Hypoxia Challenge Testing in Neonates for Fitness to Fly

Susanne Vetter-Laracy, PhD, MD, a Borja Osona, MD, b Jose Antonio Peña-Zarza, MD, a Jose Antonio Gil, MD, b Joan Figuerola, PhD, MD b

abstract

BACKGROUND: Preflight hypoxia challenge testing (HCT) in a body plethysmograph has previously been done only on infants >3 months of corrected gestational age (CGA). This study aims to determine the earliest fit-to-fly age by testing neonates <1 week old.

METHODS: A prospective observational study was carried out on 3 groups of infants: healthy term infants ≤7 days old, preterm infants (≥34 weeks CGA) 2 to 3 days before discharge, and preterm infants with bronchopulmonary dysplasia (BPD). HCT was conducted using a body plethysmograph with a 15% fraction of inspired oxygen. The oxygen saturation (SpO2) test fail point was <85%.

RESULTS: Twenty-four term (mean CGA 40 weeks), 62 preterm (37 weeks), and 23 preterm with BPD (39.5 weeks) infants were tested. One term infant (4.2%) and 12 preterm infants without BPD (19.4%) failed. Sixteen (69.3%) preterm infants with BPD failed (P < .001), with a median drop in SpO2 of 16%. At 39 weeks CGA, neither preterm infants without BPD nor term infants had an SpO2 <85%. However, 7 of 12 term infants with BPD failed the HCT.

CONCLUSIONS: Term and preterm infants without BPD born at >39 weeks CGA do not appear to be likely to desaturate during a preflight HCT and so can be deemed fit to fly according to current British Thoracic Society Guidelines.

WHAT’S KNOWN ON THIS SUBJECT: Preterm infants ≥3 months of corrected gestational age and without bronchopulmonary dysplasia are at no greater risk of hypoxia compared with term infants during a preflight hypoxic challenge test in a body plethysmograph thus can be considered fit to fly.

WHAT THIS STUDY ADDS: Preterm and term infants without pulmonary problems from a corrected gestational age of >39 weeks are not at risk for hypoxia during a preflight hypoxic challenge test in a body plethysmograph.
Commercial planes fly at 9000 to 13 000 m, requiring cabin pressurization to 1530 to 2440 m. At this altitude, the reduced pO2 is equivalent to breathing ~15% oxygen (fraction of inspired oxygen [FIO2] 0.15) at sea level. It is already well known that pulse oxygen saturation (SpO2) declines significantly in healthy children and adults (~4%, down to 94.4%) during commercial airline travel, but this is not considered pathologic.1–2 Newborns are particularly susceptible to hypoxic episodes in a hypoxic environment because of factors such as an increased tendency for ventilation-perfusion mismatch and a left shift of the oxygen dissociation curve due to fetal hemoglobin in the first months of life.3 Premature infants have more apneic pauses and periodic breathing when they reach term than term infants, and apneic pauses may be triggered by chronic hypoxemia.4–6 Thus, studies testing term infants and premature infants during the first months of life for fitness to fly have been ruled out by most other researchers despite the fact that the number of families wanting to take their newborns on flights shortly after delivery has increased.7–11

The British Thoracic Society (BTS) has published guidelines for infants stating that term newborns (>37 weeks) should wait 1 week after birth term before traveling, premature infants who have not reached term should have in-flight oxygen of 1 to 2 L/min (grade C evidence), and premature infants <1 year old with neonatal chronic respiratory problems should undergo hypoxia challenge testing (HCT).12,13

Son Espases neonatal unit is located on Mallorca, the largest of the Balearic Islands and a major tourism hub in the Mediterranean Sea. An average of 29 premature births to nonresident mothers take place annually. Approximately 9 premature infants are born on the surrounding islands each year and are transferred to our center for follow-up. It is therefore necessary to assess the safety of flying for neonates of mothers not residing on Mallorca.

No other fitness-to-fly testing has been conducted in a body plethysmograph on healthy term infants in the first week of life and premature infants at term age. The objective of this study was to determine the earliest fit-to-fly age of preterm and term infants. This was done by testing preterm infants at term age, including those with bronchopulmonary dysplasia (BPD), and comparing the results with a control group of healthy infants that were ≤7 days old.

