

# PostScript

## LETTERS TO THE EDITOR

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### Pre-flight hypoxic challenge in infants and young children with respiratory disease

Modern aircraft flying at high altitude are cabin pressurised to an atmospheric partial pressure of up to 8000 feet (2348 metres), equivalent to breathing approximately 15% oxygen. This may expose individuals with cardiorespiratory disease to the risk of developing hypoxia. In 2002 the British Thoracic Society (BTS) issued recommendations for passengers with respiratory diseases who are planning to fly.<sup>1</sup> These recommendations included the use of a hypoxic challenge test in children with a history of respiratory disease too young to undergo conventional lung function tests. While pre-flight hypoxic challenge tests have been evaluated in older children<sup>2</sup> and adults<sup>3</sup> with respiratory disease, there are few data on hypoxic responses in infants and young children with respiratory disease although one study has observed profound desaturation in a small number of healthy infants while asleep.<sup>4</sup>

In the last 6 years we have tested 20 children under 5 years of age with a history of chronic pulmonary disease in early infancy (table 1). At our institution fitness to fly testing using 15% oxygen has been performed as a routine test in older children<sup>2</sup> and adults<sup>3</sup> with respiratory disease for some years, so formal ethical approval was not sought for this study. Children were exposed to a hypoxic challenge with 15% oxygen while sitting on the lap of a carer in a whole body plethysmograph (body box). Oxygen saturation was monitored by pulse oximetry (SpO<sub>2</sub>) using a probe attached to the child's finger. After measuring SpO<sub>2</sub> of the child in air, nitrogen was passed into the body box at approximately 50 l/min to dilute the oxygen content of the air to 15% over a period of 5 minutes. Oxygen and carbon dioxide concentrations were measured via continuous flow sampling using a Centronics 200 MGA mass spectrometer. The SpO<sub>2</sub> could take up to approximately 20 minutes to reach a stable value (constant over 2–3 minutes). In none of the tests did the carbon dioxide concentration in the body box exceed 0.5%. In nine

cases oxygen was subsequently administered via nasal cannulae to restore the fall in SpO<sub>2</sub> to the original (air) value so that this flow of oxygen could then be recommended during the flight. However, because of lack of data on the range of the normal desaturation response and the clinical significance, advice was not always consistent (table 1, p 1001). No child was oxygen dependent at the time of the test although four children were receiving nocturnal or intermittent supplementary oxygen. Four children were tested a second time for subsequent flights (cases 1, 3, 4 and 5). Eight of the 20 children desaturated below 90% in 15% oxygen, six of whom had normal (>95%) saturations at rest in air. Outcome information was obtained from all seven families who had been advised to take supplementary oxygen (table 1, p 1001). Case 2 was notable for the profound desaturation episode that occurred during the flight. Information regarding the outcome of flights for children for whom supplementary oxygen was not advised was incomplete. Three cases did not fly and seven were lost to follow up.

We conclude that some children with a history of chronic pulmonary disease in early infancy may have normal oxygen saturations in room air but desaturate significantly below 90% when exposed to a 15% oxygen hypoxic challenge. These children may be at risk of hypoxia when flying at altitude. This uncontrolled observational series suggests that such infants should be advised to take supplemental oxygen during the flight. The hypoxic challenge test is a simple and practical test and may be performed in any lung function laboratory with a whole body plethysmograph, a source of nitrogen, and a means of measuring oxygen. As carbon dioxide concentrations do not reach clinically significant levels, oxygen concentrations in the body box could be measured with a conventional oxygen monitor. Further studies are required to evaluate fully the hypoxic challenge test in young children. SpO<sub>2</sub> measurements during flight on subjects and healthy control children are needed. Measurements should be undertaken both in the awake and sleep states because there is evidence that SpO<sub>2</sub> falls in some older children with cystic fibrosis while asleep during flight<sup>2</sup> and in normal infants at sea level.<sup>4</sup>

