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Air travel and venous thrombosis. Results of the WRIGHT study. Part II: Mechanism

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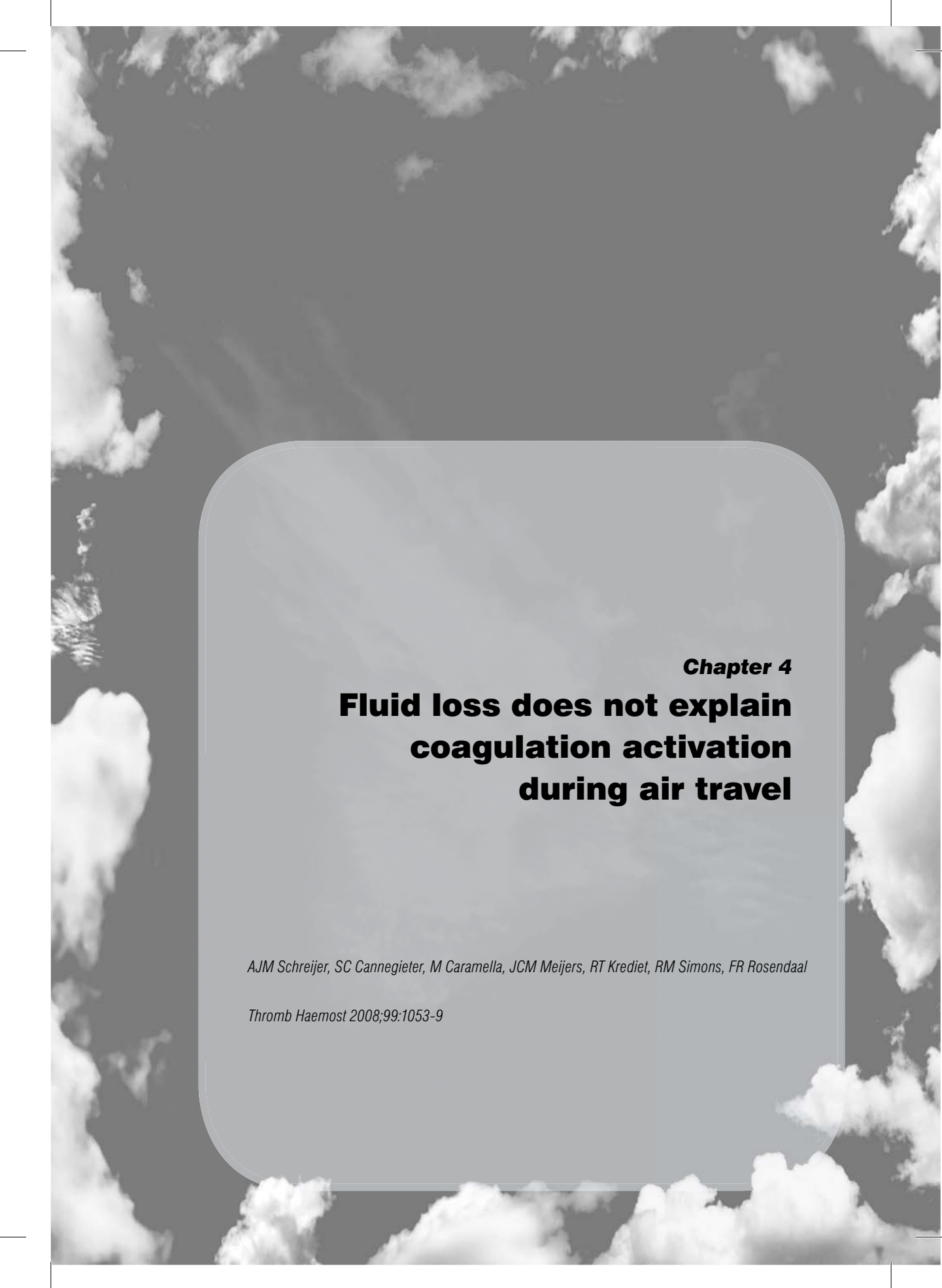
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Chapter 4
**Fluid loss does not explain
coagulation activation
during air travel**

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Summary

The mechanism of air-travel-related venous thrombosis is unclear. Although immobility plays a pivotal role, other factors such as fluid loss may contribute. We investigated whether fluid loss occurred more in individuals with coagulation activation after air-travel than in subjects without. As a secondary aim, we investigated whether fluid loss per se occurred during air-travel.

