CONGENITAL HEART DISEASE

Adult patients with Eisenmenger syndrome report flying safely on commercial airlines

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Background: Despite fears of compromised oxygen delivery in patients with Eisenmenger syndrome during flight on commercial aircraft, a clinical study has shown no adverse effects, and many patients travel frequently.

Methods: The air travel history over the past decade of 53 patients with Eisenmenger syndrome and 48 acyanotic patients was obtained. Patients listed all flights and destinations, and any major adverse event or symptoms, including, specifically, headache, palpitations, oedema or need for supplemental oxygen. For the patients with Eisenmenger syndrome, a full blood count, 6-minute walk test and p50 of the oxygen-haemoglobin dissociation curve were also obtained.

Results: 1157 flights were reported evenly between the two groups. Thirteen patients with Eisenmenger syndrome reported no travel in the past 10 years (vs 4/48 acyanotic patients, $p=0.03$), six of whom were told not to fly by healthcare providers. Of those who flew, the number and distance of flights was similar in both groups. No major adverse events were reported. One patient with Eisenmenger syndrome possibly had a transient ischaemic attack and a second patient needed supplemental oxygen when exposed to ambient cigarette smoke in flight. Other symptoms such as headache, palpitations and lower extremity oedema at the travel destination were reported with similar frequency in both groups. Patients with Eisenmenger syndrome had a raised p50 of the oxygen-haemoglobin dissociation curve (mean (SD) 29.4 (2.6) mm Hg vs 27 (3) mm Hg in laboratory controls, $p<0.01$).

Conclusions: Patients with Eisenmenger syndrome report travelling frequently and safely on commercial airlines. Shifts in the oxygen-haemoglobin dissociation curve are likely to attenuate the effects of low oxygen tension. Patients with Eisenmenger syndrome should, nevertheless, be advised to avoid inactivity and dehydration as usual, but there is no justification for limiting air travel.

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The safety of commercial air travel in severe cyanotic congenital heart disease (CHD) is often questioned by patients, their families and healthcare providers. Since aircraft are pressurised to an altitude of 6000–8000 feet (1800–2400 m), the lower partial pressure of oxygen may potentially place these fragile patients at greater risk owing to alveolar hypoxia. As a result, patients with Eisenmenger syndrome (pulmonary vascular disease resulting in reversed or bidirectional shunting and cyanosis) have often been counselled not to fly.

Despite this common recommendation, virtually no data exist to support it. Most reports about the safety of commercial air travel concern patients with chronic obstructive lung disease or cystic fibrosis. Recommendations generally include flight simulation studies before travel, following proposed algorithms for predicting levels of hypoxia, or in severe cases, not flying at all.^{1–5} Still, only rare case reports of adverse events from flight in CHD exist,⁶ and none in patients with Eisenmenger syndrome specifically.

Nearly a decade ago Harinck *et al* published an experiment involving 12 patients with cyanotic CHD studied both during simulated and actual flight, including a 2.5-hour round trip from the Netherlands to Spain.⁷ No significant drop in PO_2 was found in cyanotic patients and no patient had any adverse effect. The authors concluded that commercial air travel does not place cyanotic patients at adverse risk. However, the sample size was small and the distance travelled relatively short. Despite the publication, doctors often continue to counsel patients against flying. Still, many patients with Eisenmenger syndrome report flying repeatedly. Therefore, we sought to

retrospectively to analyse their collective experience and determine whether adverse events do occur. We designed a study to quantify frequency and distance of travel, and compare this with the results for patients with CHD without cyanosis or pulmonary hypertension.

PATIENTS AND METHODS

Patient groups

Fifty-three consecutive adult patients with Eisenmenger syndrome were asked to participate in a large prospective cross-sectional cohort study, partially described elsewhere.⁸ Eisenmenger syndrome was defined as: (a) known intracardiac or great artery shunt; (b) increased pulmonary artery pressure (tricuspid valvular regurgitation velocity ≥ 4 m/s or measured mean pulmonary artery pressure >60 mm Hg); (c) reversed or bidirectional shunt resulting in hypoxaemia. The study was approved by the institutional ethics committee and all patients gave informed consent.

