Pulmonary Thromboembolism Associated With Air Travel in Japan

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Background A link between venous thromboembolism (VTE) and air travel has been recently discussed, so the present study aimed to clarify the characteristics of acute pulmonary thromboembolism (PTE) associated with air travel in Japan.

Methods and Results The study group comprised 36 patients with acute PTE associated with air travel. Patients' characteristics, clinical risk factors for VTE and coagulation abnormalities were investigated, and compared with a group of PTE not associated with travel. Of the 36 cases, 30 cases were female, 34 were over 40 years of age and all had flown more than 6 h. Two-thirds of all cases did not leave their seats during the flight. Of the patients, 44% had no clinical risk factors for VTE or coagulation abnormalities. Idiopathic PTE (ie, PTE without clinical risk factors or coagulation abnormalities) was significantly more common in the air travel group.

Conclusion Acute PTE associated with air travel in Japan is common in elderly women and may occur without any clinical risk factors for VTE or coagulation abnormalities. Remaining seated throughout the flight increases the risk. (Circ J 2005; 69: 1297–1301)

Key Words: Economy class syndrome; Long-haul flights; Traveler's thrombosis; Venous thrombosis

A link between venous thromboembolism (VTE) and air travel has been recently discussed.^{1–4} The first case of deep vein thrombosis associated with air travel was reported in 1954⁵ and in 1977, there were 3 cases of acute pulmonary thromboembolism (PTE) after air travel, which was called “economy class syndrome”.⁶ Since the 1980s, many cases of acute VTE after air travel have been reported as “economy class syndrome”,⁷ “coach class thrombosis”⁸ or “traveler's thrombosis”⁴ in Europe and the United States.

In Japan, the number of cases with PTE is lower than in Western countries, but the incidence has been increasing in recent years.^{9–10} The first report of acute PTE associated with air travel was published in 1996¹¹ and a total of 24 case reports of acute PTE after air travel have been published up to 2004 (excluding this report).

Narita Red Cross Hospital is the closest general hospital to Narita Airport (the busiest international airport in Japan), and 36 cases of acute PTE associated with air travel were admitted from 1994 to 2004. The purpose of this study was to clarify the characteristics of acute PTE associated with air travel in Japan.

Methods

Patients

Of the 79 cases of acute PTE treated from 1994 to 2004, 36 were acute PTE associated with air travel (46%). None

of these patients had any symptoms suggesting VTE before travel. Symptoms of PTE, such as dyspnea, chest pain, palpitation or syncope, occurred for the first time during the flight or immediately after landing. Of the other 43 patients with acute PTE who had not traveled within the past 30 days (PTE without travel group), 14 cases occurred as a complication of admission.

Protocol

This study was a retrospective investigation of clinical records. The diagnosis of PTE was confirmed by scintigraphic ventilation–perfusion scanning or helical computed tomography. We recorded each patient's nationality, age, sex, height, body weight and clinical risk factors for VTE (obesity, active inflammation, smoking, recent minor surgery [within past 3 days], varicose veins, heart failure (uncontrolled), recent myocardial infarction [within 6 weeks], hormone therapy [including oral contraception], pregnancy/postpartum, lower limb paralysis, intravenous catheter, lower limb trauma [within 6 weeks], previous VTE, family history of VTE, known thrombophilia, previous cerebral vascular attack (CVA), malignancy, and recent major surgery [within 6 weeks]).⁴ A coagulation study for protein S, protein C, anti-thrombin III, lupus anticoagulant, anti-cardiolipin antibody was also performed. The origin of the flight, its duration, the class and position of seat, and the length of time patients remained seated during the flight were also investigated.

Results

Table 1 shows the characteristics of the patients with acute PTE after air travel. Their ages ranged from 39 to 75 years of age (60.1 ± 10.3 years old, mean $\pm$ SD); 34 cases (94%) were over 40 years of age; 30 cases were female.

