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Pre-flight testing of preterm infants with neonatal lung disease: A retrospective review

Kanokporn Udomittipong[1], Stephen M Stick[2,3], Maureen Verheggen[3], Jan Oostryck[3], Peter D Sly[1,3] and Graham L Hall[2,3]

1) Clinical Sciences, Telethon Institute for Child Health Research and Centre for Child Health Research, University of Western Australia, Perth, Australia.

2) School of Paediatrics and Child Health, University of Western Australia, Perth, Australia.

3) Respiratory Medicine, Princess Margaret Hospital, Perth, Australia

Corresponding Author:

Dr Graham Hall

Respiratory Medicine,

Princess Margaret Hospital

GPO Box D184, Perth 6840

AUSTRALIA

Tel: +61 8 9340 8987 Fax: +61 8 9340 8181

E-mail: graham.hall@health.wa.gov.au

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Abstract

Background: The low oxygen environment during air travel may result in hypoxia in patients with respiratory disease. However, little information exists on the oxygen requirements of infants with respiratory disease planning to fly. We aimed to identify those clinical factors predictive of an in-flight oxygen requirement from a retrospective review of hypoxia challenge tests (inhalation of 14-15% oxygen for 20 minutes) in infants referred for fitness to fly assessment.

Methods: We report data from 47 infants (median corrected age 1.4 months) with a history of neonatal lung disease but not receiving supplemental oxygen at the time of hypoxia testing. Infant's neonatal and current clinical information were analysed in terms of their ability to predict the hypoxia test results.

Results: 81% (38/47) of infants desaturated below 85% and warranted prescription of supplemental in-flight oxygen. Baseline oxygen saturation was >95% in all infants. Age at the time of the hypoxia test, either post-menstrual or corrected, significantly predicted the hypoxia test outcome (odds ratio 0.82; 95% confidence intervals 0.62-0.95; p=0.005). Children passing the hypoxia test were significantly older than those children requiring in-flight oxygen (median corrected age (10^{th}-90^{th} centiles): 12.7 (3.0-43.4) vs. 0 (-0.9-10.9) months; P<0.0001, respectively).

Conclusions: A high proportion of ex-preterm infants not currently requiring supplemental oxygen referred for fitness-to-fly assessment and less than 12 months corrected age are at a high risk of requiring in-flight oxygen. Referral of this patient group for fitness to fly assessment, including a hypoxia test may be indicated.

INTRODUCTION

The number of people including children using commercial aircraft to travel is increasing. Commercial airlines generally cruise between 9 150-13 000 metres above sea level.[1] For passenger safety during flight at these altitudes, commercial aircraft are pressurized to maintain a cabin pressure equivalent to 1 530-2 440 metres. As the altitude increases the partial pressure of oxygen (O_2) in the atmosphere falls, thus passengers in aircraft at cruising altitude are breathing the equivalent of 15%-16% of fractional inspired oxygen (FiO2) at sea level.[1] This lower oxygen environment elicits little or no clinically relevant effects in healthy adults, but may result in a lowered arterial haemoglobin oxygen saturation in these subjects.[2 3] Lee and coworkers[4] studied healthy children during air travel and reported mean pulse O_2 saturations (SpO_2) decreasing from 98% at sea level to 94%-95% during commercial air travel without notable clinical symptoms. Nevertheless, patients with pre-existing respiratory conditions, such as chronic obstructive pulmonary disease, cystic fibrosis, neonatal chronic lung disease (nCLD) or other chronic lung diseases, may develop hypoxia related respiratory distress, leading to symptom exacerbation, altitude- related illnesses, or even death during flights.[1 5 6]

