LETTERS TO THE EDITOR

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 (2438 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.1 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 with a history of respiratory disease too young to undergo conventional testing using 15% oxygen has been performed in infants and adults.2

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 to follow exposure to 15% oxygen saturation in infants: effect of altitude on pulmonary vascular function and intravascular fluid retention.3 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 selection 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 Ghl298Asp and 4b/4a polymorphisms of the endothelial nitric oxide synthase gene (eNOS) and 3447T/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 HLS 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 (Innometech, 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 (29.56) μM) (p<0.0001 for each). The NO levels in the order HLS > LLs > HAPE support earlier reports of impaired NO synthesis in HAPE and increased NO levels in mountain dwellers.5 Previous studies, however, measured the oxygen saturation and which is not the exact measure of endogenous NO production. The highest NO levels in HLS signify its importance in the
<table>
<thead>
<tr>
<th>Case no</th>
<th>Sex</th>
<th>Age (months)</th>
<th>SpO2 in air</th>
<th>SpO2 in 15% O₂</th>
<th>SpO2 in 15% O₂ + nasal cannulae O₂ (flow to achieve normal saturation)</th>
<th>Clinical</th>
<th>Destination</th>
<th>Advice given</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>2</td>
<td>98</td>
<td>88</td>
<td>100 (0.5 l/min)</td>
<td>Right hypoplastic lung</td>
<td>Malta</td>
<td>Have O₂ available</td>
<td>Did not fly</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>14</td>
<td>98</td>
<td>90</td>
<td>100 (1.0 l/min)</td>
<td>Right hypoplastic lung</td>
<td>Malta</td>
<td>Well without O₂</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>11</td>
<td>97</td>
<td>71</td>
<td></td>
<td>Severe tracheobronchomalacia; Right pulmonary artery narrowing; gastro-oesophageal reflux; Ehlers Danlos syndrome; receiving O₂ at night</td>
<td>Qatar</td>
<td>Have O₂ available</td>
<td>2 l/m</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>19</td>
<td>99</td>
<td>90</td>
<td>Ex-preterm 27 w; CLD; receiving 0.1 l/min O₂ at night</td>
<td>Ex-preterm 27 w; CLD; receiving 0.1 l/min O₂ at night</td>
<td>Pakistan</td>
<td>Have O₂ available</td>
<td>2 l/m because uncertain about sleep</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>4</td>
<td>97</td>
<td>88</td>
<td>97 (1.0 l/min)</td>
<td>Persistent tachypnoea at 4 m unknown aetiology - possible mild pulmonary hypoplasia</td>
<td>New York, USA</td>
<td>Well without O₂</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>45</td>
<td>92</td>
<td>86</td>
<td>92 (1.0 l/min)</td>
<td>Cyanotic episodes of unknown aetiology</td>
<td>Greece</td>
<td>Have O₂ available</td>
<td>Received O₂ via mask on outward and return journeys; no problems</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>54</td>
<td>98</td>
<td>92</td>
<td></td>
<td>Cyanotic episodes with colds; unknown aetiology</td>
<td>Greece</td>
<td>Wall without O₂</td>
<td>&quot;Very tired&quot; at end of flight</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>9</td>
<td>97</td>
<td>92</td>
<td></td>
<td>Left upper lobe congenital lobar emphysema</td>
<td>Switzerland</td>
<td>Well without O₂</td>
<td>Uneventful flight</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>2</td>
<td>100</td>
<td>94</td>
<td></td>
<td>Ex-preterm 25 w; CLD; on O₂ 0.1 l/min at night</td>
<td>Jamaica</td>
<td>Well without O₂</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>7</td>
<td>98</td>
<td>90</td>
<td></td>
<td>Ex-preterm 26 w; CLD; off O₂</td>
<td>Mauritius</td>
<td>Well without O₂</td>
<td>Uneventful flight</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>6</td>
<td>99</td>
<td>92</td>
<td></td>
<td>Ex-preterm 28 w; intrauterine growth retardation; CLD; off O₂</td>
<td>Pakistan</td>
<td>Well without O₂</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>11</td>
<td>100</td>
<td>94</td>
<td>100 (1.0 l/min)</td>
<td>Ex-preterm 24 w; intrauterine growth retardation; CLD; off O₂</td>
<td>UAE</td>
<td>Wall without O₂</td>
<td>Uneventful Flight</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>6</td>
<td>100</td>
<td>94</td>
<td></td>
<td>Ex-preterm 34 w; CLD; off O₂</td>
<td>Yugoslavia</td>
<td>Well without O₂</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>2</td>
<td>100</td>
<td>95</td>
<td></td>
<td>Repaired neonatal diaphragmatic hernia</td>
<td>Kuwait</td>
<td>Well without O₂</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>3</td>
<td>99</td>
<td>92</td>
<td>100 (1.0 l/min)</td>
<td>Ex-preterm 34 w</td>
<td>Thailand</td>
<td>Well without O₂</td>
<td>Uneventful Flight</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>3</td>
<td>98</td>
<td>91</td>
<td>100 (1.0 l/min)</td>
<td>Ex-preterm 34 w</td>
<td>Thailand</td>
<td>Well without O₂</td>
<td>Uneventful Flight</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>42</td>
<td>96</td>
<td>89</td>
<td></td>
<td>Cystic fibrosis</td>
<td>Majorca</td>
<td>Well without O₂</td>
<td>Uneventful Flight</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>49</td>
<td>100</td>
<td>94</td>
<td></td>
<td>Right middle lobe bronchus vascular ring</td>
<td>Greece</td>
<td>Well without O₂</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>8</td>
<td>94</td>
<td>88</td>
<td>98 (1.0 l/min)</td>
<td>Pharyngomalacia</td>
<td>Canary Isles</td>
<td>Have O₂ available</td>
<td>2 l/m</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>5</td>
<td>100</td>
<td>94</td>
<td></td>
<td>Ex-preterm 23 w; CLD; off O₂</td>
<td>S Africa</td>
<td>Have O₂ available</td>
<td>2 l/m</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>19</td>
<td>98</td>
<td>88</td>
<td>97 (1.0 l/min)</td>
<td>Spinal muscular atrophy + left lower lobe collapse</td>
<td>Phoenix, AZ, USA</td>
<td>Have O₂ available</td>
<td>2 l/m</td>
</tr>
</tbody>
</table>

