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The prediction of in-flight hypoxaemia using non-linear equations

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Summary
Background: Respiratory disease may cause profound hypoxaemia during flight. Previously derived linear equations poorly predict the need for supplemental oxygen during air travel. The current gold standard assessment is the hypoxic challenge test (HCT). Recent guidelines recommend HCT is performed for those patients with $SpO_2 < 95\%$ at sea level. The HCT protocol is a costly and time consuming investigation.
Methods: Retrospective clinical and HCT data from 138 patients were applied to previous linear equations to assess predictive value. Novel non-linear predictive models (NLMs) were constructed from these data. The linear equations and the NLMs were then applied prospectively to 44 patients undergoing HCT.
Results: Overall, 39% of historic patients had a positive HCT (PaO_2N_2 <50 mmHg). Existing linear equations varied in sensitivity (52–87%) and specificity (40–74%) at predicting positive HCT results. Seven novel NLMs (NLM1 to NLM7) were developed from the historic dataset. All NLMs predicted PaO_2N_2 more accurately than the original linear equations when tested prospectively. The best fit was observed using NLM2 which uses PaO_2RA and $PaCO_2RA$ as input terms. The NLMs are applicable to a broad range of conditions.
Conclusions: The novel NLMs represent a low cost option for the prediction of significant hypoxia during flight and perform better than SpO_2 in identifying those patients who require more formal assessment with HCT.

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Introduction

More than two billion passengers fly each year, a figure predicted to double within two decades.[1,2] Cabin pressurisation is set to a maximum altitude of 8000 feet, equivalent to breathing 15.1% oxygen at sea level. At this partial pressure of oxygen the PaO_2 in a healthy person is reduced to 7.0–8.5 kPa, an effect which is usually unnoticed. However, patients with respiratory disease who are hypoxic at sea level may experience profound hypoxia and respiratory distress.[3]

Previous studies have examined the response to hypoxia.[3–8] From these studies, a number of regression equations were developed to predict in-flight oxygenation from measurements taken at sea level.[3] However, these predictive equations were derived from measurements taken from small series of patients with chronic obstructive pulmonary disease (COPD). Therefore, their ability to reliably predict in-flight hypoxaemia may be limited, particularly in patients with respiratory disease other than COPD.

Protocols have also been developed to conduct hypoxic challenge test (HCT) assessments to titrate the level of oxygen supplementation that might be required during flight.[5–8] The HCT has been shown to reproduce degrees of desaturation in normal subjects and in passengers with COPD comparable to that observed during air travel.[9,10] Recent guidelines from the British Thoracic Society[11] recommend that clinicians consider HCT assessment in patients at risk with a $SpO_2 < 95\%$ at sea level. In-flight oxygen is recommended if $PaO_2 < 6.6$ kPa (<50 mmHg) or $SpO_2 < 85\%$ during HCT.

Despite an increasing need for HCT assessments access is limited, tests are time consuming and result in significant use of healthcare resources. Therefore, there remains a need for simple, accurate screening tools.

The Lung Function Department at the University Hospital Llandough has historical HCT data from a large cohort of patients. The current study aims to retrospectively analyse these data using statistical methods to assess the utility of current linear equations in predicting in-flight hypoxaemia, and use non-linear modelling techniques to produce new predictive equations from the retrospective data and then prospectively evaluate the usefulness of these novel equations in preflight assessment.

Methods

Clinical records, spirometry and HCT data from all patients who had undergone hypoxia challenge testing at the University Hospital Llandough Lung Function Laboratory between August 2005 and August 2008 were analysed. Subject age, sex, height, weight, FEV_1, FVC, arterialised capillary blood gas measurements and cardiorespiratory diagnosis at the time of HCT were recorded. In cases where spirometry was not performed at the time of the HCT, measurements performed closest to the date of testing were used.

For the purpose of analysis patients were stratified into broad diagnostic groups:

1. Cystic fibrosis; 2. Obstructive lung disease; 3. Pulmonary arterial hypertension; 4. Neuromuscular disease; 5. Interstitial lung disease; 6. Chest wall disease; 7. Miscellaneous.

