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## SEVERE PULMONARY EMBOLISM ASSOCIATED WITH AIR TRAVEL

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### ABSTRACT

**Background** Air travel is believed to be a risk factor for pulmonary embolism, but the relation between pulmonary embolism and distance flown has not been documented. The aim of this study was to investigate whether the duration of air travel is related to the risk of pulmonary embolism.

**Methods** From November 1993 to December 2000, we systematically reviewed all cases of pulmonary embolism requiring medical care on arrival at France's busiest international airport. Data on the geographic origins of all flights and the numbers of passengers were collected in order to evaluate the incidence of pulmonary embolism per million passenger arrivals as a function of the distance traveled.

**Results** A total of 135.29 million passengers from 145 countries or other areas arrived at Charles de Gaulle Airport during the period of the study, of whom 56 had confirmed pulmonary embolism. The incidence of pulmonary embolism was much higher among passengers traveling more than 5000 km (3100 mi) (1.5 cases per million, as compared with 0.01 case per million among those traveling less than 5000 km). The incidence of pulmonary embolism was 4.8 cases per million for those traveling more than 10,000 km (6200 mi).

**Conclusions** A greater distance traveled is a significant contributing risk factor for pulmonary embolism associated with air travel. (N Engl J Med 2001;345:779-83.)

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**A**IR travel is considered a risk factor for pulmonary embolism and has been termed "economy-class syndrome."<sup>1,2</sup> Immobility, aggravated by the limited space in economy class, is assumed to be responsible for this risk. Whereas the number of air passengers continues to increase, the relation between pulmonary embolism and the distance traveled by air has not yet been sufficiently investigated.<sup>3,4</sup> Roughly 100 cases of pulmonary embolism occurring after air travel have been reported during the past three decades.<sup>1,2,5-23</sup> Most of these re-

ports were based on small numbers of patients, included cases of both deep venous thrombosis and pulmonary embolism, or included poorly documented cases. We therefore undertook a more comprehensive evaluation of this association.

To test the hypothesis that a greater duration of air travel is a risk factor for pulmonary embolism, we systematically reviewed all documented occurrences of pulmonary embolism requiring medical care on arrival at France's busiest international airport.

### METHODS

#### Criteria for Inclusion

We systematically reviewed the records of all patients arriving at Charles de Gaulle Airport between November 1993 and December 2000 who required medical care and transport to a hospital by a French emergency medical team because of suspected pulmonary embolism. This medical-transport team is responsible for all patients requiring emergency transport from the airport. Suspicion of pulmonary embolism was based on the presence of one or more of the following clinical criteria within one hour after arrival at the airport: chest pain, malaise, syncope, or shortness of breath. The diagnosis was confirmed by scintigraphic ventilation-perfusion scanning, pulmonary angiography, or high-resolution helical computed tomographic (CT) angiography indicating a high probability of pulmonary embolism. Patients in whom the diagnosis of pulmonary embolism was subsequently ruled out were excluded from the study. Patients who died in flight or who were pronounced dead on arrival at the airport did not generate a call to the medical-transport team and were therefore not included.

#### Airport Data

A list of all passengers who arrived during the study period at Charles de Gaulle Airport in Roissy, France, according to the origin, distance, and duration of the flight, was obtained from Aéroports de Paris. A flight was defined as the period between takeoff and landing of nonstop and direct flights (including stopovers). The initial origin of passengers cannot be ascertained from Aéroports de Paris data but was known for patients with pulmonary emboli.

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### Data on Patients

The following data were obtained for all patients included in the study: origin of the flight (country or other area), distance of the flight, duration of the flight, and class of travel. Information on ambulation during the flight was recorded during an interview with the patient by the physician on the medical-transport team. Risk factors for thromboembolic events were classified as associated with high or moderate risk.<sup>24,25</sup> Factors associated with high risk were recent immobilization (within one week) for more than three days, recent surgery or multiple trauma (within three weeks), previous deep venous thrombosis or pulmonary embolism, previous or current cancer, current or recent pregnancy (within three months), previous or current congestive heart failure, and previous or current coagulation disorders. Factors associated with moderate risk were varicose veins, use of oral contraceptive or hormone-replacement therapy, age greater than 40 years, obesity, tobacco use, and the nephrotic syndrome.