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Table 1 Characteristics of the Patients With Acute PTE After Air Travel

Case no.	Age (years)	Sex	Height (cm)	Weight (kg)	BMI (kg/m ²)	Nationality	Clinical risk factors
1	67	F	147	49	22.7	Japan	–
2	53	F	165	78	28.7	Japan	Varicose vein, obesity
3	61	F	156	52	21.4	Japan	Uterine cancer
4	50	F	158	60	24.0	Japan	Contraception
5	61	M	173	72	24.1	Japan	–
6	75	F	150	50	22.2	Japan	Breast cancer
7	61	F	155	52	21.6	Japan	Varicose veins
8	50	F	158	58	23.2	Japan	–
9	39	F	162	60	22.9	Japan	–
10	57	F	155	55	22.9	Japan	Previous PTE, varicose veins
11	68	F	150	65	28.9	Japan	Obesity
12	49	F	153	55	23.5	Japan	Varicose veins
13	69	M	165	65	23.9	Chinese Taipei	Smoking
14	74	F	147	51	23.6	Japan	Previous PTE
15	71	F	149	54	24.3	Japan	–
16	70	F	155	77	32.0	Japan	Varicose veins, obesity
17	53	F	156	54	22.2	Japan	–
18	70	F	158	59	23.6	Japan	–
19	62	F	158	60	24.9	Japan	Varicose veins
20	57	F	162	62	23.4	Japan	–
21	49	F	161	58	22.4	Japan	–
22	47	F	160	53	20.7	Japan	–
23	57	F	149	55	24.8	Japan	Varicose veins
24	70	F	165	75	27.5	Japan	Obesity
25	56	F	157	60	24.3	Japan	–
26	57	M	183	95	28.4	USA	Minor surgery, obesity, smoking
27	55	M	168	69	24.4	UK	–
28	73	F	155	70	29.1	Japan	Obesity
29	57	M	168	75	26.6	Japan	Obesity, smoking
30	69	M	176	76	24.5	Japan	Smoking
31	69	F	159	43	17.1	Japan	Varicose veins
32	68	F	157	56	22.7	Japan	Varicose veins
33	40	F	162	56	21.3	Japan	–
34	69	F	160	51	19.9	Japan	–
35	70	F	150	46	20.4	Japan	–
36	39	F	158	55	22.0	Japan	–
Mean±SD	60.1±10.3		158.9±8.0	60.6±10.9	23.9±3.0		

PTE, pulmonary thromboembolism.

Height ranged from 147 to 183 cm (158.9±8.0 cm), body weight ranged from 43 to 95 kg (60.6±10.9 kg) and body mass index (BMI) ranged from 17.1 to 32.0 kg/m² (23.9±3.0 kg/m²); only 7 cases were obese (BMI >25 kg/m²). One patient was from Chinese Taipei, 1 from USA, 1 from UK, and the other 33 cases were Japanese. Of the 36 cases, 20 had clinical risk factors for VTE (obesity: 7; smoking: 4; minor surgery: 1; varicose veins: 9; contraceptives: 1; history of PTE: 2; malignancy: 2) and 16 cases (44%) did not.

Table 2 shows the travel information of the patients with acute PTE: 14 had flown from the United States mainland, 4 from Hawaii, 14 from Europe, 2 from South America, and 1 each from Australia and Asia. All flights were more than 6 h (range 6.1–24.3 h, mean 12.1±3.2 h). Only 1 patient flew in business class, and the other 35 were in economy class; 12 patients were in window seats, 16 were in center seats and 7 were in aisle seats (seat position was not recorded for 1 patient). More cases were in window or center seats than in aisle seats. Two-thirds of all cases (22) remained seated throughout the flight. The average time out of the seat during the flight was 0.8±1.3 h.

Table 3 shows a comparison of the clinical risk factors for VTE and coagulation abnormalities in the 2 groups. In the group with air travel 20 cases had at least 1 clinical risk factors and in the PTE without travel group 40 cases had clinical risk factors (obesity: 15; smoking: 7; varicose veins: 2; heart failure: 2; hormone therapy: 4; postpartum:

1; lower limb paralysis: 2; intravenous catheter: 1; lower limb trauma: 3; previous VTE: 2; previous CVA: 5; malignancy: 8; recent major surgery: 5). None of the group with air travel had coagulation abnormalities, whereas 3 cases in the group without travel did (protein C deficiency: 2, protein S deficiency: 1; these 3 cases also had clinical risk factors). There were 16 cases (44%) of idiopathic PTE (ie, PTE without clinical risk factors for VTE or coagulation abnormalities) in the air travel group and was significantly more common than in the group without travel ($p=0.0001$).