**METHODS**

This was a prospective observational clinical study. Term infants (≥37 weeks gestational age [GA]) and ≥2 days and ≤7 days old were recruited from the postnatal ward of the University Hospital Son Espases, Palma de Mallorca. Preterm infants (<37 weeks GA and ≥34 weeks of corrected gestational age [CGA]) were selected shortly before discharge from the neonatal unit. All parents of included infants were planning a flight shortly after discharge. Written informed consent was given by all parents. Ethics approval was granted by the Ethics Committee of Clinical Investigation of the Balearic Islands (IB 1231/09).

The condition for all included infants was a baseline SpO2 of >94%. Exclusion criteria were respiratory infection ≥1 week before testing, current oxygen requirement, and cardiac, respiratory (other than BPD), or metabolic disease. Birth history and all clinical data were obtained from patient reports.

The infants were divided in 3 groups: Group 1, term infants; Group 2, premature infants without BPD; and Group 3, premature infants with BPD. BPD was evaluated at 36 weeks CGA and was defined as the need for supplemental oxygen for ≥28 days, per National Institute of Child Health and Human Development criteria.12

Fitness-to-fly testing was performed according to the testing protocol in the Pediatric Pulmonary Function Testing Laboratory, Pediatric Respiratory Unit, University Hospital of Son Espases, from September 2010 to May 2013.

The HCT was performed with the infant on the caregiver’s lap sitting inside a sealed body plethysmograph (MasterScreen Body, Erich Jaeger). To test all infants in the same conditions, the infants needed to remain awake and in a half-seated position without flexing the neck and without being fed.

SpO2 and pulse rate of the newborns were measured continuously with a Masimo SET Radical-7 Electron pulse oximeter attached to the infant’s hand or foot. Readings were taken after a stable plateau was reached, and baseline SpO2 and pulse rate in room air were recorded. Nitrogen was added into the chamber with a flow of ~50 L/min, gradually reducing the FIO2 to a concentration of 15% (O2 concentration was measured by MiniOx3000, Medical Products). FIO2, SpO2, and pulse rate were continuously observed for 20 minutes, at which point timing and any changes were also noted. If SpO2 dropped to <85%, oxygen was administered immediately in a nasal cannula until the baseline SpO2 was reached. The minimum amount of supplemental oxygen given was recorded. An SpO2 of <85% was counted as a test fail, and the newborn was deemed not fit to fly.

If the newborns failed the HCT it was recommended supplemental oxygen be given on board flights, as outlined in BTS guidelines.13,14 Parents were then requested to repeat the test every 2 months until obtaining fit-to-fly status. For families living on the
surrounding islands, a ferry trip home was recommended in all cases.

After a power calculation, we simulated the recruitment of \( \geq 54 \) patients in the study with 18 patients in each of the 3 groups. Descriptive analysis was performed calculating median and quartiles, or mean and 95% confidence interval (CI) if variables were normally distributed. To contrast the hypothesis, the test of Mann–Whitney and Kruskal–Wallis, or Student \( t \) test and analysis of variance, were used. To describe qualitative variables, proportions and 95% CI were calculated. An exploratory analysis using binary logistic regression was used to calculate the adjusted effect over desaturation as a dependent variable of several independent variables. Odds ratios (ORs) are presented with 95% CIs and used for variables with significant association. All statistical tests were 2-tailed, and for differences between groups, a Bonferroni-corrected \( P \) value < .016 was considered significant. IBM Statistics SPSS 20.0 software was used.

### RESULTS

#### Demographics

From September 2009 to May 2013, 109 infants were tested: 24 term, 62 preterm without BPD, and 23 preterm with BPD. All term infants were healthy and had uneventful deliveries. Complications suffered by preterm infants during their hospital stay were resolved by the time of testing. Demographic and clinical data for all newborns are listed in Table 1.

### Test Results, Predictors of Test Failure, and Comparison Between Groups

One 5-day-old healthy term infant (38 weeks, 1 day GA) failed the test (1 of 24, 4.2%). \( \text{SpO}_2 \) dropped to 82% preterm with BPD. All term infants were healthy and had uneventful deliveries. Complications suffered by preterm infants during their hospital stay were resolved by the time of testing. Demographic and clinical data for all newborns are listed in Table 1.