The characteristics of the clinical presentation were documented, including the time of onset of the first symptom (during the flight, on standing up after landing, on leaving the airplane through the jetway, or in the airport) and any occurrence of cardiac arrest, chest pain, malaise, or dyspnea.

The presence, location, and extent of pulmonary embolism were determined from the results of scintigraphic ventilation-perfusion scanning, pulmonary angiography, or high-resolution helical CT angiography. When transthoracic echocardiography was performed, the presence of acute right ventricular dysfunction was recorded as an indicator of the severity of pulmonary embolism.<sup>26</sup> The severity of pulmonary embolism was assessed according to published criteria, including syncope, clinically apparent acute right ventricular dysfunction, shock (defined as a systemic arterial pressure of less than 80 mm Hg), tachycardia (defined as a pulse rate of more than 120 beats per minute), and a score of 17 or higher on the angiographic Miller index<sup>27</sup> (with 34 points representing complete obstruction of the pulmonary arterial bed). The duration of stay in the hospital and the final outcome were recorded.

### Statistical Analysis

The results of our analyses are expressed as means  $\pm$ SD. Quantitative data were compared by means of a two-tailed Student's *t*-test, and qualitative data by a chi-square test; *P* values of 0.05 or less were considered to indicate a significant difference. The incidence of pulmonary embolism in cases per million passenger arrivals was calculated as a function of distance traveled for increments of 2500 km (1550 mi). The exact continuity-corrected 95 percent confidence interval for a binomial probability was calculated for each incidence of pulmonary embolism, as described by Vollset.<sup>28</sup>

## RESULTS

### Airport Data

The total number of arriving passengers at Charles de Gaulle Airport during the study period was 135.29 million. Flights arrived from 145 countries or other geographic areas (Table 1).

### Data on Patients

One hundred seventy patients were transported to local hospitals with clinical suspicion of pulmonary embolism. Among these patients, 114 (67 percent) were subsequently found not to have pulmonary embolism according to clinical, laboratory, and radiographic imaging criteria and were excluded from the study, leaving 56 (33 percent) with confirmed pulmonary embolism. Forty-two patients (75 percent) were women and 14 (25 percent) were men. Their mean

age was  $57 \pm 12$  years, with no significant difference between men and women. Table 1 shows the origins of their flights, the distances flown, and the duration of their flights. The incidence of pulmonary embolism, expressed as the number of cases per 1 million passengers per 2500 km traveled, increased with the distance traveled (Fig. 1). The risk of pulmonary embolism significantly increased after 5000 km (3100 mi) to 1.5 cases per million ( $P < 0.001$ ). The total incidence of pulmonary embolism reached 4.77 cases per million passengers for distances greater than 10,000 km (6200 mi).

Among the 56 passengers with pulmonary embolism, 42 (75 percent) had traveled in economy class (also known as tourist class), 2 (4 percent) had traveled in business class, and the class of travel was unknown for 12 patients (21 percent). Only 3 patients (5 percent) reported that they had left their seats during the flight, 42 (75 percent) reported that they were completely immobile during the flight, and information on mobility was unavailable for 11 patients (20 percent).

Factors associated with high and moderate risk of thromboembolic diseases were reported in 4 patients (7 percent) and 49 patients (87 percent), respectively (Table 2).

The first symptom suggesting pulmonary embolism occurred during air travel in the cases of 8 patients (14 percent), on standing up after landing in the cases of 16 patients (29 percent), and in the jetway in the cases of 32 patients (57 percent). In no case did the primary manifestation occur beyond the jetway — that is, inside the airport. The first symptom was malaise in 54 patients (96 percent); 27 of these patients also had syncope; 36 also had dyspnea (64 percent); and 20 also had chest pain (36 percent). In the two patients for whom the chief symptom was not malaise, one patient reported dyspnea and the other was in cardiac arrest and was successfully resuscitated. Symptoms of acute right ventricular dysfunction were reported in 30 patients (54 percent); these included distended neck veins in 24 patients, hepatojugular reflux in 18 patients, and right-upper-quadrant pain in 6 patients.