**R Buchdahl, A Bush, S Ward, D Cramer**  
Royal Brompton & Harefield NHS Trust, Sydney Street,  
London SW3 6NP, UK; [rbcu@easynet.co.uk](mailto:rbcu@easynet.co.uk)

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### eNOS allelic variants at the same locus associate with HAPE and adaptation

High altitude pulmonary oedema (HAPE) is a severe form of altitude illness that may develop in individuals on rapid ascent to altitudes above 2500 m.<sup>1</sup> The disease is characterised by hypoxia induced pulmonary vasoconstriction caused by endothelial dysfunction and intravascular fluid retention.<sup>2,3</sup> While some families and individuals are at risk, those with a long ancestry at high altitude have a lower risk. Moreover, individuals who have had HAPE are at a greater risk of repeat events. Such data support a strong genetic component to HAPE susceptibility, perhaps associated with a founder effect. It is likely that long term exposure to high altitude provides a natural positive adaptive pressure to alleles that prevent the illness. We hypothesise that allelic variants at the same locus in a gene are involved in adaptation and HAPE.

We therefore investigated the Glu298Asp and 4b/4a polymorphisms of the endothelial nitric oxide synthase gene (*eNOS*) and –344T/C, intron-2 conversion and Lys173Arg polymorphisms of the aldosterone synthase gene (*CYP11B2*) in 59 patients with HAPE who developed the disease at 3400 m, 64 lowland controls (LLs) who had been to the same altitude two or three times and even to 5600 m, and 136 highland natives (HLs) from Leh, Ladakh (3400 m). The study groups consisted of unrelated and age matched men aged 30–40 years who had been inhabitants of their respective lands since ancient times. The HAPE patients and LLs were of the same ethnic origin and ascended in a similar manner. The diagnosis of HAPE was based on chest radiographs and other clinical symptoms. Blood samples were collected in the morning in the supine position after overnight fasting. Subjects abstained from smoking for 12 hours before sample collection. The institutional ethical committee approved the investigation and all subjects gave informed consent.

Genotype determination of the five polymorphisms in the two genes was performed by modified cycling conditions. Genotypes were randomly validated on a 377 DNA sequencer (Applied Biosystems, USA). Plasma nitric oxide (NO) estimated as nitrite by the enzymatic Griess method (Calbiochem, USA) and aldosterone levels were determined by radioimmunoassay (Immunotech, France). SPSS software for windows (release 10.0) was used for the statistical analysis.

This study is the first to report plasma NO and aldosterone levels in patients with HAPE and HLs. NO levels were significantly lower in the HAPE group (46.17 (13.94) μM) than in HLs (95.35 (27.56) μM) or LLs (90.53 (29.97) μM) (p<0.0001 for each). The NO levels in the order HLs > LLs > HAPE support earlier reports of impaired NO synthesis in HAPE<sup>1</sup> and increased NO levels in mountain dwellers.<sup>5</sup> Previous studies, however, measured the exhaled NO level which is not the exact measure of endogenous NO production. The highest NO levels in HLs signify its importance in the

