Air travel and deep vein thrombosis

Introduction

The WRIGHT (**W**orld Health Organisation **R**esearch **I**nto **G**lobal **H**azards of **T**ravel) is a multi-centred multi-study project investigating the association between travel and venous thrombo-embolism (VTE), a term which covers deep vein thrombosis (DVT) and/or pulmonary embolism (PE).

The project was carried out according to the WRIGHT protocol, and overseen by the Scientific Executive Committee (SEC), consisting of Dr P J Kesteven (chairman), Dr W D Toff, Prof F Paccaud, Prof H R Büller, Prof M Greaves, Dr S Mendis and Prof F.R. Rosendaal.

The WRIGHT project was designed as a series of inter-related studies with the following aims:

- to determine if the risk of venous thrombosis is increased by air travel;
- to determine the magnitude of this risk;
- to determine the effect of other factors on the association;
- to clarify the causal mechanisms.

Furthermore, these studies were performed in several general settings which included clinical endpoints (i.e., symptomatic disease) and surrogate endpoints (i.e., markers of coagulation).

The studies were organised into two groups:

1. Epidemiological studies

MEGA study: Data were collected from consecutive patients, aged less than 70 years, presenting to 6 anticoagulation clinics in the Netherlands with a first VTE. Partners served as matched controls. Information was collected by questionnaire on acquired risk factors, and genetic risk factors for VTE were determined on a blood sample. Cases of VTE were verified with hospital records and only objectively diagnosed cases were included in the analysis.

Professional Flyers Study: a retrospective cohort study amongst employees of international companies and organisations. Data concerning occurrence of VTE, risk factors for VTE and habits during air travel were linked to the organisation's travel databases. Exposure was defined as 4 weeks after a 4 hour flight.

Dutch Commercial Pilots Study: A questionnaire was sent to all members of the Dutch Airline Pilots Association who were younger than 55 years on 31 December 2002. Data concerning occurrence of VTE, risk factors for VTE and flight data were included.

2. Patho-physiological studies

Chamber Studies: Forty nine healthy subjects with no known risks of VTE, and a further 24 subjects with mild risk (12 using oral contraception and 12 aged >50 years) were seated in low atmospheric pressure and low oxygen level conditions for 8 hours, simulating flight in a commercial airliner. As a control, the subjects also sat in an identical situation in normal atmospheric pressure and oxygen level. These studies were performed in random order. A large number of haemostatic variables were assessed (involving markers of activation of coagulation, endothelium, platelets and fibrinolysis) before and after these exposures.

Volunteer Study: In a similar study, 71 healthy volunteers flew in a chartered commercial airliner for 8 hours, with the same haemostatic variables assessed before, during and after the flight. Risks factors for venous thrombosis were more abundant in this group: 26 asymptomatic carriers of the factor V Leiden mutation and 30 women using oral contraceptives (15 with, and 15 without the mutation). Two control situations were used - 8 hours watching movies and 8 hours of normal day-to-day activity.

Results

MEGA Study

Of 1851 patients, 235 had travelled for more than 4 hours in the 8 weeks preceding the VTE. Travelling for more than 4 hours in any form of transport was found to increase the risk of VTE three fold (95%CI 2.0-4.2)[1]. The risk of flying was similar to the risk of travelling by car, train or bus. The relative risk of thrombosis rose sharply for travellers with factor V Leiden mutation (as well as some other prothrombotic coagulation variations); those using oral contraception; in those who travelled for >12 hours; and for those who were >1.90m tall. Some of these synergistic effects were more pronounced in air travel than for other modes of travel.

Professional Flyers Study

The number of long-haul flights in the 45% responses (9953 employees) was 59438; and 29 probable VTEs occurred in the follow up period, 10 of which occurred in the 4 weeks after a flight.

The design of this study allowed the calculation of relative and absolute risks. A relative risk indicates how much higher the chance of disease is for those with the risk factor (in this study: flights of more than 4 hours in the previous 4 weeks) compared to those without. The absolute risk indicates the actual probability of disease, i.e. what proportion of these travellers will actually develop thrombosis.