The diagnosis of pulmonary embolism was confirmed by scintigraphic ventilation-perfusion scanning in 34 patients (61 percent), pulmonary angiography in 9 (16 percent), and high-resolution helical CT angiography in 28 (50 percent). In 40 patients (71 percent), more than one examination was performed. The pulmonary emboli were bilateral in 53 patients (95 percent). Transthoracic echocardiography was performed in 25 patients (45 percent), with acute right ventricular dysfunction found in 17.

Each patient met at least one criterion for severe pulmonary embolism: syncope in 27 (48 percent), acute right ventricular dysfunction in 30 (54 percent), shock in 6 (11 percent), tachycardia in 15 (27 percent), a Miller index score of 17 or higher in 7 (12 percent), and cardiac arrest in 1 (2 percent). The mean

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TABLE 1. CASES OF PULMONARY EMBOLISM AMONG PASSENGERS ARRIVING AT CHARLES DE GAULLE AIRPORT FROM 1993 TO 2000 AND DATA ON FLIGHTS.\*

COUNTRY OR AREA OF ORIGIN OF FLIGHT	FLIGHT DISTANCE (km)	FLIGHT DURATION (HR:MIN)	MILLIONS OF ARRIVING PASSENGERS	NO. WITH PULMONARY EMBOLISM	ORIGINS OF FLIGHTS WITH CASES OF PULMONARY EMBOLISM (NO. OF CASES; FLIGHT DISTANCE; FLIGHT DURATION)
France	<1500	<1:50	13.25	0	
Algeria, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, Germany, Gibraltar, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Libya, Macedonia, Malta, Moldova, Morocco, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tunisia, Turkey, United Kingdom, Yugoslavia	<2500	<3:00	75.24	0	
Armenia, Azerbaijan, Bahrain, Benin, Burkina Faso, Chad, Ivory Coast, Cyprus, Egypt, Gambia, Georgia, Ghana, Guinea, Guinea-Bissau, Iran, Israel, Jordan, Kuwait, Latvia, Lebanon, Lithuania, Mali, Mauritania, Niger, Nigeria, Pakistan, Qatar, Russia, Saudi Arabia, Senegal, Sierra Leone, Sudan, Syria, Togo, Ukraine	2500-4999	3:00-5:59	9.18	1	Senegal (1; 4200 km; 6.00 hr)
Afghanistan, Angola, Antigua, Bahamas, Barbados, Bermuda, Burundi, Cameroon, Canada, Cape Verde, Central African Republic, Democratic Republic of the Congo, Djibouti, Dominican Republic, French Antilles, French Guiana, Gabon, Haiti, India, Kazakhstan, Kenya, Nepal, Netherlands Antilles, Oman, Puerto Rico, Rwanda, St. Lucia, Somalia, Tanzania, Uganda, United Arab Emirates, United States, Uzbekistan, Yemen	5000-7499	6:00-8:59	22.53	9	United States Los Angeles (4; 9080 km; 10.30 hr) San Francisco (1; 8950 km; 10.30 hr) Netherlands Antilles (2; 6760 km; 8.30 hr) Angola (1; 6500 km; 8.00 hr) India (1; 6580 km; 8.25 hr)
Botswana, Brazil, China, Colombia, Comores, Cuba, Ecuador, Hong Kong, Japan, Korea, Madagascar, Malawi, Mauritius, Mexico, Mozambique, Namibia, Nepal, Reunion, Seychelles, South Africa, Sri Lanka, Taiwan, Thailand, Venezuela, Zambia, Zimbabwe	7500-9999	9:00-11:59	12.37	33	Japan (7; 9710 km; 12.00 hr) Hong Kong (6; 9630 km; 12.50 hr) Thailand (6; 9450 km; 11.00 hr) Mauritius (4; 9410 km; 11.25 hr) South Africa (4; 8730 km; 10.50 hr) Mexico (2; 9200 km; 12.00 hr) Reunion (2; 9440 km; 11.00 hr) Brazil (1; 9170 km; 11.00 hr) China (1; 8220 km; 10.75 hr)
Argentina, Australia, Chile, French Polynesia, Indonesia, Malaysia, New Caledonia, Peru, Philippines, Singapore, Tonga, Uruguay, Vietnam	≥10,000	≥12:00	2.72	13	Singapore (4; 10,740 km; 15.00 hr) Australia (2; 16,960 km; 22.75 hr) French Polynesia (2; 15,710 km; 20.0 hr) Argentina (1; 11,050 km; 13.25 hr) Indonesia (1; 12,350 km; 17.25 hr) Malaysia (1; 10,420 km; 14.00 hr) Philippines (1; 10,470 km; 15.00 hr) Vietnam (1; 10,180 km; 15.00 hr)
Total			135.29	56	