In this crossover study, 71 healthy volunteers were exposed to 8-h of air-travel, 8-h immobilization in a cinema, and a daily-life control situation. Markers of fluid loss (haematocrit, serum osmolality and albumin) and of coagulation activation were measured before and after each exposure. The study included 11 volunteers with and 55 volunteers without coagulation activation during the flight.

The change in parameters of fluid loss was not different in volunteers with an activated clotting system from those without (difference between groups in haematocrit: -0.6%, CI95: -1.9 to 0.6). On a group level, mean haematocrit values decreased during all three exposures. However, in some individuals it increased, which occurred in more participants during the flight (34%; CI95 22 to 46) than during the daily life situation (19%; CI95 10 to 28).

These findings do not support the hypothesis that fluid loss contributes to thrombus formation during air-travel.



Introduction

The complete mechanism of the increased risk of venous thrombosis after air travel is unclear (1-3). Although immobility undoubtedly plays a major role (4;5), we recently showed that clotting activation occurs more often during air travel than during immobilized or ambulant circumstances at sea level (6). In that study, 11 (17%) out of 66 volunteers showed evidence of clotting activation after a long haul flight, compared to two (3%) out of 68 volunteers after a movie marathon and one (1%) out of 70 volunteers after a day with normal activities. One of the cabin related factors that has been assumed to contribute is dehydration due to the low humidity in aircrafts or to consumption of diuretic beverages containing alcohol or caffeine (7;8). At average cruising altitudes of 10.000 meters, the humidity of the air delivered by the aircraft environmental control system is low (< 1%) and the only sources of additional moisture come from respiration and perspiration of passengers and crew. A review of studies showed that mean humidity levels in aircraft cabins ranged from 14-19% at average temperatures of 23-24 OC (9). During long haul flights, humidity is generally lower. In a study of 18 long haul passenger flights, the mean cabin relative humidity was 10.3% (range 5.5-27.5%) (10). For comparison: relative humidity at sea level in moderate climates ranges from 40-60% in buildings to 70-90% outdoors.

On the basis of this low humidity, airlines and physicians advise travellers to drink large amounts of water to prevent air travel related venous thrombosis (11-14). However, for this advice to be sensible one has to assume that air travel causes fluid loss and that fluid loss leads to venous thrombosis. Neither has been convincingly demonstrated.

Fluid loss can be divided into dehydration (pure water loss, mainly of intracellular origin) and volume depletion (loss of water and salt, primarily of intravascular origin), as with vomiting, diarrhoea and diuretic use (15). In case of dehydration, haematocrit, albumin and plasma osmolality all increase. When volume depletion (including oedema formation) occurs, only protein-free filtrate leaves the circulatory system and thus the intravascular volume decreases, reflected by increases in haematocrit and albumin (16). Plasma osmolality is primarily determined by Na⁺ salts and regulated by changes in water intake (caused by the sensation of thirst) and excretion resulting from changes in argininevasopressine (formerly antidiuretic hormone) (17). Osmolality is not affected by oedema formation, since salts can freely pass the vessel wall. A discrepancy in changes in haematocrit and albumin on the one side and osmolality on the other side can therefore distinguish between dehydration (caused by pure water loss) and volume depletion.



Only few studies focused on fluid loss during (simulated) air travel and they showed conflicting results. Some found an increase in osmolality (18;19) or viscosity (also reflected by increases in haematocrit) (20) or a reduction in plasma volume (the reciprocal of haematocrit) (21;22). In contrast, in other studies haematocrit and hemoglobin did not increase or sometimes even decreased during (simulated) air travel (23-26). Others investigated the effect of immobilisation alone on parameters of dehydration (5;8;27;28), and also reported inconsistent results. During immobilisation capillary pressure can exceed plasma colloid osmotic pressure causing filtration of fluid from the circulating plasma (i.e. oedema) (8).

Fluid loss is not an established risk factor for venous thrombosis, and has only been associated with an increased risk under specific circumstances (29-32). However, one could hypothesize that fluid loss could change blood viscosity and hence predispose to venous thrombosis. Severe hyperviscosity (e.g. in polycythemia vera) is a risk factor for venous thrombosis (especially hepatic vein thrombosis). However, there are factors other than hyperviscosity present in polycythemia vera that may cause venous thrombosis, since this disease fulfills Virchow's triad for thrombosis by perturbing the vessel wall, blood flow, as well as elements of the coagulation system (33).

