Lung Volume, Gas Mixing, and Mechanics of Breathing in Mechanically Ventilated Very Low Birth Weight Infants with Idiopathic Respiratory Distress Syndrome

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ABSTRACT. We assessed pulmonary function in 14 mechanically ventilated newborn very low birth weight infants with idiopathic respiratory distress syndrome by means of a face-out, volume displacement body plethysmograph and nitrogen washout analyses. Specially designed computer programs were used for calculations of lung volumes, ventilation, gas mixing efficiency, and mechanical parameters. In addition to very low compliance and moderately elevated resistance of the respiratory system, there were considerably impaired gas mixing efficiency and low functional residual capacity (FRC). No correlations between positive end-expiratory pressure and mean airway pressure *versus* compliance, resistance, or FRC could be found. Neither could correlations be found between FRC and compliance or FRC and the calculated right to left shunt. (*Pediatr Res* 30: 496–500, 1991)

Abbreviations

FiO₂, fraction of inspired oxygen
FRC, functional residual capacity
IRDS, idiopathic respiratory distress syndrome
MAP, mean airway pressure
NC, nitrogen clearance
PaO₂, arterial oxygen tension
PIP, peak inspiratory pressure

For methodologic reasons, lung function studies in newborn infants with IRDS have largely been focused on lung mechanics. Using applied methods makes it possible to obtain a more comprehensive picture of ventilatory conditions, even in very premature, severely affected infants. To further clarify the pathophysiology of IRDS under conditions of mechanical ventilation in this group of infants, we assessed lung volume, alveolar ventilation, gas mixing efficiency, and lung mechanics in mechanically ventilated infants with birth weights below 1500 g.

MATERIALS AND METHODS

We studied 14 very low birth weight infants with IRDS during intermittent positive pressure ventilation within 5 d (range 0–5 d) of birth. Six of the infants were boys and eight were girls. Median birth weight was 1.29 kg (range 1.00–1.50 kg) and

median gestational age was 29 wk (range 26–33 wk). Informed consent was obtained from the parents of each infant before the procedure was carried out, and the study was approved by the ethics committee of Göteborg University.

Maternal history included preeclampsia in six cases and abruptio of the placenta in three cases. One infant was a twin. Twelve infants were delivered by cesarean section. Apgar scores were below 5 at 1 min in seven infants and below 7 at 5 min in seven infants. All infants were flushed with oxygen immediately after birth, and nine were also ventilated using a mask. Ten of the infants with adequate spontaneous respiration were treated with continuous positive airway pressure by nasal prongs within 4 h of birth, and the other four were intubated and ventilated within a few minutes of birth. Mechanical ventilation was started within 27 h in all infants. The pulmonary disease was classified as IRDS in all infants (1). All initial radiographs showed a reticulogranular pattern, and no infant had positive blood cultures or hematologic signs of infection.

The following guidelines for mechanical ventilation of very low birth weight infants with IRDS were used in the intensive care unit: Nasal intubation with uncuffed endotracheal tubes 2.5–3.0 (Portex LTD, Hythe, Kent, UK) was performed. A Sechrist Infant Ventilator 400 B (Sechrist Industries Inc., Anaheim, CA) was connected to the endotracheal tube. The breathing gas was humidified and heated with a humidifier (Fisher and Paykel, Auckland, New Zealand). Initial ventilator settings were: respiratory rate 60 breaths/min, inspiratory/expiratory ratio 1/2, PIP 25–30 cm H₂O, PEEP 4–6 cm H₂O, and FiO₂ 0.5–1.0. With guidance from arterial blood gas analyses, PIP was then adjusted until normocapnia was achieved, and PEEP was increased until a distinct, sizeable rise in arterial oxygen tension was seen. FiO₂ was then gradually reduced over several hours. The respiratory rate and the inspiratory/expiratory ratio were adjusted to improve ventilation or with the intention of eliminating spontaneous breathing.

The lung function studies were performed after initial adjustments of the ventilator treatment and when the infant was in a stable condition. Median time from start of artificial ventilation until the lung function study was performed was 15.5 h (range 1–93 h). At the time of study, median FiO₂ was 0.50 (range 0.23–0.85), respiratory rate 70 breaths/min (range 59–94 breaths/min), inspiratory time 0.37 s (range 0.21–0.52 s), expiratory time 0.49 s (range 0.27–0.63 s), PIP 25 cm H₂O (range 14–37 cm H₂O), PEEP 5.4 cm H₂O (range 3.8–9.9 cm H₂O), and MAP was 14 cm H₂O (range 7.2–19 cm H₂O).

