Respiratory Medicine (2013) **107**, 298–304

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Hypoxaemia in patients with pulmonary arterial hypertension during simulated air travel

R.M. Burns, A.J. Peacock, M.K. Johnson [a], A.C. Church*[,a]

Scottish Pulmonary Vascular Unit, Golden Jubilee Hospital, Agamemnon Street, Clydebank, Glasgow G81 4DY, UK

Received 7 March 2012; accepted 15 October 2012
Available online 3 November 2012

KEYWORDS
Pulmonary hypertension;
Hypoxic challenge test;
Fitness to fly

Summary
Background: Recent air travel recommendations suggest patients with precapillary pulmonary hypertension (PCPH) in New York Heart Association (NYHA) functional class 3 and 4 should have in-flight oxygen without the need for pre-flight testing. However it remains unclear as to how best to determine patients fitness to fly.
Methods: This study (i) investigates the effect of hypoxic challenge testing (HCT) on the arterial oxygen levels in a cohort of 36 patients with PCPH and (ii) compares the relative frequency with which FC and HCT predict the requirement for in-flight oxygen.
Results: The degree of arterial hypoxaemia induced by HCT (fall in partial pressure of oxygen in arterial blood (PaO_2) 2.36 kPa, 95% CI 2.06–2.66 kPa) was similar to the drop observed in other published studies of chronic respiratory diseases.

Following current air travel recommendations based on FC, 25 patients of the cohort would require in-flight oxygen whilst 10 subjects failed the HCT. Fourteen subjects had flown post-diagnosis. Of these, nine subjects should have had in-flight oxygen based on FC but were asymptomatic without. Also one who passed the HCT had developed symptoms during the flight whilst three who failed the HCT were asymptomatic flying without in-flight oxygen.
Conclusions: Hypoxaemia induced by simulated air travel in patients with PCPH is similar to that seen in published studies of patients with other chronic respiratory diseases. HCT failed to predict correctly who had developed symptoms during an aircraft flight in a significant minority of the study subjects. Similarly guidelines based on functional class result in a major

Abbreviations: $(A–a)O_2$, alveolar–arterial oxygen tension gradient; COPD, chronic obstructive pulmonary disease; CTD-PAH, connective tissue disease-associated PAH; FiO_2, inspired fraction of oxygen; FC, functional class; HCT, hypoxic challenge testing; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PaO_2, partial pressure of oxygen in arterial blood; PCPH, precapillary pulmonary hypertension; PAH, pulmonary arterial hypertension; RV, right ventricle; SPVU, Scottish Pulmonary Vascular Unit; SpO_2, saturation of haemoglobin with oxygen measured by pulse oximetry.

* Corresponding author. Tel.: +44 0141 211 8538; fax: +44 0141 951 5442.
E-mail address: colinchurch@doctors.org.uk (A.C. Church).
[a] Both authors contributed equally to the paper.

0954-6111/$ - see front matter
http://dx.doi.org/10.1016/j.rmed.2012.10.007

increase in the proportion of patients being advised to use oxygen, many of whom had been asymptomatic on previous flights without it. More work is required to improve prediction of need for in-flight oxygen in patients with PCPH.

Introduction

Recent improvements in medical therapy have meant an improved quality of life for patients with precapillary pulmonary hypertension (PCPH) and many of these patients are now undertaking air travel. However, during a flight these patients become exposed to hypobaric hypoxia as aircraft cabins are partly pressurised and travellers may be exposed to altitudes of up to 2438 m (8000 feet), at which the partial pressure of oxygen decreases to the equivalent of breathing an inspired fraction of oxygen (FiO_2) of 15% at sea level. In patients with PCPH this altitude exposure and concomitant alveolar hypoxia leads not only to arterial hypoxaemia but also potentially to pulmonary vasoconstriction, acute right heart strain and theoretically right heart failure.

