

# Assessment of pulmonary function in resolving chronic lung disease of prematurity

R Iles, A T Edmunds

## Abstract

**Aim**—To investigate the longitudinal changes of interstitial and airways disease in resolving chronic lung disease of prematurity (CLD).

**Methods**—Thirty three infants were studied between 35 and 40 weeks of postconceptional age, and then at three monthly intervals throughout their first year. Measurements of mean arterial oxygen saturation (MSaO<sub>2</sub>) and its variability ( $\delta$ MSaO<sub>2</sub>) were recorded. PaCO<sub>2</sub> and PaO<sub>2</sub> were determined while the infants breathed steady state 50% oxygen via a hood. From these, the alveolar arterial difference (A-a) Do<sub>2</sub><sup>50</sup> was calculated. Airway disease was assessed by the measurement of partial forced expiratory flow volume curves (PEFC) to give  $\dot{V}_{\max}$  Frc.

**Results**—The cohort mean  $\pm$  95% confidence intervals measured between 35 and 40 weeks were for MSaO<sub>2</sub> (89.25  $\pm$  1.87%, range 75-96.5%) and  $\delta$ MSaO<sub>2</sub> (4.79  $\pm$  0.8%, range 0.16-9.64%), PaCO<sub>2</sub> (5.89  $\pm$  0.56 kpa, range 4.2-10.11 kpa), (A-a) Do<sub>2</sub><sup>50</sup> (22.7  $\pm$  2.56 kpa, range 6.67-31.4 kpa) and  $\dot{V}_{\max}$  Frc (41.5  $\pm$  8.65 ml/second, range 8.5-103.7 ml/second). The most significant improvement in all measurements occurred within the first three months (P = 0.05). An MSaO<sub>2</sub> of less than 90% in room air at 1 year of age was predicted between 35 and 40 weeks postconceptional age by an (A-a) Do<sub>2</sub><sup>50</sup> of greater than 29 kpa, with a sensitivity of 0.85 and a specificity of 0.88, and a PaCO<sub>2</sub> greater than 7 kpa predicted a specificity of 0.78 and a sensitivity of 0.88. Predictions were strengthened by combining the above criteria and these then gave a sensitivity and specificity of 1.

**Conclusion**—Measurements of (A-a) Do<sub>2</sub><sup>50</sup> and PaCO<sub>2</sub> taken between 35 and 40 weeks can be used to assess the degree of pulmonary dysfunction at 1 year. Quantification of the severity of CLD could be used as a measurable end point for early neonatal intervention studies.

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Since its first description in 1967,<sup>1</sup> the pathological features of chronic lung disease of prematurity (CLD) have shown abnormalities in both the airways and the interstitium of the lung. Macroscopically, the most severely

affected infants have alternating areas of atelectasis and hyperinflation.<sup>2,3</sup> Microscopically, a necrotising bronchiolitis results in alveolar septal, interlobular, and pleural fibrosis. The pathological severity of both airway and interstitial disease is extremely variable even in the most severely affected infants.<sup>4</sup> In milder disease computed tomography scans and chest x ray pictures also describe variable interstitial involvement.<sup>5,6</sup> The effect of oxygen toxicity and barotrauma on premature lungs have been characterised mainly by the mechanical properties of the lung.<sup>7-9</sup> These tests are invasive and require a high degree of technical expertise to perform and interpret, so are therefore limited to centres with an interest in infant pulmonary function. Histology and radiology suggest that the measurement of shunt is the most logical assessment of lung disease in this group of infants. In a prospective study we quantified the severity of both interstitial and airway disease in a cohort of infants with established CLD and recorded the improvement over the first year.

## Methods

Infants with CLD were recruited from the regional neonatal unit, the Simpson Memorial Maternity Pavilion, Edinburgh. This unit serves a defined geographical area of the Lothian Region of south east Scotland. Forty infants who had been born prematurely were eligible to enter the study when they had required 28 days of continuous supplementary oxygen from birth. The parents of these infants were provided with both verbal and written information at least one month before being asked to give consent for their infants to take part in the study. The parents of four infants did not consent. Three infants were initially transferred from outside the Lothian region. These infants were returned to referring hospitals, so were not included in this prospective study.