The British Thoracic Society (BTS) issued recommendations in 2002 for passengers with respiratory disease planning air travel.[7] These guidelines provide useful information for the screening of patients with respiratory disease. However, while the guidelines for adults are well supported by studies in the medical literature, the same is not true for children. The updated BTS air travel guidelines (www.brit-thoracic.org.uk) suggest a pre-flight hypoxia test be performed in older children with chronic lung disease and forced expiratory volume at 1 second (FEV1) of less than 50% predicted. Recommendations for young children, unable to perform spirometry are to wait one week after birth before allowing infants to fly, while infants with a history of neonatal respiratory disease should consult a paediatrician and a hypoxia test be considered.[7] The 2002 BTS guidelines suggest that adults with respiratory disease and a room air SpO_2 of 92-95% should undergo a hypoxic challenge, while those patients with a SpO_2 < 92% should receive in-flight oxygen. Patients undergoing a hypoxia test are considered to require in-flight O_2 if the SpO_2 falls below 85% during the test.[7] The 2004 BTS update (www.brit-thoracic.org.uk) of these guidelines suggested that a SpO_2 of less than 90% was indicative of an in-flight oxygen requirement in young children and infants with a history of respiratory disease, recommendations for adults remained unchanged.

The hypoxia test is a simple method of demonstrating a passenger's need for supplemental O_2 during flight and for determining in-flight O_2 requirements. The data on the use of hypoxia tests in infants and older children are sparse. The hypoxia test predicted cases of oxygen desaturation during flight in children with cystic fibrosis,[8] however, pre-flight spirometry predicted oxygen desaturation during flight better than hypoxia testing in those old enough to perform formal lung function testing.[9] We are aware of only two studies using hypoxia tests in infants and young children. Parkins *et al*[10] performed sleep studies on 34 healthy infants aged 1-6 months during a prolonged hypoxia test and reported that mean SpO_2 declined from 97.6% to 92.8%. Interestingly four infants demonstrated significant oxygen desaturation below 80%. More recently Buchdahl et al [11] reported the use of hypoxia tests in a case series of 20 young children with a history of respiratory disease, with six patients having SpO2 ≥95% in room air desaturating below 90% when performing the hypoxia test.

Thus the majority of healthy infants and young children do not appear to exhibit clinically relevant oxygen desaturation during air travel[4] or following a hypoxia test[10], however some healthy infants[10] and those infants and young children with respiratory disease may be at risk of significant hypoxic events.[11]

The Women's and Children's Health Service, comprising King Edward Memorial Hospital for Women and Princess Margaret Hospital for Children, provides the only tertiary obstetric, neonatal and paediatric medical service in the state of Western Australia. This study reports the results of a retrospective review of infants and young children with a history of neonatal lung disease referred

for a pre-flight hypoxia test. We aimed to identify those neonatal factors that may be predictive of a requirement for in-flight oxygen in infants with a history of nCLD.

METHODS

Subjects:

All children referred to the Respiratory Function Laboratory of Princess Margaret Hospital for Children, Perth, Western Australia for a hypoxia challenge test from January 2000 to December 2003 were identified. During this period approximately 280 children per annum were born with a gestational age (GA) of less than 36 weeks. Patients were referred by neonatal or paediatric specialists for assessment of fitness to fly prior to planned air travel, usually for transfer from tertiary neonatal and paediatric facilities to rural and regional medical units.

Forty-seven infants and young children were identified and the medical records and hypoxia test results of these children were retrospectively reviewed. Children were free of respiratory infections at the time of testing and all had a history of neonatal respiratory distress and were further categorised as either nCLD or non-nCLD. Neonatal CLD was defined as the use of supplemental O_2 at 36 weeks postmenstrual age (PMA) for infants with GA at birth of less than 32 weeks and the use of supplemental O_2 at 28 days of life for individuals with a GA at birth $\geq$ 32 weeks.[12]

The neonatal and clinical data collected were gender, GA and weight at birth, delivery mode, Apgar scores at 5 minutes, duration of mechanical ventilation and continuous positive airway pressure (CPAP), and days of supplemental O_2 in hospital and at home. The days since discontinuation of supplemental O_2, PMA, corrected age (calculated as PMA – 40) and body weight at the time of the hypoxia test were also recorded. Ethics approval to conduct the review and publish the results was obtained from the Princess Margaret Hospital Medical ethics committee.

