



respectively, until such time as appropriate adjustment is made.

A flowchart summarising the steps that should be followed when managing aberrant DPH concentrations is shown in order to fix concepts, as well as for convenience. It is helpful, initially, to pay particular attention to the units being used in a particular equation; as familiarity with procedures develops interconversion between units presents no real difficulties.

To obtain a true steady-state concentration in the therapeutic range in a patient receiving treatment with oral DPH requires meticulous compliance with a precisely determined and correct MD, constant absolute bio-availability characteristics of the DPH formulation being administered and constant absorption from the gut over a sufficiently long period of time. In the practical therapeutic setting such a condition, not requiring ongoing therapeutic monitoring, adjustment and correction, is the very rare exception rather than the rule. The only workable way in which to ensure acceptable, if not optimal, therapeutic results in less sophisticated populations is to encourage full co-operation between physician and patient in an attempt to ensure compliance; use of high-quality DPH formulations; and skilful application of adjustment and correction techniques based on high-quality routinely generated analytical [DPH] data.

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COMPLIANCE OF THE RESPIRATORY SYSTEM AS A PREDICTOR FOR SUCCESSFUL EXTUBATION IN VERY-LOW-BIRTH-WEIGHT INFANTS RECOVERING FROM RESPIRATORY DISTRESS SYNDROME

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Objective. To develop additional criteria to predict for successful extubation of very-low-birth-weight infants recovering from respiratory distress syndrome.

Design. Prospective study.

Setting. Neonatal intensive care unit at a university teaching hospital.

Interventions. Infants ready for extubation according to clinical, ventilatory and blood gas criteria were studied. Before extubation, tidal volume (V_t), minute ventilation, respiratory rate/ V_t and mean inspiratory flow were measured during two different ventilatory settings: (i) during intermittent mandatory ventilation (IMV); and (ii) while breathing spontaneously with endotracheal continuous positive airway pressure (CPAP). Tidal volume was obtained through electronically integrated flow measured by a hot-wire anemometer. Total respiratory compliance (C_{rs}) was determined during IMV and was derived from the formula $V_t/PIP-PEEP$, where the difference between peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) represented the ventilator inflation pressure.

Measurements and main results. Each of 49 infants was studied once before extubation. 33 infants (67%) were successfully extubated and 16 (32.6%) required reintubation. Infants in the success and failure groups were matched for gestation, post-conceptual age, study weight and methylxanthine therapy at the time of study. Successful extubation was associated with a higher mean absolute C_{rs} value (ml/cm H_2O) specific C_{rs} value (standardised for body length; ml/cm H_2O /cm) compared with infants in whom extubation failed (0.67 v. 0.46; $P = 0.01$ and 0.018 v. 0.014;

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$P = 0.03$, respectively). Analysis of ROC curves detected thresholds for Crs (0.5 ml/cm H₂O) and Vt (7 ml) for predicting successful extubation. An absolute Crs value 0.5 ml/cm H₂O or more improved the likelihood of successful extubation when compared with clinical/ventilator and blood gas criteria. The likelihood of successful extubation was 81% if the Crs value was ≥ 0.5 ml/cm H₂O. A tidal volume of 7 ml or more was less sensitive in contributing to successful extubation (sensitivity 69%). The major causes for extubation failure included atelectasis (diffuse and/or localised) and the presence of a patent ductus arteriosus.

Conclusions. In addition to following very precise ventilatory criteria for extubation, we found that bedside measurement of total respiratory system compliance added to the likelihood of extubation success in infants recovering from respiratory distress syndrome. Prospective studies are needed to validate the findings of this study.

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The successful weaning and extubation of neonates depends on the interaction of the ventilatory pump, lung mechanical properties and central respiratory drive, and the degree of superimposed post-extubation pathology (i.e. sub- or supraglottic oedema or lung atelectasis). The complexity of the aforementioned interactions is underscored in the very-low-birth-weight (VLBW) baby, who appears to be hampered both in respect of newly acquired lung volume and ability to sustain independent ventilation.¹

In the majority of neonatal units the decision electively to extubate infants recovering from lung disease is usually based on the attending physician's own subjective clinical experience supported by blood gas criteria.^{2,3} This is usually a trial-and-error approach. As a result a significant number of infants (15 - 40%) require reintubation and further ventilatory support, which predisposes them to develop long-term pulmonary sequelae.²⁻¹²

