Chapter 5

The effect of air travel on platelets and the vessel wall

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Summary

It is not clear which mechanisms underlie the increased risk of venous thrombosis after air travel.

We determined whether platelets or the vessel wall are involved in the prothrombotic state brought about by air travel.

Seventy-one volunteers were exposed to an 8-hour flight, 8 hours of immobilisation at ground level, and 8 hours of daily activities. We measured platelet number, markers of platelet activation (sP-selectin, β-thromboglobulin) and endothelial activation (sE-selectin, von Willebrand factor) before, during and after each exposure.

sP-selectin did not change during the flight (median change 0 μg/L, CI95:-1 to 2) but decreased during immobilisation (-2 μg/L, CI95:-3 to -1) and daily activities (-2 μg/L, CI95:-4 to -1). β-Thromboglobulin increased during the flight (median change: 2.5 IU/mL, CI95:0.9 to 4.5) but decreased during immobilisation (-2.1 IU/mL, CI95:-4.5 to -0.6) and daily activities (-2.8 IU/mL, CI95:-4.5 to -0.7; p=0.01). Platelet counts increased most during daily activities. We identified more high responders (subjects with a particularly high increase in the parameter) for sP-selectin and β-thromboglobulin after the flight than after immobilisation or daily life situation. The number of high responders in platelet counts was similar for all three exposures. sE-selectin as well as von Willebrand factor levels decreased similarly during the flight, cinema and daily activities. The proportion of high responders was similar for these assays for all three exposures.

Our findings suggest that an 8-hour flight leads to moderate platelet activation in a subset of participants, but does not affect endothelial cell function.
Introduction

With increasing awareness of air travel related thrombosis, the interest in the underlying mechanism has risen accordingly. It is still under debate whether the two to four fold increased risk for thrombosis after air travel (1) is solely attributable to immobilisation or that other cabin related factors such as hypoxia also play a role (2;3). During air travel, cabin pressure drops to 75.8 kPa, which is equivalent to an altitude of 2400 m above sea level. Consequently, oxygen saturation can become as low as 90–93% or even 80% in passengers who are asleep (4;5), and has been documented to occasionally cause acute mountain sickness (6). The studies into the mechanism of air travel related thrombosis performed so far mainly focussed on coagulation activation and fibrinolysis. However, platelet number and function are known to alter under hypoxic circumstances such as high altitude, chronic respiratory disease, neonatal hypoxia, sleep apnoea and experimentally-induced hypoxia (7).

The effect of air travel on platelets and the vessel wall has mostly been studied indirectly, i.e. during circumstances related to air travel such as hypoxia (in hypobaric chamber studies), and immobilisation. Although some studies found no effect of hypoxia on platelets or on the vessel wall (8;9), others reported increased platelet counts. The results of studies examining the effect of immobilisation on platelets and the vessel wall were not conclusive either (10;11). Only one study was performed around an actual flight from Vienna to Washington D.C. in which changes in von Willebrand factor (vWf) and platelet counts were measured in 20 volunteers. vWf decreased and platelet count remained unchanged in this study.

Previously, we showed that coagulation activation, as measured by increased TAT and F1+2 and D-dimers, occurred more during air travel than during immobilisation at normobariccircumstances (3). Here, we investigate whether platelets or the vessel wall are involved in coagulation activation after air travel. Soluble P-selectin and β-thromboglobulin were measured as markers for platelet function. E-selectin and von Willebrand factor were considered to reflect endothelial cell activation.

Material and methods

Participants

Between May 24 and July 10, 2004, we performed a crossover study in 71 healthy volunteers, 41 (58 %) of whom had major risk factors for thrombosis (i.e. carriers of the factor V Leiden mutation or users of the oral contraceptive pill or both). Exclusion criteria were previous venous thrombosis, recent (12 weeks)
surgery or immobilisation (including travel lasting >4 h or any air travel), active cancer, any drug use except oral contraceptives, pregnancy or puerperium, and diseases affecting coagulation. The institutional review board of the Academic Medical Center, Amsterdam, approved the study, and all participants gave written informed consent.

