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# Prediction of extubation failure in preterm neonates

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**Abstract** The aim of this study was to compare the results of lung function measurements made before and after extubation and ventilator settings recorded immediately prior to extubation with regard to their ability to predict extubation success in mechanically ventilated, prematurely born infants. Immediately after extubation all infants were nursed in an appropriate amount of humidified oxygen bled into a headbox. Functional residual capacity, spontaneous tidal volume and compliance of the respiratory system were measured both within 4 h before and within 24 h after extubation. The peak inspiratory pressure and inspired oxygen concentration immediately prior to extubation were recorded. The results were related to extubation failure: requirement for continuous positive airways pressure or re-ventilation within 48 h of extubation. A total of 30 infants, median gestational age 29 weeks (range 25–33 weeks) were studied at a median postnatal age of 3 days (range 1–6 days). Extubation failed in ten infants, who differed significantly from the rest of the cohort with regard to their post extubation functional residual capacity (FRC) (median 23, range 15.6–28.7 ml/kg versus 28.6, range 18.1–39.2 ml/kg, $P < 0.01$) and their requirement for a higher inspired oxygen concentration post extubation (median 0.30, range 0.21–0.40 versus 0.22, range 0.21–0.36, $P < 0.05$). An FRC of less than 26 ml/kg post extubation had the highest positive predictive value in predicting extubation failure.

**Conclusion** A low lung volume performed best in predicting extubation failure when compared to the results of other lung function measurements and commonly used 'clinical' indices, i.e. ventilator settings. A low gestational age, however, was a better predictor of extubation failure than a low lung volume.

**Key words** Extubation · Lung volume · Compliance of the respiratory system · Prematurity

**Abbreviations** *CRS* compliance of the respiratory system · $FiO_2$ fraction of inspired oxygen concentration · *FRC* functional residual capacity · *PIP* peak inspiratory pressure

## Introduction

Approximately 33% of premature neonates fail extubation [6, 12], that is they subsequently require extra respiratory support in the form of CPAP or reventilation. We have previously demonstrated that extubation failure can be predicted by a very low lung volume post extubation [10]. That finding, however, is of limited usefulness as, of course, the infant is already extubated. Ideally, infants likely to fail extubation should be identified prior to removing the endotracheal tube and that manoeuvre then delayed to a more appropriate time.

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The aim of this study was, therefore, to determine whether the results of lung function measurements prior to extubation could be used to accurately predict extubation success. In addition, we compared their performance with that of the results of the same tests performed post extubation and routinely used clinical indices, that is the level of fraction of inspired oxygen ($FiO_2$) and peak inspiratory pressure (PIP) assessed immediately prior to extubation.

## Patients and methods

Premature infants of birth weight ≤1500 g and <1 week of age receiving mechanical ventilation were studied if they were deemed by the clinician in charge to be ready to be extubated. All infants followed the routine weaning policy. At a ventilator rate of 40 breaths/min, infants were started on caffeine (a loading dose of 10 mg/kg and then maintenance of 4 mg/kg per 24 h) and changed to patient triggered ventilation. The inspiratory time (0.3–0.4 s) remained constant throughout the weaning process. The PIP was reduced as blood gas results permitted. Infants were considered ready to be extubated once their peak pressure was ≤14 cm $H_2O$ and $FiO_2$ usually ≤0.40, the decision was made by the clinical team who were unaware of the results of the lung function tests. The infant was then transferred to endotracheal CPAP for 1 h. If a respiratory acidosis (pH < 7.25 with a raised $PaCO_2$ and base excess < −5) did not develop, the infant was extubated into a headbox containing an appropriate concentration of humidified oxygen to maintain a satisfactory arterial oxygen saturation. Following extubation, blood gases were checked at least 4 hourly, but more frequently if indicated by changes in the continuous respiratory, heart rate and oxygen saturation monitoring. Extubation was deemed to have failed if the infant required nasal CPAP or reventilation within 48 h of extubation [10]. Nasal prong CPAP was instituted by the clinical team according to the routine policy that is, if a respiratory acidosis or recurrent minor apnoeas developed. Infants were re-intubated if they had a major apnoea, developed a severe respiratory acidosis (pH < 7.20) or failed to improve despite instituting CPAP.