The incidence of VTE after a flight was 4.0/1000 persons per year (py) (95%CI 1.5-6.4); compared with 1.2/1000 py (95%CI 0.6-1.7) in the non-exposed time. This yielded a relative risk of VTE after >4 hr air journey of 3.45 (95%CI 2.3-5.1), in this population.

The absolute risk of VTE per >4 hour air journey in this population was 1/5944 (95%CI 1/3433 - 1/12 714).

The absolute risk was greater if multiple flights were taken in the 4-week exposure period, and increased with duration of flight, up to one per 1000 for the longest journeys.

Comment. There has been only a 45% response rate, so far. However, data have now been collected on more than 100,000 flights >4 hrs (i.e. double the number reported here) which should strengthen these results. It should be noted that this study was performed with subjects who were in employment, which generally is a group that is healthier and younger than the whole population. Hence, the risk of thrombosis per journey may be somewhat higher when the general population is considered (estimate from the MEGA study: 1 per 2000 journeys of over 4 hours).

Dutch Commercial Pilots Study

Response rate was 73% in current members (2364/3657) and 33% in retired members (135/411). Six VTE were diagnosed yielding an incidence of 0.3/1000 py. This gives a lower incidence than for the whole general population, which is estimated at 1-2 per 1000 per year. The risk did not appear to be associated with hours flown.

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[1] 95%CI = 95% Confidence Interval.

Comment. There may have been some under-reporting due to the adverse effect this history might have on the pilot's career prospects. Furthermore, because of the frequent and rigorous medical examination requirements of commercial pilots, it is sensible to assume that this sub-group is healthier than the general population. So, while these study results are compatible with either a mildly reduced or increased risk, they exclude a very high risk among these very frequent flyers.

Chamber Studies

No significant difference was observed in any of the haemostatic parameters between the two test situations.

Comment. These subjects were screened to exclude factor V Leiden and any other risk factor for VTE, with the exception of those using oral contraception or aged >50 years. Since the test situations were applied in random order, at the same time of day, the effect of diurnal variations of the haemostatic markers was controlled.

Volunteer Study

Overall, taking the results of the whole group, there was no significant change in haemostatic markers. Some coagulation markers tested (thrombin-antithrombin complex and D-dimer) showed elevations after the flight compared to baseline (and diurnal variation). Analysis of these data showed that there was a small group (approximately 10%) who were coagulation hyper-responders in the flight situation. All were female, most of whom had one or both of the risk factors (factor V Leiden and oral contraceptives).

Comment. This study appears to demonstrate a minority whose clotting system hyper-responds during flight. All were female and most carried other risk factors for VTE. Some caution needs to be exercised in concluding what, in this experimental situation, gave rise to this hyper-response, i.e. hypoxic hypobaria or other flight-related factors.

Summary

The combined results from this group of studies provide a consistent picture, in line with previous medical literature on travellers' thrombosis. However, these data strengthen this picture in as much as far greater numbers have been involved in these studies than ever collected in previous publications. Furthermore, they make a large contribution to fleshing out the specific individual risks of this complication.

As previously suspected, it is clear from the epidemiological studies that seated immobility is a risk factor for VTE. When considering the whole population, this risk appears to be small (approximately three-fold increase) and to be present whatever form of travel. These studies confirm that the longer the period of travel, the greater the risk. Multiple flights in a short period probably reflect the same phenomenon.

The epidemiological studies also highlighted the fact that the relative risk of travellers' thrombosis increases sharply if other risks for VTE are present.

These results are supported by the patho-physiological studies. Taken overall, there were no changes in any coagulation parameters during an 8-hour flight or during a similar period of hypobaric hypoxia in a hypobaric chamber (compared to control situations). Careful analysis of the data from the Volunteer Study (which included subjects at increased risk for VTE) demonstrated a small population of 'hyper-responders'. This was not so obvious in the Chamber Studies (in which only subjects at low or modestly increased risk for VTE were included).

The WRIGHT Project Scientific Executive Committee

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