SpO₂, oxygen saturation; CLD, chronic lung disease; VSD, ventricular septal defect; NA, data not available.
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, in which aldosterone plays a pivotal role. NO inhalation therapy and the use of diuretics to treat HAPE 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 and 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. The over-representation of wild-type 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.

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)

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>HLs (n = 136)</th>
<th>LLs (n = 64)</th>
<th>HAPE (n = 59)</th>
<th>χ²</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu298Asp</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu298Glu</td>
<td>105 (78%)</td>
<td>39 (61%)</td>
<td>22 (37%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu298Asp</td>
<td>29 (21%)</td>
<td>23 (36%)</td>
<td>35 (59%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu</td>
<td>2 (1%)</td>
<td>2 (3%)</td>
<td>2 (4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp</td>
<td>239 (88%)</td>
<td>101 (79%)</td>
<td>79 (68%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4b/4a</td>
<td>113 (84%)</td>
<td>45 (71%)</td>
<td>31 (53%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4b/b</td>
<td>23 (16%)</td>
<td>19 (29%)</td>
<td>28 (47%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4b/a</td>
<td>249 (92%)</td>
<td>109 (86%)</td>
<td>90 (76%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>23 (8%)</td>
<td>19 (14%)</td>
<td>29 (24%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLs v HAPE Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypes</td>
<td>19.88</td>
<td>0.000008</td>
<td>–</td>
<td></td>
<td></td>
<td>1.84</td>
<td>6.15</td>
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<tr>
<td>Alleles</td>
<td>16.89</td>
<td>0.000004</td>
<td>3.51</td>
<td></td>
<td></td>
<td>1.94</td>
<td>6.15</td>
</tr>
<tr>
<td>LLs v HAPE Genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypes</td>
<td>4.11</td>
<td>0.04</td>
<td>–</td>
<td></td>
<td></td>
<td>1.78</td>
<td>3.41</td>
</tr>
<tr>
<td>Alleles</td>
<td>3.14</td>
<td>0.08</td>
<td>1.78</td>
<td></td>
<td></td>
<td>0.94</td>
<td>3.41</td>
</tr>
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<td>HAPE Genotypes</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotypes</td>
<td>4.28</td>
<td>0.04</td>
<td>–</td>
<td></td>
<td></td>
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<td>3.61</td>
</tr>
<tr>
<td>Alleles</td>
<td>3.78</td>
<td>0.05</td>
<td>1.89</td>
<td></td>
<td></td>
<td>0.99</td>
<td>3.61</td>
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</table>

