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Respiratory outcome in preterm ventilated infants: importance of early respiratory system resistance

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Abstract Since severity of acute respiratory distress syndrome (RDS) has been decreasing, the aetiology of long-term respiratory problems may have changed in preterm infants. We investigated whether early neonatal respiratory resistance (Rrs) and compliance (Crs) were important determinants of respiratory morbidity and lung function abnormalities during the 1st year of life in ventilated preterm infants. In 70 infants of less than 37 weeks gestation, mechanically ventilated within 24 h after birth, Rrs and Crs were assessed daily during the first 3 days of life and medians were calculated subsequently (Rrs_{neo} and Crs_{neo}). Rrs and Crs were reassessed 1 year later in 57 of 70 infants ($Rrs_{1\ year}$ and $Crs_{1\ year}$). After correction for endotracheal tube size, increased Rrs_{neo} was significantly related to respiratory morbidity during the 1st year of life (OR 1.20, 95% CI 1.04 to 1.38; $P = 0.013$), increased $Rrs_{1\ year}$ (multiplicative β per kPa/l·s 1.017, 95% CI 1.000 to 1.034; $P = 0.045$), and decreased $Crs_{1\ year}$ (multiplicative β per kPa/l·s 0.986, 95% CI 0.974 to 0.998; $P = 0.023$). Associations were not adversely affected by degree of prematurity, neonatal disease and treatment. Crs_{neo} did not show any significant associations. In the current surfactant era, increased Rrs_{neo}, and not Crs_{neo} was associated with poor respiratory outcome during the 1st year of life in preterm ventilated infants. Relationships were not adversely affected by measures reflecting degree of prematurity, neonatal disease, and ventilator conditions. *Conclusion*: Our results indicate that inborn properties of the respiratory system have become increasingly important in relation to respiratory outcome instead of neonatal disease and treatment conditions.

Keywords Artificial Respiration · Cohort studies · Preterm Infant · Respiratory system compliance · Respiratory system resistance

Abbreviations CLD: chronic lung disease of the neonate · Crs: respiratory system compliance · Crs_{neo}: median respiratory system compliance of the first 3 days of life · $Crs_{1\ year}$: respiratory system compliance at 1 year of age · CV: coefficient of variance · ERS: European Respiratory Society · FiO_2: inspiratory oxygen fraction · PIP: peak inspiratory pressure · RDS: respiratory distress syndrome · Rrs: respiratory system resistance · Rrs_{neo}: median respiratory system resistance of the first 3 days of life · Rrs_{neoC}: Rrs_{neo} corrected for endotracheal tube size · $Rrs_{1\ year}$: respiratory system resistance at 1 year of age · SBT: single breath occlusion technique

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Introduction

The introduction of prenatal corticosteroids and postnatal exogenous surfactant treatment in perinatal care have probably played a major role in the observed trend of decreasing severity of respiratory distress syndrome (RDS) during the past decades [4]. Nevertheless, the risk of developing chronic lung disease of the neonate (CLD) has remained high and may even have increased [7].

Respiratory system resistance (Rrs) and compliance (Crs) have been extensively studied in preterm infants. Results relating these parameters to respiratory outcome are conflicting, particularly with regard to the development of CLD [2, 11, 14, 15, 18, 22, 27,31]. Moreover, most of these studies were performed before the use of prenatal corticosteroids and the introduction of exogenous surfactant therapy. As a consequence of these recent developments in perinatal care, the survival of more immature infants has increased. Acute respiratory disease is often less severe and respiratory outcome seems to be mainly determined by an arrest of lung development in these infants [17]. Antenatal corticosteroid treatment may also cause impaired postnatal lung growth [16,30]. Thus, contemporary associations between early postnatal Rrs and Crs and long-term respiratory outcome may have changed compared to the pre-surfactant era.

The purpose of this study was to investigate whether neonatal respiratory mechanics are important determinants of respiratory morbidity and lung function abnormalities during infancy in preterm ventilated infants. Additionally, effects of potentially confounding factors like degree of prematurity, ventilator conditions, respiratory disease severity and therapeutic measures on associations between determinants and outcome were studied.

Subjects and methods

Preterm infants of less than 37 weeks of gestation, who were admitted to our neonatal intensive care unit between July 28th 1999 and August 31st 2000 and who were mechanically ventilated within 24 h after birth, were studied prospectively. Infants with congenital anomalies were excluded from the study. The study was approved by the Medical Ethics Review Committee of our centre and informed parental consent was obtained.