Procedure for hypoxic challenge test (HCT)

The following procedure was used for assessing the requirement for in-flight oxygen. Prior to commencing the hypoxia test the children are fitted with nasal cannula to allow O_2 administration if required. Baseline SpO_2 and pulse rate (NPB-395, Nellcor) while breathing room air over a two minute period were recorded.

Children are then exposed to high flow (15 L/minute) 14% oxygen in nitrogen (Air Liquide Healthcare, Australia); via non-rebreathing mask incorporating a one-way valve assembly (Model 1058, Hudson) for a period of 20 minutes. The face mask does not provide a leak free seal, instead the high flow 14% oxygen acts to surround the patients face in a low oxygen environment, previous work in our laboratory has demonstrated that this method maintains a FiO_2 of 14-15% measured at the nares for the duration of the study (unpublished observations)

Clinical observations including SpO_2, pulse rate and activity state (crying, settled, asleep) were recorded at 1 and 20 minutes and between the following times: 3-4 minutes, 5-7 minutes, 10-12 minutes and 15-17 minutes. A patient was considered as fit to fly without supplemental oxygen if SpO_2 remained above 85% for the duration of the test.

If SpO_2 dropped below 85% the child was considered to have failed the hypoxia test and require in-flight oxygen. At this point O_2 was administered through the nasal cannula commencing at 0.125 L/min and incremented every minute to 0.25, 0.5 and 1 L/min until SpO_2 exceeded 94-96%. Once SpO_2 exceeded 94%-96% the infant was monitored for a further five minutes to ensure oxygen saturation levels remained stable. None of the infants studied required supplemental O_2 at a rate greater than 1 L/min to achieve adequate oxygenation.

Statistical analysis

Independent variables for predicting the results of the hypoxia test in total study population were assessed as follows:

Each independent variable was analysed in terms of its ability to predict the outcome of the hypoxia test (pass or fail), using binary logistic regression. Predicting factors significantly associated with the hypoxia test result in the binary logistic regression analysis, were then included in multiple logistic regression analyses. Data are expressed as median and 10^{th}-90^{th} centiles. Mann-Whitney U test was used to compare significant univariate predicting factors between nCLD infants that passed or failed the hypoxia test. P value less than 0.05 was considered statistically significant. All analyses were performed by SPSS software version 11.5.

Sensitivity and specificity of different corrected ages for predicting hypoxia test results were calculated and used to construct a receiver operating characteristic curve to define the optimum cut-off age by plotting sensitivity and 1-specificity against possible cut-off values.

RESULTS

Forty-seven infants, (nCLD; n=32) were referred for testing during the period of the review and were included in the analyses. The median age (10^{th} -90^{th} centiles) of the study population was 46.0 (36.8-113.6) weeks PMA, equivalent to a corrected age of 1.4 (-0.7-17.0) months. All infants studied had baseline SpO_2 >95% (range 95 - 100%). The majority of infants tolerated the hypoxia test well. In the period immediately prior to discontinuing the test 27 of 32 infants with nCLD were awake and quiet, the remainder being asleep (n=2) or awake and crying or restless (n=3). All 15 infants without nCLD were awake and quiet. Demographic and hypoxic test data are shown in table 1. Nine infants were classified as not requiring in-flight oxygen and were all in the nCLD group.