#### Table 1 Demographic and Clinical Data of the Tested Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1, Term</th>
<th>Group 2, Preterm Without BPD</th>
<th>Group 3, Preterm With BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean GA, wks(^a)</td>
<td>39.6 (39.1–40)</td>
<td>32.5 (31.9–33)</td>
<td>28.2 (27–29.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (50)</td>
<td>36 (58)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>Mean birth weight, kg(^b)</td>
<td>3.3 (3.3–3.4)</td>
<td>1.8 (1.7–1.9)</td>
<td>0.9 (0.8–1)</td>
</tr>
<tr>
<td>Mean age, ( \text{d} )</td>
<td>3 (3–3.8)</td>
<td>27 (14.5–46.5)</td>
<td>78 (64.4–102.3)</td>
</tr>
<tr>
<td>Mean corrected age, wks(^a)</td>
<td>40 (39.6–40.5)</td>
<td>37 (36.5–37.6)</td>
<td>39.5 (38.1–40.9)</td>
</tr>
<tr>
<td>Days of oxygen therapy(^b)</td>
<td>—</td>
<td>1 (0–4)</td>
<td>47 (44–73)</td>
</tr>
<tr>
<td>Days of mechanical ventilation(^b)</td>
<td>—</td>
<td>2 (1–5)</td>
<td>8 (1–11)</td>
</tr>
<tr>
<td>Days of CPAP(^b)</td>
<td>—</td>
<td>0 (0–2)</td>
<td>12 (2–26)</td>
</tr>
<tr>
<td>Days without oxygen therapy(^b)</td>
<td>—</td>
<td>25 (12.3–42)</td>
<td>18 (13–36)</td>
</tr>
</tbody>
</table>

Data are \( \text{a} \) mean (95% CI) or \( \text{b} \) median (interquartile range).

#### Table 2 Test Results and Comparison of Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1, Term</th>
<th>Group 2, Preterm Without BPD</th>
<th>Group 3, Preterm With BPD</th>
<th>( P ) Group 1 vs 2</th>
<th>( P ) Group 1 vs 3</th>
<th>( P ) Group 2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ( \text{SpO}_2 ), %</td>
<td>99 (97–100)</td>
<td>98 (98–100)</td>
<td>99 (96.5–99.5)</td>
<td>NS</td>
<td>NS</td>
<td>.015</td>
</tr>
<tr>
<td>Change in ( \text{SpO}_2 )</td>
<td>9 (8–11)</td>
<td>8 (6–12)</td>
<td>16 (10–18)</td>
<td>NS</td>
<td>.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time to reach lowest test ( \text{SpO}_2 ), min</td>
<td>10 (10–15)</td>
<td>15 (10–18)</td>
<td>8 (5–12)</td>
<td>NS</td>
<td>NS</td>
<td>.003</td>
</tr>
<tr>
<td>Lowest test ( \text{SpO}_2 ), %</td>
<td>89 (88–90)</td>
<td>91 (87–94)</td>
<td>81 (80–88)</td>
<td>NS</td>
<td>.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time until failing test, min</td>
<td>20(^a)</td>
<td>10 (8–12)</td>
<td>8 (5–9)</td>
<td>—</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline pulse rate, beats per min</td>
<td>138 (121–153)</td>
<td>159 (147–170)</td>
<td>158 (138–70)</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Highest test pulse rate, beats per min</td>
<td>152 (141–162)</td>
<td>169 (160–178)</td>
<td>163 (157–177)</td>
<td>NS</td>
<td>NS</td>
<td>.015</td>
</tr>
<tr>
<td>Pulse rate during desaturation, beats per min</td>
<td>127</td>
<td>148 (143–163)</td>
<td>158 (144–177)</td>
<td>—</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Test failure ( \text{SpO}_2 ) &lt;85%, n (%)</td>
<td>1 (4.2)</td>
<td>12 (19.4)</td>
<td>16 (69.6)</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( \text{SpO}_2 ) &lt;80% during test, n (%)</td>
<td>12 (50)</td>
<td>21 (33.9)</td>
<td>19 (82.6)</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are median (interquartile range). NS, not significant.