Mechanical ventilation was started as a consequence of respiratory distress, when, despite supplemental oxygen and/or continuous positive airway pressure, the inspiratory oxygen fraction (FiO_2) remained above 0.7, the partial arterial carbon dioxide pressure exceeded 55 mm Hg, acidosis persisted with pH decreasing below 7.25, or when serious apnoeas existed. The ventilator setting was adjusted to keep the arterial oxygen saturation of haemoglobin between 90%–95% and the partial arterial carbon dioxide pressure between 40–45 mm Hg. For mechanical ventilation, one of the following infant respirators was used: Stephanie (Stephan, Gackenbach, Germany), Bear BP2001 (Bear, Palm Springs, California, USA), and Bourns BP200 (Bourns Inc., Riverside, California, USA).

RDS was diagnosed when clinical symptoms of tachypnoea (>60/min), retractions, expiratory grunting and cyanosis were present in combination with radiological signs described by Giedion et al. [13]. Exogenous surfactant (natural bovine surfactant: Alvofact, Boehringer, Ingelheim, Germany) was administered at a dose of 50 mg/kg using the following limits of peak inspiratory pressure (PIP) and FiO_2: PIP <20 cm H_2O and FiO_2 >0.6, or PIP ≥ 20 cm H_2O and FiO_2 >0.45. When PIP exceeded 25 cm H_2O, conventional ventilation was switched to high frequency oscillatory ventilation.

Measurements of passive respiratory system mechanics were performed daily during the first 3 days of life in intubated infants. No extra sedation of the infants was required. Sometimes measurements could not be performed because of clinical instability of the patient, unavailability of qualified personnel, i.e. two of the contributing authors (Y.S. and P.d.W.), or because patients were extubated before the actual time of measurement. To optimise the total number of measurement results, the median passive respiratory system resistance (Rrs_{neo}) and compliance (Crs_{neo}) of the first 3 days of life were calculated. Rrs and Crs were assessed according to the single breath occlusion technique (SBT) described by Le Souef et al. [10,20]. A heated Lilly-type pneumotachometer (8410A, linear range 0–10 l/min, dead space 1.3 ml, resistance 0.94 kPa/l·s at 5 l/min; Hans Rudolph Inc., Kansas City, MO) was placed between the endotracheal tube and ventilator tubes. A pressure transducer (Honeywell, type 163PC01D75, Morristown, NJ) and an IBM compatible personal computer with a Pentium processor running the software package Respiratory Analysis System Program (Version 007.17, PhysioLogic, Highclere, UK) were used to record signals at a sampling rate of 125 Hz using a 12 bit analogue-to-digital converter (LabMaster DMA, Scientific Solutions, Mentor, OH). Mouth pressure and flow signals were obtained after calibration before each single measurement. For flow calibration, a calibrated rotameter (Air 0–15 l/min, Medec, Aalst, Belgium) was used followed by a volume calibration using a precision syringe of 50 ml containing the actual gas mixture. For pressure calibration, a pressure transducer tester (Veri-Cal 650–900, Utah Medical Products Inc., Midvale, Utah, USA) was used. Leaks in the system or around the endotracheal tube were easily detected as mouth pressure decreased gradually during occlusion. With gentle manual compression of the trachea, leaks were minimised. Measurements with persisting tube leaks causing a decrease in occlusion pressure of 0.02 kPa or more were excluded from further analysis [5,28]. During occlusion, activity of inspiratory muscles is inhibited via stimulation of the airway receptors inducing the Hering-Breuer reflex. Analyses were performed according to the actual European Respiratory Society (ERS) standards [9]. Breath analysis was considered unreliable, when no muscle relaxation was achieved. Muscle relaxation was assumed to be present when (1) during a short occlusion period of less than 0.5 s mouth pressure did reach a plateau for at least 0.1 s during which pressure changes showed a SD of 0.01 kPa or less, and (2) the expiration part of the flow volume curve was linear for at least 50% of the volume to be expired. As a criterion for linearity, a correlation coefficient of 0.98 or more after exclusion

of the final 5% of the expired volume had to be reached. At least five occluded breaths meeting these criteria were used to calculate a mean value for both respiratory mechanics for each single measurement.