**Table 1** Hypoxic challenge test: subject details

Case no	Sex	Age (months)	SpO <sub>2</sub> in air	SpO <sub>2</sub> in 15% O <sub>2</sub>	SpO <sub>2</sub> in 15% + nasal cannulae O <sub>2</sub> (flow to achieve normal saturation)	Clinical	Destination	Advice given	Outcome
1	M	2	98	88	100 (0.5 l/min)	Right hypoplastic lung	Malta	Have O <sub>2</sub> available	Did not fly
1	M	14	98	90		Right hypoplastic lung	Malta	Well without O <sub>2</sub>	NA
2	F	11	97	71	100 (1.0 l/min)	Severe tracheobronchomalacia; Right pulmonary artery narrowing; gastro-oesophageal reflux; Ehlers Danlos syndrome; receiving O <sub>2</sub> at night	Qatar	Have O <sub>2</sub> available 2 l/m	Flew without O <sub>2</sub> until "collapse"; SpO <sub>2</sub> 40%; given via mask O <sub>2</sub> and continued for rest of trip
3	M	19	99	90		Ex-preterm 27 w; CLD; receiving 0.1 l/min O <sub>2</sub> at night	Pakistan	Have O <sub>2</sub> available 2 l/m because uncertain about sleep	Trip cancelled - non medical reasons
3	M	50	99	90		Ex-preterm 27 w; CLD; receiving 0.1 l/min O <sub>2</sub> at night	Pakistan	Have O <sub>2</sub> available 2 l/m because uncertain about sleep	Trip cancelled because chest infection
4	M	4	97	88	97 (1.0 l/min)	Persistent tachypnoea at 4 m unknown aetiology - possible mild pulmonary hypoplasia	New York, USA	Well without O <sub>2</sub>	NA
4	M	6	97	90		Persistent tachypnoea at 4 m unknown aetiology - possible mild pulmonary hypoplasia, bronchomalacia	New York, USA	Well without O <sub>2</sub>	NA
5	F	45	92	86	92 (1.0 l/min)	Cyanotic episodes of unknown aetiology	Greece	Have O <sub>2</sub> available	Received O <sub>2</sub> via mask on outward and return journeys; no problems
5	F	54	98	92		Cyanotic episodes with colds; unknown aetiology	Greece	Well without O <sub>2</sub>	"Very tired" at end of flight
6	F	20	97	87		Paraplegic with scoliosis on intermittent home O <sub>2</sub>	Malta	Have O <sub>2</sub> available 2 l/min	Received O <sub>2</sub> via nasal prongs outward, mask return; no problems
7	M	9	97	92		Left upper lobe congenital lobar emphysema	Switzerland	Well without O <sub>2</sub>	Uneventful flight
8	F	2	100	94		Ex-preterm 25 w; CLD; on O <sub>2</sub> 0.1 l/min at night	Jamaica	Well without O <sub>2</sub>	NA
9	M	7	98	90		Ex-preterm 26 w; CLD; off O <sub>2</sub>	Mauritius	Well without O <sub>2</sub>	Uneventful flight
10	F	6	99	92		Ex-preterm 28 w; intrauterine growth retardation; CLD; off O <sub>2</sub>	Pakistan	Well without O <sub>2</sub>	NA
11	M	11	100	94	100 (1.0 l/min)	Ex-preterm 24 w; intrauterine growth retardation; CLD; off O <sub>2</sub>	UAE	Well without O <sub>2</sub>	Uneventful flight
12	M	6	100	94		Ex-preterm 34 w; CLD; VSD; off O <sub>2</sub>	Yugoslavia	Well without O <sub>2</sub>	NA
13	F	2	100	95		Repaired neonatal diaphragmatic hernia	Kuwait	Well without O <sub>2</sub>	NA
14	F	3	99	92	100 (1.0 l/min)	Ex-preterm 34 w	Thailand	Well without O <sub>2</sub>	Uneventful flight
15	F	3	98	91	100 (1.0 l/min)	Ex-preterm 34 w; CLD; off O <sub>2</sub>	Thailand	Well without O <sub>2</sub>	Uneventful flight
16	M	42	96	89		Cystic fibrosis	Majorca	Well without O <sub>2</sub>	Uneventful flight
17	M	49	100	94		Right middle lobe bronchus vascular ring	Greece	Well without O <sub>2</sub>	NA
18	F	8	94	88	98 (1.0 l/min)	Pharyngomalacia	Canary Isles	Have O <sub>2</sub> available 2 l/m	O <sub>2</sub> was available but not administered. Uneventful flight
19	F	5	100	94		Ex-preterm 23 w; CLD; off O <sub>2</sub>	S Africa	Well without O <sub>2</sub>	NA
20	M	19	98	88	97 (1.0 l/min)	Spinal muscular atrophy + left lower lobe collapse	Phoenix, AZ, USA	Have O <sub>2</sub> available 2 l/m	O <sub>2</sub> available. Received on return flight after getting distressed but would not tolerate either mask or nasal cannulae; eventually went to sleep.

