

**Flight-related complications are infrequent in hereditary haemorrhagic telangiectasia/
pulmonary arteriovenous malformations patients, despite low oxygen saturations and anaemia.**

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ON LINE DATA SUPPLEMENT

CONTEXT

Flight has become an integral part of modern life and is now accessible to all, with the world's five busiest airports (in Atlanta, Beijing, Chicago, London Heathrow and Tokyo) each transporting between 64 and 89 million passengers in 2010. ¹ Whilst flying, individuals are exposed to a unique environment that clinicians would not normally seek out, or choose to subject patients to. In particular, regulations stipulate that aircraft cabin altitude pressures are no greater than 8,000 feet whilst flying at 38,000 feet. ² Although the oxygen expressed as a percentage of inspired air (FiO₂) remains constant at 0.21, this altitude results in hypobaric hypoxaemia which is equivalent to an FiO₂ of 0.151 at sea level. ³ Exposure to aircraft cabin altitude has been shown to lead to discomfort even in healthy subjects. ⁴ The potential of venous thromboembolism to be exacerbated by the relative immobility during flight is also recognised, with the World Health Organisation emphasising the need to identify risk factors and biochemical aetiology. ⁵

Whilst most people fly uneventfully, the general population is inherently heterogeneous and large studies are needed in order to draw conclusions over the risks of air travel. There are particular concerns when pre-existing medical conditions are present, stimulating management guidelines, many of which use oxygen saturation (SaO₂) and haemoglobin as factors to stratify patients' medical fitness to fly. ^{6,7,8}

Most flight studies involving patients with respiratory conditions have studied single flights in individuals suffering from obstructive or interstitial lung disease. ⁹⁻¹³ However, there are wider groups of respiratory patients who have low resting oxygen saturations. Patients with pulmonary arteriovenous malformations (PAVMs) have hypoxaemia due to the presence of right to left shunts through abnormal vessels, shunts which also lead to paradoxical embolic stroke. ¹⁴ Approximately 90% of PAVM patients have underlying hereditary haemorrhagic telangiectasia (HHT), a condition that affects 1 million individuals worldwide and has a variety of additional features that might be expected to provoke in-flight complications. ¹⁵ Anaemia in particular is common, and results from recurrent nasal and gastrointestinal bleeding. AVMs also occur in other visceral vascular beds. ¹⁵

There are very limited published data on flight tolerance in these individuals, many of whom remain undiagnosed for decades during which time they pursue full complements of normal activities such as flying. Within-series cases, and dedicated case reports, have highlighted patients with PAVMs and HHT who have suffered from venous thromboembolism¹⁶ and paradoxical embolic stroke^{17,18} after long haul flights. As a result, some patients are surprised upon diagnosis to find limitations being placed on activities that they used to perform without ill-effect.

We hypothesised that examination of flight complications in a large cohort of PAVM and HHT patients was likely to provide further relevant data regarding hypoxaemia, venous thromboembolism, and anaemia, for individuals at higher risk of in-flight complications. Here we report the results of a questionnaire-based study to investigate flight tolerance in the PAVM/HHT population.

SUPPLEMENTARY METHODS

PubMed searches

PubMed searches on 10/07/09 and 7/03/2011 using search terms: ([Pulmonary arteriovenous malformations] or [PAVMs] or [hereditary haemorrhagic telangiectasia] or [hereditary hemorrhagic telangiectasia]) AND ([altitude] or [airplane] or [aerospace medicine] or [aircraft] or [aircraft emergencies] or [air travel] or [aviation] or [fitness for air travel] or [fitness to fly] or [hypoxia inhalation simulation test] or [hypoxia inhalation test] or [passenger]) identified no studies into the effect of flight on patients with PAVM or HHT.

