Birth weight and early lung compliance as predictors of short-term outcome in premature infants with respiratory distress syndrome

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In addition to birth weight (BW), respiratory mechanics measured during the first week of life have been reported to predict outcome in ventilated newborn infants with respiratory distress syndrome (RDS). Most measuring techniques are invasive, requiring the placement of an oesophageal tube or balloon. In the present study the compliance (Crs) and resistance (Rrs) of the total respiratory system were measured without an oesophageal tube, using a commercially available system (PEDS; MAS Inc., Hatfield, Pa.). The Crs and Rrs were determined once, within 24 hours of birth, in 28 preterm infants requiring mechanical ventilation for RDS. Variables such as gestational age (GA) and BW were also evaluated for their predictive role in outcome. Poor outcome was defined as death from respiratory failure or the development of bronchopulmonary dysplasia (BPD) at 28 days. All non-survivors died of refractory respiratory failure, at a median age of 6 days. The median Crs of the 21 survivors was 0,5 ml/cm H_2O and of the non-survivors 0,21 ml/cm H_2O (P = 0,01). Crs below 0,45 ml/cm H_2O predicted 15 of the 16 infants who either developed BPD or died (positive predictive value 100%; negative predictive value 92%; sensitivity 94%; specificity 100%). Nine survivors, who subsequently developed BPD, had a median Crs of 0,38 ml/cm H_2O. Their Crs was significantly lower than that of the infants without evidence of BPD (Crs = 0,61 ml/cm H_2O) (P = 0,01). All of the 12 babies without BPD who survived had median Crs values above 0,45 ml/cm H_2O. The median Rrs of the 9 infants with BPD (96 cm H_2O/l/s) was also significantly higher than the Rrs value of the non-BPD group (59 cm H_2O/l/s) (P = 0,05). When stepwise multiple logistic regression was applied to predict outcome, the only variable that could be entered at a 0,05 level of significance was BW. Uncorrected compliance entered the second step, but did not reach statistical significance. We conclude that in premature infants with RDS, BW is a strong predictor of outcome. Although determination of the Crs within the first 24 hours after birth did not add significance to this predictive model, it was nevertheless a useful parameter to determine respiratory morbidity and mortality.

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The measurement of lung mechanics in infants has been proposed as a useful tool in neonatal respiratory care.[1,2] These measurements reflect the severity of disease and assist in the prediction of outcome of specific pulmonary disorders.[3-5] Whereas the prognostic value of lung compliance measurements has been demonstrated by some authors,[3,4] others emphasise that pulmonary resistance is a sensitive predictor of the development of chronic lung disease.[5] However, application of these techniques in routine neonatal respiratory care has yet to be determined, as controversy exists with regard to the 'ideal' method and standardisation.[6] When measuring lung compliance, some utilise invasive procedures such as oesophageal balloon placement that have been shown to provide inaccurate results in sick intubated infants,[6,7] and have also proved unnecessary when an occlusion technique was applied.[8] Controversy also exists where new variables are examined to determine respiratory outcome, without considering the contributions of more readily available factors such as birth weight (BW).[9]

The aim of this study was to determine the value of a single measurement of the compliance of the total respiratory system (Crs) within the first 24 hours of life as a predictor of the short-term outcome in premature newborn infants ventilated for respiratory distress syndrome (RDS). By identifying infants with the highest risk for a poor outcome (mortality and/or development of bronchopulmonary dysplasia (BPD)), we speculate that more timeously administered therapy such as exogenous surfactant and/or postnatal steroid treatment could influence the natural course of the RDS in these infants. Stepwise logistic regression was also used to compare the contributions of uncorrected and size-corrected Crs to the prediction of outcome achieved by BW and GA alone. Survival was defined as survival at 28 days of age. Surviving infants were further evaluated for BPD.