Discussion

Since the 1980s, many cases of acute PTE after air travel have been reported in Europe and the United States,^{7,8,12–20} but only 24 cases were reported in Japan until 2004 and ours is the most recent (Table 4). Patient characteristics were not documented in the previous reports, but the data for age, sex, flight time and clinical risk factors were similar to our report.

In our study acute PTE associated with air travel occurred more frequently in women than in men. Table 5 shows the published series of VTE associated with travel in Western countries. Lapostolle et al showed that PTE associated with air travel occurred more frequently in women,¹⁵ but Mercer et al reported opposite data¹³ and in many other reports, the incidence of VTE associated with travel is the

Table 2 Travel Information for the Patients With PTE After Air Travel

Case no.	Origin of flight	Duration of flight (h)	Stop-overs (n)	Class	Seat (W/C/A)	Leaving seat (n)
1	Hawaii	8	—	E	Unknown	0
2	Hawaii	8	—	E	A	0
3	Hawaii	8	—	E	W	0
4	London	11.8	—	E	W	0
5	New York	13.5	—	E	W	0
6	Rome	14	—	E	A	3
7	Los Angeles	11.5	—	E	C	0
8	Sydney	9.5	—	E	W	0
9	London	12	—	E	W	1
10	New York	13.5	—	E	A	2
11	Los Angeles	11.5	—	E	A	2
12	Paris	11.7	—	E	A	0
13	New York	13	—	E	C	0
14	London	11.8	—	E	W	2
15	Seattle	10	—	E	C	1
16	Hawaii	8	—	E	C	0
17	New York	13.8	—	E	C	0
18	Paris	11.5	—	E	C	0
19	Washington DC	13.5	—	E	C	0
20	Amsterdam	11	—	E	C	0
21	Brussels	11.8	—	E	W	1
22	Detroit	13	—	E	W	0
23	Milan	11.7	—	E	C	0
24	Los Angeles	11.8	—	B	C	0
25	Frankfurt	11.3	—	E	C	1
26	Bangkok	6.1	—	E	W	0
27	London	11.7	—	E	W	0
28	Sao Paulo	24.3	1	E	W	5
29	Los Angeles	11.8	—	E	C	0
30	San Francisco	10.9	—	E	C	3
31	New York	13.8	—	E	A	5
32	Paris	11.8	—	E	C	0
33	London	12.3	1	E	W	1
34	Chicago	13.1	—	E	C	1
35	Zurich	12.9	1	E	C	1
36	Lima	20.3	1	E	A	0
Mean $\pm$ SD		12.1 $\pm$ 3.2				0.8 $\pm$ 1.3

W, window; C, center; A, aisle; E, economy; B, business.

Table 3 Comparison of the Clinical Risk Factors for VTE and Coagulation Abnormalities in the Patients With PTE

	PTE with air travel (n=36)	PTE without travel (n=43)	p value (χ^2 test)
Clinical risk factors for VTE	20	40	0.0001
Positive for coagulation search	0	3*	NS
Idiopathic PTE	16	3	0.0001

VTE, venous thromboembolism; PTE, pulmonary thromboembolism.

*Protein C deficiency, n=2; protein S deficiency, n=1. These 3 cases also had clinical risk factors.

Table 4 Case Reports of Acute PTE After Air Travel in Japan

Study	Year	No. of cases	Age	Sex	Flight time (h)	Class	Clinical risk factors
Yamashita	1996	1	53	M	13.5	U	+
Sato	1996	1	52	F	9.5	E	—
Yokoyama	2000	1	69	F	12.4	U	—
Rhujin	2001	1	72	F	10.0	U	—
Kuwano	2001	3	43, 59, 82	F3	11.7, 11.8, 13.7	E3	+2/—1
Katada	2001	1	69	F	13.0	U	—
Hirano	2001	1	28	M	20.0	U	—
Furumatsu	2002	1	65	M	U	U	—
Morimoto	2002	1	66	F	12	U	+
Hata	2002	12	62 $\pm$ 9	M1/F11	15 (mean)	U	+6/—4/U2
Mii	2004	1	50	F	13	E	+
Present	2005	36	60.1 $\pm$ 10.3	M6/F30	12.1 $\pm$ 3.2	E35/B1	+20/—16
Total		60	60.2 (mean)	M10/F50	12.7 (mean)	E40/B1	+31/—27

E, economy class; B, business class; U, unknown.