Procedures

All participants were exposed to an 8-h flight, 8 h of immobilisation (in a movie marathon), and 8 h of regular daily activities, separated by 2 weeks or more. This way, we were able to investigate the effect of air travel controlled for immobilisation at ground level and for circadian rhythm. Blood was drawn before, during, and after each exposure, at the same time of day. For the first exposure situation, we chartered a Boeing 757 for a non-stop day flight of 8 h from and to Schiphol airport, Amsterdam. All participants were placed in a cinema for 8 h two to three weeks after the flight (for practical reasons two sessions with half the participants in each). For the third exposure situation, we asked participants to act as they normally would on a work day. Volunteers were instructed not to take any prophylactic measures to prevent thrombosis (e.g., heparin or aspirin use, or wearing elastic stockings). Participants were asked to keep a structured record of fluid intake, to keep their food and fluid intake constant during the three exposures and to remain seated as much as possible during the flight and movie marathon similarly. Blood was sampled by experienced technicians (each time by fresh venepuncture) who also recorded at what time blood was obtained and whether any problems arose during sampling. Blood was collected between 0800 and 0830 h (after an overnight fast), around noon, and between 1630 h and 1730 h on the day of each exposure into Vacutainer tubes (Becton Dickinson, Oxford, England) containing EDTA (4.5 mg) for platelet count and DNA extraction and trisodium citrate (3.2% wt/vol) for measurement of vWf, soluble E-selectin (sE-selectin) and soluble P-selectin (sP-selectin). Vacutainer tubes containing CTAD (citrate, theophylline, adenosine, and dipyridamole) for measurement of \( \beta \)-thromboglobulin were collected before and after each exposure.

After all blood draws, we centrifuged citrated blood twice within 15 min after venepuncture at 2500 g for 15 minutes at 15°C, and froze and immediately stored the plasma at -80°C. We extracted DNA from EDTA-anticoagulated blood and stored it at 4°C. We did the assays (all in duplicate except for the DNA tests) after all participants had completed the study. Soluble P-selectin (R&D Systems, Oxford, England) and \( \beta \)-thromboglobulin (Roche Diagnostics, Almere, the Netherlands) were measured by ELISA as markers of in vivo platelet activation. ELISAs were also used to measure soluble E-selectin (R&D Systems Ltd) and
von Willebrand factor (antibodies from Dako, Glostrup, Denmark) as markers of endothelial cell activation. β-thromboglobulin levels above 100 IU/mL were excluded (n=3) since these results were interpreted as technically unreliable. We ascertained factor V Leiden and prothrombin G20210A status by PCR. Platelet count in whole blood was determined with a hematological analyzer.

**Statistical analyses**

For general characteristics of the volunteers, we determined means and ranges for the main analytes, with medians, and 95% confidence intervals (CI95) of the concentrations of each marker for the three exposures. For each individual absolute changes were assessed by subtracting the pre-exposure value from the post-exposure value, which were expressed as median absolute differences (and their CI95). We compared the change in levels of each marker for exposure to the flight, to the movie marathon, and to the daily life situation with the Friedman test. This test is a non-parametric equivalent of a one-sample repeated measures design or a two-way analysis of variance, with one observation per cell. We identified high responders for each assay by using as cut-off points the mean plus two times the standard deviation for the absolute change in that assay during the daily life situation. Previously, we identified individuals with and without an activated clotting system. Based on the relative change in thrombin antithrombin complexes (TAT) during the flight, 66 volunteers (in 5 volunteers the change in TAT was missing due to unsuccessful blood collection or because the sample was visibly hemolytic) could be divided into volunteers with (n=11) and without (n=55) an activated clotting system (cut off point: 202.9 %). For the flight situation we compared the absolute change for each parameter in volunteers with an activated clotting system without clotting activation by Mann-Whitney U test. We compared the frequency of high-responders in volunteers with and without an activated clotting system with Fisher’s exact test and by calculating the odds ratio and its CI95. Associations between variables were investigated using linear regression.

**Role of the funding source**

The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.
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). Of these 56 women, 15 used the oral contraceptive pill, 11 were carriers of the factor V Leiden mutation and 15 women had both risk factors. The 15 men in our study did not have known risk factors for venous thrombosis. Each volunteer returned for each stage in the study as planned. There were no episodes of venous thrombosis.

