WHO RESEARCH INTO GLOBAL HAZARDS OF TRAVEL (WRIGHT) PROJECT

FINAL REPORT OF PHASE I

World Health Organization

WHO Library Cataloguing–in–Publication Data

WHO Research Into Global Hazards of Travel Project.
WHO Research Into Global Hazards of Travel (WRIGHT) Project : final report of phase I.

1.Venous thrombosis - epidemiology. 2.Venous thrombosis - physiopathology. 3.Pulmonary embolism - epidemiology. 4.Pulmonary embolism - physiopathology. 5.Travel. 6.Aircraft. 7.Research. I.World Health Organization. II.Title. III.Title: Final report of phase I.

ISBN 978 92 4 159553 7 (NLM classification: WG 610)

Printed by the WHO Document Production Services, Geneva, Switzerland

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ACRONYMS AND ABBREVIATIONS

BMI	body mass index
DVT	deep vein thrombosis
IATA	International Air Transport Association
ICAO	International Civil Aviation Organization
ICMVT	isolated calf muscle venous thrombosis
PE	pulmonary embolism
PTE	pulmonary thromboembolism
TAT	thrombin–antithrombin complex
VTE	venous thromboembolism
WHO	World Health Organization
WRIGHT	WHO Research Into Global Hazards of Travel

1. EXECUTIVE SUMMARY

The objectives of the WRIGHT (WHO Research Into Global Hazards of Travel) project were to confirm that the risk of venous thromboembolism (VTE) is increased by air travel and to determine the magnitude of risk, the effect of other factors on the risk and to study the effect of preventive measures on risk.

To address these objectives, several studies were performed during Phase I of the WRIGHT project. Additional proposed studies related to the effect of preventive interventions were deferred to Phase II.

The findings of the epidemiological studies indicate that the risk of VTE approximately doubles after a long–haul flight (>4 hours) and also with other forms of travel where travellers are exposed to prolonged seated immobility. The risk increases with the duration of the travel and with multiple flights within a short period.

The risk also increases significantly in the presence of other known risk factors of VTE. The risk factors identified as contriubtors to the increased risk of travel-related VTE were obesity, extremes of height, use of oral contraceptives and the presence of prothrombotic blood abnormalities.

The absolute risk of VTE per more than four-hour flight, in a cohort of healthy individuals, was 1 in 6000.

The pathophysiological studies supported these findings. The results of the hypobaric chamber studies in healthy volunteers failed to demonstrate any association between hypobaric hypoxia and prothrombotic alterations in the haemostatic system. However, the travel and non–travel immobility study, which included a high proportion of individuals with risk factors, suggested that some flight–specific factors may interact with pre–existing risk factors and result in increased coagulation activation in susceptible individuals over and above that related to immobility. Further study will be required to determine the identity of the culpable factors.

Based on these findings, there is a need for travellers to be given appropriate information regarding the risks and for further studies to identify effective preventive measures, which will comprise Phase II of the WRIGHT project.

2. REMIT OF THE REPORT

In March 2001, the World Health Organization (WHO) convened an international meeting on air travel and venous thrombosis at which experts on VTE and representatives of airline companies, the International Air Transport Association (IATA), the International Civil Aviation Organization (ICAO), the European Commission and consumer groups participated (1). The objectives were to review the scientific information concerning air travel and VTE, identify gaps in knowledge and develop priority areas for research.

It was concluded that a link probably existed between air travel and venous thrombosis and that similar associations possibly existed for other forms of travel. Participants agreed that the risk was not quantifiable because of a lack of data, but that it was likely to be small and to mainly affect passengers with additional risk factors for VTE. It was also concluded that there were insufficient scientific data upon which to make specific recommendations for prevention, except that leg exercise should be encouraged during travel. The indiscriminate use of pharmacological agents was to be discouraged because of their recognized side effects. The following priorities for research were identified:

- A set of multicentre international epidemiological studies, including a large prospective cohort study examining hard clinical end–points, should be conducted to determine whether there is a link between air travel and venous thrombosis; the absolute risk if such a link exists; and the size of the problem. These studies would also provide clues to other etiological factors.
- Special studies should be conducted using intermediate end–points in groups of volunteers to examine isolated independent environmental and behavioural risk factors. A prospective intervention study involving passengers, using objective diagnostic methods and examining various preventive measures, should be carried out.

