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# Fatal Pulmonary Embolism Immediately after Transatlantic Air Travel to the United States: Less than One in a Million

Dear Sir,

Recent communications in the lay press (1) and medical literature (2) have raised awareness of the need for quantitative data to estimate the incidence of fatal PE after transatlantic air travel. One study, conducted at Charles DeGaulle airport in France, estimated the incidence of fatal PE at 0.5 per one million flights (3). We are not aware of any data which has examined the rate of fatal PE occurring immediately after transatlantic air travel to the US.

The Charlotte-Douglas International Airport in Mecklenburg County, North Carolina has received at least one commercial transatlantic air flight per day since January 1992. Officials at British Airways and US Airways, the only carriers that offered overseas travel to Charlotte from 1992-July 2001, estimate that 1,120,000 persons were flown during this time. This datum was cross-checked against data supplied by US Customs, who estimate 1,380,000 transatlantic travelers were cleared for entry into the US Customs service officials also estimate that all passengers deplaning from transatlantic flights spend at least one hour in the air terminal.

Since 1992, Mecklenburg County has been served by one emergency medical system (EMS). The policy for our EMS requires that all cardiac arrests or unstable patients originating from the airport are transported to the emergency department (ED) at Carolinas Medical Center (CMC). All patients from the airport who expired in the CMC ED were referred to the county medical examiner's office, where an autopsy was performed on every decedent with unexplained cardiac arrest occurring at the airport. To determine if any person diagnosed with fatal PE originated from the airport, two independent observers examined every medical examiner's file from January 1992 – June 2001 for cases of fatal PE. Medical records of all persons diagnosed with PE (defined by objective pulmonary vascular imaging positive for PE and no other known cause of death, or autopsy) at CMC were also examined for the same time period. Out of 6006 cases at the Medical Examiner's office, we found 82 cases of fatal PE in outpatients, one of whom experienced collapse at the airport while walking from the parking lot toward the terminal prior to boarding an airplane. At CMC, 1341 patients were diagnosed with PE, 97 of whom died during hospitalization. None of these patients had symptoms originating at the airport; two occurred immediately after prolonged automobile travel.

To summarize, we were unable to identify any cases of immediately fatal PE after over one million instances of transatlantic air travel. Prior work has demonstrated that over one-half of patients with PE after air travel experience symptoms prior to or during disembarkment (3, 4). It remains possible that we missed cases of PE where symptom onset was delayed. We believe that the organization of the prehospital care system in our county, and the strict rules of the medical examiner's office, allow us to state with certainty that no person experienced fatal PE immediately after transatlantic air travel to Charlotte from 1992 to June 2001. We conclude that immediately fatal PE after transatlantic travel is exceedingly rare in Charlotte, NC.

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# Short-term Exposure to High Altitude Causes Coagulation Activation and Inhibits Fibrinolysis

Dear Sir,

With modern facilities for rapid transportation, it has become increasingly frequent that unacclimatized tourists ascend rapidly and for short periods of time from places at a normal atmospheric pressure and oxygen tension to very high altitudes, where they are suddenly exposed to hypobaric hypoxia. Typical examples of this situation occur among short-term vacationers in the Andes and in the Himalayas and high altitude skiers in the Alps and Rocky Mountains. Even though acute mountain sickness and, more rarely, cerebral edema are well established complications of the rapid ascent of unacclimatized individuals to high altitudes (1), travel agencies actively organize and promote short-term tours at high altitudes claiming that mountain sickness

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*Table* Changes in hemostasis parameters of 8 healthy individuals acutely exposed to high altitude (4000-5000 meter above sea level)

| | Prothrombin fragment 1+2, nmol/L | Thrombin-antithrombin complex, ng/mL | PAI-1 activity, IU/ml | PAI-1 antigen, ng/mL | tPA antigen, ng/mL | Factor VII antigen, % | D-dimer, ng/L | Plasmin antiplasmin complex, ng/mL | Von Willebrand factor antigen, % |
|---|---|---|---|---|---|---|---|---|---|
| BEFORE | 1.3 (0.9-1.8) | 2.8 (2.0-7.4) | 0.9 (0.26-9) | 50.7 (17.2-100) | 8.2 (4.9-11.9) | 73 (27-92) | 14.5 (9-20) | 170 (92-237) | 84 (45-135) |
| DURING | 1.8 (0.9-2.8) | 2.3 (1.4-7.0) | 10.7 (2.5-49.2) | 64.9 (48.8-100) | 12.0 (7.6-14.0) | 84 (57-96) | 13 (10-30) | 168 (115-363) | 81 (43-155) |
| AFTER | 0.9 (0.7-1.7) | 2.7 (1.4-5.4) | 0.0 (0-2.5) | 26.2 (15.4-100) | 6.0 (3.6-10.3) | 81 (55-92) | 13 (11-19) | 259 (95-409) | 73 (43-120) |
| p-value* | *P=0.004* | *P=0.11* | *P<0.001* | *P=0.023* | *P=0.002* | *P=0.75* | *P=0.90* | *P=0.69* | P=0.40 |
| Normal range | 0.6-2.7 | 0.2-4.6 | 0.1-18.4 | 7.8-97.8 | 1.7-12.3 | 70-132 | 0-60 | 120-540 | 50-148 |