Table 5 VTE Associated With Travel in Western Countries

Study	Year	No. of cases	Sex	PTE/DVT/ST	Means of travel
Eklof ¹²	1996	44	M24/F20	DVT 28/PTE 5/DVT + PTE 11	Air
Mercer ¹³	1998	33	M27/F6	DVT 16/PTE 8/DVT + PTE 9	Air
Arfvidsson ¹⁴	1999	25	M11/F14	DVT 16/DVT+PTE 9	Air
Lapostolle ¹⁵	2001	56	M14/F42	PTE 56	Air
Kesteven ¹⁶	2001	86		DVT 55/PTE 11/DVT + PTE 20	Air
Hosoi ¹⁷	2002	15	M9/F6	DVT 15	Air9/Car3/Bus1/Train1/Boat1
Kesteven ¹⁸	2002	47	M21/F26	DVT and PTE	Air28/Car11/Bus6/Train2
Paganin ¹⁹	2003	46	M19/F27	DVT 33/PTE 13	Air
McQuillan ²⁰	2003	58	M30/F28	DVT 27/PTE 24/ST 7	Air 48/Car7/Bus3

VTE, venous thromboembolism; PTE, pulmonary thromboembolism; DVT, deep vein thrombosis; ST, superficial thrombophlebitis.

same in men as in women.

Recently, 4 prospective case-control studies of the link between long-distance travel and VTE have given conflicting results. Two French studies found a positive association between VTE and long-haul flights,^{21,22} but a Dutch study²³ failed to confirm that finding. One problem of the third study was that the frequency of travel in both patients and controls was low (5% and 7%, respectively). In the most recent study by Martinelli et al, the relative risk of VTE was slightly higher (3-fold) when only long-distance flights (>8 h) were considered.²⁴ Moreover, a French study¹⁵ and a Spanish study²⁵ both showed that the incidence of PTE increased with the duration of the flight, suggesting a link between air travel and PTE. In our study, idiopathic PTE was significantly more common in the group with air travel, which coincides with data reported by Ferrari et al.²¹ These data suggest that long-haul air travel itself may be a risk factor for PTE.

In the present study, none of the patients in the air travel group had coagulation abnormalities, but there were 3 cases in the group without travel. It has been reported that Factor V Leiden and prothrombin A20210G gene mutation are pathogenetic factors for VTE.^{26,27} Although these mutations were not investigated by us, no cases of these mutations have been reported in Japan.^{28,29}

The following measures are recommended for the prevention of VTE after air travel.^{1,2,4} Passengers with no identifiable risk factors should perform frequent and regular stretching exercises, particularly of the lower limbs, during the flight. Maintaining fluid intake, but restricting alcohol, is also sensible and without hazard. Passengers with one or more identifiable risk factors should wear compression stockings and carry a supply of self-injected low molecular weight heparin.

In conclusion, acute PTE associated with air travel is common in elderly Japanese women and passenger who remain seated throughout the flight. It may occur in patients without any clinical risk factors for VTE or coagulation abnormalities.