It was agreed that these studies should be undertaken as soon as possible under the auspices of WHO and ICAO, supported by an independent scientific committee, in collaboration with IATA and airline companies.

The purpose of this report is to give an account of the activities and summary results of the first phase of this project, which was funded by the United Kingdom Departments for Transport and Health and the European Commission. The detailed scientific findings will be disseminated by publication in peer–reviewed medical journals.

The following studies were completed in Phase I:

Epidemiological studies

- Population–based case– control study
- Retrospective cohort study among employees of international organizations
- Retrospective cohort study among professional pilots (Dutch commercial pilots study)

Pathophysiological studies

- Hypobaric hypoxia study
- Travel and non–travel immobility study

The following studies, elaborated in the original protocol, have not yet been conducted:

Epidemiological studies

- Registry and meta–analysis of ongoing and completed case– control studies
- Case–control study in Australia (TRAVEL study)

3. BACKGROUND

The possible link between air travel and the development of VTE was first described in 1954 by Homans (*2*). Since then, a large number of cases have been reported (*1*). A growing number of reports over the last five years have focused on the epidemiological and pathophysiological aspects of air travel–related thrombosis. Aside from pulmonary embolism (PE) and deep vein thrombosis (DVT), other manifestations of VTE with reported associations with long–haul flights include subclavian vein thrombosis (*3*), cerebral vein thrombosis (*4*), stroke due to paradoxical cerebral embolism through a patent foramen ovale (*5*) and peripheral arterial thrombosis (*6*). However, the majority of reports have illustrated that lower limb DVT and PE are the most common manifestations of VTE (*7*). Given that increasing numbers of people embark on international and domestic air travel every year (*1*), the issue of VTE in air travellers is of significant concern.

3.1 Extent of the problem

The annual incidence of DVT in the general population is estimated to be about 1 per 1000 (*8*), however, it should be noted that much of the published data are derived from patients who present with symptoms at medical institutions. Diagnosis of DVT has traditionally been based on clinical presentation, however, evidence from postmortem studies indicates that a substantial proportion of VTE cases are asymptomatic (*9*). In one prospective study (*10*), Schwarz and colleagues recruited 964 passengers returning from long–haul flights of at least eight hours and 1213 non–travelling controls. The investigators looked at ultrasonographically diagnosed isolated calf muscle venous thrombosis (ICMVT), symptomatic PE and death as outcome measures. Venous thrombotic events were diagnosed in 27 of the passengers (2.7%) and 12 of the controls (1.0%). Of the 20 cases of ICMVT in the passenger group, 19 were asymptomatic. This study concluded that the incidence of asymptomatic ICMVT in the overall population is 1/1000 per month. While the clinical significance of asymptomatic DVT has not yet been determined, it has been suggested that the increased risk translates into an increased risk of PE and DVT. Another prospective study of long–haul air passengers over the age of 50 years found that upon duplex scanning investigation 12 of the 116 passengers had asymptomatic DVT confined to the calf (*11*).

A retrospective study reviewing the cases of pulmonary thromboembolism (PTE) among passengers arriving at Madrid Barajas Airport between January 1995 and December 2000 estimated that the overall incidence of PTE was 0.39 per one million passengers (95% CI 0.20 to 0.58) (*12*). On flights that were 6–8 hours long, the incidence was 0.25 per one

million passengers (95% CI 0 to 0.75), and on flights longer than eight hours, the incidence was 1.65 per one million passengers (95% CI 0.81 to 2.49), $P < 0.001$.

3.2 Presentation of VTE related to air travel

Symptoms of DVT are principally pain, tenderness and swelling of the affected part. Leg thrombosis can be asymptomatic, meaning that the first clinical symptoms may be chest pain and/or dyspnoea due to PE (*13*). The symptoms experienced by patients with subclavian venous thrombosis are swelling of the arm and auxiliary tenderness (*3*). In a study by Lapostolle et al. (*14*) where 56 of the 170 participants experienced PE, 14% experienced their first symptoms during air travel, 29% upon standing up and 57% at the destination airport. Only those with PE presenting at the airport were included in this study. In 96% of cases, the first symptom was malaise. Half of these patients also experienced syncope, 64% had dyspnoea and 36% had chest pain. In a study by Kesteven and Robinson (*15*), 92% of participants with VTE developed symptoms within 96 hours of their flight.