Hypoxia challenge tests

Hypoxic challenge tests were performed according using a 40% Venturi mask supplied with nitrogen to provide an FiO_2 of 15.1%.[7] Capillary ear-lobe gases were collected before and after hypoxic challenge and analysed for PO_2 and PCO_2 and SaO_2 using a Radiometer ABL810 Blood Gas Analyser.

Linear predictive equations

Previously derived predictive equations[3] were applied to the data and in-flight oxygen requirement predictions were compared with actual HCT results. The previously derived linear equations were:

1. LM1 – This relates PaO_2 at altitude (Alt) to PaO_2 at sea level (Ground):

$$PaO_2\ \text{Alt (mmHg)} = 0.410 \times PaO_2\ \text{Ground (mmHg)} + 17.65$$

2. LM2 – This relates PaO_2 Alt to PaO_2 Ground and includes FEV_1 in litres:

$$PaO_2\ \text{Alt (mmHg)} = 0.519 \times PaO_2\ \text{Ground (mmHg)} + 11.855 \times FEV_1\ \text{(litres)} - 1.760$$

3. LM3 – This relates PaO_2 Alt to PaO_2 Ground and includes FEV_1 as %predicted:

$$PaO_2\text{Alt} = 0.453 \times PaO_2\ \text{Ground (mmHg)} + 0.386 \times (FEV_1\ \%\text{pred}) + 2.44.$$

Development of non-linear models (NLMs)

New predictive equations were generated from the historical data using the NARMAX [nonlinear autoregressive moving average with exogenous input] modelling approach.[12,13] This allows the model to be built up term by term in a manner that exposes the significance of each new term that is added to the model. Individual patient's data were then fitted to these equations and compared with actual HCT results.

The previously derived predictive equations and the novel equations were then prospectively applied to data from 44 number of HCT tests performed after August 2008.

Statistical methods

The mean square error (MSE) was calculated for each predictive equation for the whole data and separate data subsets. Bland and Altman plots[14] were used to assess the agreement between the values obtained from the predictive equations and from the HCT. The sensitivity and specificity of the predictive equations were also calculated using cut off points of $PaO_2N_2 < 50$ mmHg or $SaO_2N_2 < 85\%$. The study was approved by the Local Research Ethics Review Board (Reference 08/cmc/4398).

Table 1 Demographic data.

$N = 139$	Mean ± SD
Age (years)	56 ± 19
Male:female (%)	62:38
Height (m)	1.66 ± 0.10
FEV_1 (L)	1.45 ± 0.68
FEV_1 %predicted	52 ± 25
PaO_2RA (mmHg)	73 ± 10
PCO_2RA (mmHg)	39 ± 6
SaO_2RA (%)	95 ± 2
PaO_2N_2 (mmHg)	53 ± 9
PCO_2N_2 (mmHg)	37 ± 5
SaO_2N_2 (%)	89 ± 4
Diagnostic groups (*n*)	
1. Cystic fibrosis	32
2. Obstructive lung disease	49
3. Pulmonary arterial hypertension	7
4. Neuromuscular disease	10
5. Interstitial lung disease	16
6. Chest wall disease	18
7. Miscellaneous	7

Results

Data from one hundred and ninety consecutive HCTs were collected. Complete data were available for 138 patients (Table 1). 54/138 (39%) patients had a positive HCT defined as $PaO_2N_2 < 50$ mmHg but only 20/138 (14%) had $SaO_2N_2 < 85\%$. Sixty two of the 138 patients (45%) had baseline $SaO_2 \geq 96\%$ and of these 9 (14.5%) had $PaO_2N_2 < 50$ mmHg.

Table 2 shows how well the current linear equations predict the need for in-flight oxygen in the retrospective data from the 138 patients. The MSE between the PaO_2 predicted by the current linear equations and that found on HCT, the mean ± standard deviation (SD) of the difference between the predicted PaO_2 and that found on HCT and the sensitivity and specificity of each equation in predicting a positive HCT defined as $PaO_2N_2 < 50$ mmHg or $SaO_2N_2 < 85\%$.