Lung function measurements were made as part of a clinical trial assessing the effect of fluid balance on chronic lung disease development. Routine assessment of lung function in the neonatal intensive care unit has been approved by the King's College Hospital Ethics Committee and parents gave informed written consent for their infant to take part in the "fluid trial". Infants were included in this study if they had lung function measurements within 4 h before and within 24 h after extubation. The clinicians were blinded to the results of the lung function measurements. Lung volume was assessed by measurement of functional residual capacity (FRC) using a helium gas dilution technique and a specially designed infant circuit with a volume of 95 ml. The FRC system contained a rebreathing bag (Ferraris Medical Inc), the system reservoir enclosed in an airtight cylinder. A non-intubated infant breathed through a face mask and this was connected to a rebreathing bag via a three-way valve. The three-way valve has a deadspace of 3.7 ml. The endotracheal tube of a ventilated infant was connected to the rebreathing bag via the three-way valve and the ventilator to a side port of the cylinder. The infant could be ventilated directly or, once the position of the three-way valve was changed, breathe from the rebreathing bag whilst receiving positive pressure support by changes in pressure within the cylinder resulting in compression of the rebreathing bag. After calibration of the FRC system, the circuit was filled with a mixture of 10% helium and 90% oxygen. The rebreathing bag was emptied and then filled with a volume equal to 30% of the predicted FRC (predicted FRC ≡ 25 ml/kg). After 30 s, the helium concentration was recorded and an additional volume of oxygen was added as per the manufacturer's instructions (that is an amount equal to 0.15 × predicted FRC + 10 ml). After 45 s the new helium concentration was recorded [13, 21, 23]. The infant was then connected to the circuit. The FRC system contained a helium analyser (Equilibrated Biosystems Inc, Series 7700, Melville, N.Y.) with a digital display. The latter was recorded prior to and at 15 s intervals during the measurement. Equilibration was assumed when there was no change in the helium concentration over a 30 s interval. The initial and equilibration helium concentrations were used in the calculation of FRC. FRC results were corrected for oxygen consumption, assumed to be 7 ml/kg per min [18] and the results then corrected to body temperature under pressure saturated conditions. FRC was estimated twice in each infant, with an interval of 10 min between measurements. Only recordings during quiet breathing were considered, if the infant sighed or cried then that measurement was repeated. The FRC was expressed as the mean of the paired measurements and related to body weight. The coefficient of repeatability of FRC measurements in ventilated and non-ventilated infants is 5.7 ml/kg [8] and 3.9 ml/kg [10] respectively.

Spontaneous tidal volume was measured using a pneumotachograph. In non ventilated infants a pneumotachograph (Mercury F10L) was inserted into a facemask which was placed over the infant's nose and mouth. In ventilated infants, a pneumotachograph was inserted into the endotracheal tube and tidal volume was measured during a temporary disconnection from the ventilator. The pneumotachograph was attached to a Validyne pressure transducer (range ± 2 $cmH_2O$). The flow signal from the pneumotachograph was integrated to give volume (Gould 13–4615–70). Airway pressure was measured from the infant's side of the pneumotachograph using a Validyne pressure transducer (± 50 $cmH_2O$). Tidal volume was calculated as the mean of ten regular breaths and related to body weight. Compliance of the respiratory system (CRS) was measured by the occlusion technique. Manual airway occlusion was performed at end inspiration which resulted in the Hering-Breuer reflex, provoking a temporary apnoea, indicated by a plateau in the airway pressure trace of at least 0.3 s in duration [17]. The mean plateau duration was 0.34 (SD ± 0.037). CRS was calculated from the inspiratory volume immediately prior to the occlusion divided by the height of the airway pressure plateau during the occlusion. The results of CRS from ten occlusions were meaned and CRS then related to body weight. The coefficient of repeatability of CRS is 0.08 $ml/cmH_2O$. In a previous study we have shown a good correlation between CRS measured using this technique and by relating the volume delivered to a positive pressure inflation maintained until there was no further volume delivery to the measured pressure change ($r = 0.8$, $P < 0.0001$, unpublished data).

### Analysis

Differences between infants in whom extubation failed or succeeded were assessed for statistical significance using either the Mann-Whitney-U test or Chi Square test as appropriate. The sensitivity, specificity and positive predictive value of the medians of the whole study group of FRC, tidal volume, CRS, $FiO_2$ and PIP prior to extubation and FRC, tidal volume, and CRS post extubation in predicting extubating failure were calculated. In addition, the predictive value of a tidal volume <4 ml/kg [19, 25] pre and post extubation was calculated. This tidal volume is 66% of that achieved by a spontaneously breathing, asymptomatic prematurely born infant [9]. Receiver operating characteristic plots were then constructed [1] and the area under each curve so generated was calculated [16] to compare the performance of the lung function test results to gestational age.