3.3 Investigations into the association between air travel and VTE

3.3.1 CASE CONTROL STUDIES

Several previously reported case–control studies that were conducted to investigate the potential association between air travel and VTE (*16–20)* yielded conflicting results. About 13% of patients with VTE in the four studies had a history of recent travel, compared to 3% of controls. Martinelli et al. (*16*), concluded that air travel is a mild risk factor for VTE, doubling the risk of the disease. Samama investigated the risk factors for DVT and concluded that immobilization and long–distance travel were both significant factors, and that there was an association between long–distance air travel and VTE (*17*). In another study (*18*), the travel history of 788 patients with venous thrombosis was compared with that of controls who did not have the condition. All had presented with symptoms suspicious of DVT: 4 of the patients with DVT, and 13 of those without, had travelled by aeroplane (odds ratio 1.0, 95% CI = 0.3 to 3.0), thus the results did not support an association between DVT and air travel. Conversely, Ferrari et al. (*19*) reported that a history of recent travel was almost four times more frequent in the VTE group than in controls, with an odds ratio for developing VTE among travellers of 3.98 (95% CI = 1.9 to 8.4).

3.3.2 COHORT STUDIES AND RANDOMIZED CONTROL TRIALS

Several cohort studies and randomized control trials have supported an association between air travel and VTE (*11,21–25*). Two of these studies (*24,25*) recruited patients who had responded to media advertisements and thus represented a self–selected group. Schwarz et al. concluded that long–haul flights of eight hours or more doubled the risk of calf muscle venous thrombosis (*25*). However, flight–related thrombosis occurred only in those who had established risk factors for thrombosis. A randomized control trial by Belcaro et al. was designed to evaluate the incidence of DVT occurring as a consequence of long flights (*21*). The study recruited 355 subjects at low risk of DVT and 389 at high risk who travelled by air for an average flight duration of 12.4 hours. DVT diagnosis was made by ultrasound scans after the flights. While no events were record-

ed in low–risk subjects, 11 of the high–risk subjects had DVT (2.8%), with 13 thromboses in 11 subjects and 6 superficial thromboses (total of 19 thrombotic events in 389 patients [4.9%]). Another randomized control trial by Scurr et al. showed that symptomless DVT could occur in up to 10% of long–haul airline travellers aged over 50 years (*11*). A total of 231 passengers with no history of thromboembolic problems were randomly allocated to either wearing elastic compression below knee stockings or not wearing stockings; all passengers travelled for over eight hours. Of the 116 passengers who did not wear stockings, 12 developed symptomless DVT in the calf. Two of these were heterozygous for factor V Leiden. None of the passengers who wore stockings developed DVT, however, the high incidence of VTE reported in this study has been questioned in view of the potential bias associated with unblinded ultrasonographic assessment (*26–31*).

3.3.3 CROSS–SECTIONAL STUDIES

The time relations between long–haul air travel and VTE have been investigated in a record linkage study in which data for 5408 patients admitted to hospital with VTE were matched with data for international flight arrivals during the period 1981–1999 (*32*). The risk of VTE was only increased for the two weeks following a long–haul flight. The relative risk during this period was 4.17 (95% CI = 2.94 to 5.40), with 76% of cases (n = 35) attributable to a preceding flight. The study concluded that the annual risk of VTE is increased by 12% if one long–haul flight is taken per year.

3.3.4 REVIEWS

A systematic review (*33*) identified 254 studies that estimated the risk or incidence of DVT related to travel. Only six incidence studies and four risk studies met the selected inclusion criteria. The incidence of symptomatic DVT ranged from 0 % to 0.28%, and incidence of asymptomatic DVT ranged from 0% to 10.34%. The pooled odds ratio for the two case–control studies examining the risk of DVT following air travel was 1.11 (95% CI: 0.64 to 1.94). The pooled odds ratio for all modes of travel, including two studies of prolonged air travel (more than three hours), was 1.70 (95% CI: 0.89 to 3.22). Consequently, it was concluded that there was no definitive evidence that prolonged travel of more than three hours, including air travel, increases the risk of DVT, but that there was evidence to suggest that flights of eight hours or more increase the risk of DVT if additional risk factors exist.

Available information on the association of air travel and DVT is conflicting. Some studies have concluded that that there is no firm evidence that the risk of DVT increases with air travel (*33,34*), while others have reported increased risk only in the presence of other risk factors (*35,36*), and/or only if travel duration is over 10 hours (*37*).