SpO<sub>2</sub>, oxygen saturation; CLD, chronic lung disease; VSD, ventricular septal defect; NA, data not available.

**Table 1** Genotype and allele frequencies of endothelial nitric oxide synthase (eNOS) polymorphisms in highland dwellers (HLs), lowland dwellers (LLs) and patients with high altitude pulmonary oedema (HAPE)

Polymorphism	Frequency distribution			$\chi^2$	p value	OR	95% CI
	HLs (n = 136)	LLs (n = 64)	HAPE (n = 59)				
Glu298Asp	105 (78%)	39 (61%)	22 (37%)				
Glu298Glu	29 (21%)	23 (36%)	35 (59%)				
Asp298Asp	2 (1%)	2 (3%)	2 (4%)				
Glu	239 (88%)	101 (79%)	79 (68%)				
Asp	33 (12%)	27 (21%)	39 (32%)				
HLs v HAPE							
Genotypes				28.91	0.000001	–	–
Alleles				23.92	0.000001	3.58	2.11 to 6.07
LLs v HAPE							
Genotypes				7.03	0.03	–	–
Alleles				4.47	0.03	1.85	1.04 to 3.27
HLs v LLs							
Genotypes				5.77	0.05	–	–
Alleles				5.48	0.02	1.94	1.11 to 3.39
4b/4a							
4b/b	113 (84%)	45 (71%)	31 (53%)				
4b/a	23 (16%)	19 (29%)	28 (47%)				
4b	249 (92%)	109 (86%)	90 (76%)				
4a	23 (8%)	19 (14%)	28 (24%)				
HLs v HAPE							
Genotypes				19.88	0.000008	–	–
Alleles				16.89	0.00004	3.51	1.84 to 6.15
LLs v HAPE							
Genotypes				4.11	0.04	–	–
Alleles				3.14	0.08	1.78	0.94 to 3.41
HLs v LLs							
Genotypes				4.28	0.04	–	–
Alleles				3.78	0.05	1.89	0.99 to 3.61

maintenance of regular physical activity at high altitude. NO improves the ventilation/perfusion ratio and lowers the alveolar to arterial oxygen tension difference by increasing oxygen saturation. The levels of aldosterone in the HAPE group (467.0 (339.0) pmol/l) were significantly higher in the HLs (376.3 (169.5) pmol/l;  $p = 0.05$ ), LLs (155.5 (109.9) pmol/l;  $p < 0.0001$ ), or both ( $p < 0.0001$ ). This finding is in agreement with the hypothesis that antidiuresis followed by fluid retention is one of the mechanisms leading to HAPE,<sup>3</sup> in which aldosterone plays a pivotal role. NO inhalation therapy and the use of diuretics to treat HAPE<sup>2</sup> support the decreased levels of endogenous NO and increased levels of aldosterone observed in the present study.

The three groups were in Hardy-Weinberg equilibrium for the polymorphisms. The genotype and allele frequency analysis of the Glu298Asp and 4b/4a polymorphisms of the eNOS gene revealed that the Asp and 4a alleles were over-represented in the HAPE group and that the Glu and 4b alleles were over-represented in the HLs (table 1, above). A recent study also reported an association of mutant alleles with the disorder.<sup>6</sup> The presence of the Asp variant renders the enzyme susceptible to intracellular proteases.<sup>7</sup> Proteolysis may reduce NO levels which may lead to impaired vasodilation and endothelial dysfunction in a hypoxic environment, increasing susceptibility to HAPE. The over-representation of wild-type alleles in HLs suggests that the mutant alleles associated with HAPE are eliminated in HLs as a process of natural selection. Indeed, the tolerance of Himalayan populations to hypoxia, which is reflected in their metabolic

and physiological traits, is believed to be the result of adaptation.<sup>8</sup> In the case of *CYP11B2* polymorphisms, the intron-2 conversion homozygotes were over-represented in the HAPE subjects compared with HLs ( $p = 0.03$ ) whereas the –344T/C and Lys173Arg polymorphisms were not associated with the disorder (data not shown).

