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Clinical Study

Airplane stroke syndrome

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ABSTRACT

Only 37 cases of stroke during or soon after long-haul flights have been published to our knowledge. In this retrospective observational study, we searched the Royal Melbourne Hospital prospective stroke database and all discharge summaries from 1 September 2003 to 30 September 2014 for flight-related strokes, defined as patients presenting with stroke within 14 days of air travel. We hypothesised that a patent foramen ovale (PFO) is an important, but not the only mechanism, of flight-related stroke. We describe the patient, stroke, and flight characteristics. Over the study period, 131 million passengers arrived at Melbourne airport. Our centre admitted 5727 stroke patients, of whom 42 (0.73%) had flight-related strokes. Flight-related stroke patients were younger (median age 65 *versus* 73, $p < 0.001$), had similar stroke severity, and received intravenous thrombolysis more often than non-flight-related stroke patients. Seven patients had flight-related intracerebral haemorrhage. The aetiology of the ischaemic strokes was cardioembolic in 14/35 (40%), including seven patients with confirmed PFO, one with atrial septal defect, four with atrial fibrillation, one with endocarditis, and one with aortic arch atheroma. Paradoxical embolism was confirmed in six patients. Stroke related to air travel is a rare occurrence, less than one in a million. Although 20% of patients had a PFO, distribution of stroke aetiologies was diverse and was not limited to PFO and paradoxical embolism.

1. Introduction

Almost 2 billion people travel by air every year. The age of travellers is increasing and long-haul aircraft such as the Airbus A380 and Boeing 777 are now capable of extending flight times to 18–20 hours [1]. As such, an appreciation of the associations between air travel and illness is important.

There is no standard definition of a long-haul flight. However, flight durations longer than 8 hours or distance greater than 5000 km have been shown to significantly increase the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) [1], and this association could be driven by various factors including comorbidities and dehydration.

The association between air travel and DVT, with or without PE, was labeled "economy class syndrome" by Symington et al. in 1977, based on the theory that highly congested seating arrangements put passengers at risk [2]. Although this term has been used subsequently, the exact mechanism of the association remains unclear. The first description of stroke as a complication of long-haul air travel was in 1968 by Beighton and Richards who described a 48-year-old woman who developed a lower limb DVT during a long-haul flight and had a fatal stroke soon after landing [2]. Although this condition was called "economy class stroke syndrome", it seems to affect business class travellers equally [2]. It may, therefore, be more accurate to call it "airplane stroke syndrome". Although airplane stroke syndrome has been recognised for a long time, only a few cases have been described in the literature as single case reports or small case series (Table 1).

One of the potential explanations for an association between air travel and stroke is paradoxical embolism through a patent foramen ovale (PFO), which is proposed as the aetiology in 17 of 29 published ischaemic strokes (Table 1). However, the relevance of PFO in the pathogenesis of ischaemic stroke is somewhat unclear. It has been estimated that the prevalence of PFO in the general population is 25%. In ischaemic stroke patients with no other identifiable cause the prevalence is 40%, and many of these are likely to be incidental [3].

To further understand airplane stroke syndrome, we describe all identified patients, flights, and stroke characteristics in patients with flight-related stroke at the Royal Melbourne Hospital, Australia. We also report the underlying aetiology of stroke and the presence of a PFO. We hypothesised that PFO is an important, but not the sole, underlying aetiology of flight-related strokes.

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Table 1
Flight related strokes reported in the literature

Study	n	Age in years, sex	Definition	Time of stroke	Aetiology
Beighton et al. [2]	1	48 F	Long-haul	Just after landing	PFO
Masson et al. [2]	1	62 F	10 h	Just after landing	PFO
Isayev et al. [2]	3	46 M	12 h	4 h into flight	PFO
		46 M	14 h	End of flight	PFO
		41 F	2 × 1.5 h	12 h post-flight	PFO
Foerch et al. [2]	3	21	>9000 km	End of flight	PFO
		63	>9000 km	End of flight	PFO
		64	>9000 km	End of flight	PFO
Lapostolle et al. [2]	4	53 F	10.5 h	On arrival	PFO
		67 F	11 h	On arrival	PFO/PE
		51 F	11.2 h	On arrival	PFO/PE
		56 M	8 h	5 h into flight	PFO/PE
Alonso-Canovas et al. [6]	16		Within 6 h of landing		8 ischaemic strokes (1 PFO) 8 ICH
Scacciatella et al. [7]	1	47 M	12 h flight	During landing	PFO/DVT
Pavesi et al. [8]	1	65 F	Long flight		PFO/PE
Belvis et al. [9]	1	36 F	11.35 h	After landing	PFO/PE
Lewis et al. [10]	1	56 M	7.5 h	After landing	Vertebral dissection
Heckmann et al. [11]	1	59 F	9.45 h	4 d post-flight	PFO
Civardi et al. [12]	1	39 M	12 h	During flight	Vertebral dissection
Quinn et al. [13]	1	39 F	2 h	1 d post-flight	Carotid dissection
Parees et al. [14]	1	44 F	8961 km	5 d post-flight	Pulmonary AVM
Edwardson et al. [15]	1	68 M	–	–	Cerebral air embolism/Pulmonary bronchogenic cyst