3.4 Predisposing factors for VTE related to air travel

Many studies and reports have suggested that any association between air travel and VTE is relevant mainly to those who already have predisposing risk factors (*35,38–49*). In one extensive review, 72% of patients with air travel–related VTE were reported to have coagulation defects (*42*). A case–control study by Martinelli concluded that while there is an overall 2–fold increase in risk of thrombotic disease associated with air travel, the risk of VTE increased significantly in the presence of thrombophilia and/or oral contraceptive use (*45*). Stratification of

data for thrombophilia and oral contraceptive use (*45*) yielded 16– and 14–fold increases in risk, respectively. In a prospective study by Arfvidsson, 23 of the 25 patients who had air travel–related VTE had one or more patient–related risk factors, with an average of three risk factors per patient (*44*). Similarly, a cohort by Arya et al. examined the risk factors in 568 patients with suspected DVT (*35*). Although no significant link was found between DVT and long–haul travel (odds ratio 1.0, 95% CI 0.6 to 2.8), there was an increased risk if additional risk factors were present (odds ratio 3.0, 95% CI 1.1 to 8.2).

Many reports and studies have proposed possible passenger–related and cabin–related risk factors that accentuate or lead to VTE (*38,39,45,47–52*). Possible cabin–related risk factors include prolonged immobility, cramped sitting position, low air pressure, relative hypoxia, low humidity and dehydration due to the consumption of alcohol and other diuretics such as tea and coffee. With respect to passenger–related factors, it was noted by the House of Lords Select Committee on Science and Technology that up to 20% of the total population may have some degree of clotting tendency (*53*). Given that about two billion passengers use air travel every year, this suggests a significant potential for incidents of DVT. Recognized passenger–related predisposing factors include overweight, chronic heart disease, other chronic diseases, hormone therapy, malignancy, previous VTE, family history of VTE, recent surgery or trauma, age over 40 years, pregnancy, puerperium, chronic venous insufficiency and hereditary hypercoagulability.

In a group of 20 men exposed to eight hours of hypobaric hypoxia equivalent to an altitude of 7874 feet, Bendz et al. observed a significant increase in coagulation markers, namely TAT (thrombin–antithrombin complexes), F1+2 (prothrombin fragments 1 and 2) and FVII antigen and tissue–factor–pathway–inhibitor, but no change in D–dimer (*54*). However, this study has been criticized for its lack of controls and the fact that its baseline TAT and F 1+2 levels were abnormally high. It is still accepted that Virchow's triad of endothelial lesion, venous stasis and hypercoagulability are important factors predisposing to the venous thrombosis. Various conditions during long–haul air travel may give rise to the factors included in this triad (*53, 55–57*).

Although the totality of the above evidence suggests that there is an association between venous thrombosis and air travel, there are many issues that require clarification. These include the strength of the association, the underlying mechanism that increases the risk, whether the risk is increased after air travel only or after long–distance travel in general, and the effect of combinations of other risk factors on venous thrombosis and travel.

4. MAIN STUDIES AND RESULTS OF WRIGHT PROJECT

4.1 Epidemiological studies

4.1.1 POPULATION–BASED CASE–CONTROL STUDY

A case–control study was conducted to determine whether the risk of VTE is increased by air travel. This study replaced a planned case–crossover study among carriers of frequent flyer cards who had made one to five long–haul flights in one year. These were to be selected from the database of participating airlines, including 100 000 to 150 000 individuals to detect 150 who had developed thrombosis in the one–year window. Subsequently, a detailed questionnaire would elicit information about travel in a risk period prior to the thrombotic event, to be compared to the exposure to travel in a similar time window preceding the date of thrombosis minus one year. The advantage of this approach was that confounding features would be ruled out because cases acted as their own controls. However, a pilot study of 100 such passengers, which was conducted to examine whether response would be sufficient to yield reliable results, produced less than 50% responses . Because this low response rate might easily lead to biased and, therefore, unreliable results, and because of logistic problems in cooperating with the airlines, the original full study was dropped and a new study was designed.

The new study was designed as a very large population–based case–control study, which was an extension of an ongoing project (MEGA: Multiple Environment and Genetic Assessment of risk factors for venous thrombosis), which was designed to study interaction of abnormalities in the blood in the etiology of thrombosis. Therefore, DNA and blood plasma sample measurements were integral parts of the study.