Our results suggest a significant role for NO and aldosterone in the pathogenesis of HAPE. The over-representation of eNOS Asp and 4a alleles in patients with HAPE associates these alleles with the disorder, whereas over-representation of Glu and 4b alleles in HLs suggests that they have a role in adaptation to high altitudes. These findings suggest, for the first time, that allelic variants at the same locus are involved in HAPE and adaptation.

**A Ahsan, R Charu, M A Q Pasha**

Functional Genomics Unit, Institute of Genomics and Integrative Biology, Delhi, India

**T Norboo**

Department of Medicine, Sonam Norboo Memorial Hospital and Ladakh Heart Foundation, Leh, Ladakh, India

**R Charu, F Afrin**

Centre for Biotechnology, Hamdard University, Delhi, India

**A Ahsan, M A Baig**

Department of Biochemistry, Hamdard University, Delhi, India

Correspondence to: Dr M A Q Pasha, Functional Genomics Unit, Institute of Genomics and Integrative Biology, Delhi, India; qpasha@igib.res.in

AA and RC contributed equally.

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## Prevalence of TB in healthcare workers in south west London

In the UK, and London specifically, the rise in the incidence of tuberculosis (TB) has been ascribed to reactivation of latent disease and

**Table 1** Basic demographic data for healthcare workers with tuberculosis

	No of affected staff	Non-UK born	BCG vaccinated	Pulmonary disease	Extrapulmonary disease	HIV antibody positive	African origin	Indian origin
Hospital 1	9	8	7	7	2	3	5	
Hospital 2	11	10	9	6	5	6	10	
Hospital 3	3	2	2	2	1	0	1	3
Hospital 4	2	2	0	2	0	0	2	
Total	25	22	18	17	8	9	18	3

importation of infection from recent immigrants.<sup>1</sup> The recent increase in the recruitment of healthcare workers from countries with a high prevalence of TB raises the possibility of healthcare workers being a significant source of disease. Previous estimates of TB infection among National Health Service (NHS) employees were calculated before the current levels of HIV infection and the mass migration of healthcare workers.<sup>2,3</sup> The current number of healthcare workers with TB is unknown but an estimate of this would provide data on the risk that they pose for spreading TB infection.

We conducted a retrospective interrogation of the local TB database (Integrated Tuberculosis Surveillance System, ITSS) for all healthcare workers notified in 2002. Their medical notes were then reviewed and a basic dataset was collated. A healthcare worker was defined as doctor, nurse, healthcare assistant, physiotherapist, occupational therapist, radiographer, or student equivalent. The data collected included profession, age, sex, type of disease, HIV status, country of origin, length of time in the UK when diagnosed (if applicable), history of Bacillus Calmette Guérin (BCG) vaccination, and presence of accompanying scar.

372 patients were notified as having TB in 2002 within the south west London catchment area (as of April 2003). Of these, 25 were healthcare workers (6.7%). Four were doctors, 13 nurses, five healthcare assistants, and three healthcare students. 22 (88%) were originally of overseas origin with a median (range) of 3 (0.75–22) years residence in the UK before diagnosis. Three were originally from the Indian subcontinent, 18 came from Africa, and one from the Caribbean. 18 patients had evidence of BCG vaccination (14 had a scar, 13 born overseas) and 17 (68%) had pulmonary TB. Nine patients (36%) were diagnosed as being HIV antibody positive, although not all patients agreed to be tested (table 1).