New non-linear predictive equations

Seven non-linear predictive equations were identified by using the NARMAX method. These are shown in Table 3.[12,13] The equations used between 1 and 10 independent variables (Fig. 1). The size of font used for each variable in Fig. 1 denotes the relative contribution made by that variable. In equations NLM 1, 2 and 4 PaO_2RA contributed most whilst $SaO_2RA\%$ was the greatest contributor to equations 3 and 5–7.

Prospective data

Following the development of the new nonlinear equations, full HCT data were prospectively collected from 44 consecutive patients (Table 4). 11/44 (25%) had a positive HCT defined as $PaO_2N_2 < 50$ mmHg but only 5 had $SaO_2N_2 < 85\%$. Using the data from the 44 patients, the utility of both the current linear and the newly developed non-linear predictive equations is shown in Table 5a and b. The sensitivity and specificity of the linear equations was similar to that found in the historic data (LM1 87%, 40% vs. 100%, 33%; LM2 69%, 71% vs. 72%, 83%; LM3 52%, 74% vs. 55%, 89%). The new non-linear models predict the PaO_2N_2 more accurately than the original linear equations. Looking at the group as a whole, the lowest MSE was for NLM2 which uses the 2 terms PaO_2RA and $PaCO_2RA$. The best performing linear equation was LM2. Fig. 2 shows the fitting error for each individual patient using these 2 equations and illustrates the tighter fit obtained by the nonlinear model. Fig. 3 illustrates in a Bland Altman plot the closer agreement between the HCT and predicted PaO_2N_2 derived from the nonlinear model compared to the older linear model. Whilst the mean difference between actual and predicted PaO_2N_2 is similar for both equations the standard deviation for the difference is much smaller for the non-linear equation. The sensitivity and specificity of NLM equations 1, 2, 4 and 6 is high. The NLM equations using SaO_2N_2 as an outcome measure (NLM 3 and 5) performed poorly; sensitivity being 20% for both equations, as did NLM7 which uses SaO_2RA as the single input measure. The sensitivity of LM1 is high but specificity is low whilst LM2 has a similar sensitivity to the NLM equations but has a lower specificity.

The equations are applicable to a wide patient population, although the poorest fit is for cystic fibrosis and interstitial lung disease (Table 5b). There is no difference between males and females but age does seem to be a factor.

Discussion

This is the first study evaluating the use of non linear equations for the prediction of in-flight hypoxia. The study included a reasonably sized cohort of historical data to derive the equations and prospectively tested the models on patients with various respiratory diseases. The novel

Table 2 Comparison of predicted with actual HCT results – historical data on 138 subjects.

Predictive equation	MSE ($mmHg^2$)	Bland Altman mean difference ± SD of difference (mmHg)	Sensitivity	Specificity
LM1	64.79	5.33 ± 6.04	87	40
LM2	72.15	−0.42 ± 8.54	69	71
LM3	104.01	−2.74 ± 9.89	52	74

Table 3 Derivation of non-linear predictive equations (NLMs). The best performing equation is NLM2 (bold).

	Variables tested (significant terms are underlined)	NLM equation
NLM 1	$\underline{PaO_2RA}$	$PaO_2N_2 = (0.869166 \times [PaO_2RA]) - (0.003237 \times [PaO_2RA]^2) + 7.044304$
NLM 2	$\underline{PaO_2RA}$, $\underline{PaCO_2RA}$	$\mathbf{PaO_2N_2 = (0.559496 \times [PaO_2RA]) - (0.001319 \times [PaO_2RA]^2) - (0.000189 \times [PaCO_2RA]^3 + 0.799106 \times [PaCO_2RA])}$
NLM 3	$\underline{SaO_2RA\%}$	$SaO_2N_2\% = (0.933164 \times [SaO_2RA\%])$
NLM 4	Age, diagnosis, gender, $\underline{PaO_2RA}$, $\underline{FEV_1}$, %predicted FEV_1	$PaO_2N_2 = (1.113355 \times [PaO_2RA]) - (0.00616 \times [PaO_2RA]^2) + (0.000628 \times [PaO_2RA]^2 \times [FEV_1])$
NLM 5	Age, $\underline{diagnosis}$, $\underline{gender}$, $\underline{SaO_2RA}$, $\underline{FEV_1}$, and %predicted FEV_1	$SaO_2N_2 = (0.911819 \times [SaO_2RA]) + (0.000196 \times [SaO_2RA]^2 \times [FEV_1]) - (0.092136 \times [diagnosis] \times [gender]^2$
NLM 6	Age, $\underline{diagnosis}$, $\underline{gender}$, $\underline{SaO_2RA}$, $\underline{PaO_2RA}$, $\underline{PaCO_2RA}$, $\underline{FEV_1}$, %predicted FEV_1, height and $\underline{weight}$	$PaO_2N_2 = (2.747347 \times 10^{-6} \times [SaO_2RA]^3) + (1.462488 \times 10^{-3} \times [PaO_2RA] \times [PaCO_2RA] \times [FEV_1]) - (3.506418 \times 10^{-5} \times [diagnosis] \times [weight]^2) + (0.266522 \times [PaO_2RA]) + (26.0947)$
NLM 7	$\underline{SaO_2RA}$	$PaO_2N_2 = (6.1351 \times 10^{-5} \times [SaO_2RA]^3)$