In order to overcome subjective influences and improve the success rate for extubation, investigators have focused on the measurement of pulmonary mechanics.^{4,7,10,12} Assuming intact respiratory drive and major airways, the likelihood of successful extubation should increase with improved respiratory compliance. The purpose of this study was to assess whether compliance of the respiratory system (Crs) could predict successful elective extubation in preterm infants recovering from respiratory distress syndrome (RDS)

MATERIALS AND METHODS

Subjects

A cohort of 49 VLBW infants (gestational age range 26 - 34

weeks) who had been intubated and mechanically ventilated for RDS was prospectively studied immediately before elective extubation. All the infants were clinically stable, were in the recovery phase of RDS,¹³ and had no other significant non-respiratory conditions. They had been intubated with a 2.5 mm endotracheal tube via the nasal route and were being ventilated by time-cycled, pressure-limited continuous flow ventilation. The decision to extubate (or reintubate) was made by the attending physician, who notified the respiratory technologist (DM) responsible for measuring the on-line Crs. The attending physician was blinded to the results. Infants were extubated if they were breathing comfortably without obvious subcostal and/or sternal recession and satisfied the following pre-established criteria: (i) partial pressure of oxygen (PaO₂) ≥ 6.9 kPa (52 mmHg) with a fractional inspiratory oxygen concentration (FiO₂) < 0.40 ; (ii) arterial pH > 7.26 , partial pressure of carbon dioxide (PaCO₂) < 8 kPa (60 mmHg); (iii) peak inspiratory pressure (PIP) ≤ 15 cm H₂O; and (iv) ventilator rate ≤ 15 cycles per minute (cpm). Infants with diseases other than probable RDS and those ventilated for less than 24 hours were excluded.

Infants were extubated directly to headbox oxygen without nasal continuous positive airway pressure (CPAP) as a transitional step. Humidified oxygen was delivered into a headbox. Infants were weighed on an electronic scale (model 680, Berkel) immediately after extubation. Crown-heel length (height) was measured using standard tape. Whenever possible, infants were nursed in the prone position following extubation. The clinical condition and vital signs were monitored and arterial blood gases obtained at 4 - 6-hourly intervals. Pulse oximetry was performed throughout the study and saturations were kept between 90% and 94% at all times. A chest radiograph was obtained within 4 hours of extubation. The majority of infants received chest physiotherapy. Extubation failure was defined as the need for reintubation within the first 48 hours following discontinuation of assisted ventilation. Criteria for reintubation were any one or more of: (i) recurrent apnoea episodes; (ii) respiratory failure (pH ≤ 7.25 ; PaCO₂ ≥ 8 kPa); (iii) increasing need for oxygen while receiving at least 50% supplemental oxygen; and (iv) other reasons. The clinical team who made the decision to reintubate was unaware of the results of the compliance measurements.

Compliance measurement

All the studies were performed with the babies in the supine position in neutral head-neck posture.¹⁴ No sedation was used. Pulmonary functions were measured during two different ventilatory settings: (i) intermittent mandatory ventilation (IMV) according to a pre-established protocol (see below); and (ii) while the infants were breathing spontaneously with endotracheal CPAP at 5 cm H₂O.



The neonatal volume monitor (NVM) (NVM-1; Bear Medical Systems, Riverside, Ca.) was placed in between the ventilator circuit and neonatal endotracheal tube adaptor. Five minutes were allowed for stabilisation and for the infant's physical activity to subside. Measuring times during both the ventilation and the CPAP study averaged 6 minutes. Parameters constantly monitored and digitally displayed on the NVM included inspired and expired tidal volume (Vt), minute volume, respiratory rate (RR), inspiratory and expiratory time (T) and percentage tube leakage. For the study performed during mechanical ventilation, ventilator settings were fixed at: (i) ventilator rate 40 cpm; (ii) PIP 15 cm H₂O; (iii) positive end-expiratory pressure (PEEP) 2 cm H₂O; (iv) inspiratory time (Ti) 0.45 seconds; and (v) flow 8 l/min. Ventilator pressures were not calibrated before studying each infant. The fixed, mild hyperventilation ventilator rate of 40 cpm was selected in order to suppress spontaneous breathing, which could influence variability in Vt and compliance measurements.

Volume measurement

The NVM uses a hot-wire anemometer to measure bidirectional flow at the endotracheal tube opening.^{15,16} The total dead space addition to the circuit is 1.2 ml. The device utilises a heated filament which, when exposed to flowing gas, loses heat.¹⁶ The rate of heat loss varies with the velocity of gas. Flow is electronically integrated to yield volume, which is displayed as Vt.