The control group comprised 48 acyanotic patients with known CHD attending their outpatient clinic appointment. Each patient was asked to complete a brief travel survey and had their oxygen saturation measured at rest. Age, gender and diagnosis were obtained from their available medical records. Patients were excluded if they had a history of pulmonary artery hypertension or if their resting oxygen saturation was $<95\%$.

Abbreviations: CHD, congenital heart disease; TIA, transient ischaemic attack; VSD, ventricular septal defect

Table 1 Anatomical diagnoses

Patients with Eisenmenger syndrome	No (%)	Acyanotic patients	No (%)
ASD	1 (2)	ASD/VSD	6 (13)
VSD	31 (58)	Aortic valve disease	11 (23)
PDA	6 (11)	HOCM	5 (10)
AVSD	7 (13)	TOF	10 (21)
Complex	8 (15)	Aortic coarctation	5 (10)
		TGA	5 (10)
		Complex, including Fontan	6 (13)
Total	53 (100)		48 (100)

ASD, atrial septal defect; AVSD, atrioventricular septal defect; HOCM, hypertrophic obstructive cardiomyopathy; PDA, patent ductus arteriosus; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Travel history

Each patient answered a questionnaire asking for details of their air travel history over the past 10 years. Patients were asked to include approximate travel dates and destinations, as well as any adverse events experienced during take-off, in flight or when landing. Patients were then specifically asked about the occurrence of heart failure requiring hospital admission, stroke, transient ischaemic attacks, ischaemic chest pain, oxygen requirement, headaches, lower extremity oedema, palpitations or shortness of breath. Immediately after completion, each survey was reviewed by a doctor with the patient at the time of submission to clarify any unusual travel route or listed symptoms.

One flight was defined as a take-off and landing. All flights were assumed to start and finish in London except when specified. Each destination was assumed to have been reached in a single flight unless otherwise stated. If patients were unable to recall the details of a specific trip with reasonable accuracy, it was not recorded. Patients who did not travel were asked whether this was owing to personal preference, previous adverse experience with flying, or because of a doctor's recommendation.

For each flight, mileage was determined by an available website giving direct distance between any two destinations (<http://www.indo.com/distance/>, accessed 13 August 2007). The total number of flights, total miles travelled and average miles per trip were calculated for each patient.

Physiological testing

Patients with Eisenmenger syndrome underwent a comprehensive medical interview about their history of stroke,

phlebotomy and haemoptysis. Finger oxygen saturation was measured after 5 minutes of rest and again after 5 minutes of oxygen administration through a non-rebreather mask at 15 l/min. Saturation was also measured in the toes of any patient with differential cyanosis, and this value was used in calculations.

Patients were asked to perform a 6-minute walk test, and the drop in oxygen saturation after 6 minutes was also recorded. A full blood count, reticulocyte count and iron studies were carried out for each patient. In 19 patients with Eisenmenger syndrome measurement of p50 of the oxygen-haemoglobin dissociation curve was performed (Hem-O-Scan, American Instrument Company, Silver Spring, Maryland, USA).

Statistical analysis

The following groups were compared: (a) patients with Eisenmenger syndrome who flew versus acyanotic controls who flew; (b) patients with Eisenmenger syndrome who flew versus those who did not; (c) patients with Eisenmenger syndrome reporting any complication versus those reporting none. Comparisons between groups were made using the Student *t* test and Fisher exact test for binary variables. Age at the time of survey was used for analysis, not the age at time of travel. Data are expressed as mean (SD). For all analyses a *p* value <0.05 was considered significant.

RESULTS

Table 1 shows the cardiac diagnoses of patients from the Eisenmenger and acyanotic groups and table 2 compares the two groups. By definition, patients with Eisenmenger syndrome were cyanotic (saturation range 63–92%) and had secondary erythrocytosis (haemoglobin range 14.4–24.0 g/dL). The groups did not differ with respect to age or gender. Eighty-four of the 101 patients questioned reported flying within the past decade, and on average flew 13.6 (11.3) flights, or slightly more than one round trip every 2 years. Mean flight length was 1995 (1426) miles, approximately the equivalent of a 4-hour flight. Patients with Eisenmenger syndrome flew just as often and as far as the control patients (table 2).