Materials and methods

Patient selection

During 1990, pulmonary mechanics were prospectively determined in 28 consecutive appropriate-for-gestational-age premature infants with clinical and radiological findings of RDS,[10] and who required mechanical ventilation from birth. They were all studied once within 24 hours of birth. Exclusion criteria for enrolment were congenital heart disease, a clinically significant patent ductus arteriosus, lung hypoplasia,[11] pulmonary infection and an audible air leak around the endotracheal tube.

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Outcome variables

At day 28 of life, short-term outcome was defined as: (*i*) survival without BPD; (*ii*) BPD; and (*iii*) non-survival. BPD was defined as the need for supplemental oxygen to maintain an arterial oxygen tension between 7 and 9,3 kPa or oxygen saturation between 90% and 94% at 28 days of life, and a chest radiograph with changes compatible with BPD.[12] The infants were followed up until their death or until supplemental oxygen was discontinued (oxygen saturation $\geq$ 90% in room air). Autopsies were performed to determine the presence of additional risk factors that might have contributed to the infants' death.

Method of ventilation

The infants were intubated according to their size with the best-fitting endotracheal tube to avoid air leaks. Before each measurement endotracheal tubes were additionally assessed for air leaks by documenting the return to baseline of the tidal volume measurement. All infants were ventilated with a time-cycled, pressure-limited ventilator (BP 2001; Bourns Inc., Riverside, Calif.). The flow was set at 10 l/min. The ventilator settings were adjusted to maintain an arterial oxygen tension (Pao_2) between 7 and 9,3 kPa, and an arterial carbon dioxide tension $PaCo_2$ sufficient to maintain the pH at above 7,26. Ventilator rates or frequency (f) varied between 40 and 70/min. No muscle relaxants were used, but infants were intermittently or continuously sedated with midazolam (Dormicum; Roche). None of the infants received exogenous surfactant, and fluid management was undertaken according to a standard neonatal protocol.[13] Dexamethasone was used after 10 - 14 days in an attempt to wean infants off the ventilator.

Mean airway pressure (MAP) was calculated according to the formula: MAP = (f X Ti/60) X (MIP-PEEP) + PEEP; where maximal inspiratory pressure (MIP), positive end-expiratory pressure (PEEP), and MAP are measured in cm H_2O and Ti represents the inspiratory time. Ventilator index 1 (VI1), considered to reflect the degree of lung disease and to indicate the amount of ventilatory assistance, was expressed as VI1 = f X MIP.[14]

Measurement of pulmonary mechanics

The neonates were all studied in the supine position with their heads in a neutral position. During the study most of the infants were not breathing spontaneously. Respiratory tracings distorted by spontaneous breathing activity were excluded from the analysis. The pulmonary mechanics (Crs, resistance of the total respiratory system (Rrs) and tidal volume) were measured by means of a commercially available system (PEDS; MAS Inc., Hatfield, Pa.). The system and principles of operation have previously been described by Horbar[14] and Bhutani *et al.*[15] In summary, the system consists of a heated (37°C) pneumotachometer (Fleisch model 00; OEM Medical, Richmond, Va., USA) attached to a Validyne MP45 differential pressure transducer to measure gas flow, placed in line with the infant's endotracheal tube and ventilator. Corrections for differing gas composition are applied to the flow signal and the volume is integrated from flow. Airway pressures were measured at the proximal port of the endotracheal tube via a Celesco P7D transducer. An oesophageal balloon to measure oesophageal pressure (in order to determine pleural pressure) was not used. The mechanics reported here therefore reflect those of the total respiratory system rather than the isolated lung. Air flow, volume and pressures were recorded simultaneously at a rate of 75 Hz per channel. The pressure transducer (calibrated with a water manometer) and flow channel (using constant gas flows and a flow meter) were calibrated for each patient. A minimum of 10 breaths was analysed for each infant. Values of Crs and Rrs were obtained by a two-factor least mean square analysis technique.[15]

Statistical analysis

Differences between groups were tested with the Mann-Whitney *U*-test; two-tailed tests of significance were used.[16] A *P*-value $\leq$ 0,05 was considered significant. The results of measurements are given as medians and interquartile ranges. The prediction of outcome was evaluated by stepwise multiple logistic regression (SAS Institute).