The study included 1906 patients aged less than 70 years, presenting to one of six anticoagulation clinics in the Netherlands with a first VTE along with the same number of closely matched controls (n=3812 in total). Cases of VTE were verified with hospital records and only objectively diagnosed cases were included in the analysis. Information was collected by questionnaire on acquired risk factors, and genetic risk factors for VTE were determined on a blood sample. The combined effect of travelling and the risk factors for thrombosis (factor V Leiden, prothrombin 20210A mutation, body mass index [BMI] and height) was assessed.

Of 1906 patients, 233 (12%) had travelled for more than four hours in the eight weeks preceding the index date (diagnosis of the first VTE), as compared to 182 among control subjects (9.5%). Travelling for more than four hours increased the risk of VTE 2–fold (odds ratio 2.1, 95% CI 1.5 to 3.0), compared to not travelling. The risk increase was similar for any form of travel and was highest during the first week after the travel, but remained increased

for two months. The risk of flying was similar to the risk of travelling by car, bus or train. Travel by car, bus or train led to a high risk of thrombosis in individuals with factor V Leiden mutation (odds ratio 8.1, 95% CI 2.7 to 24.7), those who were more than 1.90m tall (odds ratio 4.7, 95% CI 1.4 to 15.4) and those who used oral contraceptives (estimated odds ratio >20). These synergistic effects were more apparent with air travel. In addition, people shorter than 1.60m had an increased risk of VTE after air travel only (odds ratio 4.9, 95% CI 0.9 to 25.6). Obese individuals with a BMI of more than 30kg/m2 had an increased risk. The more pronounced risk increase observed after air travel compared to ground travel for some of these risk factors may suggest an effect of flight–related factors, which are absent during travel by other modes of transport.

4.1.2 INCIDENCE STUDIES

These studies evaluated cohorts from groups who flew frequently for their work so as to determine the actual risk.

Retrospective cohort study among employees of international organizations

This was a retrospective cohort study among employees of international companies and organizations. Data concerning the occurrence of VTE, risk factors for VTE and habits during air travel were linked to the organization's travel database. Exposure was defined as four weeks after a flight of four hours or longer. A total of 267 241 flights were included in the analysis, of which 86 748 were of more than four hours duration. The response rate was 45% as of August 2005. The total follow–up time for all respondents was 31 158 person–years, of which 27 568 person–years were unexposed time (i.e. not four weeks or less after a flight) and 3594 person–years of observation were exposed time (i.e. four weeks or less after a flight).

The incidence of VTE after a flight was 4.0/1000 persons per year (95% CI 1.5 to 6.4), compared with 1.2/1000 per year (95% CI 0.6 to 1.7) in the non–exposed time. This yielded a relative risk of VTE after a more than four–hour flight of 3.45 (95% CI 2.3 to 5.1) in this population. The absolute risk of VTE per more than four–hour flight in this population was 1/5944 (95% CI 1/3433–1/12 714). The absolute risk was greater if multiple journeys were taken in the four–week exposure period, and increased with duration of flight, up to one per 1000 for flights of 12 hours or longer.

This study was performed with a cohort of employed individuals who tend to be younger and healthier than the general population in which the absolute risk per journey is therefore likely to be greater .

Dutch commercial pilots study

This was a retrospective cohort study with a total of 2499 professional pilots (response rate: 73% in current members and 33% in past members). Total observation time was 10 165 person–years. The participants were predominantly young males (35.8 years on average, 96.2% men); 6 VTE were diagnosed yielding an incidence of 0.3 per 1000 person–year (95% CI 2.2 to 13.1). When adjusted for age and sex difference, this rate was not different from the general Dutch population (standardized morbidity ratio 0.8 (95% CI 0.3 to 1.7). There was no association between the number of hours flown. Although these results excluded a high risk of thrombosis in pilots who fly very frequently, a mildly increased risk could not be ruled out since it is difficult to estimate the expected rate of VTE for this

exceedingly healthy group. The possibility of underreporting could not be ruled out due to the possible adverse effect that this history might have on the participants' careers.

4.2 Pathophysiological studies

4.2.1 HYPOBARIC HYPOXIA STUDY

It is generally accepted that prolonged immobility predisposes to VTE and that this may be an important factor in the causation of travellers' thrombosis. However, it remains unclear whether the risk associated with long–haul flight, where passengers encounter reduced cabin pressure and hypoxia, is different from other forms of transport or from prolonged sitting at ground level. This study was designed to determine whether exposure to hypobaric hypoxia at levels comparable to those encountered during commercial air travel promotes a hypercoagulable state that could predispose to VTE.