The number of patients who reported not flying in the past 10 years was higher in the Eisenmenger group than in the cyanotic patients (25% vs 8%, *p* = 0.034; table 2). Many of these had flown safely in the remote past, but not within the target recall period of 10 years. Of these, six in the Eisenmenger group had specifically been counselled not to fly by a doctor, whereas only one patient in the acyanotic group had also been told not to fly (*p* = 0.12).

Table 2 Comparison of patients with Eisenmenger syndrome and acyanotic patients

	Patients with Eisenmenger syndrome (n = 53)	Acyanotic patients (n = 48)	p Value
Age (years), mean (SD)	38.9 (13.5)	37.5 (15.1)	0.93
Female gender	35 (66)	26 (54)	0.24
Resting oxygen saturation (%), mean (SD)	80 (7)	97 (2)	<0.001
Flights taken (n), mean (SD)	11 (14)	11 (8)	0.62
Total distance flown (miles), mean (SD)	26 974 (29 329)	25 143 (22 269)	0.81
Average flight distance (miles/flight), mean (SD)	1833 (1292)	2139 (1535)	0.37
Patients not flying (n)	13 (25)	4 (8)	0.034
Patients told not to fly (n)	6 (11)	1 (2)	0.12
Patients with any complication (n)*	12 (30)	8 (18)	0.76
Patients reporting headache (n)*	6 (15)	4 (9)	0.51
Patients reporting oedema (n)*	5 (13)	1 (2)	0.009
Patients using oxygen (n)*	1 (3)	1 (2)	1.00

Results are shown as No (%) unless stated otherwise.

*No (%) of those who flew.

Table 3 Patients with Eisenmenger syndrome compared

Characteristics	Flyers (n=40)	Non-flyers (n=13)	p Value	Flying with complications (n=11)	Flying without complications (n=29)	p Value
Age (years)	40.3 (13.5)	34.6 (13.2)	0.18	39.0 (13.1)	40.9 (13.8)	0.69
Female gender, No (%)	26 (65)	9 (69)	1.00	10 (90)	16 (55)	0.061
Resting oxygen saturation (%)	81 (7)	78 (9)	0.24	83 (6)	80 (7)	0.26
Oxygen saturation on high flow O ₂ (%)	92 (5)	87 (9)	0.031	93 (4)	92 (6)	0.45
Saturation after 6MWT (%)	58 (10)	59 (14)	0.82	58 (11)	58 (10)	0.99
Six-minute walk distance (m)	375 (107)	322 (106)	0.14	370 (118)	376 (106)	0.89
Haemoglobin (g/day)	19.6 (2.7)	20.1 (3.3)	0.59	19.8 (2.8)	19.6 (2.7)	0.85
Packed cell volume (%)	60 (8)	62 (9)	0.38	59 (9)	61 (8)	0.48
Platelet count (10 ⁹ /l)	152 (59)	125 (54)	0.16	176 (50)	143 (61)	0.14
Total flights made (n)				9 (5)	17 (16)	0.091
Total miles flown (miles)				26 351 (29 021)	27 211 (29 952)	0.94
Average flight length (miles/trip)				2767 (1847)	1479 (797)	0.004
P ₅₀ O ₂ -Hg dissociation curve (mm Hg)	29.5 (2.8)	29.8 (1.9)	0.83	29.4 (2.5)	29.6 (3.2)	0.93
New York Heart Assn Class 3–4, No (%)	11 (28)	7 (54)	0.10	2 (29)	9 (27)	1.00
Active smoker, No (%)	4 (10)	1 (8)	1.00	2 (18)	2 (7)	0.30
History of significant haemoptysis, No (%)	16 (40)	6 (46)	0.75	4 (36)	12 (41)	1.00
Routine use of supplemental O ₂ , No (%)	5 (13)	7 (54)	0.005	0	5 (17)	0.30
Iron deficient, No (%)	17 (43)	5 (39)	1.00	5 (46)	12 (41)	1.00

Results are shown as mean (SD) unless stated otherwise.
6MWT, 6-minute walk test; O₂-Hg, oxygen-haemoglobin.