Current air travel guidelines recommend that the requirement for in-flight oxygen in PCPH patients should be based upon New York Heart Association (NYHA) functional class (FC) as a surrogate marker for right heart function. Those in functional class I and II are fit to fly unless the physician feels that oxygen or an HCT is clinically required or the patient is hypoxaemic at sea level. Functional class III and IV patients are recommended to travel with in-flight oxygen irrespective of baseline saturations. This advice is expert consensus and is based upon the American Aerospace Medical Association, the European Respiratory Society/European Society Cardiology guidelines, the British Thoracic Society and the UK consensus document on pulmonary arterial hypertension (PAH).[1–5]

The problem with producing any recommendations on in-flight oxygen for patients with PCPH is a paucity of data regarding the magnitude and time course of the effect of hypobaric hypoxia on these patients. Many current recommendations on air travel are extrapolated from studies involving people with common respiratory conditions such as chronic obstructive pulmonary disease (COPD)[6–8] but it is unclear how best to assess fitness to fly in the context of pulmonary hypertension.

The aims of this study were twofold. Firstly we wished to measure the level of hypoxaemia that would develop in PCPH patients during an aircraft flight simulated by a HCT and thus determine if it is any more severe than that reported in other respiratory conditions.[9–11] Secondly, we wanted to compare the relative frequency with current air travel guidelines using FC to predict the requirement for in-flight oxygen with previous guidelines using HCT.

Methods

Ethical approval was obtained from the West of Scotland Research Ethics Service (REC:10/S0709/47) and patients who participated gave their written informed consent. All patients were recruited from the Scottish Pulmonary Vascular Unit (SPVU). Inclusion required a diagnosis of PAH or distal chronic thromboembolic pulmonary hypertension (referred to as PCPH) with saturation of haemoglobin with oxygen measured by pulse oximetry (SpO_2) $\geq$90% on air.[12]

The patients underwent a HCT and the protocol followed is summarised in Fig. 1. Hypoxaemia was assessed by both SpO_2 and measurement of capillary blood gases (CBG). To induce alveolar hypoxia, the patient breathed through a 40% Venturi mask (Intersurgical, UK) driven by 100% nitrogen (at a flow rate of 10 L min^{-1}). The FiO_2 induced at the mouth using this apparatus was measured using an oxygen sensor (Teledyne analytical instruments, Viamed, UK) and found to be 15.1%.

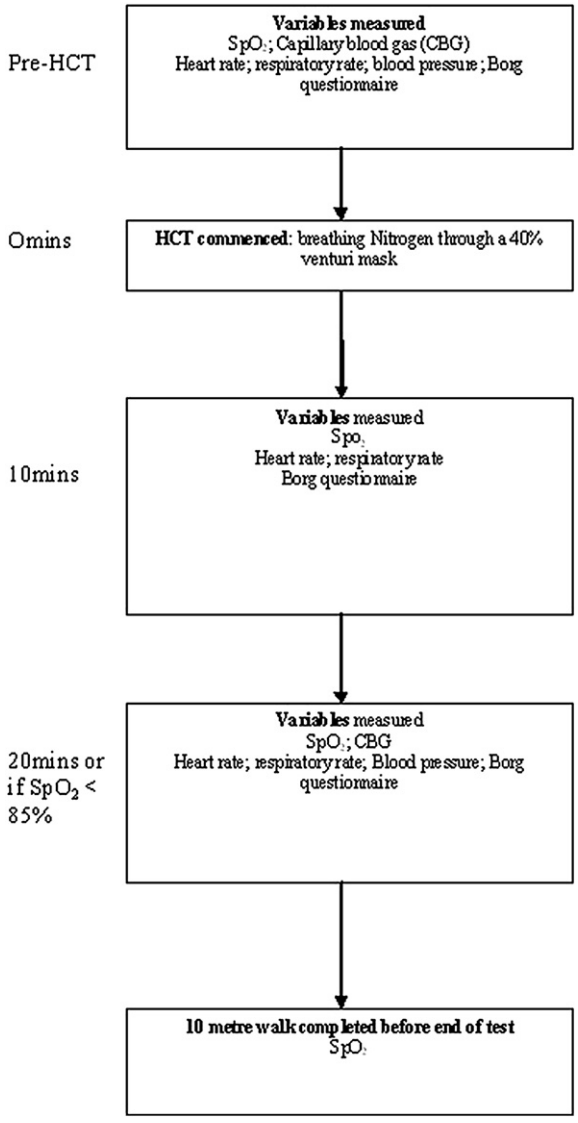

Figure 1 Study protocol.

