Pulmonary Artery Pressure Increases During Commercial Air Travel in Healthy Passengers

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Background: It is not known whether the mild hypoxia experienced by passengers during commercial air travel triggers hypoxic pulmonary vasoconstriction and increases pulmonary artery pressure in flight. Insidious pulmonary hypertensive responses could endanger susceptible passengers who have cardiopulmonary disease or increased hypoxic pulmonary vascular sensitivity. Understanding these effects may improve pre-flight assessment of fitness-to-fly and reduce in-flight morbidity and mortality. *Methods:* Eight healthy volunteers were studied during a scheduled commercial airline flight from London, UK, to Denver, CO. The aircraft was a Boeing 777 and the duration of the flight was 9 h. Systolic pulmonary artery pressure (sPAP) was assessed by portable Doppler echocardiography during the flight and over the following week in Denver, where the altitude (5280 ft/1610 m) simulates a commercial airliner environment. *Results:* Cruising cabin altitude ranged between 5840 and 7170 ft (1780 to 2185 m), and mean arterial oxygen saturation was 95 ± 0.6% during the flight. Mean sPAP increased significantly in flight by 6 ± 1 mmHg to 33 ± 1 mmHg, an increase of approximately 20%. After landing in Denver, sPAP was still 3 ± 1 mmHg higher than baseline and remained elevated at 30 ± 1 mmHg for a further 12 h. *Conclusions:* Pulmonary artery pressure increases during commercial air travel in healthy passengers, raising the possibility that hypoxic pulmonary hypertension could develop in susceptible individuals. A hypoxia altitude simulation test with simultaneous echocardiography ('HAST-echo') may be beneficial in assessing fitness to fly in vulnerable patients.
Keywords: in-flight hypoxia, pulmonary vascular response, hypoxic pulmonary vasoconstriction, pulmonary hypertension, hypoxic challenge test.

PASSENGERS ROUTINELY experience mild hypoxia during commercial air travel (26). In most healthy passengers arterial oxygen saturation (S_pO_2) falls to 90–95% in flight, although more severe hypoxemia occurs in some normal individuals and in many patients with respiratory disease (20,21,26). Although commercial air travel is very safe, if this attendant hypoxia were to endanger even 1% of passengers worldwide, this would mean up to 20 million people were at risk every year (26).

Routine in-flight hypoxia results from the reduced atmospheric pressure within the aircraft cabin, which reflects a compromise between the economic costs of higher pressurization and the dangers of hypoxia with lower pressures. Cabin pressure is conventionally expressed as its altitude equivalent and typically ranges between 5000 ft (1524 m) and a maximum limit of 8000 ft (2438 m), which is not mandated and is occasionally

exceeded (1,7). This 8000-ft ceiling arose in the World War II era, when aviators were predominantly young and healthy, but its suitability as a universal hypoxic safety limit has been questioned for at least 40 yr (16). Older and less healthy people are increasingly travelling by air and the Aviation Safety Committee of the Aerospace Medical Association recently recommended further research into the physiological effects of aircraft cabin hypoxia (1).

Air travel is already known to activate some elements of the human response to hypoxia, including an increase in ventilation and increased secretion of erythropoietin (10,14,30). Another classic response, hypoxic pulmonary vasoconstriction, could be more relevant clinically, but has yet to be studied in this setting. Through this phenomenon, hypoxia causes an increase in pulmonary artery pressure that can lead to pulmonary hypertension and ultimately right heart failure, such as in hypoxic lung disease and at high altitude (5,23,30). Textbooks and guidelines refer widely to animal work, but currently it is not known whether the mild hypoxia of air travel triggers hypoxic pulmonary vasoconstriction in humans and increases pulmonary artery pressure in flight (24).

Such an effect could be important for some passengers. Hypoxic pulmonary vasoreactivity varies greatly between individuals and high reactivity predisposes to hypoxia-related diseases such as high-altitude pulmonary edema (6). Susceptible individuals may similarly be at risk of hypoxia-induced pulmonary hypertension and its sequelae during air travel. In-flight cardiac emergencies are the most common cause of flight diversions and in-flight deaths (8), and silent pulmonary hypertension could be a contributing factor in some instances. This possibility is supported by case reports describing

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the onset of acute cor pulmonale in air passengers during commercial flights (22,33).

