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Flight assessment in patients with respiratory disease: hypoxic challenge testing vs. predictive equations

S.E. MARTIN[1,2], J.M. BRADLEY[1,3], J.B. BUICK[3], I. BRADBURY[1] and J.S. ELBORN[2,3]

From the [1]Health and Rehabilitation Sciences Research Institute, School of Health Sciences, University of Ulster, [2]Department of Respiratory Medicine, Queens University, Belfast, [3]Regional Respiratory Centre, Belfast City Hospital, Belfast, UK

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Summary

Background: Predictive equations have been proposed as a simpler alternative to hypoxic challenge testing (HCT) for determining the risk of in-flight hypoxia.
Aim: To assess agreement between hypoxic challenge testing (HCT) and predictive equations for assessment of in-flight hypoxia.
Design: Retrospective study.
Methods: Patients with chronic obstructive pulmonary disease (COPD) ($n=15$), interstitial lung disease (ILD) ($n=15$) and cystic fibrosis (CF) ($n=15$) were studied. Spirometry was recorded prior to hypoxic inhalation and oxygen saturations (SpO_2) were recorded before, after and during hypoxic inhalation. Blood gases were analysed before and after hypoxic inhalation and when $SpO_2=85\%$. An HCT was performed using the Ventimask method. The PaO_2 at altitude was estimated for each group using four published predictive equations, which use values of PaO_2 (ground) and lung function measurements to predict altitude PaO_2. Results were interpreted using the BTS recommendations for prescription of in-flight oxygen post HCT. The Stuart Maxwell test of overall homogeneity was used to assess agreement between HCT results and each of the predictive equations.
Results: Ground PaO_2 was significantly greater in patients with CF than either ILD or COPD ($p<0.05$). PaO_2 in all three groups significantly decreased following HCT. With the exception of equation 3, significantly fewer patients in each group would require in-flight O_2 if prescription was based on HCT, compared to predictive equations ($p<0.05$).
Discussion: Predictive equations considerably overestimate the need for in-flight O_2, compared to HCT.

Introduction

Hypobaric hypoxia develops as a result of the inverse relationship between oxygen partial pressure and altitude, resulting in a decrease in the partial pressure of alveolar oxygen (PaO_2) during ascent, and leads to reduced oxygenation of arterial blood. This occurs during travel in a pressurized aircraft cabin as ambient pressure is decreased. Commercial aircraft typically cruise at up to 40 000 feet (~12 000 m). Engineering and financial constraints do not allow pressurization to sea level, hence the aircraft cabin is pressurized to a maximum altitude of 8000 feet (2438 m), which, with respect to oxygenation, is equivalent to breathing 15% oxygen (O_2) at sea level.[1]

Increasing numbers of people with chronic respiratory diseases wish to travel but may be unaware that the pressurized cabin of a modern aircraft may be a physiologically challenging environment to those with lung disease.[2] There is a wide variation in the individual response to the hypobaric environment, the mechanisms of which are not clearly understood.[3] Clinical manifestations

Address correspondence to Dr J.M. Bradley, Regional Respiratory Centre, Belfast City Hospital, Belfast BT9 7BL. email: jm.bradley@ulster.ac.uk

of hypobaric hypoxia include euphoria, headache, fatigue, lassitude, dizziness and in extreme cases, if untreated, can lead to unconsciousness and even death.[3] Those patients who are hypoxic at sea level are thought to be at greater risk of experiencing a decrease in PaO_2 to a critical level, and may develop severe hypoxia during flight.[4]

The British Thoracic Society (BTS) recommend that a pre-flight assessment be considered in all patients with respiratory disease prior to air travel, to predict the likelihood of respiratory problems.[5] Hypobaric chambers are the 'gold standard' in flight assessment, but they are expensive and not widely available. Alternative methods used in clinical practice include hypoxic challenge tests (HCT) and predictive equations.[6] There is insufficient information available to establish the extent to which either method is used, but it seems reasonable to assume that predictive equations are used more frequently by clinicians (e.g. in primary health care) who do not have access to the facilities required to perform an HCT.