\(^{a}\) Only 1 term infant failed the test.
As mentioned above, a significant difference was observed between preterm infants with BPD and neonates without BPD. There was a significant drop in SpO2 ($P = .001$) during the test comparing infants who were term or preterm without BPD (median change $-9$ and $-8$, respectively) versus preterm with BPD (median change $-16$).

Minimum SpO2 during the test was significantly lower in infants with BPD (median $81\%$, interquartile range $80\%–88\%$, $P < .001$) compared with the other 2 groups. The BPD infants reached the minimum SpO2 earlier (8 minutes, $P = .003$) than preterm infants without BPD (15 min).

The 16 BPD patients who failed the test needed 0.5 to 1 L/min of oxygen to recover, and the 12 preterm infants without BPD needed 0.5 to 2 L/min (only 2 children needed 2 L/min). Twelve of the infants had mild BPD, 9 moderate BPD, and 2 severe BPD. Unexpectedly, time without supplementary O2 was not a significant factor in passing the test (Table 1).

The term infant who failed the HCT did not repeat the test 2 months later as advised. Only 2 of the preterm infants without BPD repeated the test, at 5 and 6 months CGA; both passed the second time.

Seven of 16 preterm infants with BPD repeated the test. Of these, 3 at 2 months and 2 at 6 months CGA passed. One child with BPD was retested at 6 months CGA and failed again. Another preterm infant with BPD born at 23 weeks GA was first tested at 42 weeks CGA and was retested at 7 and 17 months CGA, but failed all HCTs.

**DISCUSSION**

SpO2 declines $\sim 4\%$ in healthy children and adults while in flight.$^{12}$ Term and preterm infants without BPD in our study had an important drop in SpO2 during the preflight test ($9\%$ and $8\%$, respectively). Interestingly, we found that all neonates $>39$ weeks CGA and those without BPD passed the test.

Similar results to these were found in previous studies conducted on older infants, as in the studies of Bossley et al,$^7$ who tested term and preterm infants of 3 and 6 months CGA, and Martin et al,$^15$ who tested healthy term infants (13–221 weeks old) and found that only 1 of 24 healthy children desaturated.

Our data are not in accordance with the results of Udomitipong et al,$^16$ who found that a high proportion (38 of 47) of preterm infants with a median corrected age of 1.4 months are at a high risk of in-flight hypoxia.

The discrepancy in results with Udomitipong et al may be due to the different test methods used. We used a whole-body plethysmograph during the test, which is recommended in the BTS guidelines. Udomitipong et al$^16$ and other studies on infants of a similar age used high-flow (15 L/min) 14% oxygen in nitrogen via a non-rebreathing facemask incorporating a 1-valve assembly. This method may not be reliable when used with infants, as has been suggested by other authors.$^{15}$

Neonates $>39$ weeks CGA without BPD who reach term age have a test behavior similar to that of older infants, so the necessity for an HCT could be eliminated for this group. In-flight oxygen may not be necessary either.

BPD was highly associated with test failure, with an OR of 17.2. Infants with BPD also suffered a median drop in SpO2 of $\sim 16\%$ ($P = .001$), and 69.6% of BPD infants failed the HCT and thus were deemed unfit to fly. In 2004, Buchdahl et al$^{17}$ performed a retrospective review of test results in infants with BPD and discovered that 8 of 20 patients desaturated during...
the HCT, whereas Udomittipong et al in 2006 found that 23 of 32 preterm infants with BPD failed the HCT.

The improvement of failure rates in our study observed in term and preterm infants without BPD when they reached >39 weeks CGA was not evident among the infants with BPD (Fig 2). It has to be mentioned that infants with BPD had a considerably lower GA (28.2 vs 32.5 weeks); thus extreme prematurity might have an influence on the test result.

The strengths of this study include the relatively large number of patients tested and their young age; infants so young have not been tested before. Also, the infants were tested in a body plethysmograph, the recommended method in the BTS guidelines. Limitations include the time of testing and the conditions of testing (awake without feeding), and that accuracy of HCT results was not confirmed by comparison with actual inflight SpO₂ in the tested infants.