If SpO_2 fell below 85% for over 30 s, the test was stopped.[9] The test was classed as "failed" if PaO_2 <6.6 kPa or SpO_2 <85% after 20 min of breathing the air/nitrogen mixture. Finally, while still breathing the hypoxic gas mixture, patients were asked to walk 10 m. The rationale was to mimic the restricted movement patients may have on an aircraft and observe any changes in SpO_2 that moderate exertion at altitude may have.

A flight history was taken from each study subject. The questions asked were the date of their last flight, whether it was made pre-diagnosis or post-diagnosis, their destination and length of flight, if they experienced any symptoms (cardio-respiratory, musculoskeletal, neurological) on the flight and whether they required additional oxygen on the flight.

Statistical analysis

Data were found to satisfy the Shapiro–Wilk test for normality. Where appropriate, statistical analysis of the data was performed using paired or unpaired *t*-tests, ANOVA with Tukey's post hoc analysis, Mann–Whitney test, two sample tests of proportion and Fisher's Exact Test. The tests were carried out using GraphPad Prism v5 (Graphpad software, USA) or STATA v12 (Statacorp, USA). A p value <0.05 was taken to indicate significance.

Results

Thirty six subjects were recruited for the HCT and their baseline characteristics are shown in Table 1.

The test was well tolerated, with all subjects completing it without any serious adverse effects. Three patients reported feeling light-headed and one patient reported feeling more breathless than usual but these symptoms were not severe enough to terminate the test. Only one of these patients went on to fail the test. The mean duration of the HCT was 31 min. Partial pressure of oxygen in arterial blood (PaO_2) fell significantly during the test (mean difference 2.36 kPa, 95% CI 2.06–2.66 kPa) as shown in Fig. 2(a). At the same time, alveolar–arterial oxygen tension [$(A-a)O_2$] gradient decreased from 4.64 kPa at baseline to 1.61 kPa at the end of the test (mean difference 3.03 kPa, 95% CI 2.45–3.61 kPa) as shown in Fig. 2(b). There was no significant change in the SpO_2 between the 20 min point and the 10 m walk, despite increases in heart rate [Table 2, Fig. 3(a) and (b)].

Twenty-six of the 36 subjects passed the HCT whilst 10 failed. Tables 1 and 2 show the differences between the group who passed the HCT and the group who failed. Univariate analysis showed baseline SpO_2, PaO_2 and $A-aO_2$ gradient to be significantly different between the groups. However this significance was lost on multivariate analysis. Importantly functional class was not found as a significant predictor of those who would fail the HCT and indeed slightly more subjects in functional class II failed the HCT than in functional class III (31% vs 27%).

From the flight history data, 39% (n = 14) had undertaken air travel after their diagnosis and all these flights were intercontinental. Only one of these experienced symptoms during the flight and this subject actually passed the HCT. A further two subjects had used in-flight oxygen, with only one of these failing the HCT. Of the 14 who flew post-diagnosis four failed the HCT, but only one of them had used in-flight oxygen. Finally, 58% (n = 21) of the cohort planned to undergo future air travel.

Discussion

A complication of patients with PCPH undertaking air travel is that they might experience severe hypoxaemia. This study examined the effect a HCT would have on arterial oxygen levels and found that 28% of our cohort would fail. This is no more than observed in studies with other chronic respiratory diseases, showing up to 40% of COPD patients, 13% of cystic fibrosis patients and 58% of patients with kyphoscoliosis and/or neuromuscular disease could fail.[10,11,13] When compared with other groups of patients with respiratory diseases, the fall during the HCT in the mean PaO_2 is no larger. In our cohort the PaO_2 fell by 2.36 kPa, compared with 2.6 kPa for cystic fibrosis patients, 3.6 kPa for chest wall disease patients and 2.8 kPa for patients with COPD.[9–11] A possible explanation for this effect is the decrease observed in $(A-a)O_2$. It has been shown in both healthy individuals and more recently in patients with chest wall deformity[10,14] that the $(A-a)O_2$ gradient narrows with alveolar hypoxia. This effect could be due to hypoxic pulmonary vasoconstriction redistributing perfusion to areas of the lung with better ventilation and hence lesser degrees of alveolar hypoxia. Recent evidence has suggested that medication for PAH can worsen VQ mismatch at rest.[15] The data from this study suggest that the protective mechanism of hypoxic pulmonary vasoconstriction is sufficiently preserved in patients with PCPH despite their disease process and medication and would continue to protect these patients from excessive hypoxaemia on an aircraft.