The Vt range of the NVM-1 is 1 - 500 ml. Calibrations were performed before each study using fixed volumes injected at different rates. Known volumes of air from a 50 ml syringe were used. The measured volumes were within 1% of the syringe volume (at 50 ml, the reproducible volume was less than 0.5 ml). The output signal of the hot-wire anemometer has previously been shown to be unaffected by temperature or humidity.¹⁵

Pressure and compliance measurement

The inflation pressure (the difference between PIP and PEEP in the system) was derived from the ventilator. Crs was derived from the formula Crs = tidal volume (Vt)/PIP-PEEP. This method of determining Crs was previously validated by Baboolal and Kirpalani¹⁵ against the single-breath occlusion technique. An excellent agreement for Crs derived from both the inspiratory and expiratory volumes was obtained comparing the two methods ($r_2 = 0.97$ and 0.97 , respectively).¹⁵ The Crs values were standardised for the size (body weight and length) of the infants tested.

Indices determined during spontaneous breathing on 5 cm H₂O CPAP

In order to determine the infants' inspiratory drive we calculated mean inspiratory flow by dividing Vt by inspiratory time (Ti).¹⁷ The ratio of respiratory frequency (RR) to tidal volume (RR/Vt) was calculated to quantify the extent of rapid, shallow breathing.

Statistical analysis

Statistical significances for differences between mean values were obtained using the Statgraphics 6 programme. Parametric as well as non-parametric tests were used. Receiver operating characteristics (ROC) analysis was used to examine the Crs and Vt and its performance as a diagnostic test in predicting successful extubation. Statistical significance was accepted at $P < 0.05$.

RESULTS

Extubation was successful in 33 (67.3%) of the 49 infants. Sixteen (32.6%) of the 49 efforts at extubation failed within 48 hours. The deterioration in respiratory status was due to atelectasis (diffuse or lobar) in 4 infants, patent ductus arteriosus (PDA) (2), atelectasis and PDA (4), central apnoea

Table I. Characteristics of the patients — successful versus failed extubation

	Success (N = 33)	Failure (N = 16)	P-value
Birth weight (g) (mean (SD))	1 235 (164)*	1 229 (187)*	NS
Study weight (g) (mean (SD))	1 228 (168)	1 225 (187)	NS
Gestational age (wks) (mean (SD))	30.6 (1.9)	29.5 (2.3)	NS
Heart rate during study (bpm) (mean (SD))	152 (14)	152 (12)	NS
FiO ₂ (mean (SD))	0.28 (0.06)	0.24 (0.04)	NS
Study age (d) (mean (SD))	6.3 (4.8)	6 (5.6)	NS
Small for gestational age (N (%))	15 (45)	5 (31)	NS
Methylxanthine (N (%))	33 (100)	14 (88)	NS
Postnatal surfactant (N (%))	25 (75)	10 (62)	NS
Postnatal steroids (N (%))	3 (9)	1 (6.2)	NS
Pulse oximeter arterial saturation (%)	92	91	NS

* Range for birth weight: success 805 - 1 430 g, failure 960 - 1 484 g.



(1), generalised sepsis (1), and undefined causes (4) (excessive rib retraction accompanied by respiratory acidosis). Forty-seven (95.9%) of the 49 infants received intravenous aminophylline (loading dose 4 mg/kg, followed by 2 mg/kg at 12-hourly intervals). Four infants received a short course of postnatal corticosteroids to facilitate weaning. The clinical characteristics of the two groups are displayed in Table I. The success and failure groups were similar with regard to mean birth weight, study weight, gestational age and methylxanthine, postnatal steroid and surfactant administration. Mean heart rate and oxygenation status were similar during the study. Infants in whom extubation failed had a significantly lower PaO₂ before extubation and a significantly higher PaCO₂ and lower pH following extubation (Table II). Crs measurements revealed significantly lower mean absolute Crs values (not normalised for size) for the infants in whom extubation failed compared with those who were successfully extubated (Crs 0.46 ml/cm H₂O v. 0.67 ml/cm H₂O; *P* = 0.01) (Table III). The size-corrected Crs values between the two groups were similar for study weight but significantly different when normalised for length, with the success group having higher values than the failure group (*P* = 0.03).