Table 1: Demographic characteristics and hypoxic test results of the study population

Variables	All infants	nCLD infants	Infants without nCLD
N	47	32	15
PMA at time of HCT [weeks]			
: median (10^{th}-90^{th} centiles)	46 (36.8-113.6)	64.5 (38.0-144.6)	37.0 (34.6-42.4)
: range	34-228	38-228	34-43
Corrected age at time of HCT [months]			
: median	1.4 (-0.7-17.0)	5.7 (-0.5-24.1)	-0.7 (-1.2-0.6)
: range	-1.4-43.4	-0.5-43.4	-1.4- 0.7
Body weight at time of HCT [kg]			
: median	4.6 (2.2-10.1)	6.2 (2.6-10.5)	2.2 (2.0-3.9)
: range	1.9-14.2	2.6-14.2	1.9-4.6
Gestational age [weeks]			
: median	27.0 (24.0- 30.2)	26.0 (23.3- 29.7)	28.0 (25.0-34.8)
: range	23-36	23-31	25-36
Birth weight [kg]			
: median	0.9 (0.6-1.6)	0.9 (0.6- 1.4)	1.0 (0.7-3.1)
: range	0.5-4.5	0.5-2.0	0.7-4.5
Sex; boys: girls	25:22	19:13	6:9
SpO2 at room air (%)			
: median	98 (96-100)	98 (96-100)	98 (97- 100)
: range	95-100	95-100	97-100
Hypoxia test; pass: fail	9:38	9:23	0:15
Supplemental Oxygen (mL/min)			
: median	250 (125–500)		
: range	16-500		

Total study population

Statistically significant predicting factors for failing the hypoxia test were age and body weight at the time of testing, duration of receiving sO_2 at home and the time since discontinuing supplemental O_2 prior to the hypoxia test (P<0.05) (table 2). These factors, excepting body weight, were assessed using multiple logistic regression analysis. Body weight was excluded due to significant co-linearity with age (r=0.97, P<0.01). In the multiple logistic regression model age at the time of the hypoxia test (either PMA or corrected) remained a significant predictor of the hypoxia test result (P=0.005; PMA (weeks): odds ratio 0.96, 95% confidence interval 0.93-0.99; corrected age (months): odds ratio 0.82, 95% confidence interval 0.67-0.95). In contrast duration of home O_2 (odds ratio 1.002, 95% confidence interval 0.985-1.02 (p=0.82)) and time since O_2 administration (odds ratio 1.006, 95% confidence interval 0.996-1.016 (p=0.25)) did not contribute to the ability to predict the result of the hypoxia test

Infants failing the hypoxia test were significantly younger than infants not requiring in-flight oxygen (40.0 (36.0-87.1) and 95.0 (53.0-228.0) weeks PMA, respectively; p<0.0001) with corrected ages of 0.0 (-0.9-10.9) and 12.7 (3.0-43.4) months, respectively (p<0.0001). The median time for SpO_2 to drop below 85% in infants failing the hypoxia test was 2 (1-5) minutes and was related to the numbers of days since supplemental oxygen was discontinued (Spearman's correlation: r=0.504; p=0.001). Those infants failing the hypoxia test required a median (10^{th}-90^{th} centiles) supplemental oxygen flow of 0.25 (0.113 – 0.5) L/min to return to SpO_2 levels exceeding 94-96% whilst receiving 14% oxygen.

Table 2: Results of univariate logistic regression analysis of total study population

Predicting factors	Median (10^{th}-90^{th} centiles)	P value	Odds ratio	95% CI
PMA # [weeks]	46 (36.8-113.6)	**0.005***	0.96	0.93-0.99
Corrected age # [months]	1.4 (-0.7-17.0)	**0.005***	0.82	0.67-0.95
Body weight # [kg]	4.6 (2.1-10.1)	**0.003***	1.000	0.999-1.000
Sex; boys: girls	25: 22	0.87	1.13	0.26-4.85
Gestational age [weeks]	27.0 (24.0-30.2)	0.90	0.98	0.68-1.22
Birth weight [kg]	0.9 (0.6-1.6)	0.68	1.00	0.999-1.002
Apgar scores at 5 min	8 (4-9)	0.97	1.01	0.53-1.33
Days of CMV	9.0 (1.0-53.0)	0.87	1.00	0.97-1.02
Days of CPAP	10.0 (2.0-32.4)	0.08	1.07	0.99-1.15
Maximum FiO2 [%]	60.0 (34.0-100.0)	0.98	1.00	0.97-1.03
Days on O2 in hospital	65.0 (7.2-145.0)	0.86	1.00	0.98-1.03
Days on O2 at home	0.0 (0.0-125.8)	**0.04***	0.99	0.97-1.00
Total days of O2	71.0 (7.2-264.2)	0.15	0.99	0.98-1.00
Days off O2	18.0 (5.8-334.8)	**0.03***	0.994	0.989-0.999