AVM = arteriovenous malformation, d = days, DVT = deep venous thrombosis, F = female, h = hours, ICH = intracerebral haemorrhage, M = male, PE = pulmonary embolism, PFO = patent foramen ovale.

2. Methods

In this retrospective, observational, single centre study, we manually searched our local prospective stroke database and all discharge summaries from the Royal Melbourne Hospital Stroke Unit from 1 September 2003 to 30 September 2014 for flight-related stroke admissions. We employed a standardised search methodology using a keyword search for the following terms: "stroke", "plane", "airplane", "travel", "flight", "trip", "holiday", "PFO", and "airport". We subsequently manually reviewed the electronic discharge summary as well as the patient record in order to determine eligibility for inclusion in the study.

Patients were included in the analysis if they had a stroke during the flight or within 2 weeks of landing. The presence of DVT was diagnosed by Doppler ultrasound, and the presence of a PFO was diagnosed by transaesophageal echocardiography with or without bubble test. Stroke aetiology was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [4] and stroke severity using the National Institutes of Health Stroke Scale (NIHSS). The diagnosis of paradoxical embolism as stroke aetiology was based on the overall clinical impression of the treating physician, supported by all available investigations. Three of the study authors (H.H., N.Y., A.M.) subsequently reviewed the discharge summaries and available investigations in order to reach consensus and agree on the diagnosis of paradoxical embolism. The study was approved by The Melbourne Health Human Research Ethics Committee.

Melbourne's main domestic and only international airport is located about 20 km from the Royal Melbourne Hospital. The airport is within the catchment area of the hospital, such that acute medical emergencies requiring ambulance transport to hospital which occur at the airport are transported to the Royal Melbourne Hospital by default. During the study period, 28 million international and 103 million domestic passengers arrived at Melbourne airport [5].

Data are presented as median (interquartile range) or number (%). We compared flight-related and non-flight-related stroke patients using the chi-squared or the Mann–Whitney tests. We additionally compared within the flight-related stroke group the patients with stroke during the flight, within 2 days of the flight, and within 3–14 days of the flight with the chi-squared or the Kruskal–Wallis tests as appropriate. Statistical analysis was performed in the Statistical Package for the Social Sciences version 22 (IBM, Armonk, NY, USA).

3. Results

Over the study period we had 5727 stroke admissions. Of those, a total of 42 patients (0.73%) had flight-related strokes. Table 2 shows the baseline clinical characteristics, stroke characteristics, and outcomes in patients with and without flight-related stroke. Median patient age in the flight-related stroke group was 65 years

Table 2
Baseline characteristics, stroke characteristics, and outcomes in patients with and without flight-related stroke

	Flight-related strokes, n = 42	Non-flight related strokes, n = 5685	p-value
Age, years	65 (55–70)	73 (62–82)	<0.001
Male	22/42 (52.4%)	3181/5685 (55.0%)	0.642
Hypertension	18/42 (42.9%)	2391/5604 (42.7%)	0.980
Diabetes mellitus	6/42 (14.3%)	1424/5545 (25.7%)	0.092
Atrial fibrillation	3/42 (7.1%)	1281/5534 (23.1%)	0.014
High cholesterol	11/42 (26.2%)	1260/3327 (37.9%)	0.730
Smoking	9/42 (21.4%)	935/5551 (16.8%)	0.429
Baseline mRS	0 (0–0)	0 (0–2)	0.010
Discharge mRS	4 (2–5)	4 (2–5)	0.023
Baseline NIHSS	9 (3–16)	9 (4–18)	0.477
ICH	7/42 (16.7%)	1228/5536 (22.2%)	0.391
IV tPA	11/35 (26.2%)	562/5685 (9.9%)	0.003
Length of stay, days	9 (1–50)	6 (3–12)	0.011
Discharge destination			<0.001
Home	20/42 (47.6%)	1932/5549 (34.8%)	
Interstate/ overseas	15/42 (35.7%)	5/5549 (0.1%)	
Local institutes/ Hospitals	7/42 (16.7%)	2891/5549 (52.1%)	
In-hospital deaths	0	721/5549 (12.9%)	

