Incidence, clinical characteristics, and long-term prognosis of travel-associated pulmonary embolism

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Aims
Prolonged air travel is considered a risk factor for pulmonary embolism (PE). The clinical characteristics as well as the long-term prognosis of patients suffering from travel-associated PE (‘economy-class syndrome’, ECS) remain largely unknown. Owing to its proximity, our hospital is the primary referral centre for Frankfurt Airport, Europe’s third-largest airport. The goal of our study was to follow-up all patients with ECS, who were admitted to our hospital between 1997 and 2006.

Methods and results
We systematically reviewed all medical charts from patients presenting with acute PE to our emergency room or intensive care unit (ICU) and performed a telephone follow-up on patients discharged alive. Together with the data provided from the statistics department of Fraport Inc., the operating company of the Frankfurt International Airport, we were also able to put the medical data in context with the corresponding number of passengers and flight distances. A total of 257 patients with acute PE were admitted to our emergency and ICU between 1997 and 2006. Out of these, 62 patients suffered from ECS (45 flight-associated PE and 17 from other travel-associated PE). ECS patients were prone to more haemodynamic relevant acute events, reflected by a higher rate of initial cardiopulmonary resuscitation (4.8% vs. 1.5%; \(P = 0.153\)) and higher percentage of massive PE (8% vs. 3%; \(P = 0.064\)). Nevertheless, inhospital mortality was similar in both groups (ECS 4.8%, others 4.1%; \(P = 0.730\)). Interestingly, the long-term outcome of ECS patients was excellent (Kaplan–Meier analysis; log-rank: 0.008 vs. other entities). In general, ECS was a rare event (one event/5 million passengers), where long-haul flights over 5000 km lead to a 17-fold risk increase compared with shorter flights.

Conclusions
Travel-associated PE was a common cause of PE in our hospital, with patients showing excellent long-term prognosis after discharge. The risk of ECS is rather low and strictly dependent on the flight distance.

Keywords
Economy class syndrome • Pulmonary embolism • Long-term prognosis

Introduction
Prolonged air travel is a risk factor for pulmonary embolism (PE) mainly caused by immobilization and local venous drain deficiency.¹⁻⁴ Venous thrombo-embolic events preceded by air-travel are referred to as the ‘economy-class syndrome’ (ECS).

Two retrospective analyses of travellers arriving at the Parisian Charles de Gaulle and Madrid-Barajas airports in the last decade found a greater distance travelled is a significant contributing risk factor for PE associated with air travel.⁵,⁶ The incidence of PE was much higher among passengers travelling more than 5000 km (1.5 cases per million) as compared with those travelling...
less than 5000 km (0.01 case per million). The number of air passengers continues to increase, but the proportion of travel-associated PE in relation to other entities and the prognosis of these patients have not yet been sufficiently investigated. Recent available data focused only on a 3 month period after the index event. Furthermore, patients with ECS are not very well characterized in terms of further clinical risk factors.

Methods

Characteristics of the study: main objective
The goal of our retrospective study was to evaluate the incidence of travel-associated PE and evaluate long-term prognosis compared with other entities of PE.

Study population: inclusion criteria
We systematically reviewed medical records of all patients presenting with acute PE to the emergency room or intensive care unit (ICU) of the University Hospital in Frankfurt between 1997 and 2006. The patients were identified by the PE-specific, diagnosis-related, computer-based code (ICD-9; ICD-10) for this diagnosis during the hospital stay.

Study population: exclusion criteria
Patients with secondary PE following hospitalization were excluded: our hospital administration office identified 645 patients with coded main diagnosis of PE at discharge. After reviewing the medical charts we excluded all patients where, in retrospect, admission was primarily based on a different diagnosis other than PE. The remaining 257 patients were included in the analysis.

Procedures

Classification of patients according to cause of pulmonary embolism
Data from medical history and reports of diagnostic tests including blood tests were acquired. We categorized the population according to the cause of PE into eight groups:

1. travel associated (history of prolonged travelling in the last 2 months)
2. known or suspected neoplasm
3. thrombophilia (see definition of thrombophilia)
4. surgical procedure (during the last 2 months)
5. immobilization (>48 h during the last 2 months)
6. pregnancy/delivery (during the last 2 months)
7. other reasons [chronic diseases such as severe pulmonary hypertension, use of oral contraceptives associated with known elevated risk for venous thromboembolism (VTE)]
8. unknown cause (idiopathic PE) reflecting unexplained VTE.