The 33 remaining infants were first studied at a mean of 43 weeks (range 35-45 weeks) postconceptional age. They were born between 24 and 31 weeks gestation (median 27 weeks). Birthweight ranged from 589 to 1891 g (median of 900 g). All infants required ventilatory support within the first week of life. This was required for a median of 25 days (range 6-120 days). All infants had an oxygen requirement at 28 days of age and had chest x ray changes consistent with CLD. Thirty had required supplemental oxygen at 36 weeks postconceptional age to maintain an SaO<sub>2</sub> greater than 90%.

Department of Respiratory Paediatrics, The Royal Hospital for Sick Children, Edinburgh

R Iles  
A T Edmunds

Correspondence to:  
Dr R Iles,  
Department of Respiratory Paediatrics,  
Alder Hey Children's Hospital,  
Liverpool  
L12 2AP.

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Measurements of mean arterial saturation ( $MSaO_2$ ), the variability of the mean arterial saturation ( $\delta MSaO_2$ ), arterial blood gases, and pulmonary function were taken at four three monthly time points, until 1 year of age. A complete longitudinal data set was not complete in nine of the 33 infants, because of the failure of sedation and/or sampling methods. However, no infant had more than two absent measurements.

The study was approved by the paediatrics/reproductive medicine research ethics sub-committee of the Lothian research ethics committee.

#### PARTIAL FORCED EXPIRATORY FLOW (PEFC) CURVES

Infants were sedated with 100-150 mg/kg of triclofos sodium one hour before investigation. Rapid inflation of a jacket placed around the sedated, sleeping infant's chest wall applied a "squeeze" to produce a PEFV curve, as described by Clark and Silverman.<sup>10</sup> We used jacket inflation pressures of 10 cm  $H_2O$  to 70 cm  $H_2O$  (rising at increments of 5 cm  $H_2O$ ), five inflations being performed at each pressure. The RASP software package (Physiologic Ltd) was used to collect and analyse the data. The equipment was calibrated before and after each patient session.

Infants were monitored with a pulse oximeter and a transcutaneous  $pO_2$  monitor starting after sedation, continuing throughout the procedure, and being disconnected only when the infants were fully awake.

Visual inspection of the recorded flow gave qualitative information while the measurement of maximum flow at functional residual capacity  $\dot{V}_{max}Frc$  gave a quantitative assessment of flow through the airways. Specific criteria suggested by Clark and Silverman<sup>10</sup> were identified regarding time to peak jacket inflation, jacket inflation lead time, stable end expiratory level, and expiratory reserve volume. We excluded data that did not meet these specific criteria. The maximum value for  $\dot{V}_{max}Frc$  was taken as the reference data.

Partial forced expiratory flow volume curves were obtained from six infants with normal birth histories. These infants were studied only once and aged between 43 and 75 weeks post-conceptual age. Data were expressed relative to length and compared with predicted values calculated and published by Tager.<sup>11</sup>

#### MEASUREMENT OF (A-a) $DO_2^{50}$ AND $PaCO_2$

Measurements of alveolar arterial difference were taken one hour after measuring partial forced expiratory flow volume curves. Lignocaine hydrochloride 2.5%, prilocaine 2.5% cream (Emla, Astra) was placed on the left wrist. The infants were placed in a hood extending over their head and neck. A steady state oxygen concentration of 50% was achieved by a constant oxygen flow. Oxygen concentration was measured using an Ohmeda Ohio 5100A oxygen analyser, and transcutaneous oxygen was measured using a Kontron Minimom 7135. When values for both transcutaneous oxygen and hood oxygen concentra-