Healthcare workers contribute significantly to the number of patients with TB. A large proportion (36%) were co-infected with HIV and this is consistent with previous estimates.<sup>4</sup> The majority of patients identified were nurses which, in part, reflects the high proportion of nurses among healthcare workers. Over two thirds had pulmonary TB and would therefore be deemed a greater infection risk.

Previous estimates of TB infection among NHS workers were calculated more than a decade ago. The total number of cases reported annually ranged from 3 to 5 among nearly 22 000 NHS staff monitored.<sup>5</sup> The NHS workforce in our sector was estimated at 26 273. In order to calculate a rate of tuberculosis infection in the population we assumed that, unless otherwise indicated, all these healthcare workers worked for the NHS and that the number of cases treated within

our sector, but working outside were equivalent to the number of south west London workers treated outside the sector. The TB rate for the south west London population has been estimated at 25 per 100 000 population per year, notably lower than the rate estimated for our healthcare worker population.<sup>5</sup>

No patient was diagnosed as part of pre-employment screening but the median time of 3 years from arrival in the UK to presentation suggests that most were unlikely to have had clinically apparent disease at the time of entry. It is unclear, however, if these patients had evidence of latent disease at this time. Currently there is no uniform health screening procedure for NHS workers. The British Thoracic Society (BTS) has produced guidelines for screening immigrant employees<sup>6</sup> which rely on questionnaire evaluation of suspicious symptoms and evidence of BCG vaccination to screen for high risk individuals. 18 out of 25 (72%) of our patients had evidence of BCG vaccination and may therefore have been considered low risk if they did not report suspicious symptoms. Accordingly, a chest radiograph would not have been deemed necessary, even though this could have picked up evidence of tuberculous infection. The Department of Health in the UK has recently produced draft guidelines regarding TB screening for NHS employees.<sup>6</sup> Based on the BTS recommendations, they propose further screening manoeuvres for workers from areas of high TB prevalence (incidence levels greater than 40 per 100 000 population per year). These include universal tuberculin skin testing (TST), HIV testing for those with negative TST results, and a low threshold for chest radiography. We believe these new guidelines would increase the detection of both active and latent TB and accordingly reduce the risk represented by infected healthcare workers.

**T B L Ho, C F J Raymer**

Chest Unit, St George's Hospital, London SW17 0QT, UK

**T Lindfield, Y Young**

South West London Health Protection Unit, London SW17 7DJ, UK

**R J Whitfield**

Chest Clinic, Mayday University Hospital, Croydon CR7 7YE, UK

Correspondence to: Dr T B L Ho, Chest Unit, St George's Hospital, London SW17 0QT, UK; timho@doctors.org.uk

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## BOOK REVIEW

### Wheezing Disorders in the Preschool Child

Martinez FD, Godfrey S. London: Martin Dunitz, 2003, £40.00. ISBN 1 84184 155 2

In this monograph Martinez and Godfrey have set out to inform clinicians about preschool wheeze—a condition that has as many labels (for example, wheezy bronchitis, infant asthma, preschool viral wheeze) as theories about its pathogenesis. The chapters unfold in a logical order: the epidemiology of preschool wheeze, immunological mechanisms, and finally differential diagnosis and treatment. Indeed, there is a coherence in this book that is rare in weightier multi-author textbooks. The initial “science” orientated chapters may appear at first sight to be rather dense—with their combination of small print and infrequent illustrations. However, they do contain nuggets of clinically useful information—I immediately used the up to date data on long term prognosis to counsel parents. I also liked the authors’ pragmatic approach to treatment. For example, they correctly cited the one study assessing the effectiveness of long acting  $\beta_2$  agonists in preschool children and followed this with a sensible recommendation that cannot be found in the BTS guideline.

Overall, this book is essential reading for clinical and academic respiratory paediatricians and respiratory trainees. Furthermore, it provides an excellent and unbiased overview for anyone setting out to read the primary epidemiological literature on preschool wheeze.

**J Grigg**

Department of Child Health, University of Leicester, Leicester LE2 7LX, UK; jg33@le.ac.uk