All patients could be categorized into one or more of the above group PE, except for those with idiopathic PE. Nevertheless, patients were categorized to idiopathic PE in case of (a) negative test results from thrombophilia or (b) unavailable data or lack of thrombophilia screening if no other predefined cause occurred.

We combined all travel-associated PE cases, independent from the mode of transportation, under ECS. This definition includes PE due to prolonged sitting in a plane, bus, train, or car, and one patient in a simulation. Furthermore, we distinguished between air-travel ECS and non-air-travel ECS. Severity of PE was determined according to the guidelines of the European Society of Cardiology. Finally, we analysed the reports of the computed tomography (CT) scans to address the question whether differences in clinical presentation corresponded to differences in thrombus distribution.

Airport data
The Frankfurt Airport is the biggest German airport and 8th largest in the world, with over 50 million passengers a year. The number of passengers corresponding to flight origin was achieved from the statistics department of FRAPORT AG, the operating company of the Frankfurt International Airport. Our goal was to estimate the incidence of ECS in relation to the number of passengers and flight distance. Airport departure information was taken directly from the medical charts (in two cases the departure airport was unknown, which is noted in the manuscript). The flight distance was calculated according to the http://airtravelcenter.ch/gif/distance.htm website.

Definition of thrombophilia
Thrombophilia was defined as one of the following findings: detection of factor V Leiden (genetic or functional test), prothrombin G20210A mutations, protein C or S deficiency (if detected w/o oral anticoagulation), detection of lupus anticoagulants (positive screening test and confirmation by measuring antibody ratio and lupus-sensitive partial thromboplastin time) and detection of anticardiolipin antibodies. All thrombophilia screening tests had to be performed either before or during hospital stay, or within in the first 30 days following discharge. These data were used to categorize patients in confirmed or absence of thrombophilia.

Follow-up
Survival and death were assessed by telephone calls (patients, relatives and physicians) and information from the responsible municipal authority. All telephone follow-ups were performed between December 2005 and January 2008 with a minimum of 1 year following the index event. If no information was available via telephone, we obtained information from the local resident’s registration office, future medical charts, or the patient’s family doctor. The last date on which the patient was seen alive was included in our analysis.

Unfortunately, it was not possible to obtain contact data of all international patients from medical charts. We could not follow-up 19 patients with travel-associated PE (two in the non-ECS group), 17 of the ECS patients were not residents of Germany. The median of the follow-up time in this study population was 670 days (n= 236; interquartile range 378–1397 days). With respect to the potential bias due to the reduced survival expectancy of patients with systemic neoplastic disease and the expected higher incidence of neoplasm in the non-ECS group (other entities), we analysed the survival data in two ways, with and without patients diagnosed with neoplasm. Assuming that haemodynamic factors affect acute mortality—while recurrent VTE, cardiovascular events, and co-morbidities influence long-term prognosis following PE, we decided to include only patients discharged alive for analysis of long-term outcome.

In addition, the functional state and physical condition, including recurrent venous thrombo-embolic events, was assessed in a subpopulation (n = 130). We attempted to contact each patient and included all patients who could be contacted by telephone. Patients answered predefined questions reflecting their self assessment of participation in sports (yes/no) and occurrence of shortness of breath between daily activities (yes/no). Furthermore, patients assessed their own physical condition on a three-level scale (good, moderately reduced, and severely reduced).
Statistics

If not stated otherwise, data are expressed as mean ± standard deviation. Duration of follow-up is depicted as median and interquartile range (25th to 75th percentile). All analyses were performed as two-sided significance tests. Non-parametric tests were used (Mann–Whitney U-test) to compare continuous variables of the baseline characteristics. Comparisons between categorical variables were done by Fisher’s exact test. Survival was analysed using the Kaplan–Meier procedure in time-to-event model. Survival of travel-associated PE and other patients was compared. Comparisons between these groups were done using the log-rank test. Numbers of patients at risk were reported in life-tables. A Cox regression analysis was performed, analysing the predictability of statistically significant different baseline characteristics on survival. Statistical significance was generally assumed, if a null hypothesis could be rejected at $P < 0.05$. All statistical analyses were performed using SPSS for Windows 15.0.