Understanding the pulmonary vascular effects of commercial air travel would be helpful in assessing patients for fitness to fly. Currently many patients with cardiopulmonary disease must use supplementary oxygen in flight, while for others the risks of hypoxia are considered too great and air travel is contraindicated (2,3). Aeromedical decisions are informed by extensive international guidelines (2,3,27), but for some conditions such as pulmonary hypertension these guidelines are limited by the absence of experimental evidence (19). Evidence is also lacking in conditions that cause increased hypoxic pulmonary vasoreactivity such as Chuvash polycythemia, a rare hereditary form of erythrocytosis (29). Through the use of in-flight echocardiography, this study tested the hypothesis that air travel stimulates an increase in pulmonary artery pressure that might be clinically relevant for some passengers.

METHODS

Subjects

Eight healthy volunteers, four men and four women, participated in the study. Mean ($\pm$ SD) age was 31 ± 3 yr, with height 1.70 ± 0.10 m and weight 72.5 ± 14.8 kg. All subjects provided written informed consent. The study was approved by the Oxford Tropical Research Ethics Committee and by the airline, and was conducted in accordance with the Declaration of Helsinki.

Protocol

The study was undertaken on a Boeing 777-300 aircraft in cooperation with the Captain and cabin crew. Subjects were studied during and after a 9-h scheduled passenger flight from London, UK, to Denver, CO. This flight was chosen because the altitude in Denver (5280 ft; 1610 m) simulates the commercial aircraft cabin environment, allowing further relevant measurements after landing. Cabin altitude was recorded continuously during the flight. The primary outcome measure was the effect of air travel on systolic pulmonary artery pressure (sPAP) assessed by portable Doppler echocardiography (Vivid-i portable echocardiography machine, GE Medical Systems, Chalfont St. Giles, Buckinghamshire, UK). Baseline echocardiographic measurements were conducted at the airport immediately prior to departure from London, and in-flight echocardiographic measurements were made 3 hr and 6 hr after takeoff, with subjects reclining across the rear-most row of seats in the economy class cabin. After landing, measurements were repeated at time-points corresponding to 12 h and 24 h post-takeoff. Daily measurements continued over the following week in Denver before subjects returned to the UK, where final measurements were made 24 h after landing.

Dependent Measures

Heart rate and S_pO_2 were measured hourly throughout the flight and daily in Denver using a fingertip pulse oximeter. A standard echocardiographic technique was used to determine sPAP (28,29,31). With subjects reclining in the left lateral position, the maximum velocity of a regurgitant jet of blood through the tricuspid valve was measured during systole. Using this velocity and the modified Bernoulli equation, the maximum systolic pressure gradient across the tricuspid valve was determined and sPAP was calculated using an estimated right atrial pressure of 5 mmHg (4,34). Cardiac output was also determined by standard echocardiographic means using the left ventricular outflow tract cross-sectional area and pulsed Doppler velocity-time integral measurements.

Statistical Analysis

Changes in physiological data from baseline values were assessed statistically using Student's two-tailed t-test for paired samples and were considered significant at the $P < 0.05$ level. Values are reported as mean $\pm$ SEM unless otherwise stated.

RESULTS

Baseline venous blood analyses were normal and are shown in **Table I**. During the flight the cruising cabin altitude ranged between 5840 and 7170 ft (1780–2185 m) and is presented in **Fig. 1**, which shows altitude throughout the study. S_pO_2 fell significantly from $98 \pm 0.5\%$ at baseline to a mean of $95 \pm 0.6\%$ during the flight, which was a significant change on paired Student's t-test [$t(7) = 4.50$, $P = 0.003$]. Throughout the time in Denver the mean S_pO_2 was $97 \pm 0.5\%$, which was also significantly lower than baseline [$t(7) = 4.14$, $P = 0.004$].