At the age of 1 year, $Rrs_{1\ year}$ and $Crs_{1\ year}$ were determined during spontaneous breathing using the same technique (SBT). At this age, infants were sedated with 50–100 mg/kg chloral hydrate and measurements were performed in supine position with the head end elevated at approximately 30° relative to horizontal. A heated Lilly-type pneumotachometer (3500B, linear range 0–35 l/min, dead space 8.74 ml, resistance 0.32 kPa/l·s at 17.5 l/min; Hans Rudolph Inc., Kansas City, MO) was attached to a facemask (Laerdal Infant Mask No.1, Laerdal BeNelux BV, Valkenswaard, The Netherlands; dead space 10 ml) covered with therapeutic putty (Magic Putty, medium, Oldelft Benelux BV, Delft, The Netherlands) to prevent air leakage.

To evaluate internal validity of the tests, the intra-subject variability of both Rrs and Crs in mechanically ventilated infants was studied [29]. Coefficients of variance of Rrs and Crs were determined within subjects within each occasion and within subjects between up to three occasions that were used to calculate median Rrs and Crs of the first 3 days of life.

Clinical data, i.e. gestational age, birth weight, severity of RDS according to Giedion et al. [13], duration of mechanical ventilation, mean PIP during ventilation, number of days requiring a FiO_2 of more than 0.4, and oxygen dependency at 36 weeks gestational age, were derived from clinical charts. To achieve information about respiratory morbidity after hospital discharge, data concerning inhaled corticosteroid or bronchodilator therapy and hospital readmission for respiratory problems were obtained via questionnaires completed by the parents at the end of the 1st year. The questions in these questionnaires were similar to the key questions in the questionnaire used by Kuehni et al. [19] in children between 0 and 5 years of age. Questions included (translated from Dutch): (1) During the past 12 months, has your child taken medicine for wheezing or coughing? (2) If so, which medication was taken? (3) During the past 12 months, has your child been admitted to hospital for respiratory problems? If inhaled corticosteroids or bronchodilators were used or rehospitalisation occurred during the 1st year of life, respiratory morbidity was judged as present.

Data analysis

Characteristics of the patients who were lost to follow-up were compared to those of the patients who returned for follow-up measurements by independent Students *t*-tests, when data were normally distributed and variances were equal. Otherwise, Mann-Whitney U tests were used. For comparison of frequencies of dichotomous variables between groups, Chi squared analyses were performed.

As a first evaluation of the data, associations between early neonatal clinical and functional data (as independent variables) and respiratory morbidity, $Rrs_{1\ year}$, and $Crs_{1\ year}$ (as dependent variables) were studied by univariate regression analyses. Since endotracheal tube size substantially affects Rrs measurements during mechanical ventilation [21,23], Rrs_{neo} was subsequently corrected for this effect by including tube diameter in all regression models; referred to as Rrs_{neoC}. Respiratory morbidity during the 1st year of life was expressed dichotomously (1 for present and 0 for absent). We studied the hypothesis that early respiratory system mechanics, Rrs_{neoC} and Crs_{neo}, were associated with respiratory morbidity by using logistic regression analysis. Subsequently, effects of potentially confounding factors, i.e. gestational age, birth weight, severity of RDS according to Giedion et al. [13], duration of mechanical ventilation, mean PIP during ventilation, number of days requiring a FiO_2 of more than 0.4, and oxygen dependency at 36 weeks gestational age, on these associations were studied within the regression models.

Subsequently, we studied the hypothesis that early respiratory system mechanics, Rrs_{neoC} and Crs_{neo}, were associated with respiratory system mechanics at 1 year of age, $Rrs_{1\ year}$ and $Crs_{1\ year}$, by using linear regression analysis. $Rrs_{1\ year}$ and $Crs_{1\ year}$ were transformed by taking the natural logarithm because of their deviation from the normal distribution. Since results of regression analyses are presented after back transformation, regression coefficients and their 95% CIs should be interpreted as multiplicative instead of additive. This means that with each one-unit increase of the independent, the dependent factor is multiplied by the regression coefficient. Again, effects of potentially confounding factors on these associations were studied.

Furthermore, aetiological models were constructed and their independency from potentially confounding factors was studied. Only factors affecting the initial regression coefficients of the respiratory mechanics by more than 10% were included in the models and discussed subsequently.

