehydration. This was evidenced by the trend for a rise in the haematocrit. The degree of dehydration however, was not as substantial as might be experienced following long haul flight, although it might be enhanced in further studies by using either a longer trial period, or by pre-loading subjects with a diuretic. In addition, measurement of haematocrit alone may not be as good a measure of dehydration as for example, combing measurements of haematocrit and blood osmolarity. Measurements of the ankle, calf and leg circumference indicated that swelling of the lower limb had occurred. Somewhat surprisingly, the significant increase was seen in the calf alone and not around the ankle as might be expected (see Table 2). Lower limb swelling, with retained volumes up to one litre, can be manifest following a long haul flight[6] and, as before, it may be that a longer experimental duration is required for leg swelling to become more pronounced. Furthermore, whilst we have measured ankle, calf and leg circumferences, limb volume measurements (plethysmography) might have been a better method of assessment. The changes seen in calf circumference however, if extrapolated to a limb volume, would indicate a significant degree of fluid retention. Whatever, the below-knee, Class 1, graduated compression stockings did prevent leg swelling, as noted (see Table 2).

During the study, no subject developed clinical signs of a DVT (however reliable that may be). This was supported by the plasma D-dimer assays. Here, for the majority of subjects, a level of plasma D-dimer was not measurable, either before (30/39 subjects) or after (34/39 subjects) the trial period, with values being below the level of detection of the assay (<32 ng/ml).[24] In those few subjects where a level of plasma D-dimer was measurable, levels were very low before the trial commenced (all, <90 ng/ml) and furthermore, remained unchanged after the trial period (all remaining <90 ng/ml). The results for D-dimer were not surprising as the assay indicates only that a DVT has occurred (confirmed if plasma D-dimer is >500 ng/ml)[24] and not whether a DVT is likely to occur. Because the assay is not predictive, it's value in this setting is questionable. Furthermore, for a subject suspected to have developed a DVT during the trial period, this would have been investigated preferentially by means of Duplex ultrasound scanning, which is considerably more informative.[7,25,26]

A surprising and unexpected observation was the significantly lower numbers of circulating platelets at "0 h" in the aspirin + stockings group (see Fig. 1). Our own (unreported) studies have shown that total numbers of circulating platelets can vary considerably over the course of just a few hours. However, the differential between the control and aspirin + stockings groups in platelet numbers was maintained after the six hour experimental period and indeed, the overall percentage rise in platelet numbers by the end of the experimental period was similar within each group. This suggests that the effect seen is indeed real. Unfortunately, blood samples were not taken from the subjects before receiving aspirin, to serve as a comparison with those obtained at the start of the experimental period (0 h) – which would have helped clarify this observation. Aspirin is frequently termed an "anti-platelet" drug but more correctly, should be considered as an anti-thrombotic drug as its effects on prevention of thrombosis are mediated principally, via the prevention of platelet aggregation (through the inhibition of thromboxane A_2).[27] To the authors knowledge, there are no reports to date, of aspirin actually reducing the number of circulating platelets. From this study, we might ask therefore, does aspirin also inhibit platelet release from megakaryocytes, or alternatively, induce the loss of platelets from the circulation (perhaps via the spleen)? This finding should warrant

further investigation and indeed, might help to explain the beneficial effects of aspirin in the treatment of myocardial infarction.[28,29]

The conditions imposed during the six hour trial period induced significant rises in total WBC counts in both the control and experimental groups (Fig. 2). On differential display, significant increases were shown for lymphocytes, monocytes, neutrophils and eosinophils (Table 1). This increase in the overall cellularity of the blood might reasonably be explained as a simple volumetric effect with dehydration, but perhaps of greater importance here, it could have serious implications for the development of a DVT. For example, an increase in the number of circulating monocytes increases the possibility of cross-reaction with platelets, to form complexes which could initiate the clotting cascade and so potentially, render the individual more pro-thrombotic.[30,31] In addition, the significant rise in eosinophil count might be important, as with an increased "histamine load" circulating through vessels known to have histamine receptors,[32,33] there could be an increased potential for the induction of vasospasm. Speculatively therefore, an increase in blood cellularity, with potential activation of WBC's and the subsequent release of cytokines, are factors which could increase significantly, the predisposition to the development of a DVT. These, in combination with venous compression (due to prolonged sitting and perhaps, because of the fluid retained within the lower limbs) and also, increased histamine levels from circulating eosinophils, increases the potential for venospasm and hence, creates a focal point for the genesis of a DVT. Collectively then, these factors in combination could significantly pre-dispose to the potential of a f-DVT. The exact initiating event, or factor(s) responsible for propagation still remain to be identified.

Here, we have mimicked some features of long haul airline flight and have suggested why passengers might be at an increased risk of DVT. The mechanisms underlying the true genesis of a f-DVT remain unclear, but may be different to those developing a DVT in the hospital setting. In the meantime, the debate as to the relationship between long haul airline flight and DVT will, no doubt, continue.

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