The study was conducted between September 2003 and 2005 in the United Kingdom, whereby a single–blind crossover design was used to compare the effects of prolonged sitting in a hypobaric hypoxic environment with those of sitting for the same period in a normobaric normoxic environment. The healthy volunteers were recruited by local advertisement and individuals were excluded if they or a first–degree relative had a history of VTE, or if they had taken anticoagulant or antiplatelet medication in the two weeks before the study. Individuals were screened for factor V Leiden G1691A and prothrombin G20210A mutation and excluded if they tested positive. After the exclusion, 73 healthy volunteers participated in the study and were assigned to one of three groups (Group I: individuals between the ages of 18 and 40 years without known risk factor of VTE, n=49; Group II: women between the ages of 18 to 40 years who were taking a combined oral contraceptive pill, n=12; Group III: individuals aged 50 years or older, n=12). All participants were exposed for eight hours in random order at least one week apart to both hypobaric hypoxia and normobaric normoxia, equivalent to the prevailing atmospheric pressure at an altitude of 2438m or at ground level, respectively. The exposures took place at the same time of day to control for circadian variations in the tested parameters. Blood samples were drawn before and after exposure to assess activation of haemostatic mechanisms. The main outcome measures were comparative changes in markers of coagulation activation, fibrinolysis, platelet activation and endothelial activation. Data were available for all assays on the primary outcome for at least 63 individuals.

As expected, arterial oxygen saturation, expressed as the mean of the hourly measurements, was significantly lower in all groups during the hypobaric exposure than during the normobaric exposure: mean differences of –3.2% (95% CI –2.8% to –3.6%) for Group I; –3.6% (95% CI –2.7% to –4.5%) for Group II; and –5.1% (95% CI –4.5% to –5.8%) for Group III, $p<0.001$ for each comparison.

Significant changes in several markers of coagulation activation and fibrinolysis were observed during the normobaric exposure, attributed to prolonged sitting and circadian variation. However, no significant difference was observed in the overall change of any marker between the normobaric and the hypobaric exposures: median difference of 0ng/ml (95% CI –0.3 to 0.30ng/ml) for TAT;

–0.02nmol/l (95% CI –0.03 to 0.01nmol/l) for prothrombin fragment 1+2; 1.38ng/ml (95% CI –3.63 to 9.72ng/ml) for D–dimer; and –2.00% (95% CI –4.00% to 1.00%) for endogenous thrombin potential. In the absence of an overall effect of hypoxia, an exploratory analysis was performed to assess whether some individuals might be hyper–responsive. Although the number of high responders was greater in hypobaria than in normobaria, the difference was less apparent when response of each individual to hypobaria and to normobaria was compared.

There was no evidence of platelet activation or responsiveness attributable to hypobaric hypoxia. Nor was there evidence of endothelial activation other than a small increase in soluble E–selectin after the hypobaric exposure, with a median difference in change of 1.87ng/ml (95% CI 0.76 to 3.69; p=0.01) for the pooled data. The median difference in change was greatest in Group III, 3.93ng/ml (95% CI 1.70 to 7.68; p=0.02). A similar trend was seen in Groups I and II but the changes were not significant (p =0.20 and 0.15 respectively).

Red blood cell count, white blood cell count, platelet count and haematocrit increased after both the normobaric and hypobaric exposures in all groups; however, no significant difference was seen between normobaric normoxia and hypobaric hypoxia.

In this study, no procoagulant changes attributable to hypobaric hypoxia were found. Although changes were observed in some parameters after sitting for eight hours in a hypobaric and hypoxic environment, no significant difference was seen between the responses to hypobaric hypoxia and to normobaric normoxia, other than a small increase in soluble E–selectin. The changes observed during both the hypobaric and normobaric exposures most likely reflect the combined effects of prolonged sitting and circadian variation in clotting parameters. Changes in some parameters such as prothrombin 1+2 fragment and D–dimers were consistent with known diurnal changes. Changes in other parameters that would not be expected from the usual circadian rhythm, such as the changes in factor VIIa and factor VIIIc, tissue plasminogen activator and prothrombin time, were presumed to be attributable to prolonged sitting.

While no evident interaction was observed in those at modestly increased risk of VTE due to oral contraceptive pill use and older age in this study, these subgroups were relatively small and possible interaction between genetically determined thrombophilia or other risk factors for thrombosis and hypoxia could not be ruled out.