The aim of this retrospective study was to assess agreement between the individual hypoxic response, measured during HCT, and the extent of hypoxia calculated from predictive equations in patients with three distinct respiratory diseases: chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and cystic fibrosis (CF).

Methods

The Office for Research Ethics Committees Northern Ireland (ORECNI), determined that full ethical approval was not required for this study, although guidance on the conduct of the study was provided. We analysed data from 45 patients, with COPD ($n=15$), ILD ($n=15$) and CF ($n=15$) who attended Belfast City Hospital for routine flight assessment between August 2002 and April 2006. All procedures were performed at 29 feet (8.84 m) above sea level. Calibration of equipment and measurement of lung function indices were done in accordance with BTS guidelines.[7] Spirometry, forced expiratory volume in one second (FEV_1,) and forced vital capacity (FVC) were measured prior to an HCT, using a wedge-bellows spirometer (Vitalograph). Oxygen saturations (SpO_2) were recorded before and after hypoxic inhalation, and at 30 s intervals during hypoxic inhalation, using pulse oximetry (Ohmeda). Capillary ear-lobe gases were collected and analysed for pH, PO_2 and PCO_2 before and after hypoxic inhalation, and when $SpO_2=85\%$ (IL synthesis 10, Instrumentation Laboratory). An HCT was performed using the Ventimask method.[8] This required delivery of 100% nitrogen through a 40% Ventimask at a designated flow rate of 10.0 l/min. The Ventimask is designed to entrain room air, which mixes with the nitrogen within the mask, resulting in the equivalent inspired fraction of oxygen (FiO_2) of 15% O_2 (BOC). In order to verify the FiO_2, a 40% Ventimask was placed on a manikin head and 100% nitrogen delivered at a flow rate of 10.0 l/min. An oxygen analyser probe was then passed through a hole in the back of the manikin head to the mouth position, thus permitting verification of the FiO_2 (range 14.9–15.1).

The subject breathed the hypoxic gas mixture for a maximum of 20 min or until $SpO_2=85\%$ and a capillary ear lobe gas confirmed $PaO_2<7.4$ kPa.[5] The oxygen tension at altitude (PaO_2 (Alt)) was calculated for the three disease groups using four published predictive equations based on values of ground level PaO_2 (breathing room air) and FEV_1 to predict PaO_2 (Alt). The results were interpreted according to the BTS recommendations for the prescription of in-flight O_2 post HCT: (i) PaO_2 (Alt) >7.4 kPa, in-flight O_2 not required; (ii) PaO_2 (Alt) <6.6 kPa, in-flight O_2 required; (iii) PaO_2 (Alt) 6.6–7.4 kPa, borderline for in-flight O_2, which may require further investigation. These recommendations for the prescription of in-flight O_2 are based on a consensus of expert medical opinion.[1,5]

The predictive equations are given as examples in the current BTS recommendations.[1] Equations 1–3 were developed by Dillard *et al.*[9] from data obtained from 18 patients with severe COPD during simulated flight in a hypobaric chamber. Equation 1 incorporates PaO_2 (ground) as a variable, equation 2 incorporates PaO_2 (ground) and FEV_1 (l) and equation 3 incorporates PaO_2 (ground) and FEV_1% predicted. Equation 4 was developed by Gong *Et al.*[10] from a study of 22 patients with varying severity of COPD during normobaric flight simulation, and this equation incorporates PaO_2 (ground) as a variable.

Equations used for the calculation of PaO_2 (Alt)

(1) PaO_2 (Alt) (mmHg) $= 0.410 \times PaO_2$ (ground) (mmHg) $+ 1.7652$

(2) PaO_2 (Alt) (mmHg) $= 0.519 \times PaO_2$ (ground) (mmHg) $+ 11.855$ FEV_1 (l) $- 1.760$

(3) PaO_2 (Alt) (mmHg) $= 0.453 \times PaO_2$ (ground) (mmHg) $+ 0.386 \times (FEV_1\%) + 2.44$.[9]

(4) PaO_2 (Alt) (mmHg) $= 22.8 - (2.74 \times$ altitude in thousands of feet$) + 0.68 \times PaO_2$ (ground) (mmHg).[10]