During the exposures we took 639 samples. Some results were missing or excluded, because the results were technically unreliable or because the material was visibly haemolytic or because blood collection was unsuccessful. For soluble P-selectin and E-selectin, there were 12 samples missing. For β-thromboglobulin 31 samples were missing or excluded: 19 were visibly haemolytic, 8 were missing because of unsuccessful blood collection, in three levels were above 100 IU/mL and in one the results were technically unreliable. For vWF, 14 samples were unavailable and for platelet count 11 samples were missing.

Fluid loss (as defined by haematocrit, serum osmolality and albumin) was not different in individuals with and without clotting activation (12).

Table 1. Characteristics of the 71 volunteers*.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (range) or proportions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28 (20-39)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.0 (18-33)</td>
</tr>
<tr>
<td>Sex (ratio and % women)</td>
<td>56/71 (79%)</td>
</tr>
<tr>
<td>Risk factors in women:</td>
<td></td>
</tr>
<tr>
<td>FVL-/OC-</td>
<td>15/56 (27%)</td>
</tr>
<tr>
<td>FVL+/OC-</td>
<td>15/56 (27%)</td>
</tr>
<tr>
<td>FVL-/OC+</td>
<td>11/56 (20%)</td>
</tr>
<tr>
<td>FVL+/OC+</td>
<td>15/56 (27%)</td>
</tr>
</tbody>
</table>

* Body Mass Index (BMI) is calculated by weight/height². OC=Oral Contraceptives. FVL=Factor V Leiden mutation. +/- presence or absence of the risk factor.

Platelets

Overall, median levels of sP-selectin, β-thromboglobulin and platelet count were higher after the flight than after the cinema and daily activities. However, baseline values were also highest before the flight (Figure 1).
Figure 1. Absolute median values of markers of platelet and vessel wall function before, during and after exposure situations (n=71).

Platelets:

- sP-selectin
- β-thromboglobulin
- Platelet count

Vessel wall:

- sE-selectin
- Von Willebrand factor
On an individual level, sP-selectin did not change during the flight (median absolute individual change 0 μg/L, CI95: -1 to 2) whereas it decreased during the cinema (-2 μg/L, CI95: -3 to -1) and daily activities (-2 μg/L, CI95: -4 to -1; Friedman test for difference between the three changes: p=0.06, with most increases in sP-selectin after the flight, table 2). β-Thromboglobulin increased during the flight (median absolute increase 2.5 IU/mL, CI95: 0.9-4.5) whereas it decreased during the cinema (-2.1 IU/mL, CI95: -4.5 to -0.6) and daily activities (-2.8 IU/mL, CI95: -4.5 to -0.7; Friedman test: p=0.01, again with most increases in β-thromboglobulin after the flight, table 2). Platelet counts increased more during the daily activities (median increase 10 x 10⁹/L, CI95: 4 to 13) than during the flight (4 x 10⁹/L, CI95: -1 to 8) or cinema exposure (2 x 10⁹/L, CI95: 0 to 7, Friedman test: p=0.003 with most increases in platelet counts after the daily activities, table 2).

Table 2. Absolute individual changes after flight, cinema and daily life.

<table>
<thead>
<tr>
<th></th>
<th>Flight Median (CI95)</th>
<th>Cinema Median (CI95)</th>
<th>Daily life Median (CI95)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>sP-selectin (μg/L)</td>
<td>0 (-1 to 2)</td>
<td>-2 (-3 to -1)</td>
<td>-2 (-4 to -1)</td>
<td>0.06</td>
</tr>
<tr>
<td>β-thromboglobulin (IU/ml)</td>
<td>2.5 (0.9 to 4.5)</td>
<td>-2.1 (-4.5 to -0.6)</td>
<td>-2.8 (-4.5 to -0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelet count (10x10⁹/L)</td>
<td>4 (-1 to 8)</td>
<td>2 (0 to 7)</td>
<td>10 (4 to 13)</td>
<td>0.00</td>
</tr>
<tr>
<td>sE-selectin (μg/L)</td>
<td>-0.8 (-1.4 to -0.2)</td>
<td>-1.2 (-1.5 to -0.9)</td>
<td>-1.0 (-1.3 to -0.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Von Willebrand factor (%)</td>
<td>-8 (-12 to -4)</td>
<td>-7 (-10 to -3)</td>
<td>-5 (-7 to -1)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* Friedman test, with most increases in sP-selectin, sE-selectin and β-thromboglobulin after the flight and most increases in von Willebrand factor and platelet count after the daily life situation.