The findings from this study do not support the hypothesis that hypobaric hypoxia of the degree that might be encountered during long–haul air travel is associated with prothrombotic alterations in the haemostatic system in healthy individuals at low risk of VTE.

4.2.2 TRAVEL AND NON–TRAVEL IMMOBILITY STUDY

This study aimed to disentangle the possible etiological factors involved in the promotion of the postulated hypercoagulability occurring during flight, and was designed to complement the study described in section 4.2.1. It aimed to determine whether the risk for VTE during a long–haul flight is increased as compared to non–travelling controls and whether the risk is related to immobility or other travel or cabin–related factors. The study used a crossover design in which volunteers were exposed to an

eight–hour flight and to two control situations comprising relative immobility on the ground and daily activity.

The study was conducted between 24 May and 10 July 2004 with healthy volunteers, some of who had risk factors for thrombosis such as the factor V Leiden mutation. Individuals with a history of previous VTE, recent surgery (within the preceding 12 weeks) or immobilization (including travel lasting more than four hours or any air travel), active cancer, any drug use except for oral contraceptives, pregnancy or puerperium, and disease affecting coagulation were excluded. Volunteers with factor V Leiden mutation were recruited by contacting 60 asymptomatic female carriers identified in a previous study (performed by screening 1083 students and employees aged 18 to 40 years at a university in the Netherlands and also by screening healthy employees at participating clinics). Volunteers without factor V Leiden mutation were recruited by advertisement. All participants were exposed to an eight–hour flight, an eight–hour movie marathon and eight hours of their usual daily activities, with at least two weeks between each exposure situation. On the day of each exposure, blood samples were drawn three times between 08:00 and 08:30, around 12:00 and between 16:30 and 17:30.

The study used 71 healthy volunteers aged 20 to 39 years, of whom 56 (79%) were female. Of these, 26 women were asymptomatic carriers of the factor V Leiden mutation; 30 women used oral contraceptives (15 with and 15 without the mutation). In this population, baseline median concentrations of thrombin–antithrombin complex (TAT) were similar for each exposure; however, they were higher after the flight (2.8µg/l, 95% CI 2.4 to 3.2) than after the movie marathon (2.2µg/l, 95% CI 1.9 to 2.5) or the daily life situation (1.7µg/l, 95% CI 1.6 to 2.0). Differences between the three after–values were significant ($p<0.0001$), suggesting a strong individual effect. Compared with baseline values, TAT level increased by 30.1% (95% CI 11.2 to 63.2), while it decreased by 2.1% (95% CI –11.2 to 14) after the cinema and by 7.9% (95% CI –16.2 to –1.2) after the daily life situation (circadian rhythm). This was most clearly seen in the subgroup of women with factor V Leiden mutation who also took oral contraceptives. The proportion of subjects who were identified as "high responders" with respect to TAT (>3SD) was highest after the flight compared to the other exposure situations: 16.7% (95% CI 8.6 to 27.9), 2.9% (95% CI 0.4 to 10.2), 1.4% (95% CI 0.0 to 7.7) after the flight, cinema and daily activity, respectively.

Median baseline value of prothrombin fragment 1+2 (F1+2) was higher before the cinema than before the other two exposures. The values after the cinema and the flight were similar (0.59nmol/l, 95% CI 0.56 to 0.63), but lower than after the daily activity (0.62nmol/l, 95% CI 0.58 to 0.66, p value for difference between three after–values: 0.05). No clear difference was observed between the F1+2 values after the three exposure situations within subgroups. The proportion of high responders was the highest after the flight: 9.1% (95% CI 3.4 to 18.7), 1.5% (95% CI 0.0 to 7.9), 1.4% (95% CI 0.0 to 7.7) for the flight, cinema and daily activity, respectively.

Median D–dimer level rose to 216µg/l (95% CI 182 to 240) after the flight, but decreased to 180µg/l (95% CI 155 to 211) after the cinema and did not change after the daily activity. The proportion of the high responders was the highest after the flight: 7.9% (95% CI 2.6 to 17.6), 1.5% (95% CI 0.0 to 7.9), 2.9% (95%

CI –0.4 to 9.9) for the flight, cinema and daily activity, respectively.