tion had reached steady state for 20 minutes, arterial blood was drawn to a syringe containing heparin, and immediately analysed using an IL128 blood gas analyser. If a child roused to cry during the arterial puncture, the blood was discarded. A further attempt was made only if the child returned to sleep. No injury occurred to the radial artery from repeated arterial sampling. No child showed a decompensated respiratory acidosis. The alveolar difference (measured in kpa) was calculated using the equation:

$$(A-a)DO_2 = FiO_2 (PB - 6.7) - PaCO_2 - (PaCO_2/RQ) - PaO_2$$

Barometric pressure was recorded before each investigation. The respiratory quotient for the cohort was determined from assessment of dietary intake and age and ranged from 0.88 to 0.94.<sup>12-14</sup> The haemoglobin concentration for each child was assumed to be greater than 80 g/l.

The expected value for  $(A-a)DO_2^{50}$  was calculated using normal blood gas data and predicted  $PaO_2$  estimating a 10% shunt.  $PaCO_2$  was referenced to normal data.<sup>15</sup>

#### MONITORING OF ARTERIAL OXYGEN SATURATION

All monitoring was done on inpatients. Real time values of heart rate were taken from the analogue port of a Kontron Minimom 7135 or the serial port of a Hewlett Packard 78834A monitor. Real time values for heart rate and oxygen saturation were taken from the serial output of an Ohmeda Biox 3700 pulse oximeter. Infants were monitored for at least six continuous hours overnight. The pulse oximeter probe was attached initially on the lateral aspect of the foot, but moved to the lateral aspect of the hand if a poor signal was obtained. The probe was fixed with adhesive spots as supplied by Ohmeda and was then wrapped lightly with a coban tape bandage. Data were collected, stored in real time, and analysed using the MARY patient monitoring system (Meadowbank Medical Systems Ltd).<sup>16, 17</sup> Input data were collected and stored at a rate of 1 Hz. The mean value for each minute was used as the analysed data point. Verification of the use of the mean value for each minute was made by separate analysis of two one hour periods of collected data on each patient, using that collected at 1 Hz.

We excluded artefacts resulting from movement or probe disconnection initially by looking at the trace, and then these were re-analysed more specifically by comparing the heart rates obtained from the Hewlett Packard heart rate monitor and the Ohmeda pulse oximeter. Where there was more than a 5% difference, the  $SaO_2$  data were discarded as having been influenced by artefact.

Analysis of data collected over at least a 6 hour period, following the exclusion of artefact, provided the mean arterial oxygen saturation ( $MSaO_2$ ) and the variability of the mean arterial oxygen saturation ( $\delta MSaO_2$ ) for each infant.

Oxygen was discontinued, in infants receiving it continuously, to obtain steady state values for  $SaO_2$  while breathing air. This was done with informed parental consent when the

infant was asleep, or settled after feeding. The infants were monitored with electrocardiography and pulse oximetry. Oxygen was restarted if the infant's arterial oxygen saturation was constantly below 90% in air. For these infants, values for  $MSaO_2$  and  $\delta MSaO_2$  were obtained from the time that the infants were breathing air alone. In three infants oxygen saturation fell rapidly below 80% in air. Oxygen was restarted immediately after the lowest spot value of  $SaO_2$  had been recorded. This was taken as the  $MSaO_2$  for the infant in subsequent analysis. No value for  $\delta MSaO_2$  was recorded in these infants. Oxygen flow was then titrated to give  $SaO_2$  values of 92-93%. Infants were closely monitored throughout this procedure. No infant became bradycardic or apnoeic. Data were compared with published normal data.<sup>18</sup>

#### STATISTICAL ANALYSIS

Changes in the longitudinal cohort data for each parameter were compared using the unpaired *t* test with Bonferroni's correction. Linear correlation was used to compare measurements of  $(A-a) Do_2^{50}$  and  $PaCO_2$ ,  $MSaO_2$  and  $\dot{V}_{max}Frc$  for each study time. Longitudinal changes in  $\dot{V}_{max}Frc$  were analysed using a linear mixed effects model, PROC MIXED of SAS (SAS institute, NC, USA) in which the intercept and length of the infant were treated as random effects to reflect individual differences in patterns of growth. Initial models were constructed to include sex, length, and length-squared. Sex was not significant, and the model was therefore constructed to include only length and length squared.