With respect to sP-selectin, we identified 8 high responders after the flight (8/64, 12.5%, CI95: 5.5 to 23.2). These individuals had an absolute change in sP-selectin after the flight of more than the mean plus two standard deviations for sP-selectin during the daily activities (cut off: 5.7 μg/L). In the cinema situation one high responder was identified (1/68, 1.5%, CI95: 0.0 to 7.8). Three high responders were identified after the daily activities (3/71, 4.2%, CI95: 0.9 to 11.9) (Table 3). For β-thromboglobulin we identified 10 individuals as high responders (cut off: 11.5 IU/mL) after the flight (10/57, 17.5%, CI95: 8.7 to 29.9), compared with five after the cinema (5/62, 8.1%, CI95: 2.7 to 17.8) and one after the daily life activities (1/65, 1.5%, CI95: 0.0 to 8.3, table 3). For platelet counts, the flight caused a high-response (cut off: 41.7 x 10⁹/L) in only one individual (1/64, 1.6%, CI95: 0.0 to 8.4). The cinema did so in two individuals (2/68, 2.9%, CI95: 0.4 to 10.2) as well as the daily activities (2/70, 2.9%, CI95: 0.3 to 9.9, table 3).

During the flight, sP-selectin did not increase in the same individuals as those in whom β-thromboglobulin and platelet count increased. Also, in a linear regression analysis we found no relation between the absolute changes in
P-selectin and β-thromboglobulin (B: -0.07, CI95: -0.19 to 0.05) or P-selectin and platelet count (B: -0.01, CI95: -0.06 to 0.05).

Table 3. Proportion of high-responders per exposure*.

<table>
<thead>
<tr>
<th></th>
<th>Flight</th>
<th>Cinema</th>
<th>Daily life situation</th>
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<tbody>
<tr>
<td><strong>Platelets</strong></td>
<td></td>
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<tr>
<td>- sP-selectin</td>
<td>8/64 (12.5%, 5.5 to 23.2)</td>
<td>1/68 (1.5%, 0.0 to 7.9)</td>
<td>3/71 (4.2%, 0.9 to 11.9)</td>
</tr>
<tr>
<td>- β-thromboglobulin</td>
<td>10/57 (17.5%, 8.7 to 29.9)</td>
<td>5/62 (8.1%, 2.7 to 17.8)</td>
<td>1/65 (1.5%, 0.0 to 8.3)</td>
</tr>
<tr>
<td>- Platelet count</td>
<td>1/64 (1.6%, 0.0 to 8.4)</td>
<td>2/68 (2.9%, 0.4 to 10.2)</td>
<td>2/70 (2.9%, 0.3 to 9.9)</td>
</tr>
<tr>
<td><strong>Vessel wall</strong></td>
<td></td>
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<tr>
<td>- sE-selectin</td>
<td>1/64 (1.6%, 0.0 to 8.4)</td>
<td>0/68 (0%, 0.0 to 5.3)</td>
<td>0/71 (0%, 0.0 to 5.1)</td>
</tr>
<tr>
<td>- Von Willebrand factor</td>
<td>5/66 (7.6%, 2.5 to 16.8)</td>
<td>3/68 (4.4%, 0.9 to 12.4)</td>
<td>3/70 (4.3%, 0.9 to 12.0)</td>
</tr>
</tbody>
</table>

* Total numbers (% CI95).

**Vessel wall**

Overall, median sE-selectin and vWf values were higher after the flight than after the cinema or daily activities. Baseline values were also highest before the flight (Figure 1).