With this crossover trial, we aimed to ascertain whether fluid loss, as determined by haematocrit, albumin and serum osmolality, could explain the activation of the clotting system that we found in 17% of the volunteers after a long haul flight. As a secondary aim, we investigated whether fluid loss per se occurred during a long haul flight.

Material and methods

Study design

We exposed 71 healthy volunteers to three situations: a long distance flight, immobilisation during a movie marathon and a day with normal activities. The primary goal of the study was to ascertain whether air travel leads to coagulation activation. The details of this design were described elsewhere (6). All exposures lasted 8 hours and were separated by at least 2 weeks. Blood samples were collected at the same time, before, during and after each exposure. This way, the effects of immobilisation and circadian rhythm were accounted for. We flew without stopovers from and to the same airport to avoid potential interference due to time zone differences, jetlag and vaccinations.



Participants were not allowed to smoke, drink alcohol, take drugs or use precautions for deep vein thrombosis such as heparin, aspirin or stockings during the exposures. The number of drinks and toilet visits during each of the three exposures was reported by the participants with the use of a questionnaire. For the cinema and daily life situation, participants were asked to roughly adjust their drinking and eating behaviour to the amounts consumed during the flight exposure, which was the first of the three.

Volunteers

We included the participants after a medical, family and drug history was taken. Exclusion criteria were previous venous thrombosis, recent surgery or immobilisation (including travel >4 hours and any air travel), active cancer, any drug use except oral contraceptives (OC), pregnancy or puerperium and other co-morbidity that may influence coagulation. We recruited volunteers of whom many had risk factors for venous thrombosis (factor V Leiden mutation and oral contraceptive use). The study was approved by the medical ethics committee of the Academic Medical Center, Amsterdam and all participants gave written informed consent.

Assays and laboratory methods

Blood sampling took place between 0800 and 0830, around noon, and between 1630 hrs and 1730 hrs on each exposure day. Haematocrit, albumin and osmolality were measured before and after each exposure, while coagulation parameters were measured at all three time points. Mean cell volume and red blood cell concentration (from which haematocrit was calculated) were measured from EDTA blood, osmolality and albumin from serum and coagulation parameters from citrated plasma.

Blood samples were collected from the antecubital vein after overnight fasting by trained lab technicians. Citrate blood was centrifuged within 15 minutes after withdrawal twice at 2500g for 15 minutes at 15° C. Serum was obtained from non-anticoagulated blood after this was centrifuged once at 2500g for 15 minutes. Serum and plasma were immediately stored at -80° C. The assays were performed after all participants had completed the full study. Haematocrit (%) was calculated from the red blood cell concentration (RBC) and the mean corpuscular volume (MCV), as: $MCV (fL) \times RBC (10E12/L) / 1000 \times 100\%$. MCV and RBC were measured by the impedance method on a Cell-Dyn 4000 haematology analyzer (Abbott Diagnostics, Santa Clara, CA.). Albumin was determined by the BCG-method, a colorimetric assay on the Modular P800 (Roche Diagnostics, Basel, Switzerland). Osmolality was measured by determination of the freezing point



depression (OSMO station, Menarini). Thrombin-antithrombin complexes (TAT), prothrombin fragments 1 and 2 (F1 +2) and D-dimer were determined by methods described elsewhere (6).

Statistical analyses

The data were explored on a group and an individual level. Results were expressed as means with their 95% confidence limits (CI95). Absolute changes were calculated for each individual by subtracting the pre-exposure value from the post-exposure value. Based on the relative change in thrombin antithrombin complexes (TAT) during the flight, 66 volunteers (71-5 volunteers in whom the change in TAT was missing) could be divided into volunteers with (n=11) and without (n=55) an activated clotting system. For each parameter we compared the absolute change during the flight of volunteers with an activated clotting system (also called high-responders) to that of volunteers without clotting activation by independent t-test. Furthermore, the change in parameters of fluid loss of the whole group during the flight was compared to that during the movie marathon and that during the daily life situation (by paired t-test). Proportions and their CI95s were calculated. Relations between fluid loss and coagulation factors were analyzed by linear regression after viewing the data in scatter plots.