### Trial size

An extubation failure rate of 33% was assumed from previous data [6, 12]. A trial size of 30 patients allowed us to detect with 80% power at the 5% level a difference in FRC of 8 ml/kg between infants in whom extubation failed or succeeded.

Patients

The 30 infants had respiratory distress syndrome or respiratory distress related to severe prematurity [7] and a median gestational age of 29 weeks (range 25–33 weeks), a birth weight of 1097 g (range 744–1500 g) and postnatal age of 3 days (range 1–6 days). Their median maximum PIP was 18 $cmH_2O$ (range 14–29) and $FiO_2$ was 0.45 (0.21 − 0.98). The infants all received a PEEP level of 3 $cmH_2O$ which remained unchanged during the weaning process and immediately prior to extubation. No infant had had an intracerebral haemorrhage or pneumothorax. Only two infants developed a patient ductus arteriosus at 48 and 72 h post extubation respectively, both were in the failure group.

## Results

Ten infants failed extubation (Table 1) at a median of 7 h (range 3–36 h) post extubation. The two infants who developed patent ductus arteriosus were in the failed extubation group. The infants who failed extubation required significantly longer in supplementary oxygen than those in whom extubation was successful ($P <$ 0.02). One infant in each group died, five of the failure group were oxygen dependent at 28 days and six of the successful group (non significant). Seven infants required CPAP for an increasing inspired oxygen concentration requirement and recurrent minor apnoeas. Three infants required re-intubation as they developed recurrent apnoeas, bradycardias and severe respiratory acidosis. The only statistically significant differences between infants who failed extubation compared to those in whom extubation succeeded was that the former group were more immature ($P < 0.01$), required a higher maximum PIP ($P < 0.05$) and a longer total duration of ventilation ($P < 0.01$). They also had a lower post extubation FRC ($P < 0.01$), and required a higher post extubation $FiO_2$ ($P < 0.05$) (Table 1). A low FRC post extubation was the most sensitive predictor of extubation failure (Table 2).

As a significant difference in gestational age was found between those in whom extubation failed or succeeded, the predictive ability of a low gestational age (<30 weeks) was also calculated: sensitivity (90%), specificity (50%) and positive predictive value (47%). In addition we compared the respective FRCs of immature infants (<30 weeks) in whom extubation succeeded or failed, pre-extubation (not significant) and post extubation (median 30.7 ml/kg, range 18.2–39.2 versus median 22.3 ml/kg, range 15.6–28.7, $P < 0.01$). Pre-extubation, gestational age performed better as a predictor of failure than lung function results (Fig. 1); post extubation, however, gestational age (area under the curve 0.89) and FRC (area under the curve 0.81) results performed similarly (Fig. 2).

**Table 2** Prediction of non-successful extubation

| | Sensitivity (%) | Specificity (%) | Positive predictive value (%) |
|---|---|---|---|
| Pre-extubation | | | |
| FRC < 26 ml/kg | 60 | 50 | 38 |
| Tidal volume < 5.5 ml/kg | 60 | 60 | 43 |
| Tidal volume < 4 ml/kg | 10 | 85 | 25 |
| CRS < 0.8 ml/$cmH_2O$/kg | 60 | 55 | 40 |
| $FiO_2$ > 0.21 | 70 | 45 | 39 |
| PIP > 11 $cmH_2O$ | 60 | 45 | 35 |
| Post extubation | | | |
| FRC < 26 ml/kg | 70 | 70 | 54 |
| Tidal volume < 5.8 ml/kg | 30 | 45 | 21 |
| Tidal volume < 4 ml/kg | 0 | 90 | 0 |
| CRS < 1.0 ml/$cmH_2O$/kg | 50 | 50 | 33 |

**Table 1** Comparison of infants in whom extubation did and did not succeed. Data are expressed as median (range) or number (*IPPV* intermittent positive pressure ventilation, *NS* not significant)