Data are presented as median (interquartile range) or n (%).
ICH = intracerebral haemorrhage, IV tPA = intravenous tissue plasminogen activator, mRS = modified Rankin Scale, NIHSS = National Institute of Health Stroke Scale.

and 22 were males. Median baseline NIHSS was 9 (1–25), indicating moderate stroke severity. The stroke subtype was ischaemic stroke in 35 patients and intracerebral haemorrhage in seven.

Median flight duration was 10.5 hours (ranging from 1.5 hours from Sydney to 21.5 hours from London) and median distance travelled was 8204 km (ranging from 713 km to 16,898 km). Twelve strokes occurred in-flight, 18 within 2 days post-flight, and 12 between 3–14 days post-flight, with no significant differences observed between these groups in any of the variables shown in Table 2. The TOAST aetiology of the ischaemic strokes was large artery atherosclerosis in two patients, cardioembolic in 14, small vessel disease in two, other determined (dissection) in three and undetermined (with no single identifiable cause) in 14 (Fig. 1), the distribution being no different to non-flight related strokes ($p = 0.41$). In the cardioembolic group, seven patients had a PFO (two with associated atrial septal aneurysm), four had atrial fibrillation, one had an atrial septal defect, one had endocarditis, and one had aortic arch atheroma.

Based on the treating physician assessment, paradoxical embolism was diagnosed in six patients (Table 3). Two of the identified PFO were considered incidental. In one of these, the stroke occurred in the context of myocardial infarction with left ventricular thrombus visible on echocardiography. In the second, the patient was 67 years of age with a history of hypertension, and the treating physician impression was that PFO was incidental. However, echocardiography (either transthoracic or transaesophageal) was performed only in 17/35 (48.5%) ischaemic stroke patients. Therefore, a PFO was observed in 20% of ischaemic strokes but there might have been more identified if every patient had the full cardiac workup.

Eleven patients received intravenous thrombolysis, three of whom had subsequent endovascular clot retrieval. Two of these had their stroke in-flight and received thrombolysis upon arrival at their destination. The first patient was a 68-year-old woman who was travelling from Thailand and developed sudden onset right-sided weakness and depressed consciousness 1 hour before landing. Imaging demonstrated a left carotid T-junction occlusion and thrombolysis was administered 2 hours after onset with subsequent clot retrieval. The second patient was a 54-year-old woman who was travelling from Dubai and had a sudden onset of headache and left-sided weakness about 2 hours before landing. Imaging demonstrated a right internal carotid dissection with occlusion of the right middle cerebral artery. The patient received thrombolysis 3.5 hours after onset and subsequently had clot retrieval.

Table 3
Patients with paradoxical embolism

Age, years	Sex	Stroke type	Time of stroke	Mechanism
62	Male	Right PCA	1 hour after landing	PFO and ASA
55	Female	Left MCA	4 hours after landing	Right lower limb DVT, bilateral PE, PFO
43	Female	Left PCA	1 hour after landing	PFO with positive bubble test and DVT
66	Female	Left MCA	2 hours after landing	PFO and ASA with right to left shunt
40	Male	Right MCA	6 days after landing	PFO with positive bubble test
67	Female	Right MCA Right PCA	1 day after landing	ASD with PE

ASA = atrial septal aneurysm, ASD = atrial septal defect, DVT = deep venous thrombosis, MCA = middle cerebral artery, PCA = posterior cerebral artery, PE = pulmonary embolism, PFO = patent foramen ovale.

The rate of thrombolysis in flight-related stroke patients was higher than non-flight related stroke patients (26.2% *versus* 9.9%, $p = 0.003$) perhaps indicating early detection and referral. There was no observed difference in cardioembolic aetiology between flight and non-flight ischaemic stroke groups (40.0% *versus* 31.0%, $p = 0.249$). No in-hospital deaths occurred in the flight-related stroke patients, compared to 12.9% in-hospital mortality in non-flight related patients ($p = 0.012$).

4. Discussion

Although airplane travel is a very common experience, flight-related stroke is fortunately uncommon. We identified 42 flights-related strokes during a period with >100 million passengers landing in Melbourne. Therefore flight-related strokes are probably a less than a one in a million occurrence.