Results

General

The flight took place on May 24th 2004, between 08.30 and 16.19 hrs. 71 healthy volunteers aged 20-39 years participated in the study, 56 (79%) of whom were women (Table 1). Each volunteer returned for each stage in the study as planned.

Because of unsuccessful blood collection 10 samples were missing. There were 68 blood samples available before the flight, 67 after the flight, 69 before the cinema and 70 after the daily life situation. After the cinema and before the daily life situation there were no missing blood samples (n=71).

Overall, fluid intake was similar during the three exposures (Table 2), with most participants drinking 4-6 drinks. We also analysed drinking behaviour on an individual level (Wilcoxon signed rank test) and found no difference between drinking behaviour during the flight and the cinema situation or the daily life situation. However, volunteers drank more during the cinema than during the daily life situation.



Table 1. Characteristics of the 71 volunteers.

Characteristic	Mean (range) or proportions (%)
Age (years)	28 (20-39)
BMI (kg/m ²)	23.0 (18-33)
Sex (ratio and % women)	56/71 (79%)
Use of OC	30/56 (54%)

Body Mass Index (BMI) is calculated by weight/height². OC=Oral Contraceptives.

Table 2. Consumption of non-alcoholic drinks during each of the exposures*.

Drink category	Flight	Cinema	Daily life
<2 drinks	4%	1%	6%
2-4 drinks	13%	11%	21%
4-6 drinks	51%	49%	37%
>6 drinks	32%	38%	34%

* Using the Wilcoxon signed rank test we found that volunteers drank more during the cinema than during the daily life situation ($p=0.012$). No differences were found between the other situations.

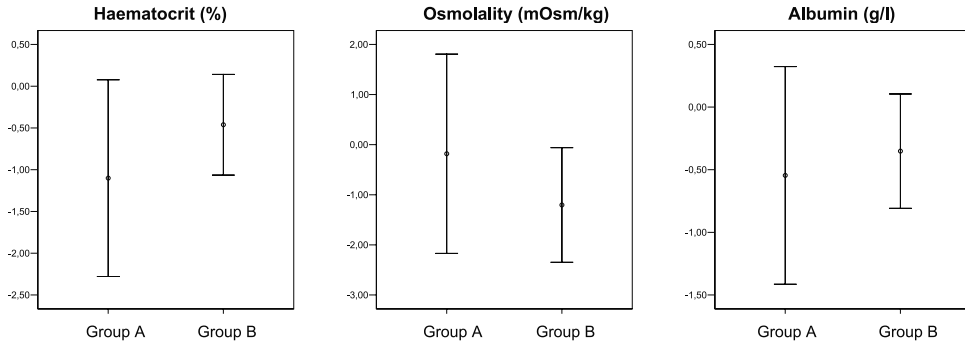
Fluid loss in volunteers with and without clotting activation after the flight

Haematocrit decreased to a similar extent during the flight in both groups: the absolute change was -1.1% (-2.3 to 0.1) in subjects in whom coagulation activation occurred after the flight, compared to -0.5% (-1.1 to 0.1) in volunteers without an activated clotting system (Figure 1, difference between groups: -0.6% (CI95: -1.9 to 0.6)). The change in osmolality was -0.2 mOsm/kg (CI95: -2.2 to 1.8) for subjects with clotting activation and -1.2 mOsm/kg (CI95: -2.3 to -0.1) for those without (Figure 1), indicating no difference (difference: 1.0 mOsm/kg; CI95: -1.2 to 3.2). The absolute change in albumin during the flight for subjects with clotting activation (-0.6 g/L; CI95: -1.4 to 0.3) was also comparable to that of those without (-0.4 g/L; CI95: -0.8 to 0.1, figure 1, difference:-0.2 g/L; CI95: -1.1 to 0.8).

We analysed the association between levels of haematocrit after each exposure with the corresponding levels of TAT, F1+2 and D-Dimer by linear regression and did not find an association. Figure 2 shows that individuals who had evident increases in haematocrit were not the same as those who showed strong changes in TAT levels (or changes in F1+2 or D-dimer levels, which occurred in roughly the same individuals). Changes in albumin and osmolality were also not associated with coagulation activation.