Results

Baseline characteristics

A total of 257 patients with acute PE were admitted to our emergency or ICU between 1997 and 2006. Here, ECS-associated PE was the third most common cause of PE in our hospital ($n = 62; 24%$; Figure 1). Only patients with idiopathic PE ($n = 83; 32%$) and thrombophilia ($n = 78; 30%$) were more common. In 45 patients (18%), flying causes travel-associated PE (ECS). The remaining cases were due to travel by bus ($n = 13; 5%$) or by car ($n = 3; 1%$). The remaining patient was exposed to a travelling simulation with longer sitting in an altitude chamber and was categorized as non-air-travel ECS.

The mean age of ECS patients was 54 ± 13 years as compared with 60 ± 17 years in patients with other predisposing factors ($P = 0.002$; Table 1). Gender was equally distributed among ECS patients, which were on average overweight (BMI 28 ± 8 kg/m²). Patients with ECS due to bus, car, or train travelling were significantly overweight compared with ECS due to air travelling (96 ± 25 vs. 76 ± 12 kg, $P = 0.002$). Other baseline parameters such as age, gender, usage of thrombolytic therapy, C-reactive protein, D-dimer, and creatinine were not statistically different (see also Supplementary material online).

Diagnostic procedures

Diagnosis of PE has been confirmed in most cases by high-resolution helical CT angiogram (performed in 82% of cases), scintigraphic ventilation-perfusion scanning or, in some fatal cases, by integrating criteria for clinical probability (i.e. the Wells’ score[12]) or other empirical criteria including history, clinical presentation, venous ultrasonography, and echocardiogram. Six acute intrahospital fatal cases were diagnosed by the responsible physicians, solely based on clinical probability, ECG, physical examination, blood tests, and echocardiogram.

Clinical presentation on admission

Economy-class syndrome patients showed a trend to more haemodynamically relevant acute events, reflected by the higher rate of patients admitted following successful cardiopulmonary resuscitation (4.8% vs. 1.5%; $P = 0.153$), a higher rate of massive PE (8% vs. 3%; $P = 0.066$), and a slightly higher rate of elevated troponin and treatment by thrombolysis (Table 1). Nevertheless, intrahospital mortality remained similar (4.8% vs. 4.1%, $P = 0.730$). The occurrence of deep vein thrombosis (DVT) in ECS patients was significantly lower compared with non-ECS patients (48% vs. 68%; $P = 0.038$). Patients in the non-ECS group presented far more often with a history of neoplasms (21% vs. 7%, $P = 0.011$), congestive heart failure (11% vs. 2%, $P = 0.033$) or chronic pulmonary diseases (32% vs. 16%, $P = 0.022$; Table 1). Regarding the symptoms that led to admission, it is remarkable that syncope occurred twice as often in the ECS group in comparison to the other patients (29% vs. 13%, $P = 0.006$; Figure 2). In contrast, swelling of lower limbs, indicating oedema, occurred less often (16% vs. 31%; $P = 0.022$; Figure 2). In patients with ECS, the proportion of S1Q3 pattern of the ECG axis on admission (41% vs. 26%, $P = 0.032$; Table 2) was more frequent as opposed to a lower mean pulmonary artery pressure (38 ± 12 vs. 47 ± 17 mmHg, $P = 0.004$) measured by echocardiography. There was no difference in the initial clinical presentation or severity of PE between air-travel ECS and non-air-travel ECS.

Figure 1 Causes of pulmonary embolism (per cent).
Computed tomography scan documentation and thrombus distribution

We analysed data from multislice CT scans, which were performed in nearly 81% of patients (Table 2). Two-thirds of the scans showed a bilateral distribution. Isolated one-sided emboli could be detected twice as often in the right vs. left pulmonary artery, without any difference between the two groups. Isolated subsegmental emboli could only be detected in ECS patients (5%), whereas involvement of the main pulmonary artery was less common in ECS patients (31% vs. 50%, \( P = 0.046 \); Table 2).
Long-term outcome of patients with economy-class syndrome

The 3-month mortality rate in our patients was similar in both groups (ECS 7.0%, others 7.3%; P = 0.999, including neoplasms). Independent from analysing long-term outcome including or excluding neoplasm, survival was significantly better in the ECS group (Figure 3A and B). We did not detect any fatal event in the ECS group in patients without concomitant neoplasm after discharge. Short- and long-term prognosis of ECS patients was independent from means of travel.