Still, in our enriched population, 0.7% of stroke admissions were flight-related and the present series of 42 patients is by far the

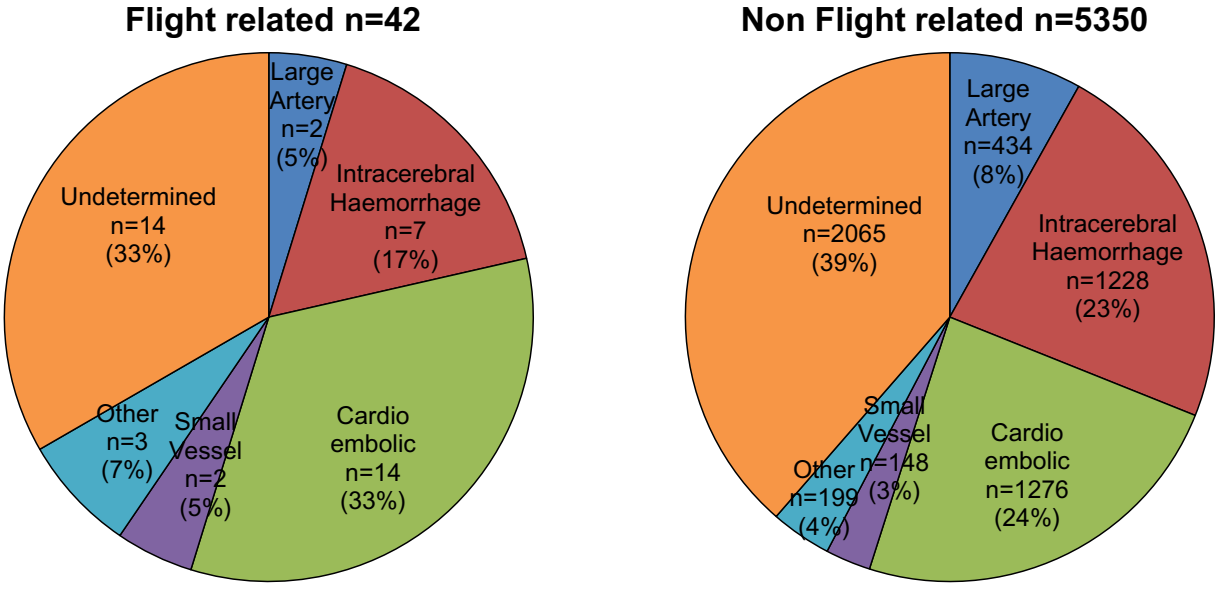

Fig. 1. Pie charts showing flight-related and non-flight-related stroke aetiology.

largest published to our knowledge (Table 1). Unlike the previous literature, our distribution of stroke aetiologies was no different to stroke patients in general. All stroke types were observed, including intracerebral haemorrhage, and only 20% of the ischaemic stroke patients had a PFO, which had been considered the dominant aetiology in the previous literature.

This study is the first to describe in-flight intracerebral haemorrhage, seen in two patients. We also showed that it is feasible to administer thrombolysis to patients with in-flight ischaemic stroke upon arrival at their destination, adding to the previous literature of three cases. We report here the first endovascular clot retrieval cases in flight-related strokes in two patients.

Limitations of this study include its retrospective nature, and the possibility that some cases may not have been included due to presentation to other hospitals, outpatient management, or death prior to arrival to hospital. However, given that the Royal Melbourne Hospital is the primary referral hospital for Melbourne airport, it is likely that the vast majority of in-flight strokes or strokes occurring shortly after landing presented to our centre. Lack of routine data on the class of travel prevented an analysis of the association between travel class and stroke. Given that this study occurred within a clinical stroke service, investigations were not standardised and not all patients were fully investigated for an underlying aetiology, particularly if they had a poor premorbid functional status or a poor prognosis.

Still, we demonstrated paradoxical embolism in 17% compared to 59% in the previous literature of flight-related stroke. Instead of this being the dominant cause of stroke, we observed a wide range of aetiologies with a spectrum not different to stroke patients in general.

Being a rare condition affecting less than one in a million, not many of us will see flight-related strokes. As the risks are likely to increase with longer flights, Australians might see more of these than other nationalities. The key finding of our study is that the aetiologies of flight-related strokes should be fully worked up as with any stroke, as paradoxical embolism suggested mostly by single cases in the previous literature was not the sole or even the dominant aetiology in our series.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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