Eleven infants were extubated within 1–8 d and later had normal outcomes. One infant developed bronchopulmonary dysplasia and had to be ventilated for several months. Two infants died, one at 2 d and the other at 1 mo, of severe respiratory insufficiency.

Received January 9, 1991; accepted April 24, 1991.

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Supported by Grants No. 5703 and 7543 from the Swedish Medical Research Council.

We used a measuring system constructed to record respiratory flow continuously, as well as airway pressure and nitrogen concentration in breathing gas during mechanical ventilation and intensive care. This system has been described in detail elsewhere (2). Infants breathing vigorously against the ventilator were given a muscle relaxant (vecuronium bromide 0.1 mg/kg body weight) as a part of a clinical routine. Ventilatory flow was recorded by means of a face-out, volume displacement body plethysmograph placed inside the infant's incubator. A pneumotachograph (Fleisch no. 1; Siemens-Elema, Gothenburg, Sweden) was mounted in the wall of the plethysmograph and connected to a differential pressure transducer (ES EMT 32; Siemens-Elema). Airway pressure was measured in the proximal end of the endotracheal tube. Nitrogen washouts were performed and analyzed by means of a gas sampling device built into the endotracheal tube connector for nitrogen concentration measurement in a nitrogen analyzer (HP 47302A; Hewlett-Packard Co., Palo Alto, CA).

The mechanical parameters of the respiratory system were calculated by means of a least mean square analysis-based computer program (3). Work and work rate were calculated taking both resistive and elastic work into account (4). FRC, dead space, and alveolar ventilation were calculated according to Sjöqvist *et al.* (5). NC index, *i.e.* the amount of ventilation, normalized by the FRC, needed to wash out a nitrogen volume from 10 to 90% of its initial volume, expresses the gas mixing efficiency and was also calculated from the nitrogen elimination curve (6). The right to left shunt was calculated according to the alveolar-arterial oxygen tension gradient, using a nomogram (1).

Monitoring of the infants' vital functions was continued during the procedure. ECG, transcutaneous oxygen tension, and respiratory rate were continuously monitored in all infants. Arterial blood gases were analyzed before each measurement. The samples were drawn either from a radial or an umbilical arterial line. In some infants, arterial blood pressure was measured continuously. Rectal and skin temperature were also monitored.

RESULTS

In Table 1, mean values, SD, and ranges of data from the nitrogen washout analyses are presented. FRC varied from 9.3 to 30 mL with a mean value of 20 mL. Alveolar ventilation varied from 79 to 343 mL/min, with a mean value of 178 mL/min. NC varied from 4 to 19 with a mean value of 11.

Mean values, SD, and ranges of data on the mechanical parameters of the respiratory system are presented in Table 2. Compliance of the respiratory system varied from 0.25 to 0.52 mL/cm H₂O, with a mean value of 0.37 mL/cm H₂O. Resistance varied from 61 to 166 cm H₂O/L/s with a mean value of 95 cm H₂O/L/s.

Under the conditions of mechanical ventilation described, there were no evident correlations between compliance of the respiratory system, conductance, or calculated shunt and FRC (Fig. 1). Neither were there correlations between PEEP or birth weight and FRC (Fig. 2).

To test whether the duration of disease with ventilator treat-

Table 1. Mean values, SD, and ranges of data from nitrogen washout analyses*

Parameter	Mean	SD	Range	Mean/kg body weight
FRC (mL)	20	6.5	9.3–30	15.5
V _E (mL/min)	542	126	312–745	424
V _A (mL/min)	178	73	79–343	141
V _T (mL)	7.7	1.8	5–11	6.1
V _D (mL)	5.2	1.2	3.2–6.5	4.0
NC	11	3.8	4–19	

* V_E, total ventilation; V_A, alveolar ventilation; V_T, tidal volume; V_D, dead space.

Table 2. Mean values, SD, and ranges of data from analyses of mechanical parameters of respiratory system*

Parameter	Mean	SD	Range
Crs (mL/cm H ₂ O)	0.37	0.09	0.25–0.52
Rrs (cm H ₂ O/L/s)	95	31	61–166
Crs·Rrs (ms)	36	14	17–68
Crs/FRC (L/cm H ₂ O)	0.021	0.011	0.011–0.053
G/FRC [L/(cm H ₂ O·s)]	0.65	0.33	0.22–1.4
Work/breath (cm H ₂ O·mL)	120	43	47–221
Work rate (mW)	15	5.6	4.7–24
Work/mL V _T (cm H ₂ O)	17	3.6	9.5–34

* Crs, compliance of the respiratory system; Rrs, resistance of the respiratory system; G, conductance; V_T, tidal volume.