#### Results

At the time of first study, six infants required supplementary oxygen to maintain arterial oxygen saturation above 90%. Only three infants required supplementary oxygen throughout the year, all of whom had evidence of right ventricular hypertrophy on electrocardiogram and all of whom had raised carbon dioxide tensions on arterial blood gases for the first three months. These became normal with time. All other infants had normal electrocardiograms and capillary blood gases at the time of study.

Twenty of the 40 infants (50%) were readmitted to hospital. Five of the six (83%) infants who received oxygen, and 15 of the 34 (44%) of those that did not, were readmitted. On hospital admission, 11 of the infants had confirmed respiratory syncytial virus infection, one parainfluenza, and one rhinovirus infection. Eight infants were admitted with a clinical history of an acute life threatening event. Infection was not confirmed in these infants.

One infant died unexpectedly. The post mortem examination was performed by a paediatric pathologist who was aware of the child's neonatal history. The cause of death was cited as sudden infant death syndrome. The changes in CLD were noted to be minimal and felt to be an insignificant factor in the child's death. This child did not require supplementary oxygen at the time of death.

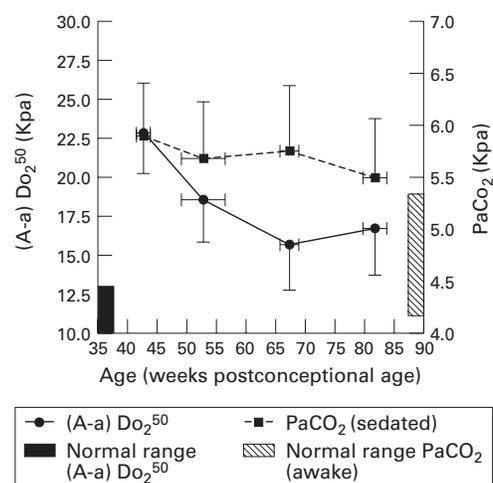


Figure 1 Longitudinal changes in  $(A-a) Do_2^{50}$  and  $PaCO_2$  (group means and confidence interval).

There was no linear correlation between measurements of  $(A-a) Do_2^{50}$  and  $PaCO_2$ ,  $MSaO_2$  and  $\dot{V}_{max}Frc$  taken at each study time. Notably, infants with high  $(A-a) Do_2^{50}$  did not necessarily have high values for  $PaCO_2$ . However, individual infants were consistent in their disease pattern throughout the study period. Ten infants had a  $PaCO_2$  greater than 7 kpa. The longitudinal changes for  $(A-a) Do_2^{50}$  and  $PaCO_2$  are shown in fig 1.

For  $(A-a) Do_2^{50}$ , neither the mean nor 95% CI fell within the normal range. For  $PaCO_2$ , the lower 95% CI fell within the normal range by 50-55 weeks postconceptional age, while the mean remained outside the normal range throughout the year.

The longitudinal change for  $\dot{V}_{max}Frc$  is shown in fig 2. Predicted data<sup>11</sup> were plotted using the equation:

$$\dot{V}_{max}Frc = -36.99 + 0.5 * length + 0.056 * length^2 - 15.6 \text{ (mean adjusted for sex).}$$

The longitudinal change for infants with CLD was plotted from the equation:

$$\dot{V}_{max}Frc = 264 - 9.3 * length + 0.09 * length^2$$

Both equations were modelled using PROC MIXED SAS. The mean values for the cohort of infants with CLD were all less than 50% of the predicted data. The difference in the slope of the data for the infants with CLD suggests that the rate improvement in pulmonary function expected by disease resolution and lung growth is well below that seen in normal lung growth.