In this study hypoxaemia is used as a measure of the impact of hypobaric hypoxia on the subjects but it may not be the most appropriate test to determine fitness to fly in PCPH patients, as it does not assess the effect of the cabin environment on the right ventricle (RV). Indeed it has been suggested that the most important issue in a patient with pulmonary hypertension on an aircraft flight is the risk of RV failure. However, this appears to be uncommon with very few actual reported cases[16] and there are no published studies to our knowledge which have specifically looked at RV function in patients with PCPH while on commercial aircraft travel. Moreover the actual cabin pressure (and therefore equivalent sea-level FiO_2) experienced by air travellers can vary and may not be as low as the patients undergoing the HCT actually experience.[17]

There are more data looking at the effect of acute hypoxia on the RV. In healthy volunteers during acute hypoxia the systolic performance measured by ejection fraction, stroke volume and end-diastolic volume of the RV is well maintained despite the increase in pulmonary artery pressure and afterload.[18] One study has looked at the right and left ventricular contractility in patients with connective tissue disease-associated PAH (CTD-APAH) exposed to hypoxia. Patients were exposed to a reduced FiO_2 of 14% and then 10% for a period of 30 min and underwent right

Table 1 Baseline characteristics of study subjects and comparison of those who passed and failed the HCT.

Baseline characteristics	All subjects $n = 36$	Passed HCT $n = 26$	Failed HCT $n = 10$	p value[a]
Sex, % female	61.1% (22)	61.5% (16)	60% (6)	0.932
Age (years)*	58 [47—66]	57 [45—67]	61 [53—67]	0.61
Diagnosis				
IPAH	42% (15)	46% (12)	30% (3)	
CTD-APAH	25% (9)	23% (6)	30% (3)	
POPAH	6% (2)	8% (2)	0% (0)	0.785
CHD-PAH	3% (1)	4% (1)	0% (0)	
CTEPH	25% (9)	19% (5)	40% (4)	
mPAP (mmHg)	50.6 [11.5]	50.8 [9.9]	50.3 [15.5]	0.914
CO (L min^{-1})	3.8 [1.2]	3.8 [1.2]	4.1 [1.1]	0.459
PCWP (mmHg)	8.8 [4.9]	8.4 [4.2]	9.8 [6.6]	0.433
NYHA FC*				
I	3% (1)	4% (1)	0	
II	36% (13)	35% (9)	40% (4)	0.606
III	61% (22)	62% (16)	60% (6)	
IV	0	0	0	
6MWD (m)	370 [98]	378 [92]	350 [112]	0.449
6MWD SpO_2 nadir (%)	90	91	88	0.403
Smoking history (%)				
Non-smoker	39%(14)	35% (9)	50% (5)	
Ex-smoker	44% (16)	46% (12)	40% (4)	1.0
Current smoker	17% (6)	19% (5)	10% (1)	
Medications				
PDE5I monotherapy	14	11	3	
ETRA monotherapy	7	5	2	
Prostanoids monotherapy	0	0	0	
Combination therapy	12	7	5	
No therapy	3	3	0	
FEV_1 (% pred)	84.3% [19.2]	84.1% [19.4]	84.9% [19.6]	0.748
FVC (% pred)	98.5% [18.7]	98.5% [19]	98.9% [18.9]	0.659

Actual numbers are shown in brackets (n). All continuous variables are mean [SD] except * which indicates median [interquartile range]. IPAH—idiopathic pulmonary arterial hypertension, CTD-APAH—connective tissue disease associated pulmonary arterial hypertension, POPAH—portopulmonary arterial hypertension, CHD-APAH—congenital heart disease associated PAH, CTEPH—chronic thromboembolic pulmonary hypertension, 6MWD—6 minute walk distance, mPAP—mean pulmonary arterial pressure, CO—cardiac output, PCWP—pulmonary capillary wedge pressure, FEV_1—forced expiratory volume in 1 s, FVC—forced vital capacity.