Fig. 1. Correlations between compliance of the respiratory system (Crs), conductance (G), calculated shunt, and FRC.

Fig. 2. Correlations between PEEP, body weight (bw), and FRC.

ment before the lung function study affected the results, the material was divided into two moieties according to time of ventilator treatment (above or below the median value of 15.5 h). Ventilatory index $[(\text{FiO}_2 \times \text{MAP})/\text{arterial oxygen tension}]$, NC, and the calculated right to left shunt were higher in the infants investigated early during the course of the disease. No differences were seen in FiO_2 , FRC, compliance, resistance, or MAP. Neither were there any differences in gestational age or birth weight between the two groups.

We also wanted to test whether the severity of disease, expressed as calculated right to left shunt, influenced any other calculated parameter at the time of study. Dividing the material at the median shunt value (33%), we found no significant differences between the groups, except for a higher ventilatory index in the group with the larger shunt.

DISCUSSION

Assessment of pulmonary function in the sick, premature newborn infant needing intensive care has long been a challenge, not only because of the fragility of the newborns and their inability to cooperate, but also because of a limitation of available techniques. The use of whole body plethysmography in combination with a multiple breath nitrogen washout technique has several advantages. Air leaks around the endotracheal tube can be disregarded, because the ventilatory volume is recorded from the volume displacement of the chest movement. Extra dead space in a flowmeter in the artificial airway can be prevented. Mechanical ventilation does not have to be interrupted for

measuring maneuvers, and both short and long studies can be performed, providing information on both mechanics of the respiratory system and simultaneous lung volumes.

One of the main findings of this study, in addition to generally low compliance and reduced FRC, was the greatly impaired capacity for efficient mixing of inspired and alveolar gas in lungs afflicted with IRDS. The mean value of NC in the ventilated infants with IRDS was 11 (SD 3.8), which can be compared with that of term healthy newborns, 5 (SD 0.4) (recalculated from Sandberg) (7). This reduced efficiency of gas mixing may be a result of a reduction of alveolar and small airway space in IRDS owing to disseminated atelectases and alveolar influx of fluid. Distended remaining air-filled structures and high ventilatory flow rates also contribute to the impaired gas mixing. Thus, gas mixing efficiency seems to be a characteristic feature of the pathophysiology of very preterm infants with IRDS.

The infants in the present study had very low respiratory system compliance, with a mean value of 0.37 mL/cm H_2O . This is in agreement with other findings (Tables 3 and 4) (8–19). Immaturity and poor development of alveolar tissue, lung surfactant deficiency, and increased leak of proteinaceous fluid into the alveolar space are probably contributing factors.

Airway resistance in spontaneously breathing, nongrunting infants with IRDS is hardly affected, or slightly elevated (20). Most studies on resistance of the respiratory system in mechanically ventilated infants with IRDS show increased values as compared with healthy preterms. The mean pulmonary resistance value of the infants in our study was 95 cm $\text{H}_2\text{O}/\text{L}/\text{s}$, which was lower than values in other studies (Tables 3 and 4) (8–19). It is, however, difficult to make comparisons with data from

Table 3. Observations on mechanical parameters of lung and respiratory system*

Author	Parameter			
	Crs (mL/cm H_2O)	Cl	Rrs (cm $\text{H}_2\text{O}/\text{L}/\text{s}$)	RI
Philips <i>et al.</i> (8)	0.60† 0.46† 0.35†			
Thomson and Silverman (9)‡	0.21–0.71		120–380	
Bhutani <i>et al.</i> (10)		0.44		106
Bhutani <i>et al.</i> (11)		0.30–0.43		116
Davis <i>et al.</i> (12)		0.38		64
Couser <i>et al.</i> (13)		0.33–0.43		141–160
Goldman <i>et al.</i> (14)		0.48–0.56		85–150

* Crs, compliance of the respiratory system; Cl, compliance of the lung; Rrs, resistance of the respiratory system; RI, resistance of the lung.

† Values for different levels of PEEP; 0, 5, and 10 cm H_2O .

‡ Different technique for respiratory flow measurement.

Table 4. Observations on mechanical parameters of respiratory system*

Author	Parameter	
	Crs (mL/cm H_2O)	Rrs (cm $\text{H}_2\text{O}/\text{L}/\text{s}$)
LeSouef <i>et al.</i> (15)	0.76	124
Simbruner <i>et al.</i> (16)	0.51–0.60	
Popow and Simbruner (17)	0.58	
Dreizzen <i>et al.</i> (18)	0.53	
Prendiville <i>et al.</i> (19)	0.61	195–224

* Crs, compliance of the respiratory system; Rrs, resistance of the respiratory system.

nonintubated spontaneously breathing infants and mechanically ventilated infants as well as with different materials of mechanically ventilated infants for several reasons. One contributing factor to the raised flow resistance is the endotracheal tube (21). The tube size and the type of connector is of major importance, as is the size of air flow that is forced through by the mechanical ventilator (22). Kinking of the tube, improper position, and tracheal secretions are other factors that might affect endotracheal tube resistance and possibly also explain the very wide range of values seen in most investigations.