On an individual level, sE-selectin decreased during the flight (median individual change -0.8 μg/L, 95CI: -1.4 to -0.2), as well as during the cinema (-1.2 μg/L, 95CI: -1.6 to -0.9) and daily activities (-1.0 μg/L, 95CI: -1.3 to -0.6; Friedman test: p=0.17 with most increases in sE-selectin after the flight, table 2). vWf levels decreased during the flight (-8%, CI95: -12 tot -4), cinema (-7%, CI95: -10 to -3) and daily activities (-5%, CI95: -7 to -1; Friedman test: p=0.25 with most increases after the daily life situation, table 2).

With respect to sE-selectin we only identified one high responder (cut off: 1.5 μg/L) during the flight (1/64 (1.6%, CI95: 0.0 to 8.4) and none during the cinema (0/68, 0%, CI95: 0.0 to 5.3) and daily activities (0/71, 0%, CI95: 0.0 to 5.1, table 3). The flight caused a high response in vWf (cut off: 21.5%) in five individuals (5/66, 7.6%, CI95: 2.5 to 16.8), while the cinema and daily life situation triggered a high response in three individuals (cinema: 3/68, 4.4%, CI95: 0.9 to 12.4; daily activities: 3/70 (4.3%, 0.9 to 12.0, table 3). sE-selectin did not increase in the same individual(s) as those in whom vWf increased.

**Relation between markers of platelet and endothelial function**

Absolute changes in sP-selectin or β-thromboglobulin during the flight were not related to absolute changes in sE-selectin, vWF or platelet count during the flight, as assessed by linear regression.
Platelet and endothelial function in individuals with and without clotting activation

Based on the relative change in thrombin antithrombin complexes (TAT) during the flight, 11 volunteers were identified as individuals with an activated clotting system (3). In one of these, sP-selectin results were missing. During the flight, sP-selectin levels were higher in individuals with an activated clotting system, (median change 3.5 μg/L, CI95: -3.0 to 10.0) than in volunteers without an activated clotting system (median change -0.5μg/L, CI95: -2.0 to 2.0, Mann-Whitney U-test: p=0.02). Furthermore, 4 out of 10 (40%, CI95: 14 to 71) individuals with an activated clotting system were identified as high responders in sP-selectin, whereas only 4 out of 52 (8%, CI95: 2 to 18) individuals without an activated clotting system showed a high response in sP-selectin (OR 8.0; CI95: 1.6 to 40.6, p=0.02). We did not find such associations between TAT and one of the other parameters of platelet or endothelial function (β-thromboglobulin, sE-selectin, vWF or platelet count).

Discussion

In our study, sP-selectin and β-thromboglobulin increased in more individuals after a long distance flight than after immobilisation in a cinema or a day with normal activities. Therefore, our findings suggest that an 8-hour flight leads to platelet activation in certain individuals, but it does not seem to affect platelet number or endothelial cell function. Furthermore, the changes in sP-selectin were related to changes in TAT. This suggests that sP-selectin is directly related to the thrombin formation in these subjects.

P-selectin is a member of the selectin family, localized in the membranes of the alfa-granules of platelets and the Weibel-Palade bodies of endothelial cells and expressed on the surface of activated platelets and endothelial cells (23). P-selectin augments vein wall inflammation, promotes thrombus generation when stimulated by a thrombotic stimulus, is responsible for leukocyte rolling and is upregulated early during venous thrombosis (13). P-selectin is rapidly translocated to the cell surface when cells are exposed to stimuli such as histamine or thrombin. Some inflammatory cytokines can also induce P-selectin transcription. One case-control study found that P-selectin was raised in subjects who suffered from venous thrombosis. The authors concluded that excess platelet activation may be related to the development, or be a consequence, of venous thrombosis (14). β-Thromboglobulin is present in the α-granula of platelets, is secreted after activation of the platelet and is known to be elevated in patients suffering from venous thrombosis (15).
E-selectin and vWF were measured as markers for endothelial cell activation. E-selectin is only found on endothelial cells and binds ligands on circulating granulocytes, monocytes and some memory lymphocytes. It is only detectable after several hours exposure to cytokines (TNFα or IL-1) or bacterial endotoxin, which induce transcription of the E-selectin gene (16). E-selectin temporally follows P-selectin upregulation, enhances the thrombotic response and amplifies the effects of P-selectin (13). Studies in mice showed that high circulating levels of P-selectin are associated with thrombosis, whereas a lack of P-selectin and E-selectin was associated with less thrombosis, suggesting the importance of selectins to venous thrombogenesis (13). VWF is synthesized by megakaryocytes and endothelial cells and can be secreted from endothelial storage pools (i.e. Weibel Palade bodies) after a specific stimulus. Activated VWF serves as a ‘glue’ between platelets and the damaged vessel wall and between platelets themselves (19).