Results

The 28 infants had a median BW of 1 410 g (range 710 - 2 850 g) and a median GA of 30 weeks (range 25 - 35 weeks). Twenty-one infants survived (75%) and 7 died of respiratory failure, at a median age of 6 days. The relevant autopsy findings of the patients who died are given in Table I.

Table I. Clinical and autopsy findings of the non-survivors

Patient No.	Clinical and autopsy characteristics
1	ICH grade 3 with right-sided parenchyma extension Severe HMD; bilateral PTX
2	Severe HMD, bilateral PIE and PTX Bilateral ICH grade 3
3	Severe HMD, PIE, left-sided PTX
4	Moderate-severe HMD, right-sided PTX
5	Severe HMD, BPD changes, alveolar bleeding
6	Severe HMD, left-sided PIE ICH grade 3 (left-sided)
7	Severe HMD, bilateral PTX, pneumomediastinum, pneumoperitoneum

ICH = intracranial haemorrhage;[25] PTX = pneumothorax; PIE = pulmonary interstitial emphysema; HMD = hyaline membrane disease.

Clinical findings, ventilatory settings and pulmonary mechanics of the surviving infants and non-survivors are shown in Table II. Significant differences existed between these two groups in respect of BW, fractional inspired oxygen concentration Fio_2, MAP, f, VI1, Crs and Crs/body length (Crs/L).

Nine of the infants (43%) who survived developed BPD. Statistically significant differences existed between this group of babies and babies who did not develop BPD with regard to BW, GA, duration of ventilation, duration of oxygen therapy, Crs, Crs/L, and Rrs (Table III). The median Crs (0,38 ml/cm H_2O) of the BPD group was significantly lower than that of the babies without BPD (0,61 ml/cm H_2O) (*P* = 0,01).

Table II. The clinical, ventilatory and pulmonary mechanics characteristics of the survivors and non-survivors (median and interquartile ranges)

	Survivors	Non-survivors	*P*-value
No.	21	7	
GA (wks)	30	28	NS
	(29 - 33,5)	(26 - 31)	
BW (g)	1 480	840	0,05
	(1 120 - 2 100)	(740 - 1 200)	
M/F ratio	14/7	6/1	
FiO_2	0,60	0,97	0,05
	(0,45 - 0,7)	(0,6 - 1,0)	
Vent. rate	42	60	0,05
	(37 - 50)	(50 - 63)	
PIP	26	30	NS
(cm H_2O)	(23,5 - 30)	(26 - 31)	
MAP	10	12	0,01
(cm H_2O)	(7 - 10)	(12 - 15)	
VI1	1 152	1 500	0,05
	(822 - 1 478)	(1 352 - 2 065)	
Vt	6,5	6,5	NS
(ml/kg)	(5,4 - 8)	(5,7 - 6,7)	
Ve	406	406	NS
(ml/kg/min)	(326 - 510)	(349 - 486)	
Crs	0,5	0,21	0,01
(ml/cm H_2O)	(0,39 - 0,62)	(0,18 - 0,37)	
Crs/BW	0,32	0,25	NS
(ml/cm H_2O/kg)	(0,26 - 0,45)	(0,23 - 0,32)	
Crs/L	1,2	0,74	0,05
(ml/cm H_2O/m)	(0,9 - 1,3)	(0,55 - 1,23)	
Rrs	68	100	NS
(cm H_2O/l/s)	(55,5 - 99,5)	(72 - 169)	

PIP = peak inspiratory pressure; Vt = tidal volume; Ve = minute ventilation.