Study Protocol

Ethical approval was obtained from the London-Surrey Borders Research Ethics Committee (NRES 10/H0806/8). Written consent was obtained at the time the completed questionnaire was returned. Adult patients who had attended a tertiary UK referral centre HHT service, and had been given a definite diagnosis of HHT¹⁹ were identified from cohorts previously reported,¹⁶ and more recently reviewed. As previously described,¹⁷ all patients had undergone PAVM screening with oxygen saturations (SaO₂) recorded at rest in supine and erect postures, and imaging (thoracic CT scan excepting occasional individuals with chest x-ray/angiogram). Serial SaO₂, haemoglobin, and serum iron concentrations were available over the periods in which patients had been seen in the Hospital Trust. Participants were sent a questionnaire asking them to document the number and length of flights they had taken on an aeroplane throughout their life; list any symptoms they experienced during or shortly afterwards; and any subsequent treatment they received. The study invitation letter asked for consent for their responses and hospital records to be used for flight study analyses.

Definitions

Flights of less than six hours' duration were classed as short haul, and those of over six hours as long haul. Flight hours for each patient were calculated by adding up the total number of hours of all flights taken. Where patients provided an estimate of the number of short and long haul flights, the average duration was calculated from responses received. As a result, where otherwise not specified, an average of 3 hours for short haul flights and 8 hours for long haul was used. PAVMs were only diagnosed if radiologically confirmed.

Data recording and Statistics

Paper questionnaires were stored alongside patient hospital records where only the authors had access. A coded Excel spread sheet was generated on the Trust computers, delineating self reported flight in-flight outcomes, and post-flight VTE if these occurred within 4 weeks of flight. Relevant physiological variables were accessed from hospital records, namely oxygen saturation (SaO₂) on air, at sea level after 7-10 minutes in the erect posture as previously described,^{17,20,21} and serial haemoglobin concentrations over the periods when the patients had been reviewed. For patients experiencing complications, serial values were recorded, otherwise, the latest available measurements were recorded. Variable statistics were calculated using Graph Pad 5 (Graph Pad Software Inc, San Diego, California, USA). The relationship between outcome variables dyspnoea, nosebleeds, DVT and ischaemic stroke were examined in univariate analyses using Mann-Whitney.

SUPPLEMENTARY RESULTS

Demographics of respondents and flights

159 replies were received from 308 questionnaires sent out (response rate 51.6%). The average age at the time of reply was 55 (range 18-90) years, 34% of respondents were male, and 147 respondents had flown. Two had flown extensively due to their occupation, reporting over 10,000 flights between them (pilot with HHT, PAVMs and pre-embolization SaO₂ 91% erect; cabin crew with HHT and no PAVMs). As this was a self-selecting group who would substantially skew the data, their data were not incorporated into the bulk of the analyses. Excepting those two individuals, 145 HHT-affected respondents (96 [66%] with PAVMs) had flown for 18,943 hours over 3,950 flights. As demonstrated in Supplementary Table 1, of the 145 non-professionals, 111 (77% [95% confidence intervals 69.6, 83.5%]) reported no complications. Six individuals (4.1 [0.86, 7.4]%) reported dyspnoea, two had a deep vein thrombosis, and one suffered an ischaemic stroke whilst flying. The most common complication was nosebleeds related to the underlying HHT. Complications occurred in similar proportions of men and women (10 [20%] males; 22 [23%] females, χ^2 p value = 0.18).

Supplementary Table 1: Flights and complications

A)	<i>Flights</i>	<i>All complications</i>	<i>Nosebleeds</i>	<i>Dyspnoea</i>	<i>DVT</i>	<i>Ischaemic Stroke</i>
Short haul	2,981	117 (4.0 [3.2, 4.6])	78 (2.6 [2.0, 3.2])	39 (1.3 [0.9, 1.7])	0 (0 [0,0])	0 (0 [0,0])
Long haul	969	132 (13.6 [11.5, 15.8])	112 (11.6 [9.6,13.6])	17 (1.8 [0.9, 2.5])	2 (0.2 [-0.08, 0.49])	1 (0.1 [-0.10, 0.30])
Total	3,950	249 (6.3 [5.5, 7.1])	190 (4.8 [4.1, 5.5])	56 (1.4 [1.1, 1.8])	2 (0.05 [-0.02, 0.1])	1 (0.03 [-0.02, 0.08])