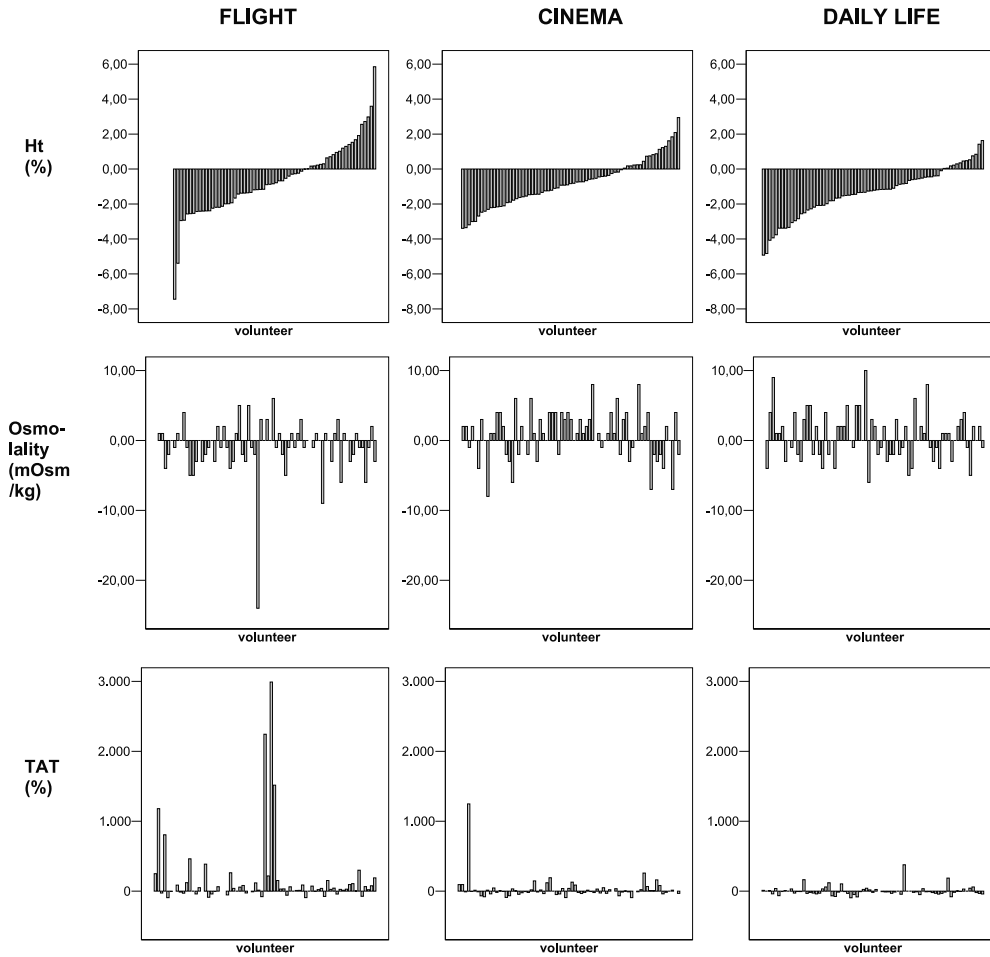


Figure 1. Absolute change in hydration state during air travel in volunteers with and without coagulation activation.



Group A consists of volunteers with coagulation activation and group B consists of volunteers without coagulation activation. Errorbars show means and CI95.

Figure 2. Individual data of absolute changes in haematocrit during the three exposures compared to osmolality and TAT.



Order of bars (individuals) consistent for each exposure. Change in TAT is relative change (%), change in Ht (%) and osmolality (mOsm/kg) are absolute changes.



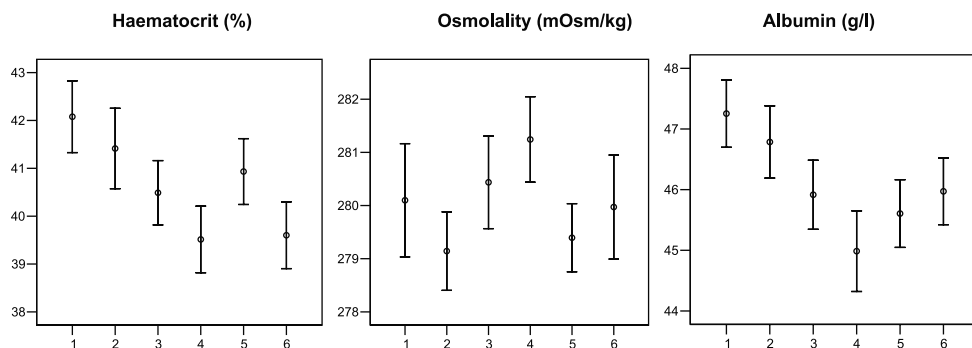
Fluid loss after the flight as compared to cinema and daily life