NLMs are able to predict in-flight hypoxia more reliably than the previously derived linear equations with high sensitivity and specificity.

The NLMs performed well in a variety of respiratory conditions, although did so least well in patients with cystic fibrosis and interstitial lung disease. In addition, age seemed to affect fit but this may be because the youngest age group had the greatest preponderance of cystic fibrosis.

The BTS guidelines suggest that patients with $SpO_2 < 95\%$ plus additional evidence of significant respiratory disease should undergo HCT assessment.[11] However, a recent study found that 23% of patients tested with HCT and baseline $SpO_2 \geq 96\%$ had a positive HCT with partial pressure of oxygen falling to <6.6 kPa.[15] Our results showed 14.5% of patients with $SaO_2 \geq 96\%$ have a positive HCT. This emphasises that baseline SpO_2 is a poor predictor of those who may be at risk of in-flight hypoxia and that this should not be used to identify those who would benefit from more formal assessment. From our results, SpO_2 of 85% does not correlate sufficiently with a PaO_2 of 50 mmHg to allow its substitution as an end point for the HCT.

No patient who had a negative HCT was predicted to need oxygen using the NLMs. However, for the most sensitive models, 3 of the 11 patients considered to require oxygen based on HCT would not have been prescribed oxygen using the NLM predictive equations alone. Diagnoses for these patients included interstitial lung disease, chest wall disease and obstructive lung disease. The best linear model would also have failed to prescribe oxygen to 3 patients but would have prescribed oxygen to 5 patients who

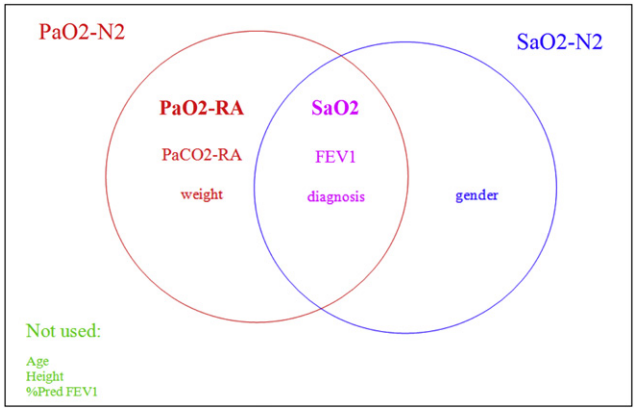

Figure 1 Contribution of variables predictive equation. The size of the font of each variable denotes the relative contribution made by that variable. The suffix —RA denotes where a measurement has been taken whilst the patient was breathing room air at sea level. The suffix $-N_2$ denotes where a measurement has been taken whilst the patient was breathing a nitrogen mix during the hypoxic challenge test.

Table 4 Demographic data of cohort of 44 patients tested prospectively.