Supported by grants from the Council of Scientific and Industrial Research.

References


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
importation of infection from recent immi-
grants. The recent increase in the recruit-
ment of healthcare workers from countries 
with a high prevalence of TB raises the 
possibility of healthcare workers being a 
significant source of disease. Previous esti-
mates of TB infection among National Health 
Service (NHS) employees were calculated 
based on the current levels of TB infection 
and the migration rate of healthcare work-
ners. 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 equiv-
alent. The data collected included profession, 
age, sex, 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 catch-
ment area (as of April 2003). Of these, 25 
were healthcare workers (6.7%). Four were 
doctors, 13 were 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 
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 esti-
mates. The majority of patients identified 
were nurses which, in part, reflects the high 
proportion of nurses among healthcare work-
ers. Over two thirds had pulmonary TB and 
would therefore be deemed a greater infec-
tion 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 
approximately 22 000 NHS staff monitored. 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 equiva-
 lent 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. 1

No patient was diagnosed as part of pre-
employment screening but the median time 
of 3 years from arrival in the UK to presenta-
tion 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 screen-
ing procedure for NHS workers. The British 
Thoracic Society (BTS) has produced guide-
lines for screening immigrant employees2 which 
rely on questionnaire evaluation of 
suspicious symptoms and evidence of BCG 
vaccination to screen for high risk indivi-
duals. 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 
needed, even though this could have picked up 
evidence of tuberculosis infection. The Department of Health in the 
UK has recently produced draft guidelines 
regarding TB screening for NHS employees. 3

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 
infectious healthcare workers.

Table 1 Basic demographic data for healthcare workers with tuberculosis

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

2 Capewell S, Leaker AR, Leitch AG. Pulmonary 
tuberculosis in health service staff: is it still a 

3 Lunn JA, Mayho V. Incidence of pulmonary 
tuberculosis by occupation of hospital employees 
in the National Health Service in England and 
30–2.

4 Bowen EF, Rice FS, Cooke NT, et al. HIV 
seroprevalence by anonymous testing in patients 
with Mycobacterium tuberculosis and in 

5 Ad Hoc Risk Assessment Group. Health clearance 
for serious communicable diseases. London: Depart-
.uk/healthclear (accessed 7 January 2004).

BOOK REVIEW

Wheezing Disorders in the Preschool Child

Martinez FD, Godfrey S. London: Martin 

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 bronchi- 

tis, infant asthma, preschool wheeze) as 
theories about its pathogenesis. The chapters 
unfold in a logical order: the epidemiology of 
preschool wheeze, immunological mechani-
isms, 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 infor-
mation—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 B2 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 paediatri-
cians and respiratory trainees. Furthermore, 
it provides an excellent and unbiased over-
view for anyone setting out to read the pri-
mary epidemiological literature on preschool 

t wheeze.

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www.thoraxjnl.com
eNOS allelic variants at the same locus associate with HAPE and adaptation

A Ahsan, R Charu, M A Q Pasha, T Norboo, F Afrin and M A Baig

*Thorax* 2004 59: 1000-1002
doi: 10.1136/thx.2004.029124