[a] Comparing those who passed and failed the HCT.

and left heart catheterisation. During hypoxia there was an increase observed in the right ventricular end-diastolic and systolic volume, cardiac index and heart rate, an identical response to healthy volunteers. Baseline mean pulmonary artery pressure (mPAP) was 32 mmHg which showed a modest increase to 38 mmHg at FiO_2 14% and 41.5 mmHg with a profound hypoxic insult of 10%.[19] There were no reports of problems during the test. A similar response has

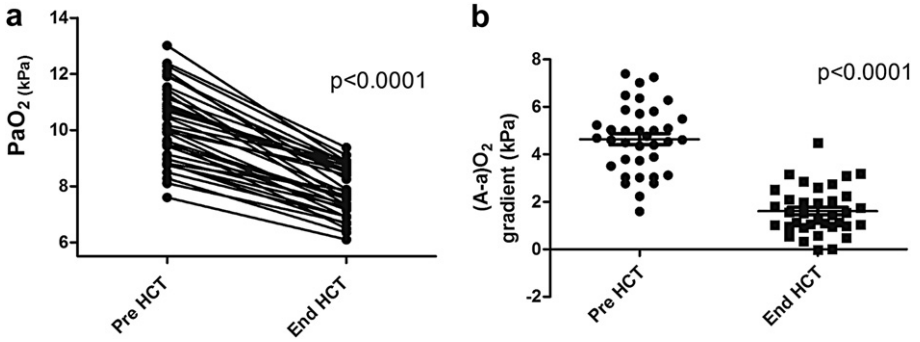

Figure 2 (a). Partial pressure of oxygen (PaO_2) in arterial blood before HCT and at the end of HCT. Individual patient data are shown. (b). The (A—a)O_2 gradient is shown before HCT and at the end of HCT. Individual data points are shown and mean values are indicated by the horizontal lines through the data points.

Table 2 Comparison of measured variables between subjects who passed and failed the HCT.

	Passed HCT	Failed HCT	*p* value
Pre HCT			
SpO_2 (%)	95 [2]	93 [2.2]	0.027
PaO_2 (kPa)	10.6 [1.2]	9.2 [1.1]	0.002
$(A-a)O_2$ (kPa)	4.3 [1.4]	5.5 [1.2]	0.026
Heart rate (min^{-1})	75 [12]	77 [10]	0.597
Systolic blood pressure (mmHg)	119 [19]	108 [15]	0.110
Diastolic blood pressure (mmHg)	80 [14]	74 [16]	0.296
Respiratory rate (min^{-1})	18 [6]	16 [3]	0.4
Borg score*	0 [0–0.6]	0.5 [0–1]	0.42
End of HCT			
SpO_2 (%)	89 [3]	83 [1]	<0.0001
PaO_2 (kPa)	8.2 [0.7]	6.6 [0.5]	<0.0001
$(A-a)O_2$ (kPa)	1.4 [0.9]	2.3 [1.1]	0.008
Heart rate (min^{-1})	74 [13]	80 [10]	0.456
Systolic blood pressure (mmHg)	116 [20]	106 [13]	0.164
Diastolic blood pressure (mmHg)	77 [14]	73 [17]	0.442
Respiratory rate (min^{-1})	18 [6]	16 [4]	0.256
Borg score*	0.3 [0–1]	0.5 [0–1]	0.67
10 m walk			
SpO_2 (%)	89 [3]	83 [2]	<0.0001
Heart rate (min^{-1})	88 [10]	99 [9]	0.01
Respiratory rate (min^{-1})	20 [7]	19 [4]	0.73
Borg score*	0.5 [0–2]	1 [0–2]	0.62

Actual numbers are shown in brackets (*n*). All continuous variables are mean [SD] except * which indicates median [interquartile range].
SpO_2—pulse oximetry oxygen saturation, PaO_2—partial pressure of oxygen in arterial blood, $PaCO_2$—partial pressure of carbon dioxide in arterial blood, $(A-a)O_2$—alveolar–arterial oxygen gradient.

been seen in patients with COPD some of whom had pulmonary hypertension.[20–22] It would appear that even with severe alveolar hypoxia (FiO_2 10%) the effect on pulmonary haemodynamics may be modest and unlikely to affect the RV adversely for the short period required for an aircraft flight and indeed maximal hypoxic vasoconstriction is achieved by 2 h.[23] However one study showed that 2 children out of a cohort of 22 with congenital heart disease and pulmonary hypertension, developed a large increase in pulmonary vascular resistance (PVR) when exposed to hypoxia (although others actually decreased their PVR).[24] The extent by which this effect is relevant to adults with non-congenital heart disease associated PAH is unclear.