C-reactive protein was significantly higher in the non-ECS-patients. In the univariable Cox regression analysis, an elevated C-reactive protein did not reach statistical significance in terms of prognostic relevance. This was the case for either 30 day mortality [hazard ratio (HR) 0.7 all patients; P = 0.630] or long-term follow-up (HR 2.1 all patients; P = 0.203). These findings did not change when excluding patients with neoplasms. Furthermore, our follow-up data showed a markedly better functional state of ECS patients, represented by self-assessment of participation in sports, occurrence of shortness of breath between daily activity, and a three-level self-assessed condition (Figure 4).

As we already outlined in Methods section, information on survival was missing in 19 patients with travel-associated PE. Seventeen of these patients were not residents of Germany. The patients who were lost to follow-up showed no differences regarding age, gender, initial clinical haemodynamic severity, use of thrombolytic therapy, troponin level, C-reactive protein, creatinine, D-dimer, left ventricular ejection fraction, pulmonal arterial pressure, thrombus distribution in the CT scan, or medical history (data not shown).

Table 2 Diagnostic procedures

<table>
<thead>
<tr>
<th></th>
<th>Travelling (n = 62)</th>
<th>Others (n = 195)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG performed</strong></td>
<td>62 (100%)</td>
<td>195 (100%)</td>
<td>–</td>
</tr>
<tr>
<td>S1Q3</td>
<td>26 (42%)</td>
<td>49 (25%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>10 (16%)</td>
<td>41 (21%)</td>
<td>0.468</td>
</tr>
<tr>
<td>Neg T-wave V1–V4</td>
<td>11 (18%)</td>
<td>44 (23%)</td>
<td>0.481</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>0 (0%)</td>
<td>12 (6%)</td>
<td>0.076</td>
</tr>
<tr>
<td><strong>Echo performed</strong></td>
<td>59 (95%)</td>
<td>182 (93%)</td>
<td>0.768</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>56 (90.3%)</td>
<td>153 (78.5%)</td>
<td>0.231</td>
</tr>
<tr>
<td>Slight reduction</td>
<td>2 (3.2%)</td>
<td>17 (8.7%)</td>
<td></td>
</tr>
<tr>
<td>Moderate reduction</td>
<td>0 (0.0%)</td>
<td>8 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Severe reduction</td>
<td>1 (1.6%)</td>
<td>5 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (4.8%)</td>
<td>12 (6.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>PAPsys (mm Hg)</strong></td>
<td>38 ± 12 (n = 33)</td>
<td>47 ± 17 (n = 85)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>CT scan performed</strong></td>
<td>50 (81%)</td>
<td>161 (83%)</td>
<td>0.708</td>
</tr>
<tr>
<td>Thrombus distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>4 (10%)</td>
<td>15 (10%)</td>
<td>0.849</td>
</tr>
<tr>
<td>Right</td>
<td>9 (23%)</td>
<td>31 (22%)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>26 (67%)</td>
<td>99 (68%)</td>
<td></td>
</tr>
<tr>
<td>Proximal level</td>
<td>12 (31%)</td>
<td>72 (50%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Main</td>
<td>20 (51%)</td>
<td>56 (39%)</td>
<td></td>
</tr>
<tr>
<td>Lobus</td>
<td>5 (13%)</td>
<td>17 (12%)</td>
<td></td>
</tr>
<tr>
<td>Subsegmental</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>V/P scan performed</strong></td>
<td>6 (10%)</td>
<td>34 (17%)</td>
<td>0.163</td>
</tr>
<tr>
<td>Venous compression sonography performed</td>
<td>57 (92%)</td>
<td>178 (76%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Thrombophilia tests (positive/not performed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>8 (13%)/15 (24%)</td>
<td>19 (10%)/62 (32%)</td>
<td>0.470</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>3 (5%)/24 (39%)</td>
<td>11 (6%)/79 (41%)</td>
<td>0.927</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>6 (10%)/30 (48%)</td>
<td>2 (1%)/90 (46%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>6 (10%)/29 (47%)</td>
<td>6 (3%)/90 (46%)</td>
<td>0.087</td>
</tr>
<tr>
<td>Lupus anticoagulants</td>
<td>11 (18%)/17 (27%)</td>
<td>31 (16%)/62 (32%)</td>
<td>0.799</td>
</tr>
<tr>
<td>Anticardiolipin AB</td>
<td>0 (0%)/18 (29%)</td>
<td>3 (2%)/63 (32%)</td>
<td>0.528</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction.
Economy-class syndrome and flight distance

The number of passengers per year has increased continuously during the observation period (Figure 5). From 1997 to 2006, nearly 240 million passengers arrived at the Frankfurt Airport. One-third of all passengers were on long-haul flights (over 5000 km; Table 3). Based upon these data, we calculated an overall incidence of symptomatic PE following air-travel of about one case per 5 million passengers. With the risk of a symptomatic PE at nearly one case per 2 million passengers travelling further than 5000 km, this incidence would reflect a 17-fold increase compared with shorter flights.