Individuals who showed high response to all three variables (TAT, F1+2, and D–dimers) were found after the flight (n=4, 6.3%), but not in other two exposure situations. The proportion of high responders was consistently highest for those volunteers who carried two risk factors.

These findings suggest that one or more flight–associated factors, possibly hypobaric hypoxia or the type of seating in the aeroplane lead to increased thrombin generation after air travel in some individuals, especially those with the factor V Leiden mutation who also took oral contraceptives. Higher response was observed for TAT and for the combination of an increase in TAT, F1+2, and D–dimer values after a flight than after a movie marathon or a period of normal daily activity. All three variables showed clotting activation to a certain extent after a flight, but TAT showed the most apparent change both in the group as a whole and in high responders. This could be explained by the shorter half–life of the TAT (10min vs 90min for F1+2).

This study included only young and healthy individuals with no history of VTE and the effect of flight in an older population or those with other risk factors should be investigated. Nonetheless, this study showed that coagulation and the fibrinolytic system are activated in some susceptible individuals after an eight–hour flight, suggesting that a mechanism, additional to immobilization, may play a part in air travel–related thrombosis.

5. CONCLUSIONS

The WRIGHT project had several goals:

- to confirm if the risk of VTE is increased by air travel;
- to determine the magnitude of the risk;
- to determine the effect of other factors on the association;
- to study the effect of interventions on risk.

To reach these goals, several studies were performed during Phase I of the WRIGHT project to investigate the magnitude of the risk, the effect of other factors on the risk and the mechanism by which air travel leads to VTE. The studies into the effect of interventions were deferred to Phase II.

The combined results from these studies provide a consistent picture in line with previous reports, which highlighted the possible link between air travel and VTE and a similar association for other types of travel. The data from this project enabled the investigators to quantify the risk by involving far greater numbers of individuals than were collected in previous publications and, furthermore, demonstrated the possible existence of individuals with an increased propensity to activation of the coagulation system during long–haul air travel.

The findings of the epidemiological studies indicate that the risk of VTE approximately doubles after a long–haul flight (>4 hours). The data also showed that this increased risk applies to other forms of travel (such as car, bus or train) where travellers are exposed to prolonged seated immobility. The risk increases with the duration of the travel and with multiple flights within a short period.

Obesity, extremes of height, use of oral contraceptives and the presence of prothrombotic blood abnormalities or variants were identified as contributors to the increased risk of travel–related VTE.

The absolute risk of VTE per more than four-hour flight, in a cohort of healthy individuals, was 1 in 6000.

The pathophysiological studies supported these findings. Hypobaric hypoxia is one of the factors that travellers will encounter during air travel but not during ground travel. The results of the hypobaric chamber studies with healthy volunteers predominantly without risk factors for VTE failed to demonstrate any association between hypobaric hypoxia (of a degree that might be encountered during commercial air travel) and prothrombotic alterations in the haemostatic system. However, the travel and non–travel immobility study, which included a high proportion of individuals with risk factors, such as the use of oral contraceptives and/or carriage of the factor V Leiden mutation, suggested that some flight–specific factor may interact with pre–existing risk factors and

result in increased coagulation activation in susceptible individuals over and above that related to immobility. Further study will be required to determine the identity of the culpable factors.

Each study had limitations, some of which have been indicated in the foregoing descriptions. Nonetheless, the findings of Phase I of the WRIGHT project demonstrated that the increased risk of VTE observed in long–haul travellers is due mainly to prolonged immobility. It is possible that there is an interaction between pre–existing risk factors and flight–specific factors, which may further increase the risk during air travel. In view of the substantial number of people undertaking long–haul air travel and the fact that many travellers will have one or more known or unknown risk factors for thrombosis, air travel–related VTE is an important public health issue. There is a clear need for travellers to be given appropriate information regarding the risks and for further studies to identify effective preventive measures, which will comprise Phase II of the WRIGHT project.

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ABSTRACTS:

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9. ACKNOWLEDGEMENTS

Phase I of the WRIGHT project was conducted under the auspices of the World Health Organization (WHO) and the International Civil Aviation Organization (ICAO), supported by an independent scientific committee and in collaboration with IATA and airline companies. The studies were partially funded by the United Kingdom Department for Transport, in collaboration with the Department of Health, and the European Commission.
Catherine Le Galès Camus, D. Yach, R. Bengoa are thanked for their advice. D. Abegunde, M. Nassef, K. Fukino, G. Verma, and F. Besson are thanked for their assistance.