$N = 44$	Mean ± SD
Age (years)	60.7 ± 15.6
Male:female (%)	58:52
Height (m)	1.67 ± 0.10
FEV_1 (L)	1.48 ± 0.69
FEV_1 %pred	56.6 ± 24.4
PaO_2RA (mmHg)	75.2 ± 9.7
PCO_2RA (mmHg)	36.3 ± 5.5
SaO_2RA (%)	96.0 ± 1.7
PaO_2N_2 (mmHg)	55.7 ± 8.1
PCO_2N_2 (mmHg)	34.5 ± 5.7
SaO_2N_2 (%)	90.3 ± 4.0
Diagnostic groups (*n*)	
1. Cystic fibrosis	6
2. Obstructive lung disease	22
3. Pulmonary arterial hypertension	3
4. Neuromuscular disease	0
5. Interstitial lung disease	5
6. Chest wall disease	7
7. Miscellaneous	1

Table 5 Comparison of predicted with actual HCT results using old and new predictive equations — prospective data on 44 subjects. a) Mean square error, Bland and Altman mean difference and sensitivity and specificity of predictive equations using data from all 44 subjects. b) Mean square error for individual subsets.

Predictive equation	MSE	BA mean difference ± SD of difference	Sensitivity	Specificity
	($mmHg^2$)	(mmHg)		
LM1	79.01	5.33 ± 6.04	100	33
LM 2	67.41	−0.39 ± 8.29	72	83
LM 3	105.07	−2.74 ± 9.89	55	89
	($mmHg^2$)	(mmHg)		
NLM1	35.56	−1.59 ± 5.81	72	100
NLM2	34.27	−0.50 ± 4.21	64	100
NLM4	39.38	−0.54 ± 4.28	72	100
NLM6	37.09	−1.85 ± 5.86	72	100
NLM7	44.94	0.036 ± 5.17	27	100
	$SaO_2\%^2$	$SaO_2\%$		
NLM3	9.37	−0.33 ± 2.76	20	98
NLM5	8.80	−0.33 ± 2.56	20	98

	LM1 1	LM2	LM3	NLM1	NLM2	NLM4	NLM6	NLM7
All patients	79.01	67.41	105.07	35.56	34.27	39.38	37.09	44.94
Dx group								
1	143.56	115.78	63.13	57.77	63.40	94.57	65.75	76.80
2	63.85	59.44	99.32	33.58	31.12	32.46	32.28	40.68
3	35.68	112.01	433.53	1.87	0.96	10.47	4.95	2.11
5	116.81	106.86	102.41	64.52	64.49	78.82	80.48	55.56
6	64.67	21.30	45.39	20.65	16.40	7.13	14.45	44.63
7	111.34	6.32	0.20	25.28	26.80	21.95	40.89	33.88
Male	87.03	77.18	73.31	35.37	33.87	32.81	34.00	46.94
Female	71.33	58.04	135.51	35.74	34.65	45.69	40.04	43.02
<25 = 25	73.44	23.30	44.35	53.91	109.90	227.28	96.50	108.75
26—65	82.90	69.68	84.15	25.90	24.18	25.19	27.09	31.88
>65	75.37	67.05	128.63	44.42	41.07	45.41	44.50	55.23

Diagnostic groups: 1 Cystic fibrosis; 2 Obstructive lung disease; 3 Pulmonary arterial hypertension; 5 Interstitial lung disease; 6 Chest wall disease; 7 Miscellaneous.

did not have a positive HCT. Whilst this may be due to inadequacy within the predictive equations, consideration should also be given to the variability inherent within HCT derived PaO_2N_2.

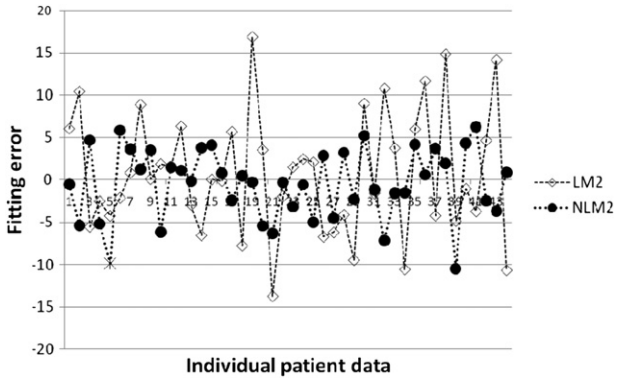

Figure 2 Mean square errors between individual patient predictive values derived from equations NLM2 and LM2 and HCT result for the 44 prospective patients.