An alternative way to stress the RV which results in equivalent rises in mPAP and hence RV afterload is exercise. It has been shown using ambulatory pulmonary artery catheters that during exercise mean increases in mPAP of 9.6 mmHg can be seen, with some patients increasing by as much as 19 mmHg.[25] Most of these subjects manage such effort without adverse effect. What is more, we actively encourage our patients to undertake exercise regularly despite being aware of these acute effects on RV afterload. In addition it has been demonstrated in patients with coexistent COPD and pulmonary hypertension that during eight hour periods of sleep the mPAP can rise to levels seen during exercise.[26] Clearly during sleep the RV copes in general with these increases in the mPAP and many flights are shorter than eight hours.

From our flight history questionnaire, 10 of the people who have been on a flight since their diagnosis would be advised to use supplementary oxygen based on current recommendations, although only 4 actually failed the HCT. Moreover only 1 of these patients had actually used in-flight oxygen. None of these patients experienced symptoms during the flight. This agrees with previous studies which have shown that despite being hypoxaemic during aircraft flight very few actually experienced any symptoms or needed unscheduled respiratory healthcare.[27] In addition some patients had symptoms during the HCT and still passed suggesting that some patients may experience symptoms above the threshold for failing a HCT. Therefore both HCT and FC assessment are not perfect at identifying patients who may have symptoms during aircraft travel.

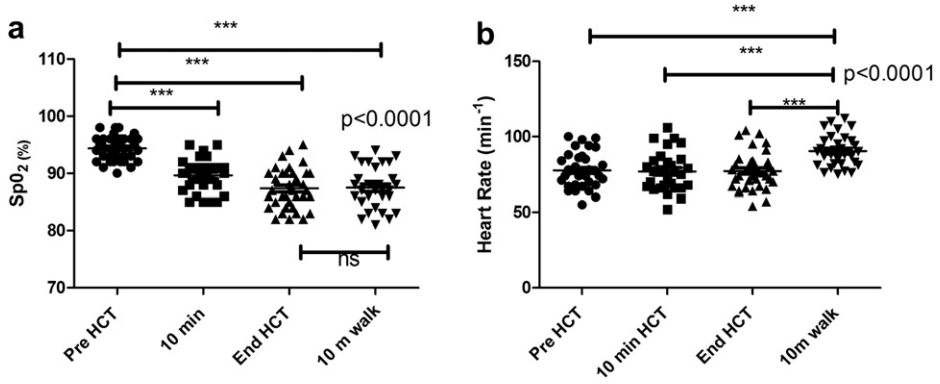

Figure 3 (a) Pulse oximetry oxygen saturation (SpO_2) and (b) heart rate are shown before, during, at the end of the HCT and after the 10 m walk. Individual patient data are shown. Mean values are indicated as horizontal line through data points.

With nearly 2 billion people travelling by air each year and numbers increasing, more people with chronic health problems such as PCPH will want to fly.[28]The consequences of the current recommendations and their implications for air travel in these patients should not be underestimated as it could limit their potential to travel by air and impair their quality of life. There is great disparity in the attitudes of airlines to the provision of in-flight oxygen, demonstrated by a recent report by the UK Pulmonary Hypertension Association.[29] Some airlines do not allow additional in-flight oxygen, some can charge in excess of £200 for a round trip, while others require the purchase of an additional seat if oxygen is required.[29] Perhaps one of the principal aims of air travel guidelines should be to minimise the proportion of patients to whom we recommend in-flight oxygen without jeopardising their safety. Whilst failing a HCT is not a definite predictor of acute RV failure and subsequent problems during air travel, it does indicate the likelihood of developing significant arterial hypoxaemia during a flight. Using recommendations based on functional class may both increase the proportion of patients who must now be advised to arrange oxygen for their flight whilst at the same time is not proven to improve the accuracy of predicting problems should oxygen not be provided. In addition in this study functional class did not predict whether a subject would fail the HCT (31% with FC II vs 27% FC III) and so was a poor indicator of the potential development of severe arterial hypoxaemia. This study is not suggesting that use of HCT is better than using FC to determine need for in-flight oxygen but merely aiming to compare and contrast two different approaches to assessing the in-flight oxygen requirement. The HCT is an imperfect test for assessing this as it measures arterial hypoxaemia whereas in patients with PAH the ideal end-point would be the effect on RV function. In addition the need for in-flight oxygen for a patient who actually fails a HCT has not been proven conclusively in clinical trials but is based on expert consensus. There are further cost implications if all patients with PAH were to undergo a HCT, with no data available to suggest that this would be a cost effective strategy.