\*Data on flights are from Aéroports de Paris, Charles de Gaulle Airport, 95700 Roissy, France. To convert kilometers to miles, multiply by 0.62.

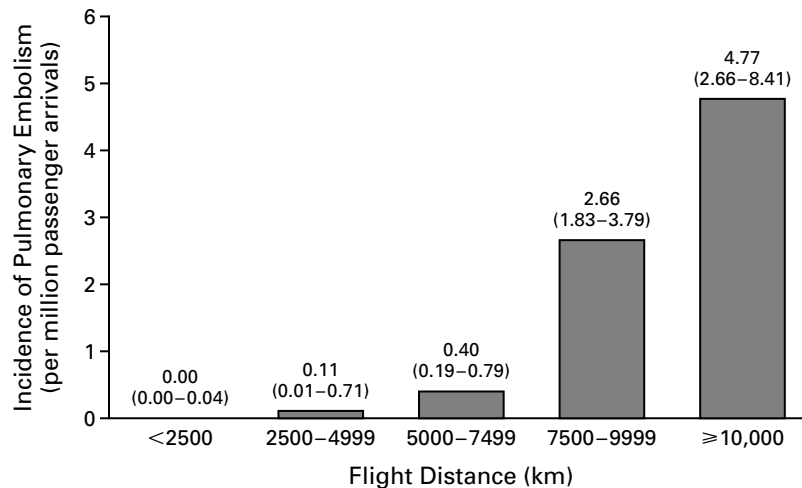
duration of the hospital stay was 7±4 days. There was one death, in a patient whose pulmonary embolism was complicated by an ischemic cerebral stroke due to paradoxical embolism.

DISCUSSION

A relation between the duration of air travel and the risk of pulmonary embolism is strongly suggested by this study. The incidence of pulmonary embolism was markedly higher among passengers who traveled by air for more than 5000 km or spent approximately six hours or more in flight; these results thus demonstrate that a longer distance traveled is a significant risk factor for pulmonary embolism (Fig. 1). All patients

with pulmonary embolism had traveled at least 4000 km (2480 mi). The increased incidence of pulmonary embolism with increased duration of air travel was apparently not due to an increased duration of the observation period alone (i.e., the fact that passengers who took longer flights were observed for longer periods than passengers who took shorter flights). If this were the case, the incidence would be expected to be constant.

The incidence of pulmonary embolism was low in our study. The duration of the observation period was short, corresponding to the duration of flight plus up to one hour spent in the airport; therefore, the comparison of this incidence with the reported incidence



**Figure 1.** Incidence of Pulmonary Embolism According to Distance Traveled by Air.

Values shown above the bars are numbers of cases per million passenger arrivals, with 95 percent confidence intervals. To convert kilometers to miles, multiply by 0.62.

of pulmonary embolism in the population would be of questionable value.

It is possible that we underestimated the incidence of pulmonary embolism during air travel because of our inability to detect relatively mild cases, cases occurring after passengers had left the airport, and cases that resulted in death in flight (for which the medical-transport team would not have been notified). Severe pulmonary embolism accounts for approximately 20 percent of clinical presentations with pulmonary embolism, and therefore, one might expect an incidence of approximately 25 per million passengers for pulmonary embolism after flights of more than 10,000 km. In our study, only the presence of severe clinical signs, particularly syncope, resulted in a call for emergency medical services. It seems unlikely that pulmonary embolism during air travel is always severe. Passengers with minor signs, such as mild-to-moderate chest pain, fever, or calf pain, may leave the airport without medical consultation and thus without a diagnosis. Several reports have suggested that pulmonary embolism may develop in passengers several weeks after air travel.<sup>17,18,20,29</sup> We therefore speculate that the incidence not only of pulmonary embolism, but also of deep venous thrombosis (which was not a subject of our study), is probably higher after long-distance air travel than our study would suggest.