Mean haematocrit levels (normal range 38 to 45% in women and 41 to 49% in men) were higher before the flight than before the other situations (Figure 3). After the flight, mean values were also higher (41.4%, CI95: 40.6% to 42.3%) than after the cinema (39.5%, CI95: 38.8% to 40.2%) or daily life situation (39.6%, CI95: 38.9% to 40.3%, figure 3). On average haematocrit values decreased over the day during all three exposures (Figure 3). However, in some individuals it increased, and this occurred in more participants during the flight (22/64, 34%; CI95: 22 to 46%) than the cinema (18/69, 26%; CI95: 16 to 36%) or ordinary day (13/70, 19%; CI95: 10 to 28%, figure 2).

Mean osmolality levels (normal range: 275-295 mOsm/kg) increased during the course of the exposure in the cinema and the daily life activities, but decreased during the flight. Since mean osmolalities were similar before the three exposures, they were lower after the flight (279 mOsm/kg, CI95: 278 to 280) than after the cinema (281 mOsm/kg, CI95: 280 to 282) or daily life situation (280 mOsm/kg, CI95: 279 to 281 figure 3). Osmolality increased in more participants during the cinema (41/70, 59%; CI95: 47 to 71%) and daily life situation (35/71, 49%; CI95: 37 to 61%) than during the flight (23/70, 32%; CI95: 21 to 43%). These were not the same participants as those in whom haematocrit increased (Figure 2).

Mean albumin levels (normal range: 35-50 g/L) decreased during the flight and cinema exposure, and slightly increased during the daily life blood exposure. Baseline albumin levels followed the pattern observed for haematocrit, with higher values before the flight than before the other two exposures. Albumin levels were higher after the flight (46.8 g/L, CI95: 46.2 to 47.4) than after the cinema (45.0, CI95: 44.3 to 45.7) or daily life situation (46.0, CI95: 45.4 to 46.5, figure 3). Albumin increased in more participants after the daily life situation (36/71, 51%; CI95: 39 to 63%) than after the flight (17/70, 24%, CI95: 14 to 34%) or movie marathon (12/70, 17%; CI95: 8 to 26%).

Figure 3. Haematocrit, osmolality and albumin before and after the flight, the cinema and the daily life situation.



Errorbars show means and CI95. 1=before the flight, 2=after the flight, 3=before the cinema, 4=after the cinema, 5=before the daily life situation, 6=after the daily life situation.



Discussion

We compared changes in hydration state between volunteers with and without an activated coagulation system and found no difference. Also, we found no relationship between hydration parameters and TAT, F1+2 and D-dimer. Therefore, our results do not support the hypothesis that changes in hydration level trigger coagulation activation. When we compared fluid loss in all volunteers after an 8-hour flight to that after 8-hour exposure to immobilisation or daily life activities, we found that haematocrit decreased during the course of a day in all three exposures with the smallest decrease during 8 hours of air travel. Consequently, the proportion (34%) of individuals in whom haematocrit increased was highest during an 8-hour flight.

Fluid loss due to the low humidity within the aircraft cabin is often assumed to be involved in the pathogenesis of venous thrombosis after air travel. There are two conditions that have to be fulfilled for fluid loss to cause air travel related thrombosis: first, there has to be a relationship between fluid loss and thrombin generation; secondly, fluid loss actually has to occur during air travel. As we found that fluid loss was not associated with coagulation activation, the first condition seems very unlikely. Whether or not the second condition occurs could not be answered conclusively from this study. Although haematocrit values decreased during all three exposures, fluid loss occurred in more subjects during air travel than during the ambulant situation. However, in general there is no evidence for the theory that exposure to a low humidity environment (even in the nude) can lead per se to dehydration (34).