Observations on endotracheal CPAP did not add any significant predictive power to the present study. Similar mean Vt, inspiratory flows and ratios to quantify rapid, shallow

Table II. Blood gas results of all patients before and within 4 hours of extubation (mean (SD))

	Success (N = 33)	Failure (N = 16)	P-value
Before extubation			
PaO ₂ (kPa)	11.4 (2.6)	8.2 (2.3)	< 0.001
PaCO ₂ (kPa)	5.6 (1.1)	5.7 (1.3)	NS
pH	7.34 (0.05)	7.31 (0.06)	NS
After extubation:			
PaO ₂ (kPa)	11.6 (4.5)	11.6 (7.9)	NS
PaCO ₂ (kPa)	5.9 (0.89)	6.6 (1.6)	NS
pH	7.32 (0.04)	7.26 (0.08)	< 0.001

Table III. Inspiratory respiratory mechanics (mean (SD))

	Success (N = 33)	Failure (N = 16)	P-value
Tidal volume (ml/kg)	8.7 (2.9)	7.2 (1.4)	0.07
Minute ventilation (ml/kg/min)	321 (103)	286 (92)	0.07
Respiratory compliance (ml/cm H ₂ O)	0.67 (0.22)	0.46 (0.12)	0.01
Standardised compliance:			
Per weight ml/cm H ₂ O/kg	0.52 (0.2)	0.45 (0.12)	0.07
Per length ml/cm H ₂ O/cm	0.018 (0.006)	0.014 (0.003)	0.03

Table IV. Observations on nasotracheal continuous positive airway pressure (5 cm H₂O) (mean (SD))

	Success (N = 33)	Failure (N = 16)	P-value
Tidal volume (ml/kg)	4.1 (1.4)	3.7 (1.0)	NS
Inspiratory time (sec)	0.36 (0.11)	0.39 (0.09)	NS
Mean inspiratory flow (ml/kg/sec)	12 (7.3)	12.5 (3.1)	NS
Arterial saturation (%)	92 (2.5)	92 (3.6)	NS
Respiratory rate/min	58 (12)	60 (11)	NS
RR/ tidal volume (breaths/min/ml/kg)	13.6 (6.7)	14.8 (4.1)	NS
Heart rate (bpm)	145 (13)	149 (12)	NS

breathing (RR/Vt ratio) were documented in the success and failure groups of infants (Table IV).

ROC curves for Crs and Vt detected thresholds for Crs (0.5 ml/cm H₂O) and Vt (7 ml) for predicting successful extubation. A Crs threshold of 0.5 ml/cm H₂O and a Vt level of 7 ml predicted successful extubation with a sensitivity and specificity of 81% and 41% and 69% and 47%, respectively.

DISCUSSION

Sixty-seven per cent of the VLBW infants in the present study were successfully extubated to headbox oxygen or ambient air according to pre-established clinical criteria. We have shown that in patients who fulfil clinical and arterial blood gas criteria for extubation, success is significantly more likely in the group with a total Crs value of more than 0.5 ml/cm H₂O. An absolute tidal volume exceeding 7 ml was less accurate.

In recent years several studies have identified differences in lung function between infants in whom a trial of extubation succeeded or failed.^{2,4,7,10,12} The majority emphasise the lack of predictive capacity of a single measurement of respiratory function to assess optimal timing of extubation reliably.

Low Crs values are invariably associated with extubation failure.^{2,4,10} Reported Crs values vary (with different methodology) between 0.9 ml/cm H₂O and 2 ml/cm H₂O (absolute values),^{2,4} and mean standardised Crs between 0.57 and 0.74 ml/cm H₂O/kg body weight.^{2,10} One study, however, failed to show a relationship between standardised Crs (Crs corrected for body weight) and extubation success.³ This study included infants who suffered from a variety of conditions, i.e. asphyxia, transposition of the great arteries, pulmonary hypertension, aspiration and RDS. Correction of compliance for size presents a major problem, as body weight fluctuates by a large percentage over time in neonates. Lung volumes and compliance have previously been related to height.^{18,19} In a previous study¹⁹ we showed that Crs corrected for body length was a better predictor of poor outcome than Crs standardised



for body weight. Dynamic Crs is a useful, direct measurement of the distensibility of the lung and reflects the visco-elastic properties and alveolar volume of the respiratory system as well as airways disease. Dimitriou *et al.*²⁰ found that a low lung volume is associated with extubation failure in the first 10 days of life. In their study infants in whom extubation failed had a median functional residual capacity (FRC) of 19 ml/kg within 1 hour of extubation. This value was significantly lower than the FRC of infants in whom extubation succeeded (28 ml/kg). In neonates recovering from RDS, a low compliance usually reflects atelectasis or low lung volumes. Although the absence of FRC measurements in our study precludes interpretation of Crs values in terms of changes in FRC, it could be speculated that our significantly lower Crs values obtained before extubation in the infants in whom extubation failed corroborate the findings of Dimitriou *et al.*²⁰ A low baseline Crs could decrease to a critically lower level (within 1 hour) following extubation.