B)	<i>Patients</i>	<i>All complications</i>	<i>Nosebleed</i>	<i>Dyspnoea</i>	<i>DVT</i>	<i>Ischaemic Stroke</i>
Short Haul	141	17 (12 [6.6, 17.5])	14 (9.9 [4.9, 14.9])	3 (2.1 [-0.28, 4.5])	0 (0 [0,0])	0 (0 [0,0])
Long Haul	80	29 (36 [25.5, 47.0])	20 (25.0 [15.3, 34.7])	6 (7.5 [1.6, 13.4])	2 (2.5 [-1.0, 6.0])	1 (1.3 [-1.2, 3.7])
All Flights	145	35 (24.1 [17, 31])	26 (17.9 [11.6, 24.3])	6 (4.1 [0.8, 7.4])	2 (1.3 [-0.5, 3.3])	1 (0.69 [-0.67, 2.0])

Legend: Data expressed A) as proportion of flights taken, and B) as proportion of participants who flew, since individuals contributed more than one flight each. All data reported as number (% [95% confidence intervals]). Note that complications were more frequent during long haul flights (χ^2 p values < 0.0001 in each case). DVT, deep venous thrombosis.

Dyspnoea

As illustrated in the main text and Figure, there was a wide range in SaO₂ levels for participants with PAVMs who had not reported in-flight dyspnoea, but no relationship was detected between SaO₂ and in-flight dyspnoea. Since anaemia is common in HHT patients, reduces oxygen carriage by the blood, and is used as an indicator of fitness to fly,^{6,7,22} serial haemoglobin values were examined. For the HHT participants who had not reported in-flight dyspnoea, there was a wide range in haemoglobin values (Supplementary Figure 1A). There was no difference in median haemoglobin between those who reported in-flight dyspnoea, and those who did not (Supplementary Figure 1B). Flights where dyspnoea was reported did not correspond to times when haemoglobin concentrations were lowest for that particular individual (Supplementary Figure 1C).

Iron deficiency exacerbates hypoxic pulmonary vasoconstriction (HPV)²³ that could elevate pulmonary arterial pressure when alveolar hypoxia is widespread, as during flight^{23,24} There was however, no difference in serum iron between those who reported in-flight dyspnoea, and those who did not (Supplementary Figure 1D). Flights where dyspnoea was reported did not correspond to times when serum iron was lowest for that individual (Supplementary Figure 1D).

Thrombotic and haemorrhagic complications

There was no difference in oxygen saturations or haemoglobin concentrations between the individuals reporting in-flight ischemic stroke or deep venous thromboses attributed to a flight, and those that did not (Supplementary Figure 2).

Twenty six (18%) of all participants, 17 with PAVMs, reported nosebleeds due to their HHT. A larger proportion of individuals experienced nosebleeds during long haul flights (Table 1, $p=0.0029$). HHT nosebleed severity varies,²⁵ but the proportion of participants reporting in-flight nosebleeds was similar for patients who normally experienced nosebleeds at least once per month (Supplementary Figure 3A). There was no difference between tendency to suffer nosebleeds whilst on a flight and average haemoglobin (Supplementary Figure 3B).

Anecdotal comments:

Three participants only reported in-flight dyspnoea during long haul flights. Two (with sea level SaO₂ of 92% and 94%) stated that they asked for, and used, in-flight oxygen, each recording that this was of benefit, feeling more breathless when it was taken off in-flight for meals.

One of the two professionals and seven (5%) of the remaining 145 respondents reported that their nosebleeds were more intense whilst flying; both longer in duration and severity of bleeding. One individual described the need for surgical intervention of a major nosebleed that commenced in-flight.

Two women (both with PAVMs) reported flying when pregnant and noted that they did not experience any adverse symptoms.

SUPPLEMENTARY DISCUSSION

The principal findings of this study were that flying appears safe for the majority of individuals with PAVMs and HHT despite abnormal oxygen saturations and haemoglobin concentrations. With the exception of nosebleeds, complications, when they occurred, were usually self limiting. The best predictor of individuals who would be prone to dyspnoea or nosebleeds appeared to be previous flight experience. The findings are surprising, and raise difficulties in recommendations for in-flight oxygen and prophylactic heparin.