Fig. 1 shows sPAP throughout the study. During the first in-flight echocardiographic measurements, the cabin altitude was 5840 ft (1780 m) and the mean S_pO_2 was $96 \pm 0.7\%$. At the time of the second in-flight measurements, cabin altitude was 6530 ft (1990 m) and mean S_pO_2 was $95 \pm 0.9\%$. During the flight sPAP increased by 6 ± 1 mmHg to 33 ± 1 mmHg, which was significantly higher than baseline [$t(7) = -4.85$, $P = 0.002$]. This was an increase of approximately 20% and varied over a fivefold range between the subjects. After landing in Denver, sPAP was still 3 ± 1 mmHg higher than baseline and remained elevated for a further 12 h at 30 ± 1 mmHg, significantly higher than baseline on paired Student's t-test [$t(7) = -3.64$, $P = 0.008$]. After this point sPAP gradually returned to the normal baseline level. There were no significant changes in heart rate or cardiac output.

TABLE I. BASELINE VENOUS BLOOD ANALYSES.

Hemoglobin (12.0–17.0 g · dl^{-1})	14.0 ± 1.1
Hematocrit (0.36–0.50 L/L)	0.43 ± 0.03
Mean Cell Volume (83–105 fl)	90.7 ± 5.2
Serum Iron (11–31 μmol · L^{-1})	20.2 ± 4.9
Serum Ferritin (10–300 μg · L^{-1})	75.4 ± 69.9
Serum Transferrin (1.8–3.6 g · L^{-1})	2.7 ± 0.5

Mean $\pm$ SD values are shown. Where normal ranges vary with sex, the widest range is given.
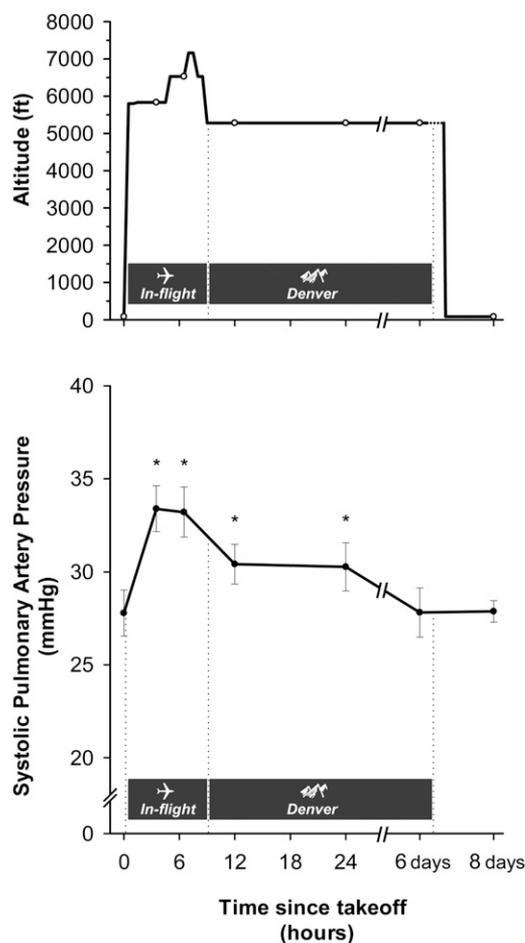
Fig. 1. Altitude (top) and systolic pulmonary artery pressure (bottom) during and after a commercial airline flight. For the duration of the flight, the altitude presented is the equivalent cabin altitude, which should not normally exceed 8000 ft (2438 m). Measurement time points are indicated by white symbols in the upper panel and black symbols in the lower panel. Data are mean ± SEM and asterisks denote a significant change from the baseline value ($P < 0.05$).

DISCUSSION

This study has established that pulmonary artery pressure increases during commercial air travel in healthy passengers. Mean in-flight values approached the sPAP threshold for pulmonary hypertension, which has been defined as 36 mmHg (17). Airlines commonly maintain higher cabin altitudes and fly much longer ultra-long-haul routes of up to 19 h (e.g., Singapore–Newark), carrying a potential for greater hypoxia and higher pulmonary artery pressures even into the pulmonary hypertensive range.

Prior to this study, acute hypoxic pulmonary vasoconstriction had not been demonstrated in humans at such modest altitudes and with such mild hypoxia. These findings support previously controversial reports claiming that, in rare individuals who are otherwise healthy, high-altitude pulmonary edema can develop at altitudes below 8000 ft (2438 m) (12,25). While the phenomenon we observed is inconsequential for the vast majority of air passengers, it may be less benign in those with exaggerated pulmonary vasoreactivity and the potential for

exacerbating or precipitating cardiopulmonary disease. At the extreme, this includes critically ill patients undergoing aeromedical transportation, which is an expanding area of civilian and military intensive care medicine where even subtle changes in cardiopulmonary function can be hazardous (32).