Table 3 compares flyers versus non-flyers within the Eisenmenger group. Non-flyers had lower oxygen saturation on supplemental oxygen and were more likely to use nocturnal oxygen. There was a trend towards a lower New York Heart Association (NYHA) class among the non-flyers. Otherwise there were no significant differences in blood count, history of phlebotomy, haemoptysis, oxygen saturation, diagnostic complexity or 6 minute walk test results.

There was a rightward shift in the oxygen-haemoglobin dissociation curve in the patients with Eisenmenger syndrome (n=19). Mean p₅₀ was 29.4 (2.6) mm Hg, which is a significant shift from the laboratory normal average of 27 (3) mm Hg (p<0.01).

Specific adverse events

No major adverse events requiring admission to hospital, such as stroke, ischaemic chest pain, syncope or heart failure, were reported in any patient. Minor adverse events were reported by 12/40 (30%) Eisenmenger flyers versus 8/44 (18%) acyanotic flyers (not significant). The most common symptom was headache, followed by lower extremity oedema.

Patients with Eisenmenger syndrome who reported any adverse events were compared with those without complications (table 3). No differences were noted in age, oxygen saturation at rest or with supplemental oxygen, haemoglobin, packed cell volume, drop in oxygen saturation after 6-minute walk test, total miles travelled or number of trips. However, there was a significantly higher average miles per trip in those with any complication versus those without (2767 (1847) miles/trip vs 1479 (797) miles/trip respectively, p=0.004). Patients generally, however, did not report that they flew less because of complications.

Transient ischaemic attack

Only one patient described symptoms that might have been related to a transient ischaemic attack (TIA). A 41-year-old woman with a ventricular septal defect (VSD) and oxygen saturation 88% noted leg swelling on a transatlantic flight. When she left the plane upon arrival she noted transient blurred vision and frontal headache, but the symptoms resolved completely after a few hours of sleep. She noted no other neurological problems, including numbness or tingling, motor dysfunction, diplopia or trouble speaking. Since then the same

patient has flown extensively without problems, albeit always within Europe. The same patient reported subsequently two further episodes suggestive of TIA, neither associated with air travel. She has since started treatment with warfarin.

Oxygen requirement

One Eisenmenger patient and one acyanotic control patient used supplemental oxygen during flight. The Eisenmenger patient (a 41-year-old woman with a VSD, oxygen saturation 76%) recalled sitting near another passenger who was smoking on a flight from London to Los Angeles and feeling bothered by passive smoke. She was given supplemental oxygen for about 2 hours before descent. After a layover of several hours in Los Angeles she continued her journey to Auckland without difficulty. Subsequent flights, including transatlantic flights, have all been uneventful.

The acyanotic patient who required oxygen was a 32-year-old woman with double outlet right ventricle and previous Rastelli repair with extensive travel. She reported breathlessness during all eight of her most recent flights, all within the past 2 years. On one of these flights, she felt anxiety, dyspnoea and palpitations. A crew member offered oxygen, which she used for the final third of the flight. On other flights since then she has also experienced dyspnoea and palpitations but has not used oxygen.

Three other patients with Eisenmenger syndrome reported elective oxygen use. One, a 30-year-old man with Down syndrome and atrioventricular septal defect (oxygen saturation 73%) had tonsillitis at the beginning of his trip. The aircraft was delayed on the tarmac for considerable time before take-off, and the patient's family asked for oxygen. Oxygen was stopped before take-off, and the patient was well throughout the flight. A 33-year-old woman with an aorto-pulmonary window (oxygen saturation 80%) was told that she should use oxygen on flights over 6 hours in duration. Thus each year when she flies to the Mediterranean (3 hour flight) she does not use oxygen, but when she flies to western Africa (6–7 hour flight) she arranges oxygen at her own expense. She has had no adverse events. Another 32-year-old patient with congenitally corrected transposition and a large VSD (oxygen saturation 69%) used oxygen electively on ascent and descent but not during a flight to the Canary Islands as recommended by her doctor. She reported no problems.