Our data were analysed with the Statistical Product and Service Solutions 10.0 for Windows (SPSS Inc, Chicago, IL, USA). For all analyses, a P -value of < 0.05 was considered statistically significant.

Results

Initially, 88 infants were randomly recruited. Eleven infants died during the neonatal period leaving 77 infants for follow-up at the age of 1 year. Six infants died of respiratory insufficiency, four due to neurological problems and one due to circulatory problems. Rrs_{neo} and Crs_{neo} results in seven infants were considered unreliable according to the ERS criteria and, therefore, excluded from further analysis. Eventually, data of 70 infants were analysed. Patient characteristics of this group are listed in Table 1.

Table 1 Patient characteristics. (*PDA* patent ductus arteriosus)

	Median (range)/number (%)
Neonatal period: ($n = 70$)	
Gestational age (weeks)	29.5 (25.3–36.3)
Birth weight (g)	1277 (630–3020)
Sex (male)	39 (56%)
Prenatal exposure to tobacco smoke	16 (23%)
Prenatal corticosteroids administration (≥24 h antenatally)	45 (64%)
Radiological RDS severity[a]	3 (0–4)
Duration of mechanical ventilation (days)	9 (1–67)
Maximum PIP (cm H_2O)	22 (14–40)
Number of days with $FiO_2 > 0.4$	1 (0–48)
Surfactant administration	46 (66%)
Hour of life of surfactant instillation	9 (1–52)
Diagnosis of PDA[b]	27 (39%)
Day of PDA diagnosis	2 (1–9)
Size of endotracheal tube (internal diameter):	
2.5 mm	35 (50%)
3.0 mm	32 (46%)
3.5 mm	2 (3%)
Switched from 2.5 to 3.0 mm on 2nd day of life	1 (1%)
Rrs_{neo} (kPa/l·s)	15.1 (8.8–30.4)
Crs_{neo} (ml/kPa)	5.4 (2.3–22.2)
Oxygen dependency at 36 weeks	4 (6%)
Postnatal corticosteroid administration	23 (33%)
First degree relative with asthma	18 (26%)
First degree relative with either asthma, eczema or hay fever	30 (43%)
Maternal smoking during pregnancy:	16 (23%)
< 5 cigarettes per day	4 (25%)
5–10 cigarettes per day	5 (31%)
> 10 cigarettes per day	6 (38%)
not otherwise specified	1 (6%)
Outcome during the 1st year of life:	
Inhalation therapy with bronchodilators and/or steroids ($n = 66$)	27 (41%)
Rehospitalisation for respiratory problems	9 (14%)
Respiratory morbidity[c]	28 (42%)
$Rrs_{1\ year}$ (kPa/l·s) ($n = 57$)	4.6 (2.7–8.3)
$Crs_{1\ year}$ (ml/kPa)	99.2 (59.6–169.3)
Age at follow-up measurement corrected for gestation (days)	303 (270–437)
Weight at follow-up measurement (kg)	8.8 (6.6–12.0)
Height at follow-up measurement (cm)	72.3 (65.0–80.0)

[a]Radiological score for severity of RDS according to Giedion et al. [13] (0–4)
[b]Diagnosed by ultrasound performed by a paediatric cardiologist
[c]Inhaled corticosteroids or bronchodilator therapy, or hospital readmission due to respiratory problems during the 1st year of life