More generally, our results suggest that there may be an important role for echocardiography in evaluating patient fitness to fly. The hypoxia altitude simulation test (HAST) is a standardized pre-flight assessment tool that has increasingly been used in patients with chronic obstructive pulmonary disease (COPD) over the past 25 yr (13,18). The patient breathes a hypoxic gas mixture of 15.1% oxygen, replicating the effects of an altitude of 8000 ft (2438 m), and the resultant changes in S_pO_2 and arterial blood gases are used to predict the severity of in-flight hypoxemia. The patient is also monitored for symptoms and for myocardial ischemia or arrhythmias, and the overall aim is to reduce in-flight morbidity and mortality.

In selected patients, expanding the HAST to include simultaneous echocardiography (termed here 'HAST-echo') could allow prediction of in-flight changes in pulmonary artery pressure and ventricular function, allowing more accurate assessment of whether air travel is safe and whether in-flight supplementary oxygen is indicated. Potentially this could reduce the incidence of in-flight medical emergencies, flight diversions, and in-flight deaths in patients with COPD, pulmonary hypertension, other obstructive and restrictive lung disease, and cardiac disease (2,3,27). HAST-echo could also be beneficial in non-cardiopulmonary conditions that are associated with increased hypoxic pulmonary vasoreactivity, such as Chuvash polycythemia (29) [and related genetic diseases (11)] and iron deficiency (28,31), and the pulmonary vascular effects of air travel should be investigated in these groups. Pulmonary vasoconstriction intensifies for at least 2 h with sustained hypoxia (9) and HAST-echo of a similar duration would presumably have the greatest predictive benefit. Although it is likely that the normobaric HAST and the hypobaric hypoxia of air travel induce similar pulmonary vascular responses (15,21), this may not necessarily be the case, and confirmatory studies are required.

In summary, this study provides experimental evidence demonstrating that pulmonary artery pressure increases during a commercial airline flight. Further research is warranted to determine whether excessive in-flight pulmonary hypertensive responses can endanger susceptible passengers and whether incorporating HAST-echo into aeromedical assessments can improve the safety of air travel.