To our knowledge this is the largest study of patients with PCPH undergoing a hypoxic challenge test. Patients with baseline SpO_2 >95% and <92% were included, allowing conclusions to be drawn on patients not always tested. A further strength was the addition of a 10 m walk, which is not routinely performed during a HCT, to mimic mild exercise on an aircraft. This study has a number of limitations. The current most accepted standard to test for in-flight oxygen requirement and potential issues arising during a flight would be to use a hypobaric chamber. For practical purposes a hypoxic challenge test was used assuming that normobaric hypoxia experienced by the patient equated to the hypobaric hypoxia of altitude. There is no physiological rationale to think that this would be otherwise.[30] Furthermore the Venturi modification HCT has been validated as an equally effective test against the standard of measuring oxygenation in a hypobaric chamber.[31] The duration of the test is not as long as even a short haul flight would be. However studies have shown that after 20 min there is equilibration of the hypoxic gas mixture.

In conclusion, patients with precapillary pulmonary hypertension have similar degrees of hypoxaemia during the HCT to patients with other respiratory diseases. Current guidelines based on functional class result in a major increase in the number of patients being advised to use oxygen in-flight compared with older guidelines based on HCT. Both approaches recommend oxygen in patients who were asymptomatic on flights undertaken post-diagnosis but before this study. HCT did not identify one patient who developed symptoms during a flight. Further work is required to identify more accurate predictors for determining the need for in-flight oxygen in patients with PCPH.

Acknowledgements

We would like to thank the staff in the pulmonary function laboratory for their assistance with the hypoxic challenge test. We also acknowledge the essential help of the nursing and secretarial staff in the SPVU.

Funding

University of Glasgow.

Author contribution

RB — undertook the HCT and contributed to writing the manuscript.
AJP — contributed to writing and advised during the project.
MKJ — contributed to writing and advised during the project.
ACC — conceived the project, undertook the HCT and contributed to writing the manuscript and is guarantor.

Competing interests

None.

References

1. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *The European Respiratory Journal* 2009;**34**(6):1219—63.
2. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. *Thorax* 2008;**63**(Suppl. 2):ii1—41.
3. Smith D, Toff W, Joy M, et al. Fitness to fly for passengers with cardiovascular disease. *Heart (British Cardiac Society)*; **96**(Suppl. 2):ii1—16.
4. Medical guidelines for airline travel, 2nd ed. *Aviation, Space, and Environmental Medicine* 2003;**74**(5 Suppl.):A1—19.
5. Shrikrishna D, Coker RK. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax* 2011;**66**(9):831—3.
6. Dillard TA, Beninati WA, Berg BW. Air travel in patients with chronic obstructive pulmonary disease. *Archives of Internal Medicine* 1991;**151**(9):1793—5.
7. Dillard TA, Berg BW, Rajagopal KR, Dooley JW, Mehm WJ. Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. *Annals of Internal Medicine* 1989; **111**(5):362—7.
8. Akero A, Christensen CC, Edvardsen A, Skjonsberg OH. Hypoxaemia in chronic obstructive pulmonary disease patients