Information about respiratory morbidity during the 1st year of life was complete for 66/70 (94%) infants. In 57/70 (81%) infants, respiratory function measurements were performed at the age of 1 year. Parents of ten infants decided not to return for follow-up respiratory function measurements for various personal reasons, in two cases no reason was given, and one infant was tested 3 months late and therefore excluded for further analysis. The 13/70 (19%) infants, in whom follow-up data were missing, did not substantially differ from the 57/70 (81%) infants, in whom these data were available, with respect to gestational age (median 29.9 range 26.6 to 33.7 weeks versus 29.4 weeks range 25.3 to 36.3 weeks, respectively; $P = 0.794$), birth weight (1536 g range 875 to 1860 g versus 1240 g range 630 to 3020 g; $P = 0.572$), sex (54% versus 56% male; $P = 0.881$), maximum PIP (23 cm H_2O range 14 to 40 cm H_2O versus 22 cm H_2O range 15 to 35 cm H_2O; $P = 0.387$), Giedion score (3 range 0 to 4 versus 3 range 0 to 4; $P = 0.268$), and oxygen dependency at 36 weeks post-conceptional age (0% versus 7%; $P = 0.325$). However, groups did differ with respect to duration of mechanical ventilation (5 days range 1 to 15 days versus 11 days range1 to 67 days; $P = 0.014$) and number of days requiring FiO_2 of > 0.4 (0 range 0 to 1 day versus 1 range 0 to 48 days; $P = 0.008$). Rrs_{neo} and Crs_{neo} were comparable between both groups (14.9 kPa/l·s range 9.8 to 22.1 kPa/l·s versus 15.3 kPa/l·s range 8.8 to 30.4 kPa/l·s; $P = 0.381$, and 5.9 ml/kPa range 3.6 to 12.1 ml/kPa versus 5.2 ml/kPa range 2.3 to 22.2 ml/kPa; $P = 0.962$, respectively), as was the occurrence of respiratory morbidity, i.e. inhalation therapy or hospital readmission, during the 1st year of life (50% versus 41%; $P = 0.557$).

Respiratory function measurements during mechanical ventilation

The median number of occluded breaths on which results of each single measurement were based, was

6 (range 3 to 12). The CVs of Rrs and Crs assessments were calculated within subjects within measurements. The median CV of Rrs was 6.4 (range 1.8 to 51.3). The median CV of Crs was 7.7 (range 1.5 to 38.7). Subsequently, median values of respiratory function measures of the first 3 days were calculated. The median Rrs of the first 3 days (Rrs_{neo}) was based on a single measurement at either day 1, 2 or 3 in 25/70 (36%) infants, on two measurements in 17/70 (24%) infants and on three measurements in 28/70 (40%). The median Crs of the first 3 days (Crs_{neo}) was based on a single measurement on either day 1, 2 or 3 in 21/70 (31%) infants, on two measurements in 20/70 (27%) infants and on three measurements in 29/70 (41%). The median CV between Rrs measurements was 15.6 (range 4.2 to 62.1) and between Crs measurements 24.9 (range 0.8 to 60.0).

Relationships between early postnatal lung mechanics and respiratory outcome during infancy

Univariate regression analyses revealed no significant associations between early neonatal clinical data (gestational age, birth weight, radiological RDS severity according to Giedion et al. [13], duration of mechanical ventilation, maximal PIP, number of days requiring a FiO_2 of more than 0.4, and oxygen dependency at 36 weeks gestational age) and respiratory morbidity during the 1st year of life and $Rrs_{1\ year}$. We did find, however, significant associations between gestational age, birth weight, and duration of mechanical ventilation and $Crs_{1\ year}$ (Table 2).

Increased Rrs_{neoC} was associated with respiratory morbidity during the 1st year of life (OR 1.20; 95% CI 1.04 to 1.38; $P = 0.013$). The association between the actually measured values of Rrs_{neo} and respiratory morbidity is presented in Fig. 1. Although independent of gestational age, birth weight, radiological RDS severity according to Giedion et al. [13], duration of mechanical ventilation, number of days requiring a FiO_2 of more than 0.4, and oxygen dependency at 36 weeks gestational age, the association between Rrs_{neoC} and respiratory morbidity was affected by the maximal PIP used during mechanical ventilation. After including maximal PIP as an independent factor in the regression model, the initial relation between Rrs_{neoC} and respiratory morbidity became stronger (i.e. the regression coefficient of Rrs_{neoC} increased) and more significant (OR 1.23; 95% CI 1.05 to 1.43; $P = 0.009$), but maximal PIP itself was not associated with respiratory morbidity (OR 0.90; 95% CI 0.78 to 1.04; $P = 0.149$). Secondly, increased Rrs_{neoC} was related to increased $Rrs_{1\ year}$ (multiplicative β per kPa/l·s 1.017; 95% CI 1.000 to 1.034; $P = 0.045$) and this association was independent of all potentially confounding factors. Thirdly, Rrs_{neoC} was negatively associated with $Crs_{1\ year}$ (multiplicative β per kPa/l·s = 0.986; 95% CI 0.974 to 0.998; $P = 0.023$). Of all potential confounding factors, the number of days requiring a FiO_2 of more than 0.4 substantially affected this association. After including this variable in the regression model, the initial association between Rrs_{neoC} and $Crs_{1\ year}$ became more significant (multiplicative β per kPa/l·s = 0.984; 95% CI 0.972 to 0.995; $P = 0.007$) and the number of days requiring a FiO_2 of more than 0.4 itself was negatively associated with $Crs_{1\ year}$ (multiplicative β per day = 0.992; 95% CI 0.986 to 0.999; $P = 0.019$).