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REFERENCES

1. Aerospace Medical Association, Aviation Safety Committee, Civil Aviation Subcommittee. Cabin cruising altitudes for regular transport aircraft. Aviat Space Environ Med 2008; 79:433–9.
2. Aerospace Medical Association, Medical Guidelines Task Force. Medical Guidelines for Airline Travel, 2nd ed. Aviat Space Environ Med 2003; 74(5, Suppl.):A1–19.
3. Ahmedzai S, Balfour-Lynn IM, Bewick T, Buchdahl R, Coker RK, et al. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. Thorax 2011; 66 (Suppl. 1):i1–30.
4. Allemann Y, Sartori C, Lepori M, Pierre S, Melot C, et al. Echocardiographic and invasive measurements of pulmonary artery pressure correlate closely at high altitude. Am J Physiol Heart Circ Physiol 2000; 279:H2013–6.
5. Barberà JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. Eur Respir J 2003; 21:892–905.
6. Bärtsch P, Mairbäurl H, Maggiorini M, Swenson ER. Physiological aspects of high-altitude pulmonary edema. J Appl Physiol 2005; 98:1101–10.
7. Cottrell JJ. Altitude exposures during aircraft flight. Flying higher. Chest 1988; 93:81–4.
8. DeJohn CA, Wolbrink AM, Veronneau SJ, Larcher JG, Smith DW, Garrett JS. An evaluation of in-flight medical care in the U.S. Aviat Space Environ Med 2002; 73:580–6.
9. Dorrington KL, Clar C, Young JD, Jonas M, Tansley JG, Robbins PA. Time-course of the human pulmonary vascular response to 8 hours of isocapnic hypoxia. Am J Physiol 1997; 273(3, Pt. 2):H1126–34.
10. Fatemian M, Kim DY, Poulin MJ, Robbins PA. Very mild exposure to hypoxia for 8 h can induce ventilatory acclimatization in humans. Pflugers Arch 2001; 441:840–3.
11. Formenti F, Beer PA, Croft QP, Dorrington KL, Gale DP, et al. Cardiopulmonary function in two human disorders of the hypoxia-inducible factor (HIF) pathway: von Hippel-Lindau disease and HIF-2α gain-of-function mutation. FASEB J 2011; 25:2001–11.
12. Gabry AL, Ledoux X, Mozziconacci M, Martin C. High-altitude pulmonary edema at moderate altitude (< 2,400 m; 7,870 feet): a series of 52 patients. Chest 2003; 123:49–53.
13. Gong H, Tashkin DP, Lee EY, Simmons MS. Hypoxia-altitude simulation test - evaluation of patients with chronic airway-obstruction. Am Rev Respir Dis 1984; 130:980–6.
14. Gunga HC, Frommhold M, Hildebrandt W, Kirsch K, Rocker L. Erythropoietin production during flights with pressurised aircrafts. Lancet 1996; 348:416.
15. Levine BD, Kubo K, Kobayashi T, Fukushima M, Shibamoto T, Ueda G. Role of barometric pressure in pulmonary fluid balance and oxygen transport. J Appl Physiol 1988; 64:419–28.
16. McFarland RA. Human factors in relation to the development of pressurized cabins. Aerosp Med 1971; 42:1303–18.
17. McGoon MD. The assessment of pulmonary hypertension. Clin Chest Med 2001; 22:493–508, ix.
18. Mohr LC. The hypoxia altitude simulation test: an increasingly performed test for the evaluation of patients prior to air travel. Chest 2008; 133:839–42.
19. Mohr LC. Hypoxia during air travel in adults with pulmonary disease. Am J Med Sci 2008; 335:71–9.
20. Muhm JM, Rock PB, McMullin DL, Jones SP, Lu IL, et al. Effect of aircraft-cabin altitude on passenger discomfort. N Engl J Med 2007; 357:18–27.
21. Naughton MT, Rochford PD, Pretto JJ, Pierce RJ, Cain NF, Irving LB. Is normobaric simulation of hypobaric hypoxia accurate in chronic airflow limitation? Am J Respir Crit Care Med 1995; 152:1956–60.
22. Noble JS, Davidson JA. Cor pulmonale presenting in a patient with congenital kyphoscoliosis following intercontinental air travel. Anaesthesia 1999; 54:361–3.
23. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation 2007; 115:1132–46.
24. Pickard JS, Gradwell DP. Respiratory physiology and protection against hypoxia. In: Davis JR, Johnson R, Stepanek J, Fogarty JA, eds. Fundamentals of aerospace medicine. Philadelphia: Lippincott Williams and Wilkins; 2008.
25. Raymond LW. Altitude pulmonary edema below 8,000 feet: what are we missing? Chest 2003; 123:5–7.
26. Silverman D, Gendreau M. Medical issues associated with commercial flights. Lancet 2009; 373:2067–77.
27. Smith D, Toff W, Joy M, Dowdall N, Johnston R, et al. Fitness to fly for passengers with cardiovascular disease. Heart 2010; 96(Suppl. 2):ii1–16.
28. Smith TG, Balanos GM, Croft QP, Talbot NP, Dorrington KL, et al. The increase in pulmonary arterial pressure caused by hypoxia depends on iron status. J Physiol 2008; 586:5999–6005.
29. Smith TG, Brooks JT, Balanos GM, Lappin TR, Layton DM, et al. Mutation of von Hippel-Lindau tumour suppressor and human cardiopulmonary physiology. PLoS Med 2006; 3:1178–85.
30. Smith TG, Robbins PA, Ratcliffe PJ. The human side of hypoxia-inducible factor. Br J Haematol 2008; 141:325–34.
31. Smith TG, Talbot NP, Privat C, Rivera-Ch M, Nickol AH, et al. Effects of iron supplementation and depletion on hypoxic pulmonary hypertension: two randomized controlled trials. JAMA 2009; 302:1444–50.
32. Teichman PG, Donchin Y, Kot RJ. International aeromedical evacuation. N Engl J Med 2007; 356:262–70.
33. Toff NJ. Hazards of air travel for the obese: Miss Pickwick and the Boeing 747. J R Coll Physicians Lond 1993; 27:375–6.
34. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984; 70:657–62.