A target altitude of 8000 feet (2438 m) was substituted into equation 4. The equations originate

Table 1 Comparison of hypoxic challenge test versus predictive equations

	Mean ± SD value	Mean difference between PaO_2 HCT and PaO_2 predicted by equations (KPa) [95%]	In-flight O_2 recommended?		
			N	Y	B
COPD patients (n = 15)					
Age (years)	62 ± 8				
FEV_1%	38 ± 13				
PaO_2 (ground) (kPa)	8.37 ± 0.85				
HCT PaO_2 (Alt) (kPa)	6.9 ± 0.65	–	4	6	5
Equation 1 PaO_2 (Alt) (kPa)	5.8 ± 0.35	1.1 [0.75 to 1.4]	0	15	0
Equation 2 PaO_2 (Alt) (kPa)	5.6 ± 0.67	1.2 [0.90 to 1.5]	0	14	1
Equation 3 PaO_2 (Alt) (kPa)	6.1 ± 0.7	0.8 [0.47 to 1.1]	1	13	1
Equation 4 PaO_2 (Alt) (kPa)	5.8 ± 0.58	1.1 [0.68 to 1.4]	0	14	1
ILD patients (n = 15)					
Age (years)	69 ± 13				
FEV_1%	83 ± 28				
PaO_2 (ground) (kPa)	8.9 ± 0.53				
HCT PaO_2 (Alt) (kPa)	7.3 ± 0.64	–	6	1	8
Equation 1 PaO_2 (Alt) (kPa)	6.0 ± 0.22	1.3 [0.97 to 1.64]	0	15	0
Equation 2 PaO_2 (Alt) (kPa)	7.1 ± 1.19	0.2 [−0.38 to 0.72]	3	2	10
Equation 3 PaO_2 (Alt) (kPa)	8.6 ± 1.47	−1.3 [−2.07 to 0.56]	11	1	3
Equation 4 PaO_2 (Alt) (kPa)	6.2 ± 0.36	1.13 [0.79 to 1.5]	0	13	2
CF patients (n = 15)					
Age (years)	27 ± 6				
FEV_1%	44 ± 19				
PaO_2 (ground)* (kPa)	9.6 ± 0.86				
HCT PaO_2 (Alt) (kPa)	7.5 ± 0.91	–	8	2	5
Equation 1 PaO_2 (Alt) (kPa)	6.3 ± 0.35	1.2 [0.80 to 1.57]	0	12	3
Equation 2 PaO_2 (Alt) (kPa)	7.0 ± 1.32	0.5 [−0.01 to 0.96]	5	8	2
Equation 3 PaO_2 (Alt) (kPa)	6.9 ± 1.23	0.5 [0.06 to 1.04]	4	7	4
Equation 4 PaO_2 (Alt) (kPa)	6.7 ± 0.58	0.8 [0.50 to 1.17]	2	7	6

HCT, hypoxic challenge test; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CF, cystic fibrosis; PaO_2, partial pressure of arterial oxygen. *CF patients had significantly higher PaO_2 (ground) than both COPD and ILD ($p < 0.05$). Results were interpreted according to the BTS recommendations for the prescription of in-flight O_2 post HCT: N, no (PaO_2 (Alt) >7.4 kPa); Y, yes (PaO_2(Alt) <6.6 kPa); B, borderline (PaO_2 (Alt) 6.6–7.4 kPa).

from studies that quote feet and mmHg,[9,10] thus the following conversion factor was used to convert mmHg to kPa in the current study: 1 kPa = 7.5 mmHg.

Statistics

Data were analysed using SPSS for Windows, version 11.5. The following (means ± SD) were calculated for each disease group: age, FEV_1, FEV_1% predicted (FEV_1%), PaO_2 (ground) and predicted PaO_2 (Alt). The difference between PaO_2 (Alt) measured during HCT and PaO_2 (Alt) estimated from the equations were calculated in each disease group on a patient-by-patient basis. The Stuart Maxwell test of overall homogeneity was used to assess agreement between HCT results and each of the predictive equations; a significant result indicates that the marginal frequencies are not homogeneous, or have poor agreement.