Table III. Clinical, ventilatory and pulmonary mechanics characteristics of the BPD v. non-BPD groups (median and interquartile ranges)

	Non-BPD	BPD	*P*-value
No.	12	9	
GA (wks)	32,5	29	0,01
	(32 - 34)	(25 - 30)	
BW (g)	1 825	1 120	0,01
	(1 320 - 2 375)	(845 - 1 410)	
Days on	6	25	0,001
ventilator	(5,9 - 6,5)	(14 - 39)	
Days on	9	80	0,001
oxygen	(5,5 - 15)	(33 - 100)	
Crs	0,61	0,38	0,01
(ml/cm H_2O)	(0,5 - 0,75)	(0,34 - 0,42)	
Crs/L	1,3	0,9	0,01
(ml/cm H_2O/m)	(1,2 - 1,6)	(0,8 - 1,1)	
Crs/BW	0,29	0,33	NS
(ml/cm H_2O/kg)			
Rrs	59	96	0,05
(cm H_2O/l/s)	(46,5 - 78,5)	(69 - 186)	
FiO_2	0,60	0,55	NS
Vent. rate	43	43	NS
PIP (cm H_2O)	26	24	NS
Vt (ml/kg)	7	6	NS
Ve (ml/kg/min)	419	406	NS
MAP (cm H_2O)	10	8,5	NS
PEEP (cm H_2O)	4	3	NS
VI1	1 105	1 194	NS

PIP = peak inspiratory pressure; Vt = tidal volume; Ve = minute ventilation.

A Crs value below 0,45 ml/cm H_2O predicted 15 of 16 infants who either developed BPD or died (PPV 100%, NPV 92%, sensitivity 94%, specificity 100%). All 12 infants without BPD who survived had a Crs value of 0,45 ml/cm H_2O or more. The Crs value allowed stratification of the infants into three groups, according to their outcome. In 5 out of 7 infants who died, the Crs was below 0,3 ml/cm H_2O. In 8 of 9 infants with BPD who survived, Crs was between 0,3 and 0,45 ml/cm H_2O, and a Crs of 0,45 ml/cm H_2O or more was found in all 12 surviving infants without BPD.

When stepwise multiple logistic regression was applied to predict outcome, the only variable that could be entered at a 0,05 level of significance was BW. Neither Crs, size-corrected Crs nor GA significantly affected the model.

Discussion

To a large extent, the maturational status of the newborn lung at birth determines ultimate survival. The early identification of those babies with moderate/severe RDS who are at greatest risk of dying or developing chronic lung disease, i.e. BPD, could assist clinicians to provide more timely and appropriately targeted therapy, such as postnatal exogenous surfactant or steroid administration. Poor respiratory outcome might therefore be prevented.

Compliance and resistance measurements as predictors of the course and outcome of RDS have been determined by several investigators using different techniques.[3,4,9] Simbruner *et al.*[3] first measured static respiratory compliance (Cst) by means of an occlusion method. They reported a Cst below 0,5 ml/cm H_2O in 7 of 8 ventilated infants who died, and a value above this in 8 of 10 infants who survived. Subsequently Graff *et al.*[4] used a pneumotachometer to measure dynamic respiratory compliance (Cdyn) in infants with RDS, at 2,3 ± 1,4 days of life. They correctly predicted survival in 45 of 47 infants with a Cdyn above 0,45 ml/cm H_2O and non-survival in 11 of 13 infants who had a value below this. Kirpalani *et al.*[9] determined passive respiratory system mechanics by an occlusion technique in premature newborns with respiratory failure. They concluded that BW was a strong predictor of compliance whereas compliance entered the last step on their logistic model. Neither size-corrected nor uncorrected compliance and resistance significantly increased the predictive value of BW. Infants in Kirpalani *et al.*'s study also included those with respiratory diagnoses other than hyaline membrane disease. As in the study of Kirpalani *et al.*[9] the results of the present study confirm BW as the best predictor of a poor outcome. Uncorrected Crs followed on the second step with GA and size-corrected Crs thereafter. None of these variables added significantly to the predictive power. The close correlation between BW and Crs found in this study will not necessarily hold in populations with a high incidence of intra-uterine growth retardation. Under these circumstances, BW may no longer be an acceptable alternative to Crs for predicting outcome.