The data for  $MSaO_2$  and  $\delta MSaO_2$  (fig 3) became normal by 65-77 and 50-55 weeks. An  $MSaO_2$  of less than 90% in room air at 1 year of age was predicted between 35 and 40 weeks by an  $(A-a) Do_2^{50}$  of greater than 29 kpa, with a sensitivity 0.85, a specificity of 0.88, and a  $PaCO_2$  greater than 7 kpa was predicted with a specificity 0.78 and a sensitivity of 0.88. Prediction was strengthened by including both an  $(A-a) Do_2^{50}$  greater than 29 kpa or a  $PaCO_2$  greater than 7 kpa, to give a sensitivity and specificity of 1.

#### Discussion

$(A-a) Do_2^{50}$  and  $PaCO_2$ ,  $MSaO_2$  and  $\dot{V}_{max}Frc$ , are numerical measurements of intrapulmo-

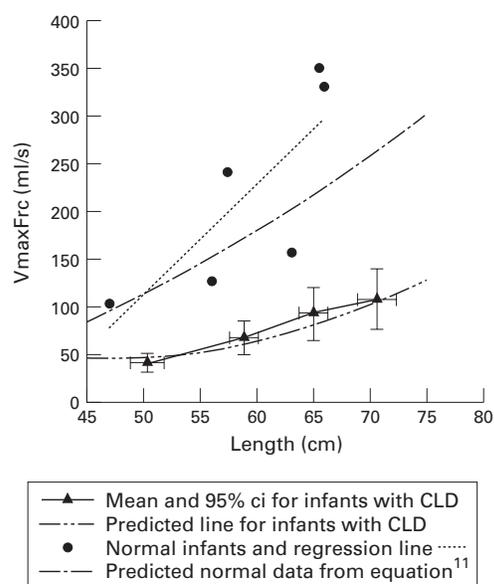


Figure 2 Longitudinal changes in  $\dot{V}_{\max}\text{Frc}$ .

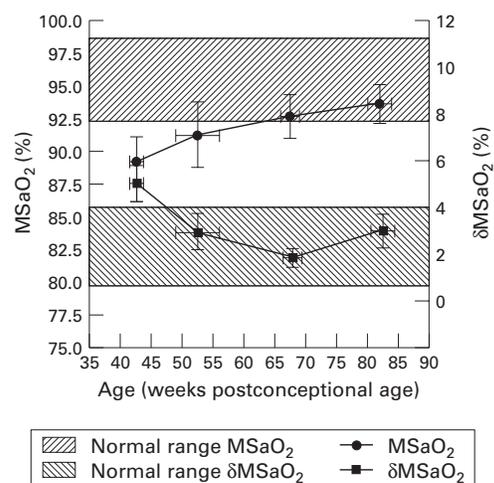


Figure 3 Longitudinal changes in  $\text{MSaO}_2$  and  $\delta\text{MSaO}_2$  (cohort means and 95% confidence intervals).

nary shunt, alveolar ventilation, arterial haemoglobin oxygen saturation and flow through small airways. They are all directly influenced by lung volume. In a cohort of infants with mild to severe disease we have shown that measurements of  $\text{PaCO}_2$  and  $\text{MSaO}_2$  may become normal within the first year of life. The longitudinal changes in pulmonary mechanics in CLD have been well described,<sup>7 19–21</sup> with residual lung disease detectable in children aged 7 to 10 years<sup>22</sup> and even into the third decade.<sup>23</sup> Interpretation of the severity of CLD depends on the chosen method of measurement.  $(\text{A-a})\text{Do}_2^{50}$  and  $\dot{V}_{\max}\text{Frc}$  provide a more sensitive index of resolving lung function than  $\text{PaCO}_2$  and  $\text{MSaO}_2$ .