#: Patient characteristics at the time of the hypoxia test. CMV = conventional mechanical ventilation; CPAP = continuous positive airway pressure; * p<0.05.

Neonatal chronic lung disease group

Infants with nCLD passing the hypoxia test were significantly older and had been off sO_2 for longer, while differences in the duration of home oxygen use were not different (Table 3). A multiple logistic regression including age at the time of testing (either PMA or corrected) and days since oxygen use demonstrated that age at the time of testing was the primary characteristic influencing the outcome of the hypoxia test (PMA (weeks): odds ratio 0.954, 95% confidence interval 0.913-0.997 (p=0.035); days off oxygen: odds ratio 1.005, 95% confidence interval 0.996-1.013 (p=0.29)).

Table 3: Comparison of nCLD infants passing or failing the hypoxia test.

Factor	Pass	Fail	p
PMA	95.0 (53.0-228.0)	51.0(38.0-97.0)	0.006
Corrected age	12.7(3.0-43.4)	2.5 (-0.5-13.2)	0.006
Days off O_2	155.0 (70-365.2)	13.0 (4.8 – 341.8)	0.009
Days on O2 at home	31.0 (7.2-205)	27 (0.0 – 125.8)	0.24

Receiver operator characteristic curve

The sensitivity and specificity of specific corrected ages (term, 3, 6, 9, 12, 18 and 24 months) for predicting those infants failing the HCT were calculated and used to construct a receiver operator curve. The optimum corrected age for predicting an in-flight oxygen requirement was less than 12 months with a sensitivity and specificity of 95% and 56%, respectively (figure 1).

DISCUSSION

This retrospective review of infants referred for pre-flight hypoxia tests with history of neonatal respiratory problems demonstrated that a high proportion of infants (81%) exhibit significant oxygen desaturation below 85% when breathing a hypoxic gas mixture (FiO_2= 0.14). Interestingly, all infants displayed normal oxygen saturations (SpO_2 > 95%) in room air, suggesting that baseline SpO_2 is not a useful screening tool for in-flight oxygen requirement in this patient group.

British Thoracic Society guidelines[7] recommend in-flight oxygen is not required in those adults in whom sea level SpO_2 > 95% or between 92-95% depending on the absence or presence of additional risk factors, respectively. Buchdahl *et al.* [11] reported their experience of pre-flight hypoxia testing in 20 young children with a mixture of chronic lung diseases. Eighteen infants and young children had normal baseline SpO2. Of these, six individuals exhibited oxygen desaturation below 90% with one infant recording a SpO_2 of less than 85% during exposure to 15% oxygen. The present data support these earlier findings and suggest that a normal SpO_2 in room air in infants and young children with a history of neonatal respiratory disorders is insufficient to determine the safety of this patient group in the low oxygen environment encountered during flight or at high altitude.