No controlled studies have been done so far into the effect of air travel on platelets and the vessel wall. One study (without a control situation) measured vWF and platelet counts during air travel, and the results were similar to our findings (17). Some research has been done into the effect of circumstances related to air travel (hypoxia or immobilisation) on platelets and the vessel wall. Studies that focussed on the effect of short term hypoxia on platelet or vessel wall function found no effect (8;18), while the results of platelet counts under hypoxic circumstances were conflicting (8;9;18-20). No studies have been performed on the effect of immobilisation on platelet function; the effect on vessel wall function has only been studied by measurement of thrombomodulin, which decreased in all studies (10;21;22). The results of studies that measured vWF during immobilisation were not conclusive (10;11), while platelet counts seemed unaffected by immobilisation (11). It is difficult to compare our study results with those of others. Firstly, most of the studies done in this field presented results on a group level, diluting individual effects. We have shown before that it is likely that only some individuals are susceptible to venous thrombosis after air travel (3), which makes it important to report results at an individual level. Secondly, most studies did not control for immobilisation or circadian rhythm whereas our study design accounted for such effects. Proper design will particularly unmask effects in the opposite direction as the circadian rhythm, as we observed for sP-selectin. Finally, there may be air cabin-related factors other than immobilisation and hypoxia related to air travel, such as air pollution, fluid loss (dehydration), or anxiety that are responsible for the increased risk of venous thrombosis after air travel.
There are various general limitations to our study, which also have been described in our previous publication (3). Although there is no evidence that our assays could be affected by haemolysis in vitro, we excluded all visibly haemolytic material. Also samples with technically unreliable data in other assays (TAT) were excluded as well as unreliable data in the current assays. Furthermore, there was a slight difference in pre-exposure values between the three situations especially in sP-selectin and β-thromboglobulin. We took this into account by comparing the absolute changes of the several parameters instead of comparing their absolute values after the three situations. Lastly, although some of our subjects had common risk factors for thrombosis, most were young and healthy individuals with no history of thrombosis. It would be of interest to investigate the effect of flying on the coagulation system in older volunteers, individuals with other risk factors for venous thrombosis, or those with a personal history of venous thrombosis.

How do our results add up? Firstly, sP-selectin and β-thromboglobulin, both markers of platelet activation, were highest after the flight. Also, the individual changes were most positive during the flight and most high responders for these markers were found after the flight. Furthermore, changes in sP-selectin were related to changes in TAT in the same subjects. Possibly, platelets were activated by thrombin that was formed during the flight. Alternatively, both thrombin formation and platelet activation may have been induced concurrently by one underlying condition, such as hypoxia. It is difficult to explain why β-thromboglobulin did not increase in the same individuals as in whom sP-selectin increased. Perhaps in these subjects platelets were activated through a different mechanism. Another explanation could lie in artefacts in the β-thromboglobulin results. Secondly, markers of endothelial cell activation (i.e. sE-selectin and vWF) were not affected by the 8-h flight. Since it can take a few hours for sE-selectin to increase after a specific stimulus, it is possible that blood was drawn too soon after the rise in sP-selectin and it was therefore too early to find an increase in sE-selectin. Platelet count remained unchanged during the flight, so we did not find evidence for “shedding” of trombocytes by megakaryocytes during acute hypoxia, a phenomenon that has been described during severe acute hypoxia in mice (20).

In conclusion, the results of our study suggest that an 8-h flight does not affect the vessel wall, whereas moderate platelet activation occurs in a subset of patients which is to some extent related to thrombin generation.
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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Reference List