| | Success | Failure | *P* |
|---|---|---|---|
| Gestational age (weeks) | 30 (27–33) | 27 (25–30) | < 0.01 |
| Birth weight (g) | 1092 (744–1500) | 1107 (770–1462) | NS |
| Antenatal steroids | 17 | 10 | NS |
| Maximum PIP ($cmH_2O$) | 17 (14–28) | 19 (14–29) | < 0.05 |
| Maximum $FiO_2$ | 0.38 (0.21–0.92) | 0.58 (0.26–0.98) | NS |
| Total duration of IPPV (days) | 2 (1–6) | 6 (1–46) | < 0.01 |
| Duration of oxygen dependency (days) | 4 (1–49) | 20 (1–68) | < 0.02 |
| Exogenous surfactant | 8 | 6 | NS |
| Postnatal age at extubation (days) | 2 (1–6) | 4 (1–6) | NS |
| Pre-extubation | | | |
| FRC (ml/kg) | 26.1 (13.5–38.5) | 22.1 (16.4–36.9) | NS |
| Respiratory rate (bpm) | 60 (48–84) | 60 (55–102) | NS |
| Tidal volume (ml/kg) | 5.8 (2.0–8.6) | 5.4 (3.1–8.7) | NS |
| CRS (ml/$cmH_2O$/kg) | 0.94 (0.30–1.54) | 0.74 (0.42–1.05) | NS |
| Specific compliance ($cmH_2O^{-1}$) | 0.03 (0.013–0.068) | 0.03 (0.016–0.051) | NS |
| $FiO_2$ | 0.23 (0.21–0.36) | 0.22 (0.21–0.38) | NS |
| PIP ($cmH_2O$) | 12 (10–14) | 12 (10–14) | NS |
| Post extubation | | | |
| FRC (ml/kg) | 28 (18.1–39.2) | 23.0 (15.6–28.7) | < 0.01 |
| Respiratory rate (bpm) | 75 (48–102) | 72 (60–90) | NS |
| Tidal volume (ml/kg) | 5.5 (3.1–7.7) | 6.7 (4.1–9.9) | NS |
| CRS (ml/$cmH_2O$/kg) | 0.98 (0.43–1.6) | 0.97 (0.58–1.26) | NS |
| Specific compliance ($cmH_2O^{-1}$) | 0.036 (0.014–0.057) | 0.038 (0.030–0.057) | NS |
| $FiO_2$ | 0.22 (0.21–0.36) | 0.30 (0.21–0.40) | < 0.05 |

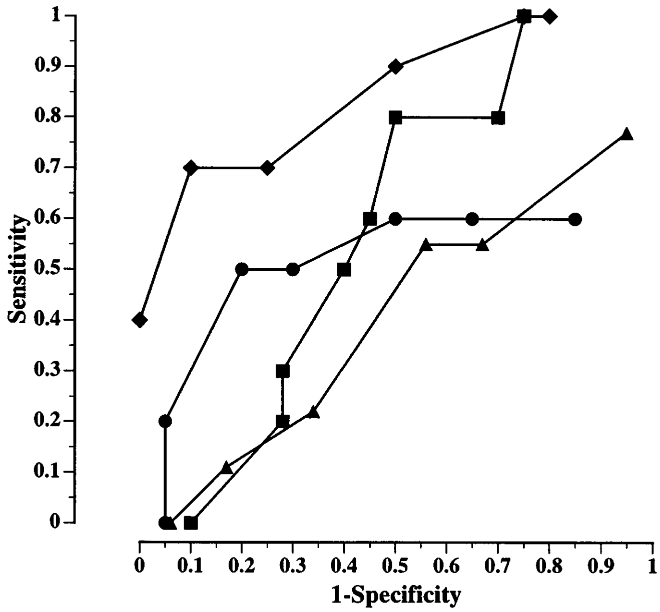


**Fig. 1** Receiver operating characteristic curve for gestational age (*closed diamonds*, area under the curve = 0.89) and the lung function test results (FRC, *closed circles*, area under the curve = 0.54, tidal volume, *closed triangles*, area under the curve = 0.57, CRS, *closed squares*, area under the curve = 0.57) pre-extubation