Crs_{neo} was positively associated with $Crs_{1\ year}$ (multiplicative β per ml/kPa = 1.015; 95% CI 1.000 to 1.030; $P = 0.049$). However, after correction for birth weight this association lost statistical significance (multiplicative β per ml/kPa = 1.001; 95% CI 0.984 to 1.018; $P = 0.885$) and birth weight itself was significantly associated with $Crs_{1\ year}$ (multiplicative β per kg = 1.181; 95% CI 1.052 to 1.310; $P = 0.007$). Crs_{neo} was neither associated with $Rrs_{1\ year}$ (multiplicative β per ml/kPa = 0.998; 95% CI 0.990 to 1.007; $P = 0.653$) nor with respiratory morbidity (OR 0.96; 95% CI 0.84 to 1.09; $P = 0.495$).

Discussion

We found that in the current surfactant era, early neonatal Rrs (Rrs_{neoC}), and not Crs (Crs_{neo}), was associated with respiratory outcome during infancy. Increased Rrs_{neoC} was associated with respiratory morbidity during the 1st year of life, increased Rrs ($Rrs_{1\ year}$) and decreased Crs ($Crs_{1\ year}$) at 1 year of age. These causal relationships were not affected by factors

Table 2 Results of univariate regression analyses with $Crs_{1\ year}$ as a dependent variable

Early neonatal factor ($n = 57$)	Multiplicative β per unit of independent	95% CI of β	P
Gestational age (weeks)	1.035	1.013–1.057	0.002
Birth weight (g)	1.0002	1.000–1.000	0.001
Radiological RDS severity[a]	1.005	0.954–1.055	0.851
Duration of mechanical ventilation (days)	0.996	0.992–0.999	0.018
Maximum PIP (cm H_2O)	0.995	0.979–1.011	0.510
Number of days with $FiO_2 > 0.4$	0.993	0.986–1.000	0.062
Oxygen dependency at 36 weeks post-conceptional age	1.229	0.991–1.466	0.059
Rrs_{neoC} (kPa/l·s)	0.986	0.974–0.998	0.023
Crs_{neo} (ml/kPa)	1.015	1.000–1.030	0.049

[a]Radiological score for severity of RDS according to Giedion et al. [13] (0–4)

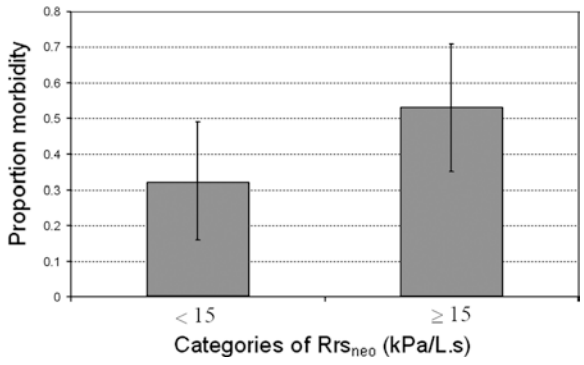

Fig. 1 Mean proportions of infants with respiratory morbidity (i.e. inhaled corticosteroid or bronchodilator therapy, or rehospitalisation) during the 1st year of life for two categories of Rrs_{neo}. *Error bars* indicate 95% confidence intervals of the mean

indicating degree of prematurity and neonatal disease. The relationship between Rrs_{neoC} and respiratory morbidity was strengthened by inclusion of maximal PIP required during mechanical ventilation in the neonatal period into the regression model. The relationship between Rrs_{neoC} and $Crs_{1\ year}$ was strengthened by the number of days requiring a FiO_2 of more than 0.4. Early postnatal Crs_{neo} was not associated with respiratory outcome during the 1st year of life. Degree of prematurity and duration of mechanical ventilation were also associated with $Crs_{1\ year}$.