Results

Demographic characteristics for each group of subjects are summarized in Table 1, and the individual hypoxic responses for each group of subjects in Figure 1. No subject reported any hypoxic symptoms. PaO_2 (ground) was significantly greater in patients with CF than patients with ILD or COPD ($p < 0.05$), but there was no significant difference between groups in PaO_2 (Alt) measured during HCT (Figure 2). The mean difference between PaO_2 (Alt) measured during HCT and the PaO_2 (Alt) predicted by the equations is shown in Table 1. In each group, significantly fewer patients

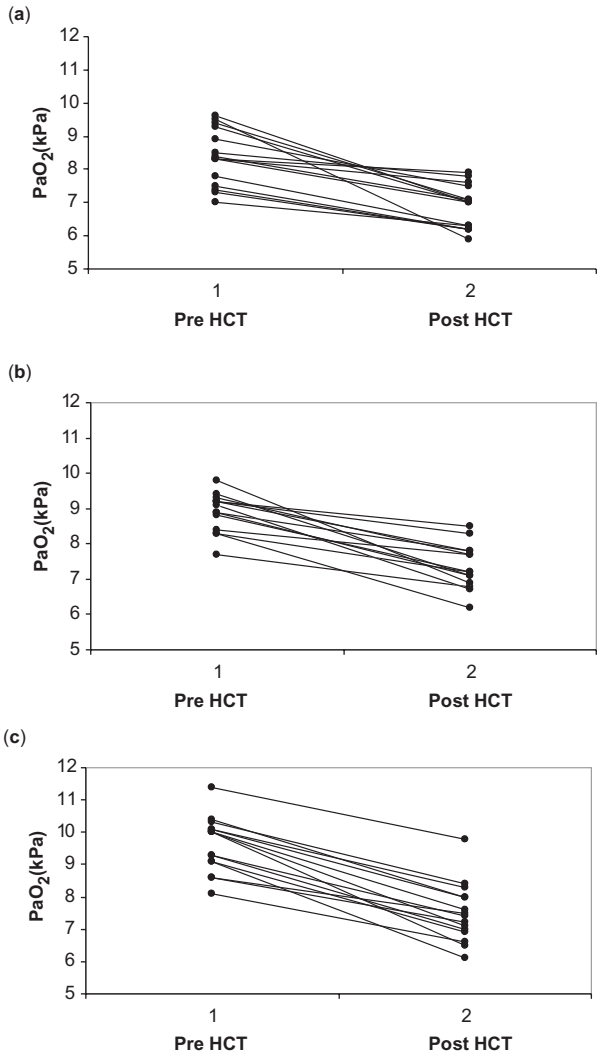

Figure 1. PaO_2 before and after HCT in patients with **a** COPD, **b** ILD and **c** CF.

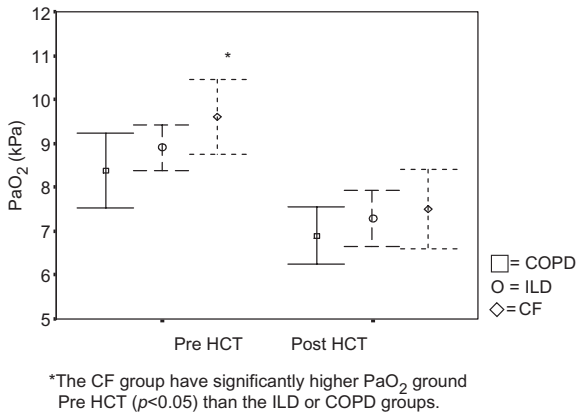

Figure 2. Mean (SD) PaO_2 before and after HCT for each disease group.