Headaches

Ten patients reported headaches during travel, six patients with Eisenmenger syndrome and four acyanotic controls (not significant). Headaches were reported both on short and long flights (range 213–5371 miles). Patients with Eisenmenger syndrome who reported headaches seemed to travel less often than other patients with Eisenmenger syndrome without headache but the difference was not significant (6.0 (3.3) vs 16.5 (15.0) flights/patient, $p=0.09$). Two patients with Eisenmenger syndrome who reported recurrent headache purposely reduced their frequency of flying. However, the other four patients with a history of headaches continued to fly; and in two of these patients headaches are consistent each time they fly. Similarly, of the four acyanotic patients reporting headache, two patients experience headaches with every flight.

Lower extremity oedema

Five patients with Eisenmenger syndrome reported lower extremity oedema only while at their travel destination, but no problems during the flight itself and no swelling after returning from the trip. All were women, but otherwise did not differ from the rest of the group. Oedema occurred on both long and short trips (range 712–11 390 miles). In almost all cases the patients believed the swelling was weather related (warmer climates at the destination). One acyanotic control patient (29-year-old with Mustard repair of transposition of the great arteries) reported lower extremity swelling on a single flight.

DISCUSSION

Despite theoretical concerns that patients with Eisenmenger syndrome are at risk for complications during commercial air travel, such complications have not been reported. Our survey found that significant clinical events did not occur in nearly 600 flights to destinations throughout the world. This is in harmony with the report by Harinck *et al*, who demonstrated that pressurised cabin altitudes of 6000–8000 feet (1800–2400 m) had a smaller effect on oxygen delivery, even negligible, in patients with cyanotic CHD compared with acyanotic controls.⁷ Cyanosis in these patients is not related to poor alveolar oxygen tension but to right-to-left shunting of unoxygenated blood. Thus small changes in alveolar oxygen tension are less likely to have an impact on arterial oxygen saturation. Furthermore, these patients have developed chronic adaptations that allow them to achieve homeostasis in tissue oxygen delivery. Harinck *et al* postulated that a shift in the oxygen–haemoglobin dissociation curve was present,⁷ which our study confirms. The average p_{50} for the patients with Eisenmenger syndrome we measured was shifted rightwards. This shift does not affect oxygen binding in the lungs but favours oxygen release at tissue level. This is further evidence of the chronic adaptation made in cyanotic heart disease.

When all complications were considered, we found no difference between those who reported problems and those who did not (table 3). One may hypothesise that older patients, those with lower resting oxygen saturation, or those with compromised oxygen carrying capacity due to iron deficiency, for example, may be more prone to symptoms in flight. We found no such differences, even considering those with previous strokes or significant haemoptysis. The data suggest that minor complications occur more frequently on longer flights, but overall we show similar complication rates in acyanotic controls. Some of the data suggest that patients with more advanced or severe disease (NYHA 3–4 or using supplemental oxygen) flew less frequently or not at all, either because they chose not to or were told not to fly, yet there was no significant difference in the 6-minute walk distance.

One patient with Eisenmenger syndrome from our study reported a mild headache with lower extremity oedema and transient blurring of vision after a flight. In retrospect she may have had a TIA. Air travel in general is associated with a two- to fourfold increased risk of thrombosis,^{9–10} and this risk increases with flight duration.¹¹ The risk for flight-related thromboembolic complications is known to be higher in the presence of clotting disorders such as factor V mutation or the use of oral contraceptives.¹² Shunt thrombosis after air travel has been reported in a patient with cyanotic heart disease.⁶ Since embolic thrombi in a patient with an intracardiac communication can shunt across to the systemic circulation causing a stroke, this risk is worth considering. However, we do not feel that our patient's experience justifies general limitations on flight in this population. Despite the result of our study, a patient with Eisenmenger syndrome, just as any traveller, should justifiably be encouraged to remain well hydrated, avoid alcohol use and excessive physical inactivity during the flight. Anticoagulation could be considered, especially for long distance flights, and low molecular weight heparin has been shown to reduce the occurrence of deep venous thrombosis in high risk groups.¹³