Predisposing factors

It appears that isolated ECS without any associated risk factor is a very rare event (13%; Figure 6). In 40% of the ECS patients, thrombophilia was confirmed. Seven per cent of ECS patients had neoplastic disease and 10% had other predisposing factors (e.g. pulmonary hypertension, Behcet disease, use of oral contraceptives, etc.). Despite the retrospective evaluation and the therefore non-systematic documentation of medical history regarding VTE (recurrent event or hereditary disease), we found in 10% of the medical reports evidence of a VTE family history and in 16% evidence of a recurrent event. Even on the basis of incomplete screening during clinical practice (about 30% of ECS patients did not undergo any screening procedure), thrombophilia had been diagnosed in 40% of the study population. Thirteen per cent of the ECS patients were diagnosed for Factor V Leiden, and in 18% of the ECS patients, lupus anticoagulant as a prothrombotic factor was detected. Only protein C deficiency was more frequent in the ECS group compared with other entities (10% vs. 1%; P = 0.002), although screening of proteins C and S deficiency occurred infrequently (nearly 50% of the patients were not tested or tested under oral anticoagulation). Only six ECS patients (13%) had no additional predefined risk factor including a history of VTE in the past or in the family. Interestingly, the mean BMI of these patients was 35 (range 23–60), unveiling a trend to higher values compared with ECS patients with predisposing factors (mean BMI 28; P = 0.364).

Discussion

Incidence of travel-associated pulmonary embolism

The incidence of flight-associated PE was relatively low in our study (0.2 cases per 1 million passengers arriving at the Frankfurt Airport). Other trials estimated a risk roughly twice as high for PE. A previously suggested correlation between the duration of air travel and the risk of PE is confirmed by our study. In contrast to previous studies, we performed a hospital-based rather than an airport medical service-based analysis. Despite the proximity of our University Hospital to the airport, we cannot exclude the possibility that patients had been brought to other hospitals. When comparing data from the airport-based ambulance organization (which is the primary destination for medical advice or primary care at the airport) to the number of patients admitted to our hospital for the year 2005, we confirmed that more than 60% of their patients were transferred to our clinic. Unfortunately, we have no data regarding the preclinical selection. But what can be mentioned is that all alternative healthcare facilities have comparable possibilities of medical supply including, for example, 24 h percutaneous coronary intervention on-call service and high-level ICUs. Due to this fact the main consideration for selection of the destination is the actual availability of ICU capacity and not clinical presentation of the patients.

Some uncertainty in drawing conclusions from this study is the possibility of missed preclinical fatal cases, which we did not detect, and missed subclinical events. The only study screening for subclinical venous thrombo-embolic events detected about one in 10 passengers developing symptomless DVT after airline travel despite excluding patients with known predisposing factors. It must be assumed that asymptomatic PE is much more common compared with symptomatic PE. Therefore, the true frequency of (symptomatic and asymptomatic) PE during long-haul air travel is unknown. The fact that pulmonary emboi
following travel are smaller compared with patients with non-ECS PE. Some reports have suggested that PE may occur several weeks after air travel. This presents a further limitation for all airport-bounded analysis of one area. Nevertheless, symptomatic ECS seems to be a very rare phenomenon in relation to the number of passengers despite all the limitations of our and previous studies. Unfortunately, it is not possible to perform any estimation about the incidence of travel-associated PE due to travel by bus, car, or train. We can only assume that the risk of PE due to ground travelling is much lower because of the commonly shorter trip duration.