Table 2 Agreement between HCT and predictive equations

	χ^2	*p*
COPD patients		
HCT vs. Equation 1	9.00	0.0111
HCT vs. Equation 2	8.00	0.0183
HCT vs. Equation 3	7.00	0.0302
HCT vs. Equation 4	8.00	0.0183
ILD patients		
HCT vs. Equation 1	14.00	<0.0009
HCT vs. Equation 2	3.33	0.01889
HCT vs. Equation 3	3.85	0.1462
HCT vs. Equation 4	12.26	0.0022
CF patients		
HCT vs. Equation 1	11.64	0.0030
HCT vs. Equation 2	6.43	0.0402
HCT vs. Equation 3	5.45	0.0654
HCT vs. Equation 4	7.42	0.0245

χ^2 was calculated at two degrees of freedom. HCT, hypoxic challenge test; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CF, cystic fibrosis.

would require in-flight O_2 if prescription were based on HCT compared to the predictive equations. For COPD: HCT 6, equations 13–15 (range). For ILD: HCT 1, equations 1–15 (range). For CF: HCT 2, equations 7–12 (range). The Stuart Maxwell test of overall homogeneity indicated poor agreement between PaO_2 (Alt) measured during HCT and the PaO_2 (Alt) predicted by the equations. With the exception of equation 3 in the ILD and CF groups, the differences in the number of subjects requiring in-flight O_2 were statistically significant ($p < 0.05$) (Table 2).

Discussion

The current BTS recommendations provide four equations for predicting PaO_2 (Alt), all developed exclusively from studies investigating the hypoxic response of COPD patients.[5,9,10] Predictive equations are a cheap, readily available method of flight assessment, but this study shows poor agreement between their predictions and the measured individual hypoxic responses during HCT.

When assessing a patient with chronic respiratory disease planning air travel, careful consideration must be given to their overall clinical status. The response to hypobaric hypoxia is variable and influenced by a number of factors, including cardiac and respiratory status, anaemia, sea-level arterial blood gases, blood carboxyhaemoglobin and age.[3]

Passengers are also more likely to sleep during long-haul flights, resulting in hypoventilation which may further decrease PaO_2 (Alt).[11]

An HCT simulates one aspect of altitude exposure, i.e. the inhalation of a low inspired fraction of oxygen (FiO_2) such as is encountered at altitude, typically 8000 feet (2438 m). This is normally the maximum operational cabin altitude; however, this altitude can be exceeded to avoid adverse weather conditions and is also dependent on individual aircraft design characteristics.[3] An HCT also allows correction of induced hypoxia by titration of supplemental O_2, thus enabling correct prescription of in-flight O_2.

Naughton *et al*.[12] compared the hypoxic response of six normal control subjects and nine patients with chronic airflow obstruction using HCT and a hypobaric chamber at 6000 feet (1829 m) and 8000 feet (2438 m). They found no significant difference between arterial blood gas measurements obtained using either method. Kelly *et al*.[13] compared SpO_2 measured during HCT and during an actual flight in 15 normal subjects. They found no significant difference between the final HCT SpO_2 and the mean in-flight SpO_2.

Dillard *et al*.[9] studied the hypoxic response of eighteen subjects with severe COPD, FEV_1 31(10)%. The results showed that PaO_2 (ground) had the highest correlation with PaO_2 (Alt) ($r = 0.587$; $p < 0.01$), equation 1. They also found that the variability in PaO_2 (Alt) could only be partially explained by PaO_2 (ground), and that using lung function measurements as the additional predictor variables significantly increased the correlation between PaO_2 (ground) and PaO_2 (Alt) ($r = 0.847$; $p < 0.0001$) (equations 2 and 3). Gong *et al*.[10] also studied the hypoxic response of 22 subjects with COPD with a range of airflow obstruction FEV_1 44(17)%. They also found PaO_2 (ground) to be the best predicator of PaO_2 (Alt) ($r = 0.87$; $p < 0.0005$) equation 4. Unlike Dillard, Gong found that inclusion of lung function measurements did not improve the predictability of the PaO_2 (Alt). Our study examined the hypoxic response of 15 subjects with moderate COPD, FEV_1 38(13)% and the results show that the application of equations 1, 2, 3 and 4 in the COPD group significantly overestimates PaO_2 (Alt) and thus the need for in-flight O_2 (Table 1). This finding is supported by a previous study, which also found equation 4 overestimated PaO_2 (Alt) in subjects with moderate/severe COPD.[14]