It should be emphasized, nonetheless, that the incidence of severe pulmonary embolism during air travel appears to be low. Among 135.29 million passengers arriving at Charles de Gaulle Airport during the study period, only 56 had confirmed pulmonary embolism, for an incidence of roughly 0.4 case per million passengers. Pulmonary embolism was ruled out in 67 percent of suspected cases.

Only four patients had factors generally accepted as associated with a high risk of pulmonary embolism (Table 2).<sup>25</sup> Most patients had factors associated with moderate risk.<sup>30</sup> Our methods did not permit us to discern the importance of risk factors other than duration of flight (because these factors are unknown for passengers without pulmonary embolism), including travel class and immobility. Still, it seems prudent to recommend that, in the case of suspected thromboembolic events, physicians should always consider long-distance air travel as a risk factor.

The percentage of cardiac arrests that occur in flight or immediately after landing that might be attributable to pulmonary embolism is unknown. This issue has been partially addressed by autopsy studies,<sup>13,31,32</sup> but data on survivors of cardiac arrest are lacking. The low mortality rate in our study may be due in part to the fact that the medical-transport team is not called when death is pronounced by airport medical personnel on the patient's arrival.

Homans described thromboembolic complications during travel in 1954.<sup>33</sup> He reported five cases of thromboembolic events after travel, including two deep venous thromboses. A case of pulmonary embolism after air travel was reported in 1968.<sup>5</sup> Nine years later, Symington and Stack proposed the term economy-class syndrome,<sup>1</sup> which has since been used by others to describe the condition of decreased mobility of passengers in economy seating (relative to other classes of travel).<sup>2,15,18</sup> The sitting position is associated with venous stasis and increased blood viscosity, and after only one hour is associated with a substantial decrease in blood flow, increased hematocrit, and increased concentrations of blood proteins in the legs.<sup>34,35</sup> Immobility increases thrombus forma-

**TABLE 2.** REPORTED RISK FACTORS FOR THROMBOEMBOLIC DISEASES.

RISK FACTOR	NO. OF PATIENTS
<b>High risk</b>	4
Immobilization >3 days	1*
Recent surgery (within past 3 wk)	1*
Multiple trauma	0
Previous deep venous thrombosis or pulmonary embolism	3*
Cancer	1
Pregnancy or postpartum period	0
Heart failure	2
Coagulation disorders	0
<b>Moderate risk</b>	49
Varicose veins	14
Estrogen or progesterone treatment	18
Age >40 yr	49
Obesity	5
Tobacco use	4
Nephrotic syndrome	0

\*One patient reported undergoing recent surgery for varicose veins associated with immobilization.

tion.<sup>35,36</sup> Finally, vessel lesions due to the compression by the seat have been suggested as a cause of thrombosis.<sup>34</sup> Thus, the three factors of Virchow's triad — venous stasis, vessel-wall injury, and hypercoagulability — appear to be present during air travel, thus increasing the risk of venous thrombosis.<sup>29,34</sup> Even minor activity might be effective in attenuating venous stasis.<sup>36</sup> However, whether physical activity during flight is protective against pulmonary embolism remains to be demonstrated.

None of our patients reported a stopover during the flight. However, it was not possible, on the basis of available data, to be sure that stopovers did not occur during extremely long flights. Even in such cases, the final leg of these flights generally exceeded 12,000 km (7440 mi).

Given the risk of air travel of long duration, simple behavioral and mechanical prophylactic measures should be considered, even if their efficacy has not yet been established.<sup>15</sup> These include adequate consumption of fluids, with avoidance of alcohol, refraining from smoking, avoidance of constrictive clothing, use of elastic support stockings, avoidance of leg crossing, frequent changes of position while seated, and minor physical activity, such as walking, or at least moving the legs.

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