In the present study, age at the time of testing (either PMA or corrected), irrespective of disease severity at the time of the hypoxia test, significantly predicted the requirement for in-flight O_2. The median age of infants without nCLD referred for hypoxia testing was 37 weeks PMA, significantly younger than the median corrected age of infants who passed the test (12.7 months). Additionally all infants less than 3 months corrected age failed the hypoxia test. This result may explain the failure of the young infants without nCLD to pass the hypoxia test despite the fact that one may expect these infants to have less severe initial lung disease. The reasons that younger infants are more susceptible to hypoxia and thus fail the hypoxia test are not clear, but may be due to the relative immaturity of respiratory system, leading to increased ventilation-perfusion mismatch.[1 13] Additionally, the

response to the hypoxic challenge in infants with a history of premature birth is liable to be more pronounced in the first months of life due to the influence of lung damage, resulting from mechanical ventilation and oxygenation in the neonatal period. Furthermore, the preterm children without nCLD in the present study all had respiratory distress in the neonatal period. Therefore, we are cautious about extrapolating the conclusions from our observations to preterm children in general although post-menstrual age appears to be a critical independent determinant of failure of the hypoxia test in our population.

Using ROC analysis we demonstrated that infants less than 12 months corrected age are significantly more likely to fail the hypoxia test when conducted in accordance with current recommendations ($p<0.001$). Thus, a pre-flight hypoxia test may be indicated in infants, with a history premature birth, less than 12 months corrected age. Additionally, based on current recommendations, all infants in the present study with a corrected age below three months would require in-flight oxygen, suggesting that young infants with a history of neonatal lung disease should not undertake air travel without supplemental O_2 before performing a pre-flight hypoxia test.

We routinely use a 20 minute hypoxia challenge for the assessment of fitness to fly in infants and young children. The hypoxia test, as used by our department, has a SpO_2 lower limit of 85% for the administration of in-flight oxygen. While this differs from the current BTS recommendations of a 90% limit, it is in agreement with the original BTS guidelines[7] and reported practices of other tertiary paediatric units[11]. Altering the lower limit for prescription of in-flight oxygen from 85 to 90% is likely to increase the proportion of infants with a history of premature birth defined as requiring in-flight oxygen. While the relevance and accuracy of the hypoxia test has been tested in adults and adolescents[7], this is not the case in infants and young children. We use a face mask and non-rebreathing valve to deliver a high flow of 14% oxygen and this is in contrast to the approach suggested by the BTS guidelines[7]. However, neither approach has been validated with subsequent measurements of in-flight SpO_2 nor therefore we are unable to comment on the clinical validity of the hypoxia test as we use it to predict the actual in-flight O_2 requirement. Additionally, the current study did not seek to evaluate clinical symptoms and oxygen saturation during flying. We therefore cannot draw conclusions as to the clinical relevance of the hypoxia test in infants with neonatal lung disease. Prospective studies comparing pre-flight hypoxia test results and clinical and oxygen status during flying in young children are required. In addition, disease-specific studies are required, as different diseases, with differing pathophysiologies, may contribute to distinctive responses to the hypoxia test.

In conclusion, a high proportion of ex-preterm infants not currently requiring supplemental O_2 referred to us for assessment of fitness-to-fly, exhibited significant oxygen desaturation when exposed to 14-15% oxygen. Critically, baseline oxygen saturation was normal in all infants indicating SpO_2 in room air is not predictive of in-flight oxygen requirements in infants with a history of neonatal lung disease. Age at the time of the hypoxia test was a significant predictor of the test outcome, suggesting that infants and young children with a history of neonatal respiratory problems under 12 months corrected age may require in-flight oxygen during flight and should undergo a fitness to fly test prior to considering air travel. Further information is required to determine the effect of prematurity alone on hypoxia test results and the clinical significance of failing current guidelines for safety during flight for infants with a history of neonatal lung disease.

Competing Interest statement

All authors declare that the answer to the all questions on the BMJ competing interest form [http://bmj.com/cgi/content/full/317/7154/291/DC1] are all No and therefore have nothing to declare

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Figure legend:

The optimum corrected age for predicting the hypoxia test result was a corrected age of < 12 months with a sensitivity and specificity of 95% and 56%, respectively.

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