Seccombe *et al*.[15] studied the hypoxic response of 15 subjects with ILD and 10 subjects with COPD. They found that PaO_2 (Alt) differed significantly between both groups. The current study however found no significant difference in PaO_2 (Alt) between the ILD and COPD groups. This difference in results may be explained by differences in the subjects' PaO_2 (ground) and also the hypoxic inhalation termination point. Seccombe *et al*.[15] studied ILD and COPD subjects with mean PaO_2 (ground) values of 11.2 kPa and 10.5 kPa, respectively, whereas the mean PaO_2 (ground) values in the current study were much lower at 8.9 kPa (ILD) and 8.37 kPa (COPD). The termination point of the hypoxic inhalation also differed. The current study terminated the hypoxic inhalation when $SpO_2 = 85\%$, in keeping with current BTS recommendations, whereas Seccombe *et al*. continued the hypoxic inhalation until $SpO_2 < 80\%$, which would result in lower PaO_2 (Alt) values. What both studies do show, however, is the high individual variability of hypoxic response in both groups of subjects (Figure 1).

The subjects with CF investigated in the current study showed significantly higher PaO_2 (ground) than those subjects with either ILD or COPD; however, during hypoxic inhalation, PaO_2 (Alt) in each group did not differ. Peckham *et al*.[16] studied a sub-group of patients ($n = 18$) with similar FEV_1% and PaO_2 (ground) to those in the current study. The hypoxic responses were consistent between studies. The high inter-variability in hypoxic response in subjects with CF has been documented previously, and is in keeping with the current study results[17] (Figure 1).

Given the complex physiological variables that influence an individual's hypoxic response, it is not surprising that there is poor agreement between the measured individual responses and the results obtained from the predictive equations. The current BTS recommendations state that some centres still use predictive equations as a method of flight assessment.[5] All predictive equations used to assess fitness to fly include PaO_2 (ground) as a predictor variable, but there is conflicting evidence with regard to its usefulness in predicting PaO_2 (Alt).[1,9,10,14,16,18] Predictive equations also do not allow the signs and symptoms of hypoxia to be evaluated. For this reason the American Thoracic Society now recommends that predictive equations be used as a screening tool to identify patients with borderline PaO_2 (Alt) estimates, for further investigation with HCT.[18]

The sensitivity of all four equations in the three diseases groups ($n = 45$) was high (range 78–100%), but specificity was low (range 11–55%). All four equations in the current study overestimate the need for in-flight O_2 in the CF and COPD groups. Equations 1, 2 and 4 also overestimate the need for in-flight O_2 in the ILD group, although equation 3

in the same group shows a significant underestimation. This result is probably explained by the fact that FEV_1% predicted is included as an additional variable in this equation, and that subjects with ILD may well have higher FEV_1 values than those subjects with either COPD or CF.

Two studies have shown subjects with PaO_2 (ground) >9.3 kPa (SpO_2 > 95%) values in whom further assessment was not recommended, but who developed significant hypoxia during flight.[14,19] Other studies have found that although at altitude PaO_2 (Alt) dropped below the recommended critical value, none of the subjects developed any hypoxic symptoms.[20] In centres that use predictive equations as a method of flight assessment, it should be highlighted that determining the requirement for in-flight O_2 and the specific flow rate at which it should be administered has important implications for the patient. General practitioners can prescribe portable O_2, and some airlines permit its use,[21] but an accurate flow rate is needed to ensure that cylinder capacity is adequate for the flight duration. This degree of specificity can only be achieved by individual assessment of the hypoxic response, and cannot be achieved using predictive equations.

Predictive equations may be a cheaper and simpler alternative to an HCT, particularly in the primary-care setting, but they considerably overestimate the need for in-flight O_2 in the majority of patients. Thus, with the exception of equation 3 in subjects with ILD, the results of the current study would support the use of predictive equations as screening tools only. Patients for whom the equations indicate fitness to fly should be allowed to fly without further testing, but patients for whom the predictive equations indicate critical or borderline in-flight PaO_2 (Alt) values should be re-evaluated in a centre with HCT facilities or with access to a hypobaric chamber, before discouraging such patients from flying or alternatively prescribing in-flight oxygen based on the predictive equation calculation alone.

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