during a commercial flight. *European Respiratory Journal* 2005;**25**(4):725—30.
9. Gong Jr H, Tashkin DP, Lee EY, Simmons MS. Hypoxia-altitude simulation test. Evaluation of patients with chronic airway obstruction. *The American Review of Respiratory Disease* 1984;**130**(6):980—6.
10. Mestry N, Thirumaran M, Tuggey JM, Macdonald W, Elliott MW. Hypoxic challenge flight assessments in patients with severe chest wall deformity or neuromuscular disease at risk for nocturnal hypoventilation. *Thorax* 2009;**64**(6):532—4.
11. Martin SE, Bradley JM, Buick JB, Bradbury I, Elborn JS. Flight assessment in patients with respiratory disease: hypoxic challenge testing vs. predictive equations. *Qjm* 2007;**100**(6):361—7.
12. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology* 2009;**54**(1 Suppl.):S43—54.
13. Seccombe LM, Kelly PT, Wong CK, Rogers PG, Lim S, Peters MJ. Effect of simulated commercial flight on oxygenation in patients with interstitial lung disease and chronic obstructive pulmonary disease. *Thorax* 2004;**59**(11):966—70.
14. Hoffstein V, Duguid N, Zamel N, Rebuck AS. Estimation of changes in alveolar-arterial oxygen gradient induced by hypoxia. *The Journal of Laboratory and Clinical Medicine* 1984;**104**(5):685—92.
15. Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine*;**181**(3):270—8.
16. Noble JS, Davidson JA. Cor pulmonale presenting in a patient with congenital kyphoscoliosis following intercontinental air travel. *Anaesthesia* 1999;**54**(4):361—3.
17. Kelly PT, Swanney MP, Seccombe LM, Frampton C, Peters MJ, Beckert L. Air travel hypoxemia vs. the hypoxia inhalation test in passengers with COPD. *Chest* 2008;**133**(4):920—6.
18. Oliver RM, Peacock AJ, Challenor VF, Fleming JS, Waller DG. The effect of acute hypoxia on right ventricular function in healthy adults. *International Journal of Cardiology* 1991; **31**(2):235—41.
19. Batyraliev TA, Niyazova ZA, Akgul F, et al. Effects of the hypoxic test on left and right ventricular contractility in progressive systemic sclerosis with pulmonary arterial hypertension. *International Journal of Angiology* 1998;**7**(1):25—7.
20. Weitzenblum E, Apprill M, Oswald M, Chaouat A, Imbs JL. Pulmonary hemodynamics in patients with chronic obstructive pulmonary disease before and during an episode of peripheral edema. *Chest* 1994;**105**(5):1377—82.
21. Biernacki W, Flenley DC, Muir AL, MacNee W. Pulmonary hypertension and right ventricular function in patients with COPD. *Chest* 1988;**94**(6):1169—75.
22. Akgul F, Batyraliev T, Karben Z, Pershukov I. Effects of acute hypoxia on left and right ventricular contractility in chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease* 2007;**2**(1):77—80.
23. 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. *The American Journal of Physiology* 1997;**273**(3 Pt 2):H1126—34.
24. Waldman JD, Lamberti JJ, Mathewson JW, et al. Congenital heart disease and pulmonary artery hypertension. I. Pulmonary vasoreactivity to 15% oxygen before and after surgery. *Journal of the American College of Cardiology* 1983;**2**(6):1158—64.
25. Raeside DA, Smith A, Brown A, et al. Pulmonary artery pressure measurement during exercise testing in patients with suspected pulmonary hypertension. *European Respiratory Journal* 2000;**16**(2):282—7.
26. Raeside DA, Brown A, Patel KR, Welsh D, Peacock AJ. Ambulatory pulmonary artery pressure monitoring during sleep and exercise in normal individuals and patients with COPD. *Thorax* 2002;**57**(12):1050—3.
27. Coker RK, Shiner RJ, Partridge MR. Is air travel safe for those with lung disease? *European Respiratory Journal* 2007;**30**(6): 1057—63.
28. WHO. *International travel and health*. WHO; 2010.
29. PHA-UKassociation. *The right to breathe free report*, http://www.phassociation.uk.com/living_with_ph/airline_rules_on_oxygen.php; 2009.
30. Naeije R. Preflight medical screening of patients. *European Respiratory Journal* 2000;**16**(2):197—9.
31. Dine CJ, Kreider ME. Hypoxia altitude simulation test. *Chest* 2008;**133**(4):1002—5.