Several studies investigated changes in hydration state during (simulated) air travel and during sole immobilisation, but with conflicting results (5;8;18;20;22-28). There are explanations for these discrepancies. Firstly, different parameters for fluid loss were used. Some studies measured osmolality, which is not affected by oedema formation. Others measured plasma volume or haematocrit but could not distinguish between reasons for fluid loss (dehydration and volume depletion as in oedema formation). We measured haematocrit, albumin and osmolality in order to disentangle pure dehydration from other causes of fluid loss, such as oedema formation. Secondly, several studies were small and did not take circadian variation of parameters into account. Our study size was large and we had effects of circadian rhythm (daily life) and immobilisation (cinema) accounted for. Discrepancies between other studies can also be explained by differences in duration of exposure and differences in altitude levels, which are both related to the relative humidity. Also, in some studies, fluid intake was tightly controlled, while we allowed participants to drink freely during the flight, corresponding with



the normal situation during air travel. Lastly, most studies presented data at a group level which consequently diluted individual effects. We studied both group patterns as well as individual changes.

When we compared exposure to an 8-h flight to exposure to immobilisation only or to daily life activities, we found a discrepancy between changes in haematocrit and osmolality. Haematocrit decreased less during the flight compared to the daily life situation, whereas osmolality decreased during the flight and hardly changed over a day of normal activities. From an individual perspective, haematocrit increased in more participants during the flight than the daily life situation, while osmolality increased in more participants during the daily life situation. These observations suggest that pure water loss (i.e. dehydration) does not occur during air travel, but that isotonic fluid loss from the vasculature does occur. An obvious explanation for this fluid loss is oedema formation during air travel. In oedema, protein free fluid leaves the circulatory system, with an increase in haematocrit and albumin, while osmolality remains constant. Besides this discrepancy between haematocrit and osmolality, we observed that osmolality decreased more during the flight than during the other situations. This suggests overconsumption of fluid during the flight, i.e., the volunteers drank more than necessary for maintaining isotonicity. It is unclear whether this was due to a greater urge to drink, or to the widespread belief that a large fluid intake during air travel is beneficial. This idea is possibly reinforced by the sensation of dry eyes and dry skin during air travel. Albumin showed a similar pattern as haematocrit, except for the daily life situation in which it slightly increased while haematocrit decreased. This could be due to the higher activity level during the ambulant situation than the seated ones, during which albumin is known to increase (35).

One of the limitations of our study is that the mean baseline haematocrit value was higher before the flight than before the two control situations. This may reflect a more strict commitment to fasting instructions before the flight (which was the first exposure of the three) than before the other situations. Of the individuals with high haematocrit levels before the flight, many also had high levels after the flight (data not shown). To solve this, we used changes in parameters for the analyses, rather than just post exposure values. Another limitation is that we did not measure leg circumference to assess oedema formation in order to explain changes in parameters of fluid loss. Finally, the amount of fluid intake was not imposed, hence we do not know what would have happened when individuals who drank copiously had drunk less and vice versa.

Although for logistical reasons humidity levels could not be assessed, it is justifiable to assume that onboard relative humidity levels in our study were well within the range of average relative levels provided by the literature (9;10). The



study flight had all the characteristics of a long haul flight and was carrying only 91 passengers, whereas the maximum capacity of the aircraft was 220 passengers. Therefore, the quantity of additional moisture produced by the passengers on the study flight will have been lower than on most commercial long haul flights.

In conclusion, this study does not support the hypothesis that fluid loss during air travel contributes to thrombus formation. The current guidelines that advise to drink a lot of water may therefore not be as beneficial as assumed in preventing travel-related thrombosis.

WRIGHT scientific executive committee

The study has been conducted as part of the WRIGHT project (World Health Organisation Research Into Global Hazards of Travel), which is an international research project under auspices of the World Health Organisation. The scientific committee consists of P Kesteven, Freeman Hospital, Newcastle upon Tyne, UK; W D Toff, University of Leicester, Leicester, UK; F Paccaud, Institute for Social and Preventive Medicine, Lausanne, Switzerland; M Greaves, University of Aberdeen, Aberdeen, UK; H R Büller, Academic Medical Centre, Amsterdam, Netherlands; F R Rosendaal, Leiden University Medical Centre, Leiden, Netherlands; S Mendis, WHO, Geneva, Switzerland.

The WRIGHT project monitoring group is chaired by B M Psaty, University of Washington, Seattle, WA, USA.

Conflict of interest statement

We declare that we have no conflict of interest.

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