We found no linear correlation between measurements of  $(\text{A-a})\text{Do}_2^{50}$  and  $\text{PaCO}_2$ , taken at any study time. This agrees with pathological findings which show that even in the most severely affected infants the severity of both airway and interstitial disease is extremely variable.<sup>4</sup>

The  $\dot{V}_{\max}\text{Frc}$  for the cohort was below the 95 CI for the normal predicted range during the first year. As  $\dot{V}_{\max}\text{Frc}$  is closely related to body length we standardised our results against length. Lack of acceleration of the slope of the line formed by data from the CLD cohort suggested that catchup growth and/or disease resolution did not occur in the first year.

There is good evidence that infants with CLD have poorly developed alveoli, with a reduction in total numbers and consequent loss of alveolar surface area.<sup>3 24 25</sup> Areas of collapsed lung represent a significant loss of alveolar numbers. The use of  $\text{Frc}$  is a floating reference point, and may lead to erroneous data when there is severe airway obstruction. It has been suggested that lung volume should be measured concurrently.<sup>26</sup> Volume estimation using gas based techniques measure the accessible volume of gas in the lungs and underestimate lung volume in airway obstruction (the desired variable to be measured by  $\dot{V}_{\max}\text{Frc}$ ). Plethysmographic methods include all of the intrathoracic gas volume. Both methods require a sedated infant, highly specialised equipment, and trained staff. Measurement of lung volume by helium dilution was attempted in a number of infants from the cohort. Gas equilibration time was in excess of 7 minutes. The total study time available from one dose of sedative limited the collection of PEFC data. The measurement of lung volume was therefore discontinued.

Intrapulmonary shunt and  $\dot{V}/\dot{Q}$  mismatch are the major contributors to  $(\text{A-a})\text{Do}_2^{50}$ . Failure of the diffusion equilibrium of alveolar oxygen with capillary blood is common in CLD.<sup>19</sup> The calculation of  $(\text{A-a})\text{Do}_2^{50}$  as a measure of shunt and  $\dot{V}/\dot{Q}$  mismatch has the theoretical disadvantage that it is influenced by the inspired  $\text{PO}_2$ . A given degree of shunt or  $\dot{V}/\dot{Q}$  mismatch will produce a higher calculated  $(\text{A-a})\text{Do}_2^{50}$  as the  $\text{PiO}_2$  is increased.  $\text{PaO}_2$  measurements were only taken at a steady state  $\text{FiO}_2$  of 50%.

The use of 50%  $\text{PiO}_2$  in the less severely affected infants gave a  $\text{PaO}_2$  within linear range of the II128 blood gas analyzer. A  $\text{PiO}_2$  of 80% or 100% gave values outside this range. A  $\text{PiO}_2$  of 100% may also increase the intrapulmonary shunt. Alveolar collapse of a respiratory unit with a sufficiently low  $\dot{V}/\dot{Q}$  can occur when breathing pure oxygen, as oxygen uptake by pulmonary capillary blood exceeds that delivered by alveolar ventilation. When a gas with a lower  $\text{PiO}_2$  is breathed, the insolubility of nitrogen helps to stabilise these units, preventing their collapse. A  $\text{PiO}_2$  of 50% also allowed measurements to be made safely in oxygen dependent infants.

A high degree of variability of  $\text{MSaO}_2$  ( $\delta\text{MSaO}_2$ ) is associated with an increased incidence of an acute life threatening event.<sup>27</sup> Our data suggest that the degree of variability decreases after 50 weeks postconceptional age and therefore matches the clinical observation that infants of this age and older have less risk of this. The cause of the variability in infants with CLD has been suggested to be due to the sensitivity of infants to hypoxia.<sup>28</sup>

The pathological description of CLD describes both disease of the airways and interstitium. We have recorded the physiological improvement in both these modalities and have shown that (A-a)  $\text{Do}_2^{50}$  and  $\text{PaCO}_2$  predict long term disease severity. Quantification of CLD by this method may provide helpful information to clinicians and could be used as a measurable end point for early neonatal intervention studies.

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