The important and crucial question, in which case primary prevention should be recommended, remains unanswered. In hospitalized patients, where VTE occurs at a rate of about one case per 200 patients, primary prevention leads to an absolute risk reduction of ~29%. This translates into an estimated number needed to treat of 345. The suspected ~25 000 times lower incidence of ECS would not justify primary prevention such as low-molecular-weight heparin for all passengers. Nevertheless, in patients with known risk factors such as thrombophilia, positive history for VTE, or obesity, preventive measures on long-haul flights over 5000 km should be encouraged.
Travel-associated pulmonary embolism due to air travelling vs. travelling by bus or car

Patients with PE due to non-air-travel ECS were significantly overweight compared with air-travel-associated PE, indicating that obesity might be a crucial risk factor for prolonged car, bus, or train travelling. We did not detect further differences between these groups regarding their baseline characteristics, initial clinical presentation, and prognosis.

Predisposing factors and clinical presentation

The majority of ECS patients had additional predisposing risk factors such as neoplasm, thrombophilia, obesity, or history of VTE in the past or in the family history. In the ICOPER Registry, death in the long-term follow up due to neoplasm occurred in 17.6%,5 which averages the proportion of predisposing neoplasm in our population. It must be assumed that we missed some risk factors in the retrospective analysis of medical charts. Owing to the non-systematic screening for thrombophilia it may be that the true prevalence of thrombophilia is underestimated. Intrahospital mortality is mainly driven by acute right heart failure and the following multiple organ disorder. This is similar to other entities of PE (ECS 4.8%, others 4.1%, P = 0.730).

The higher occurrence of syncope as the leading symptom, a higher rate of S1Q3 ECG-pattern, and more cases requiring cardiopulmonary resuscitation indicate that ECS patients present with more acute haemodynamic relevant events in ECS patients instead of smaller emboli shown at CT scan.

It is well known that in the long-term follow-up of PE death, in contrast to acute mortality, is not regularly caused by pulmonary hypertension and cor pulmonale.16 Owing to the different pathology, we considered it necessary to analyse predictors of acute and long-term prognosis separately for our patients. Unfortunately, we could not investigate the cause of death during long-term follow-up, which would have given us more insights into the pathophysiology leading to a fatal course in PE patients. It has been shown that cardiovascular events are more common in patients with idiopathic PE compared with those patients associated with transient risk factors. Cardiovascular events were also the major cause of death in patients with idiopathic PE.17

Long-term outcome of patients with economy-class syndrome

Intrahospital mortality was not statistically different between both groups (4.3% overall). If preclinical fatal cases (not detectable by our study) would have been added, acute mortality due to PE would have still been substantially high, despite great advancement in acute preclinical and clinical management of patients with PE over the last years. Fortunately, our patients had an excellent prognosis once discharged from our hospital. We also hypothesize that patients with asymptomatic travel-associated PE will not suffer from significant mortality due to an expected smaller thrombus load and therefore less cardiopulmonary restriction. Furthermore, our follow-up data show a markedly better functional state of ECS patients.

Little data exist thus far concerning the long-term outcome of patients following PE. In one of the largest registries (ICOPER), 3 month overall mortality (which included patients lost to follow-up) was 17.6%.5 Longer outcome data are not available from this database. The 3 month mortality in our patients was similar in both groups (ECS 7.0%, others 7.3%; P > 0.999, including neoplasm). Unfortunately, long-term follow-up was not available in 19 ECS patients (vs. two patients in the non-ECS group), limiting the strength of our data. This difference is explained by the very heterogeneous group of ECS patients, a large proportion of which came from outside the European continent. Nevertheless, the ECS group showed a markedly better long-term survival, regardless of whether we included patients with neoplasm or not.

Limitations of the study

The non-systematic screening for additional risk factors in clinical practice (e.g. thrombophilia or neoplasm) caused some uncertainty in estimating the relevance of additional risk factors. The main limitation of the study is that the calculation of ECS incidence is hampered by missing data from potential preclinical fatal cases, missing subclinical events, and inadequate detection of subacute
cases (which continue travelling to other destinations). Despite the proximity of our clinic to the airport, the number of patients being admitted to other hospitals was estimated to be <40%. This certainly represents another important limitation to our study. Finally, the high proportion of lost to follow-up patients in the ECS group (19 patients with travel-associated PE; 17 of these patients were not residents in Germany) slightly weakens our conclusion on the excellent prognosis following hospital discharge of these patients.

Conclusions
Symptomatic patients with ECS requiring medical care are a rare phenomenon concerning the high number of passengers. After surviving the acute phase, long-term prognosis is excellent with a better functional outcome compared with other entities of PE. Interestingly, most patients with ECS-associated PE do have further predisposing factors.

Supplementary material
Supplementary material is available at European Heart Journal online.

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