Rrs_{neoC} was the most consistent factor related to respiratory outcome during the 1st year of life in ventilated preterm infants. Rrs represents the sum of the resistive properties of chest wall, airways and, especially in immature infants, the lung parenchyma [26]. Acute respiratory disease in preterm infants is dominated by parenchymal changes like surfactant deficiency, alveolar hyaline membrane deposition, interstitial oedema, and pulmonary interstitial emphysema. As treatment facilities for acute respiratory disease have improved dramatically, early postnatal Rrs increasingly reflects inborn properties of the respiratory system [10] depending on gestational age, intra-uterine lung development, and familial predisposition. Nowadays, determinants of respiratory course in ventilated preterm infants may become similar to those in healthy term infants, described by Martinez et al. [24,25]. It has been suggested before that both interruption of antenatal lung development by preterm birth [7,17] and intra-uterine growth retardation [8] are important indicators of respiratory outcome in preterm infants. In a study of very low birth weight infants, Chan et al. [3] found that conductance (the reciprocal of resistance) in the 1st year of life was not associated with neonatal oxygen score and duration of mechanical ventilation. Lui et al. [22], who found that Rrs, measured during the 1st week of life in 46 infants with birth weights of < 1000 g, was related to respiratory outcome, while Crs was not. They also found that Rrs was a better predictor of CLD development than RDS and surfactant use. These findings support our findings and argue that inborn properties of the respiratory system more strongly affect respiratory outcome than acute neonatal lung injury by RDS or ventilator conditions.

Both gestational age and birth weight, as markers of intra-uterine body growth, did not affect the relationships between Rrs_{neoC} and respiratory outcome. Intra-uterine lung growth may be completely reflected by Rrs_{neoC}, and may therefore not be a real confounder. We found that inspiratory pressures during mechanical ventilation (maximal PIP) and duration of supplemental oxygen exposure did affect the relationships between Rrs_{neoC} and respiratory morbidity, and Rrs_{neoC} and $Crs_{1\ year}$, respectively. Hence, correction for these factors seems important to reveal more pure aetiological relationships.

Since the compliance of the chest wall is very high in preterm infants [12], Crs_{neo} is predominantly affected by changing conditions of lung tissue. In severe RDS, surfactant deficiency together with alveolar deposition of hyaline membranes and interstitial oedema are known to decrease Crs [6]. As a consequence of decreased RDS severity [4], neonatal Crs decreased less and is therefore not related to long-term respiratory outcome. In preterm infants developing CLD, Baraldi et al. [1] showed that, instead of Rrs, Crs was strongly associated with forced expiratory flow ($V'max_{FRC}$) at the age of 2 years; however, Crs was measured between 10 and 20 days of life. By that time, CLD is usually worsening, thereby causing Crs to decrease. Alternatively, the increased variability of early neonatal Crs measurements makes this a less sensitive tool in relation to respiratory outcome. The poor relationship between Crs_{neo} and respiratory outcome in this study may well have been influenced by the use of surfactant. In 66% of the infants in our study population, exogenous surfactant was instilled at a median age of 9 h. Surfactant is known to immediately improve Crs values [5] and to decrease RDS severity [4]. Postnatal corticosteroid administration did not show any confounding effect.

Assessment of passive respiratory mechanics using the SBT according to Le Souef et al. [20] is simple and can be easily performed in intubated preterm infants with minimal disturbance to the patient. We are well aware of the limitations of this technique, especially in intubated preterm infants [29]. By using strict criteria recommended by the ERS, neonatal respiratory function results can be considered reliable. CVs of Rrs and Crs within subjects and within measurements were acceptable, indicated by low median CVs. CVs of Rrs and Crs within subjects between the daily measurements during the first 3 days of life were larger, especially for Crs assessments. This indicates that Rrs and Crs may change considerably during the first days of life.

More studies are needed to explore which factors contribute to intra-uterine lung development, postnatal lung function and respiratory outcome in the current surfactant era. We intend to follow our study population

into childhood to explore future respiratory development in relation to early respiratory system mechanics.

To conclude, we found important causal relationships between early postnatal Rrs (but not Crs) and respiratory outcome during the 1st year of life in preterm ventilated infants. Relationships were not adversely affected by measures reflecting degree of prematurity, neonatal disease, and ventilator conditions. This indicates that inborn properties of the respiratory system have become increasingly important in relation to respiratory outcome instead of neonatal disease and treatment conditions.

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