It is possible that the testing time of 20 minutes may not be long enough and thus not generate sufficient data to predict safety limits for long-distance flights, as SpO₂ usually decreases in proportion to the duration of hypoxemia. Most of our test patients who failed desaturated in 8 to 10 minutes; however, the only term child who failed did not drop to <85% until the end of the testing period.

The HCT was carried out with the infant awake without feeding and without decubitus position. The authors are aware that all those factors and others (duration of the test, humidity, infections of the upper airways, noise, etc) vary greatly during flight. It is true that active sleep, changes of position (which can influence the obstruction of the upper airway), and feeding may have an impact on oxygen saturation. Therefore, we decided to standardize conditions as much as possible and tried to avoid introducing variables. The BTS guidelines do not establish recommendations in reference to the mentioned conditions even though they can have an important impact on the results. Further studies are needed that analyze similar populations for the significance of sleep or change of body position.

Many studies have proved the HCT to be equivalent to in-flight conditions and hypobaric chamber results in adults and children. Two studies were recently conducted by an Australian group to assess HCT accuracy by using a non-rebreathing mask on infants. They published data of 46 preterm (35.8 weeks) and 24 term infants >2 weeks old, finding false-positive and false-negative HCT results compared with in-flight SpO₂.

The studies that concluded that the HCT is unreliable in infants both used facemasks to do the testing, and this is thought to be a flaw, as false-positive results due to immediate exposure to FIO₂ of 14% or crying or false-negative results due to insufficient sealing of the mask and air room entrainment can be responsible for the discrepancy of test and in-flight results.

In the first study, done on preterm infants, the range of time between HCT and flight was 1 to 15 days. A delay of 2 weeks might change the condition of a premature infant considerably and could explain the differences between the results. In the study done on term infants, the inflight SpO₂ nadir was 5% lower than the HCT nadir. Flight duration may also play a role, as 3 children had SpO₂ both below and above 85% on different flights. Sitting in a sealed chamber in 15% oxygen is presently the best method available for simulation of in-flight conditions.
but further studies are needed to prove the accuracy of the HCT in a plethysmograph in term and preterm infants.

In another recent study from Australia, \( \text{SpO}_2 \) of infants <6 months old was monitored during aircraft transport, and no difference in the incidence of desaturation was found between children <6 and >6 weeks old. This could support our data that young infants are able to fly. The cutoff limit in the study was 94%, which explains the high incidence of desaturations in all age groups (one-third). In 2011, the cutoff limit of the HCT was changed in the BTS guidelines from \( \text{SpO}_2 \geq 90\% \) to 85%,.[14] If it is set to 90%, the probability to fail the test increases in all groups, especially in healthy infants (Table 2).[15,25] An explanation for the high failure rate of term infants in our study if \( \text{SpO}_2 \) is set to <90% in comparison with preterm infants could be the younger chronological age of term infants and a shorter adaptation period to extrauterine life (e.g., higher amount of fetal hemoglobin in term infants). If a temporal \( \text{SpO}_2 \) of 85% to 90% has any negative impact on infants, it is still not clear.[8]

The HCT via body plethysmograph represents a reasonable approximation of the physiologic changes infants undergo in a hypoxic environment and is useful for advising a family about the risk of commercial air travel and the need for oxygen during a flight.

CONCLUSIONS

This study shows that over a period of 20 minutes in a controlled environment with an \( \text{FIO}_2 \) of 15%, \( \text{SpO}_2 \) levels remain within safe limits for healthy term infants >39 weeks CGA and also for preterm infants >39 weeks CGA without BPD. The majority of infants with BPD do not maintain safe levels of \( \text{SpO}_2 \) even in a simulated in-flight environment, and therefore testing at this early age might not be useful. It is recommended to delay the test until the infant is \( \geq 1 \) year old.

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia

BTS: British Thoracic Society

CGA: corrected gestational age

Cl: confidence interval

\( \text{FiO}_2 \): fraction of inspired oxygen

GA: gestational age

HCT: hypoxia challenge testing

OR: odds ratio

\( \text{SpO}_2 \): pulse oxygen saturation

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