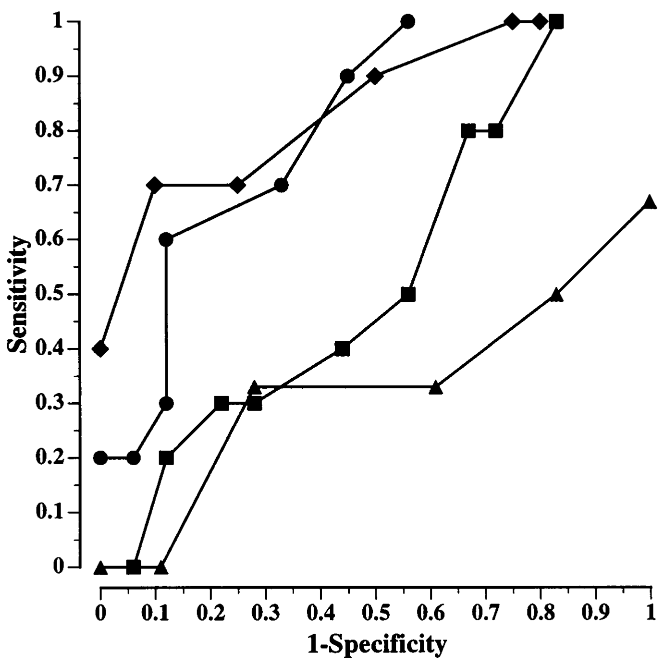


**Fig. 2** Receiver operating characteristic curve for gestational age (*closed diamonds*, area under the curve = 0.89) and the lung function test results (FRC, *closed circles*, area under the curve = 0.81, tidal volume, *closed triangles*, area under the curve = 0.65, CRS, *closed squares*, area under the curve = 0.54) post extubation

## Discussion

We have demonstrated in a population of very low birth weight infants, compared to other lung function test results, the most sensitive predictor of extubation failure was an FRC <26 ml/kg measured post extubation. In clinical practice, the infant's ability to maintain blood gases in a predetermined range on low ventilatory settings is the usual criteria on which a decision to extubate is made. Despite measuring FRC at any time within 24 h after extubation, the result of this test performed better than the ventilator settings recorded immediately prior to extubation.

The usefulness of lung function test results in predicting extubation failure in infants has been debated [3, 14, 26]. We have previously argued [10] that differences in the predictive ability of lung function measurement results prior to extubation may be due to the influence of the ventilator settings, particularly the level of PEEP [11]. An alternative explanation for the conflicting results may be differences in policies in relating lung function data to body weight. Changes in dynamic compliance are highly correlated with body weight [15] and in one series [4], when results were corrected for body weight, there was a clearer differentiation between results from infants in whom weaning succeeded and those from infants in whom weaning failed. We related our results to body weight, but nevertheless found that only FRC post extubation differed significantly between the groups.

Failure to achieve a tidal volume >4 ml/kg has been invariably associated with extubation failure in adults [19, 25]. Similarly in children and infants born at term [20], a low tidal volume predicted extubation failure. As a consequence, it was postulated [20] that it is not the effort of breathing, but rather the outcome of that effort which determines the ability to sustain spontaneous breathing. Our results demonstrate that a low tidal volume is not an accurate predictor of extubation failure in preterm neonates. It is interesting to speculate why, even when related to body weight, a low tidal volume performed so poorly in the present population. Adults who fail extubation have frequently required prolonged ventilatory support and diaphragmatic fatigue, hence their inability to maintain an adequate tidal volume. In contrast, the present population studied had, by definition, all been ventilated for <1 week and were receiving caffeine. Methylxanthines are known to improve diaphragmatic contractility [2]. One strategy the preterm neonate adopts to maintain his or her lung volume is to increase respiratory rate and it is possible that the immature infants in whom extubation failed, did not achieve a compensatory respiratory rate. It would, therefore, be interesting to assess if an integrated index, that is the respiratory rate to tidal volume ratio, was a more accurate predictor of extubation failure, although it should be noted that the rate to volume ratio, as an index of rapid shallow breathing, has had mixed success in adult populations [27].

The median FRC post, but not pre-extubation, differed significantly between infants in whom extubation did or did not succeed. The coefficient of repeatability of FRC measured in ventilated infants is higher than in non ventilated patients, which may partially explain this difference. In a previous study [10] we demonstrated that a low lung volume immediately after extubation was a sensitive and specific predictor of extubation failure. We now demonstrate that even when the FRC is measured at any time within 24 h post extubation it remains a useful predictor of weaning failure. Although we had previously demonstrated that a very low lung volume predicted extubation failure, we did not apply it as a criterion in this cohort on which to institute early CPAP. We did this as we wished to both confirm our earlier results [10] in a further series prior to changing clinical policy and also wished to assess the performance of a low FRC against more readily available clinical data, that is ventilator settings.

One-third of our study group failed extubation. We used a relatively low dose of caffeine [22], but other studies [6, 12] have also reported a similar extubation failure. Infants who failed extubation were significantly more immature. We related our lung function results to body weight to try and reduce bias. Post extubation the FRC results performed similarly to gestational age as a predictor of extubation failure. In a subgroup analysis, however, that considered only infants of $< 30$ weeks of gestational age, the FRC was significantly different between infants in whom extubation failed or succeeded. Use of CPAP post extubation is not successful in preventing extubation failure in all infants [5, 24] and has side-effects [5]. We therefore suggest that in very low birth weight infants, particularly those born very immaturely, identification of a low lung volume post extubation should be used as an indication for use of CPAP and hopefully such a policy would reduce extubation failure.

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