Headaches occurred in 6/40 (15%) patients with Eisenmenger syndrome who flew. Headaches are reported commonly in such patients. Dehydration potentially affecting viscosity can make patients more prone to headache. Further, travel can often be associated with psychological tension. The fact that 9% of the acyanotic flyers also complained of headache is indirect evidence that the hassle and stress inherent in travel may all contribute to headache.

Our survey anecdotally highlights the various recommendations patients receive from healthcare providers. One young man with an Eisenmenger VSD (oxygen saturation 84%) was counselled to organise formal air simulation testing before a flight to Africa. Another was told to take oxygen during yearly trips to the Mediterranean, but she never did and had no problems. A patient with Down syndrome wanted to travel to Disney World for his birthday, but was told he should not fly. Meanwhile, another patient with Down syndrome travelled to Orlando every year without trouble. Another patient flew to Australia twice without problems, but was later told never to fly. Although the purpose of this study is not to assess the efforts of healthcare providers to offer vigilant advice to patients, since such counsel is nearly always made with the patient's ultimate safety in mind, we suggest that overcautious advice based on theoretical risk is not always in the patient's best interest since in today's global society many of life's various pursuits will at some point require air travel. Our survey supports the findings by Harinck *et al*⁷ and should give healthcare workers the confidence to allow stable patients with Eisenmenger physiology the freedom to travel as they wish.

Doctors should still be encouraged to discuss travel with their patients with Eisenmenger syndrome, and encourage them to avoid excessive inactivity during the flight and to actively move about the cabin when occasion permits. Factors such as dehydration can contribute to hyperviscosity, and should be avoided specifically in these patients. More particularly, we are aware of patients who have died of exertionally related tachyarrhythmia while trying to make a connecting flight. Hence it is important to underline the fact that exposure to high altitude is not the only risk associated with travel, and that patients should plan well ahead and not exert themselves to extremes.

Limitations

This is a retrospective self-reported survey. Inaccuracies may have occurred on precise destination, year travelled, number of trips to a particular destination or whether smaller journeys were covered by air or ground. However, this potential recall

bias would have affected both groups similarly. Furthermore, most people tend to recall easily misadventures during travel, particularly if health problems occurred. Recall bias should therefore favour over-reporting travel-related complications rather than under-reporting. A 10-year period only was surveyed to minimise the recall bias. Possibly, those with more advanced disease flew less often, and these findings should not automatically be extrapolated to unstable patients.

At the time of the survey, 12 patients with Eisenmenger syndrome were using warfarin and five were using aspirin. However, as a retrospective study, it was impossible to determine whether a given trip was taken while the medication was being used, and no conclusions could be made about the efficacy of warfarin or aspirin.

We report a limited sample size, and it is impossible to know with certainty that more serious adverse events would not be experienced in a larger group. It is important that doctors report travel complications as they may help determine the type of patients or events that should be avoided to ensure safe travel. Also, this study did not assess the safety of exposure to high altitudes in non-pressurised aircraft.

CONCLUSIONS

This retrospective study of self-reported complications during flight adds clinical evidence to support previous experimental data suggesting that commercial air travel is safe in patients with Eisenmenger syndrome. Furthermore, it suggests that the risk of cerebrovascular events during air travel is small. Stable patients with Eisenmenger syndrome, as patients with other CHD, should not be discouraged from flying provided that they remain well hydrated and stay active and mobile during the flight. Patients should be encouraged to avoid time constraints and excess physical or mental stress that often accompanies travel. Such guidelines are appropriate for any passenger, but even more essential in this susceptible group.

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