The strengths of the study were the large number of participants; data regarding multiple flights per participant, including different durations of flights; and correlation with known pre and post flight parameters. The weaknesses of the study were its retrospective nature, particularly, reliance on patient recall. In addition, the focus on symptoms will have underestimated the total number of thrombotic complications compared to studies which examined asymptomatic DVTs. One such study indicated that 10% of individuals over 50 years of age with no previous thromboembolic disease experienced asymptomatic DVTs whilst on long haul flights.²⁶

Other studies have examined outcomes in participants with different respiratory conditions over the course of a single flight.⁹⁻¹³ This method allows prospective clinical measurements and an accurate account of the complications that each patient suffers, but is limited because it provides only a snapshot during a single flight. Our study is the largest involving patients with HHT and PAVM, and recorded individuals' experiences during 3,950 flights. The advantage of this retrospective database is that a trend could be built up for individuals, providing a greater understanding of the risks to a population group. Furthermore, less common complications such as stroke could be observed in an unselected population to provide a more accurate account of their prevalence.

The first surprising finding from the study for policy makers was the good toleration of flights despite many participants having chronically low oxygen saturations (main text, Figure 1A). Previous flight guidelines used SaO₂ and the forced expiratory volume in 1 second (FEV₁), or regression equations and previous flight experience, to determine which patients should be recommended to undergo hypoxic challenge testing.⁶⁻⁸ We were unable to predict which individuals would experience dyspnoea based on sea level SaO₂. This is in line with other recent flight studies which no longer suggest SaO₂ alone as a reliable marker of desaturation and morbidity whilst flying.^{10,11} Furthermore,

the UK Flight Outcomes Study that followed 431 patients with various lung diseases on a single flight after specialist respiratory assessment, concluded that air travel appeared safe for the majority of patients following such an evaluation.⁹ While this makes it difficult to produce guidelines based on sea level SaO₂ regarding who is likely to benefit from in-flight oxygen, since two individuals in the current series found that this relieved the sensation of dyspnoea, it would be prudent that individuals with HHT and PAVM who experience dyspnoea should be recommended to use in-flight oxygen for future flights, with face masks potentially preferable to nasal cannulae that might be predicted to provoke nosebleeds.

Our second objective was to examine thrombotic complications, and, again surprisingly, overall rates of symptomatic thrombotic complications were low. In our study only two respondents (1%) reported DVTs, and one reported an ischemic stroke (<1%). We recognize that the questionnaire did not capture all flight-provoked DVTs as the two reported here are two of four in the full cohort of HHT patients seen by CLS since 1999 (Livesey et al, manuscript in review). Furthermore, asymptomatic events are likely to have been even more frequent.²⁶ The questions regarding recommended thromboprophylaxis are therefore difficult. Based on the evidence from²⁶ in which no DVTs were detected in participants wearing thromboembolic deterrent stockings (TEDs), recommendation of this safe prophylaxis appears justifiable, even if the prevention rates are not as high in all studies (compare²⁷). Use of prophylactic anticoagulation as might have been recommended²⁸ is more problematic in HHT patients than in the general population, because of the high prevalence of nosebleeds which may lead to individuals being barred from taking a flight.²⁹ In addition, there is a recent report of two cases of in-flight PAVM haemorrhage (one hemoptysis, one hemothorax).³⁰ Based on these data, for the general HHT population, the risks of additional low molecular weight heparin may not be justifiable except in patients who have had a previous DVT, pulmonary embolus or ischemic stroke. As always, the clinician must weigh up the risk of thrombosis against the risk of bleeding for each individual patient.