Values are expressed as median (range)
* Friedman's test with exact significance

rarely strikes within the first 24 h of rapid ascent (1). On the basis of reports indicating that thrombotic manifestations are frequent and serious complications of exposure to high altitude (2, 3), we chose to monitor selected measurements of coagulation and fibrinolysis in 8 healthy but unacclimatized individuals (5 men, 3 women, age ranging from 36 to 62 years) who visited the Mount Everest region in Nepal. A first sample of citrated venous blood was obtained in Italy on the day before the departure, and centrifuged immediately to obtain platelet poor plasma that was snap-frozen and stored at –80° C. The 8 individuals departed from Italy on April 2001 and flew to Kathmandu (altitude 1200 meters). After two days in this city they flew by helicopter to Syangboche (3940 meters) where they stayed for approximately 24 h resting or engaging in mild physical activities. The next morning they flew by helicopter to the Ev-K2 laboratory of the Italian Research Council (CNR) at an altitude of 5060 meters, where another blood sample was obtained and processed as above with snap-frozen plasma stored in small containers containing dry ice. After one hour, they descended by helicopter to Syangboche and immediately to Kathmandu to return after two days to Italy where a third sample of venous blood was obtained and processed as above. On the control samples obtained before and following the visit to Nepal and on the sample obtained during the short stay at high altitude, the following coagulation and fibrinolysis measurements were investigated: prothrombin fragments 1 plus 2, thrombin-antithrombin and plasmin-antiplasmin complex (Enzygnost $F_{1+2}$, TAT and PAP, Behring, Marburg, Germany); D-dimer and factor VII antigen (Asserachrom D-Di and VII: Ag, Diagnostica Stago, Asnières-sur Seine, France); tissue plasminogen activator (tPA) antigen, plasminogen activator inhibitor 1 (PAI-1) activity and antigen (Imulyse tPA and Chromolyze PAI-1, Biopool, Umea, Sweden; and Immotest PAI-1, Byk-Sangtec, Dietzenbach, Germany). Von Willebrand factor antigen was measured with an in-house enzyme immunoassay. Repeated measures Friedman's ANOVA was used to test for changes of the measurements over time and to test for changes over the three time points.

Table indicates that in the blood sample obtained at high altitude there was a significant increase of the prothrombin fragment 1+2, compared with the values obtained in Italy before and after the trip. There was also a significant increase in tPA antigen and PAI-1 activity and antigen, with a return to baseline levels after returning to Italy. Thrombin-antithrombin complex, D-dimer, plasmin-antiplasmin complex, factor VII antigen and von Willebrand factor antigen did not change significantly.

These data indicate that the short-term stay at high altitude of unacclimatized healthy individuals determines a transient prothrombotic imbalance, expressed by an increase of a key fibrinolysis inhibitor such as PAI-1 (tPA antigen levels are an indirect measurement of PAI-1) accompanied by heightened thrombin generation reflected by mildly elevated plasma levels of prothrombin fragment 1+2. To our knowledge, no similar study has been carried out before. Bendz et al. (4) investigated 20 healthy male volunteers acutely exposed to experimental conditions of hypobaric hypoxia similar to those encountered within airplane cabins (altitude 2400 meters, ambient air pressure about 76 KPa). They found a transient two- to eightfold increase in markers of activated coagulation (4). In our study, altitude was much higher (between 4000 and 5000 meters) and ambient air pressure much lower (about 51 KPa). The increase of prothrombin fragment 1+2 was smaller than in the study of Bendz et al. (4) but there was a marked increase in PAI-1, a key fibrinolysis inhibitor. It is likely that the short term increase of PAI-1, reversed upon return to lower altitude, is due to release of this moiety in plasma from vascular endothelial cells due to hypoxia (5). High values of PAI-1 and tPA antigen have been found to be consistent predictors of incident atherothrombotic disease in prospective epidemiological studies (6). On the whole, these findings provide information that should discourage short-term exposure of unacclimatized individuals at high altitudes.

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