Hypoxia challenge testing is considered the gold standard test for predicting in-flight hypoxia, however, little work has been done to assess its reproducibility. Robson et al. reported on 2 patients who underwent a repeat HCT after an interval of several months both of whose results placed them in the same category of fit/not fit to fly.[7] PaO_2N_2 values were not given so it is not possible to say what variation was found. Variation in response to exposure to high altitude however has been noted in staff manning an astronomical observatory 4200 m above sea level[16] and differences of up to 9 mmHg for an individual's PaO_2 were found.

Furthermore, even under rigorous conditions there can be variability in PaO_2 measurement. A previous study examining the repeatability of blood gas quality control solutions showed that for an arterial blood gas PaO_2 measurement of 50 mmHg, 95% of measurements are between 45.9 and 54.1 mmHg[17] Kapelmacher et al. also found a standard deviation of 1.46 mmHg variability between different blood gas analysers.[18] Therefore, a range of ±2SD (5.84 mmHg) would encompass the normal variation between analysers and would influence whether patients were deemed in need of in-flight oxygen or not. As well as

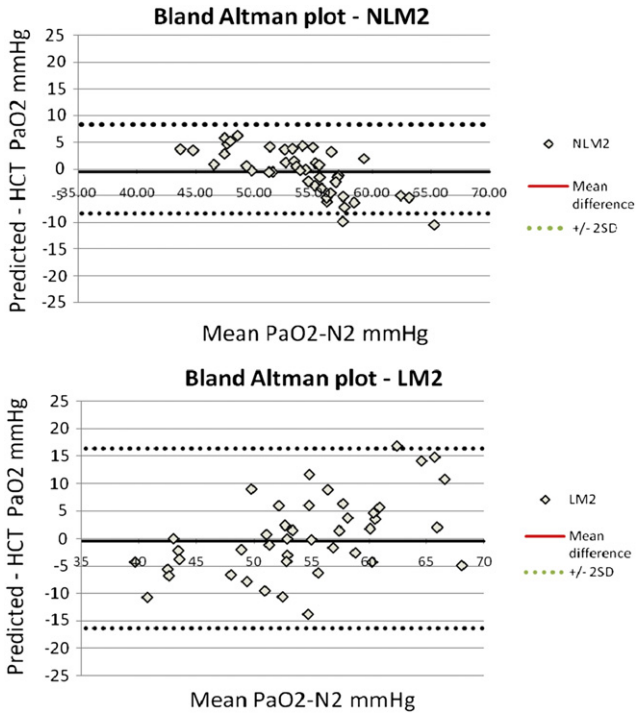

Figure 3 Bland—Altman plots of the difference between the predicted PaO_2 and the HCT SaO_2 plotted against the mean of the 2 from the 2 methods. The solid line is the mean difference between the 2 methods and the dotted lines are ±2SD the difference between the methods.

analyser variation, sampling variation may further affect the repeatability of HCT. Ladegaard-Pedersen[19] reported on 30 patients in whom blood samples were taken from both radial arteries and analysed for blood gases. The 95% confidence level for PaO_2 measurements was ±8.8 mmHg.

Given this variability in the measurement of PaO_2, the fitting errors found from the predictive equations are within the normal variation of PaO_2 measurements suggesting that the NLM equations we have developed could be used to provide a reasonable prediction of in-flight oxygen requirements that in practice has comparable usefulness to the current gold standard.

The HCT provides an opportunity to determine the flow rate of supplemental oxygen needed during flight to correct substantial hypoxia. The NLMs do not provide this information and are limited to determining whether or not a patient should receive supplemental oxygen during flight.

This study has its limitations as, although the NARMAX predictive equations have been derived from data from a large number of HCTs, all the tests were performed in a single laboratory. The NARMAX method works most effectively with more than 400 data sets. Therefore, a larger study would enable the development of even stronger predictive equations.

In conclusion, this is the largest study of the use of predictive equations for the assessment of the need for in-flight oxygen in patients with a broad range of respiratory diseases. The NLMs represent a further option for the prediction of significant in-flight hypoxia and perform better than the use of SpO_2 in identifying those patients who require more established methods of assessment such as HCT.

Conflict of interest

None declared.

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