References

- Gallus AS, Goghan DC. Travel and venous thrombosis. *Curr Opin Pulm Med* 2002; **8**: 372–378.
- O'Keefe DJ, Baglin TP. Traveller's thrombosis and economy class syndrome: Incidence, aetiology and prevention. *Clin Lab Haematol* 2003; **25**: 277–281.
- Mendis S, Yach D, Alwan A. Air travel and venous thromboembolism. *Bull World Health Organ* 2002; **80**: 403–406.
- Bagshaw M. The Air Transport Medicine Committee, Aerospace Medical Association. Traveller's thrombosis: A review of deep vein thrombosis associated with travel. *Aviat Space Environ Med* 2001; **72**: 848–851.
- Homans J. Thrombosis of the deep leg veins due to prolonged sitting. *N Engl J Med* 1954; **250**: 148–149.
- Symington IS, Stack BHR. Pulmonary thromboembolism after travel. *Br J Dis Chest* 1977; **71**: 138–140.
- Cruickshank JM, Gorlin R, Jennett B. Air travel and thrombotic episodes: The economy class syndrome. *Lancet* 1988; **ii**: 497–498.
- Arfvidsson B, Eklof B, Kistner RL, Masuda EM, Sato DT. Risk factors for venous thromboembolism following prolonged air travel: Coach class thrombosis. *Hematol Oncol Clin North Am* 2000; **14**: 391–400.
- Ota M, Nakamura M, Yamada N, Yazu T, Ishikura K, Fujioka H, et al. Association between antithrombotic treatments and prognosis of patients with acute pulmonary thromboembolism. *Circ J* 2003; **67**: 612–616.
- Sakuma M, Nakamura M, Nakanishi N, Miyahara Y, Tanabe N, Yamada N, et al. Inferior vena cava filter is a new additional therapeutic option to reduce mortality from acute pulmonary embolism. *Circ J* 2004; **68**: 816–821.
- Yamashita M, Mori Y, Shimada T, Kawakami K. A case of economy class syndrome. *Rinsyo-Kakuigaku* 1996; **29**: 105–107 (in Japanese).
- Eklof B, Kistner RL, Masuda EM, Sonntag BV, Wong HP. Venous thromboembolism in association with prolonged air travel. *Dermatol Surg* 1996; **22**: 637–641.
- Mercer A, Brown JD. Venous thromboembolism associated with air travel: A report of 33 patients. *Aviat Space Environ Med* 1998; **69**: 154–157.
- Arfvidsson B, Eklof B, Kistner R, Masuda EM, Sato D. Risk factors for venous thromboembolism following prolonged air travel: A "prospective" study. *Vasc Surg* 1999; **33**: 537–544.
- Lapostolle F, Surget V, Borron SW, Desmaizères M, Sordet D, Lapandry C, et al. Severe pulmonary embolism associated with air travel. *N Engl J Med* 2001; **345**: 779–783.
- Kesteven PJL, Robinson BJ. Clinical risk factors for venous thrombosis associated with air travel. *Aviat Space Environ Med* 2001; **72**: 125–128.
- Hosoi Y, Geroulakos G, Belcaro G, Sutton S. Characteristics of deep vein thrombosis associated with prolonged travel. *Eur J Vasc Endovasc Surg* 2002; **24**: 235–238.
- Kesteven P, Robinson B. Incidence of symptomatic thrombosis in a stable population of 650,000: Travel and other risk factors. *Aviat Space Environ Med* 2002; **73**: 593–596.
- Paganin F, Bourdè A, Yvin JL, Génin R, Guijarro JL, Bourdin A, et al. Venous thromboembolism in passengers following a 12-h flight: A case-control study. *Aviat Space Environ Med* 2003; **74**: 1277–1280.
- McQuillan AD, Eikelboom JW, Baker RI. Venous thromboembolism in travellers: Can we identify those at risk? *Blood Coagul Fibrinolysis* 2003; **14**: 671–675.
- Ferrari E, Chevallier T, Chapelier A, Baudouy M. Travel as a risk factor for venous thromboembolic disease: A case-control study. *Chest* 1999; **115**: 440–444.
- Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: The Sirius study. *Arch Intern Med* 2000; **160**: 3415–3420.
- Kraaijenhagen RA, Haverkamp D, Koopman MMW, Prandoni P, Piovella F, Büller HR. Travel and risk of venous thrombosis. *Lancet* 2000; **356**: 1492–1493.
- Martinelli I, Taioli E, Battaglioli T, Podda GM, Passamonti SM, Pedotti P, et al. Risk of venous thromboembolism after air travel: Interaction with thrombophilia and oral contraceptives. *Arch Intern Med* 2003; **163**: 2771–2774.
- Pérez-Rodríguez E, Jiménez D, Diaz G, Pérez-Walton I, Luque M, Guillén C, et al. Incidence of air travel-related pulmonary embolism at the Madrid-Barajas airport. *Arch Intern Med* 2003; **163**: 2766–

- 2770.
26. Ridker PM, Miletich JP, Stampfer MJ, Goldhaber SZ, Lindpaintner K, Hennekens CH. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. *Circulation* 1995; **92**: 2800–2802.
 27. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996; **88**: 3698–3703.
 28. Seki T, Okayama H, Kumagai T, Kumasaka N, Sakuma M, Isoyama S, et al. Arg506Gln mutation of the coagulation factor V gene not detected in Japanese pulmonary thromboembolism. *Heart Vessels* 1998; **13**: 195–198.
 29. Miyata T, Kawasaki T, Fujimura H, Uchida K, Tsushima M, Kato H. The prothrombin gene G20210A mutation is not found among Japanese patients with deep vein thrombosis and healthy individuals. *Blood Coag Fibrinolysis* 1998; **9**: 451–452.