Although probably not the optimal technique, we chose to measure the transtracheal pressure and opted not to use an invasive procedure such as oesophageal balloon placement. Thoracic compliance in preterm infants is very high, hence contributing only a small component to the measurement of total respiratory compliance.[17] Oesophageal pressure changes may not reflect mean pleural pressure changes accurately but may measure local pressure, which can be different from the mean.[6,18] Inclusion of the chest wall in the lung compliance calculation incurs a loss in resolution of 5% in infants with RDS.[17] During the present study, infants were continuously sedated in an attempt to prevent any spontaneous breathing activity and chest wall distortion. Breaths that showed distortion of the flow signal were excluded from the final analysis. With this technique for measuring pulmonary mechanics, compliance results comparable with those of Graff *et al.*[4] were documented. The extreme Crs values of the infants in our study who succumbed, 0,17 - 0,56 ml/cm H_2O, are also very similar to those reported by the abovementioned authors: 0,15 - 0,66 ml/cm H_2O.[4]

Correction of compliance for size presents a major problem, as body weight fluctuates by a large percentage over time in neonates. Lung volumes and CI have previously been related to height.[19] Because lung compliance varies directly with lung volume, we preferred to correct for lung volume by relating the determined compliance to the infants' length.[19] In the present study, univariate analysis showed Crs corrected for body length to be a better discriminant of poor outcome then uncorrected Crs. No such difference existed when Crs was corrected for BW in any of the abovementioned groups.

The infants in this study who developed BPD were smaller and more immature than those who did not, and required more days of mechanical ventilation and supplemental oxygen. Moriette *et al.*[20] showed that birth before 30 weeks' gestation, RDS, and mechanical ventilation for more than 15 days are the most important predictive factors for the development of pulmonary functional abnormalities at 1 year of age. Although the development of BPD is also partly related to peak ventilator pressures and oxygen concentration,[21] the significantly lower median Crs value of the BPD infants (0,38 ml/cm H_2O) compared with the non-BPD infants (0,61 ml/cm H_2O) in this study could not be explained by the amount and degree of initial ventilatory support (VI1, peak inspiratory pressure, f, FiO_2, minute ventilation) as these values did not differ significantly between the two groups.

The Rrs value, 96 cm H_2O/l/s (range 69 - 186 cm H_2O/l/s), found in the BPD infants in this study compares well with the values observed by Goldman *et al.*,[5] 50 - 200 cm H_2O/l/s in infants with prolonged oxygen dependence and radiographic changes of BPD. Although it may be possible to identify the infants at risk of developing BPD by using elevated Rrs values within the first 24 hours of life, the data on increased Rrs values in intubated infants are difficult to interpret.[5,22-24] The combination of a narrow tube and relatively high ventilator flow rates and ventilation rates may lead to the generation of turbulent flow and thus increase resistance. Increased resistance may also be caused by airway secretions or a change in the configuration of the endotracheal tube, and may be influenced by the relationship of the tip of the tube to the tracheal wall.[22]

Stratification according to Crs revealed three distinct groups related to outcome. Crs above 0,45 ml/cm H_2O was related to a normal respiratory outcome. Infants in this group were also ventilated for a short period (median 6 days). A Crs below 0,45 ml/cm H_2O was related to a poor respiratory outcome (development of BPD) or death. BPD infants required assisted ventilation for a median period of 26 days. Whether the abovementioned findings would influence the administration of exogenous surfactant to babies with HMD remains speculative.

Nevertheless, our findings do suggest that surfactant administration could be limited to the group of babies with HMD and Crs values below 0,45 ml/cm H_2O, as babies with Crs values above this seem to survive without chronic lung sequelae. This finding may be of value in neonatal intensive care units with limited resources, but remains to be tested in a larger series.

In conclusion, we found changes in measured Crs within 24 hours of birth in premature infants ventilated for RDS that proved to be sensitive and specific in predicting poor short-term respiratory outcome. However, when a multiple logistic regression model is applied to predict outcome, BW is the strongest predictor. It needs to be determined whether these findings also hold for growth-retarded infants.

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