We believe caution is required before these data are applied to members of the general population who have low oxygen saturations with or without anemia. First, it is well recognized by airlines that the situations of flight suitability in the setting of recent onset and stable anemia are different.²⁹ Secondly, longstanding hypoxemia in PAVM patients results in adaptive responses (such as polycythaemia). Most importantly, hypoxemia in PAVM patients results from anatomical shunting, and not alveolar hypoxia (Supplementary Figure 4). For general respiratory patients, in-flight hypobaric conditions accentuating pre-existing alveolar hypoxia, risk not only lowering arterial PO₂, but also elevating pulmonary artery pressure as a result of widespread hypoxic pulmonary vasoconstriction (HPV). As recently reviewed,²⁴ HPV is advantageous at the time of focal alveolar hypoxia, when low alveolar PO₂ is sensed, leading to reflex constriction of adjacent pulmonary

arterioles, diverting blood away from the unventilated alveoli, and attenuating the resultant mismatch between ventilation and pulmonary blood flow. In the setting of extensive alveolar hypoxia pulmonary artery pressure rises, providing an additional mechanism for in-flight dyspnoea in general respiratory patients that does not apply to the majority of HHT/PAVM patients.

In conclusion, we have conducted the largest flight study on individuals with PAVMs and HHT. The vast majority of participants flew without experiencing complications. Previous flight experience was a useful indicator of future complications. Nosebleeds were the most common complication, and were often more severe than at ground level, whereas symptomatic DVTs and ischemic stroke were rare events. The sensation of dyspnoea was uncommon, but re-occurred in the same individuals. In this population, it is difficult to recommend in-flight oxygen for patients purely based on low sea level SaO₂. Unanswered questions concern the risk-benefits of prophylactic heparin in specific individuals with HHT, and relevance of the findings to the general respiratory populations, for which further study is required.

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LEGENDS TO SUPPLEMENTARY FIGURES

Figure 1: Haemoglobin concentrations in 145 participants who flew with HHT

A: Earliest and most recent haemoglobin values for HHT patients who did not report in-flight dyspnoea. Falls in haemoglobin reflected onset of iron deficiency anemia, or correction of secondary polycythaemia post PAVM embolization and concomitant rise in SaO₂. Rises in haemoglobin resulted from corrective treatments for haemorrhage and iron deficiency. **B:** Mean haemoglobin at sea level for individuals who reported in-flight dyspnoea, and those who did not. **C:** Serial haemoglobin in participants who reported dyspnoea, over periods of 1-17 (median 7.5) years. Circles indicate periods in which flights were reported to cause dyspnoea. **D:** Serial serum iron concentrations in participants who reported dyspnoea, over periods of 1-17 (median 7.5) years. Circles indicate periods in which flights were reported to cause dyspnoea. Inset indicates spread of median values in patients with and without dyspnoea. Note data excludes the two professionals.

Supplementary Figure 2. In-flight thromboembolic complications:

A: Comparison of average recorded SaO₂ in individuals who suffered either a stroke or deep venous thrombosis (DVT), and those who did not. **B:** Comparison of average recorded haemoglobin (Hb) concentrations in individuals who suffered either a stroke or deep venous thrombosis (DVT), and those who did not. **C:** Serial haemoglobin concentrations from patients' who suffered a stroke or DVT. The values closest to the complications reported are circled.

Supplementary Figure 3. In-flight Nosebleeds

A: Percentage of patients reporting in-flight nosebleeds according to maximum reported frequency of nosebleeds in adult life. Total bar size (grey +black) represents number of participants reporting nosebleeds of at least daily; at least weekly (but not daily); at least monthly (but not weekly); at least annually (but not monthly) and at least once per year. Black bars represent number reporting in-flight nosebleeds within each group. **B:** Comparison of mean recorded haemoglobin (Hb) concentrations in individuals who suffered in-flight nosebleeds compared to those who did not.

Supplementary Figure 4: Illustration of different mechanisms of hypoxaemia

Figure adapted from JB West, with permission. **i)** Normal pulmonary arterial blood flow to capillaries associated with oxygenated alveoli. **ii)** Blood flow through PAVMs representing anatomical right to left shunts. The fraction of blood passing through the PAVMs (shunt fraction) determines the level of hypoxaemia; pulmonary artery pressure does not rise.³² **iii)** Reduced blood flow to hypoxic alveoli resulting from hypoxic pulmonary vasoconstriction- if this is widespread, pulmonary artery pressure will rise.³²