The time constant is a variable of great importance to adjustments of the ventilator settings. Too high a time constant might give rise to a risk of air trapping and inadvertent PEEP (16). In our infants, time constants varied from 17 to 68 ms with a mean value of 36 ms. Considering the highest time constant among our infants, a 50% increase of resistance would mean a risk of air trapping at a ventilatory rate of 60 breaths/min and an inspiratory/expiratory ratio of 1/1.

Only a limited amount of data is available on measurements of FRC in preterm newborns with IRDS. Richardson *et al.* (23) presented data on 32 intubated, spontaneously breathing newborn preterms on continuous positive airway pressure with a mean body weight of 2.013 kg and a mean FRC of 21.4 mL, using a nitrogen washout technique. They have also presented later work on a similar material with intermittent positive pressure ventilation, using the same technique, with a FRC of 14.5 mL/kg body weight (24). Heaf *et al.* (25) measured FRC with a closed-circuit helium dilution technique in nine mechanically ventilated preterm infants with IRDS and found FRC to vary between 13.3 and 18.1 mL/kg body weight during the first 48 h of life. Bose *et al.* (26) described a multiple gas rebreathing technique with which they found a mean FRC of 10.8 mL/kg body weight in 10 mechanically ventilated preterm newborns. Our data are in good agreement with data from two of these investigators, although our values were slightly higher than those of Bose *et al.* and those in the first work of Richardson *et al.* Differences in mode of ventilation may have contributed to these discrepancies (23, 26). We can consequently confirm the observations that infants with IRDS and a demand for respiratory support have lower FRC than comparable groups without lung disease (27–30).

As shown in Figure 2, there was no correlation between PEEP level and FRC. Bose *et al.* (26) showed that a change in PEEP level is strongly correlated with a change in FRC. In our group of infants, however, effects of changes in ventilator settings in the individual infant were not included in the measurements, and the combined impact of the pulmonary disease rather than PEEP or any other single variable seemed to be the determinant of the lung volume. Thus, we found no correlation between compliance or conductance and FRC as a possible effect of distension and overdistension of airways and alveoli (Fig. 1).

Work rate of breathing was considerably higher in our mechanically ventilated preterm infants than in spontaneously breathing infants of comparable sizes with IRDS and with the same total ventilation (4). This was mainly attributable to the much lower compliance in the ventilated infants. This increased work rate can be considered a measure of the increased net effect the respiratory muscles would have to develop to overcome the respiratory insufficiency. The evident failure of the respiratory muscles to do this is, however, probably a consequence of poor muscular effect due to the soft thoracic walls.

The impact of ventilator treatment time and duration of disease was studied by dividing the material in two moieties according to duration of the ventilator treatment. The higher ventilatory index, calculated right to left shunt, and NC index found in infants investigated early during the course of the disease indicate that these infants had a more severe pulmonary disease. Inasmuch as the majority of the infants improved and were extubated within 8 d and because infants with IRDS usually start to improve clinically after 2–3 d, this difference is not surprising.

We were not able to sort out any specific entity in the pulmonary function tests that indicated the development of chronic lung disease, nor was any particular variable attributed to a longer duration of ventilator treatment. Neither was any mechanical or ventilatory variable strongly correlated to the calculated right to left shunt.

The observation by Richardson *et al.* (24) that there was a linear correlation between alveolar-arterial oxygen gradients and FRC could not be confirmed in our study. Extrapulmonary shunting or pulmonary ventilation-perfusion mismatch may contribute to this difference in data.

In conclusion, very immature infants with severe IRDS requiring mechanical ventilation have considerably impaired gas mixing efficiency in addition to low FRC, very low compliance, and moderately elevated resistance of the respiratory system. The results of the measurements of FRC, compliance, and resistance are similar to values measured by other techniques in similar populations of infants. FRC varied considerably without evident correlation to PEEP or any other parameter of the ventilator settings. To maintain normal blood gases, ventilation had to be elevated, and the work rate required to ventilate the sick lungs was considerably higher than in spontaneously breathing infants. Within the group, there were no correlations between FRC, mechanical parameters, or severity of disease expressed as calculated right to left shunt. Neither did differences in duration of ventilator treatment affect any mechanical parameters.

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