A significant relationship exists between compliance and gas exchange parameters, with gas exchange improving earlier than Crs.²¹ Successfully extubated infants in our study had a significantly higher mean arterial PO₂ before extubation for identical ventilator settings than those in whom extubation failed, and their mean FiO₂ was similar. These findings could be interpreted as representing decreased ventilation/perfusion mismatch (less intrapulmonary shunting) secondary to lesser degrees of subsegmental atelectasis. The major cause of reintubation of our infants was related to the respiratory system. Eight infants (50%) had either diffuse or lobar atelectasis, associated with a concomitant haemodynamically significant PDA in 4 cases. Four infants (25%) were reintubated because of moderate or severe rib retraction accompanied by a respiratory acidosis the cause of which was not well documented. A similar finding to that of Balsan *et al.*⁴ is that apnoea was not a major cause for reintubation, occurring in only 1 infant.

The majority of infants in our study received methylxanthine therapy, which has been reported to decrease the incidence of post-extubation apnoea.^{22,23} In addition, aminophylline administration to preterm infants results in improved lung compliance and increased excursions of the diaphragm, without significantly altering respiratory rate, pH or arterial PaCO₂.^{6,24} The similarity of mean inspiratory flow (Vt/Ti) while on CPAP in both groups in our study indicates that both groups had similar respiratory muscle performance and central drive before extubation. Following extubation, the failure group developed significant respiratory acidosis indicating alveolar hypoventilation. Whether there was failure to transform neural drive into improved mechanical performance of the respiratory muscles in these infants is unknown.²⁵

Prone posture has been shown to be beneficial for neonates being weaned from mechanical ventilation.^{26,27} In full-term neonates, a change from supine to prone posture improved

both ventilation and respiratory drive (Vt/Ti).²⁸ Although the extubation protocol of our unit stipulates that VLBW infants should preferably be placed in the prone position following extubation, this was not well documented in the present study. It therefore remains to be shown whether 'posturing' contributes significantly to extubation outcome.

A patent ductus arteriosus was diagnosed in 6 (37.5%) of the infants in our study in whom extubation failed. Increased pulmonary blood flow has been shown to alter the mechanical properties of the lung significantly, i.e. reducing lung compliance in the presence of left-to-right shunts.²⁹⁻³¹ Conversely, to improve extubation outcome of VLBW infants, the exclusion of a significant PDA by echocardiography seems indicated.

The present study has certain shortfalls. Single pulmonary function measurements should be interpreted with caution, and the data generated from this study should not be extrapolated to evaluate lung conditions other than RDS. Intrasubject reproducibility was not assessed, though great care was taken to analyse only mechanical breaths during the IMV study. During the present study we tried to minimise the effect of intrasubject variability on results by using fixed ventilator settings between subjects studied.^{32,33} Since ventilator pressures were not calibrated before the procedure, actual transpulmonary pressure measurements could have been less than accurate.³⁴ Recently Khan *et al.*³⁵ described increasing failure rates for extubation with worsening physiological variables (decreasing Vt indexed to body weight, decreasing inspiratory flow, increasing FiO₂, increasing fraction of total minute ventilation). The present study could not confirm this, since we were unable to identify an accurate cut-off point for any of the variables that could discriminate with sufficient specificity and sensitivity between extubation success or failure.

In conclusion, weaning and successful extubation depends on multiple factors, i.e. definitions of weaning failure, weaning methods, extubation criteria, and a host of interrelated physiological factors. Our study was non-invasive and required inexpensive equipment. We demonstrated significant differences in absolute Crs values as well as specific Crs (standardised for body length) values between infants who were successfully extubated and those in whom extubation failed within 48 hours. We have shown that, when precise clinical/ventilator and arterial blood gas criteria for extubation are fulfilled, success is more likely in the group with a total respiratory compliance (Crs) value of more than 0.5 ml/cm H₂O and/or an absolute tidal volume value of 7 ml. Furthermore, extubation outcome could be improved further through carefully excluding medically treatable causes for extubation failure such as a PDA. The predictive power of the cut-off levels mentioned for Crs and Vt, however, requires further investigation.



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