Changes in Lung Volume and Ventilation during Surfactant Treatment in Ventilated Preterm Infants

Martijn Miedema¹, Frans H. de Jongh¹, Inez Frerichs², Mariëtte B. van Veenendaal¹, and Anton H. van Kaam¹

¹Department of Neonatology, Emma Children’s Hospital, Academic Medical Center, Amsterdam, The Netherlands; and ²Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Germany

Rationale: The immediate and regional effects of exogenous surfactant in open lung high-frequency oscillatory ventilated (HFOV) preterm infants are unknown.

Objectives: To assess regional changes in lung volume, mechanics, and ventilation during and after surfactant administration in HFOV preterm infants with respiratory distress syndrome (RDS).

Methods: Using electrical impedance tomography, changes in lung volume were continuously recorded during a stepwise recruitment procedure before, during, and after surfactant administration in 15 preterm infants (gestational age: 28.3 wk; birth weight: 1,000 g). Deflation limbs of the pressure-impedance curve before and after surfactant were mapped and the effect of surfactant on oscillation volumes and ventilation was determined. Data were analyzed for the whole cross-section and the left, right, ventral, and dorsal lung regions.

Measurements and Main Results: Surfactant increased lung volume by 61 ± 39% within a median time of 241 seconds. The ventral to dorsal ratio in lung volume changed significantly from 1.16 before to 0.81 after surfactant administration. The upper inflection point of the deflation limb after surfactant (10.4 ± 2.4 cm H2O) was significantly lower compared with before surfactant (16.4 ± 3.1 cm H2O). Surfactant increased maximal compliance of the respiratory system, and this effect was reached at lower airway pressures. Surfactant caused a transient decrease in oscillatory volume but did not alter its regional distribution.

Conclusions: Surfactant treatment in HFOV preterm infants with RDS causes a rapid increase and subsequent stabilization of lung volume, which is most prominent in dependent lung regions. Maximal lung compliance increases but at lower airway pressures. Ventilation distribution is not affected by surfactant.

Keywords: premature infant; surfactant; high-frequency oscillatory ventilation; electrical impedance tomography

Despite the increasing use of noninvasive respiratory support, almost one-half of extremely preterm infants with respiratory distress syndrome (RDS) need invasive mechanical ventilation and are treated with exogenous surfactant (1).

The effect of exogenous surfactant on lung function was initially studied in animal models, which showed that surfactant increases and stabilizes functional residual capacity (FRC), improves lung compliance, and results in more homogeneous ventilation (2–4).

Studies in preterm infants have mainly explored the effect of exogenous surfactant on lung function in RDS and exclusively during conventional ventilation. These studies also showed a positive effect of surfactant on FRC (5). However, data on the changes in lung compliance have been less consistent, varying from a reduction, to no change, to an increase in compliance after surfactant treatment (6–13). This inconsistency may, in part, be explained by the fact that most studies assessed the effect of surfactant on lung function at different points in time after treatment, ranging from 15 minutes to several hours. To date, no study in preterm infants continuously measured the acute changes in lung volume and mechanics during surfactant administration. This is also true for the regional effects of surfactant on lung volume and ventilation.

This gap in knowledge is mainly caused by the limitations of the available bedside lung function monitoring tools. This has recently changed with the introduction of electrical impedance tomography (EIT), a noninvasive bedside tool capable of continuously measuring (regional) changes in lung impedance, which are highly correlated with changes in gas volume (14). Studies have shown that EIT measurements are also feasible in preterm infants (15, 16). In this study, we used EIT to monitor (regional) changes in lung volume and ventilation during and after surfactant administration in high-frequency ventilated premature infants with RDS. We hypothesized that exogenous surfactant would increase and stabilize lung volume, improve compliance, and result in a more homogeneous distribution of ventilation.

METHODS

A detailed description of the methodology is provided in the online supplement.

The study was performed in the neonatal intensive care unit of the Emma Children’s Hospital, Academic Medical Center (Amsterdam,
the Netherlands). Preterm infants (< 37 wk) were included if they failed nasal continuous positive airway pressure (nCPAP) and needed high-frequency oscillatory ventilation (HFOV) for a suspected diagnosis of RDS within 72 hours after birth. All patients were ventilated in the supine position and were not sedated or paralyzed. The study was approved by the institutional board and written informed consent was obtained from both parents.

HFOV was used as a primary mode and combined with an open lung ventilation strategy using oxygenation as an indirect marker for lung volume. Briefly, the continuous distending pressure (CDP) was increased stepwise (1–2 cm H2O) until oxygenation no longer improved or fractional inspired oxygen (FiO2) was less than or equal to 0.25 (CDPc). Next, CDP was decreased with 1- to 2-cm H2O steps until oxygenation deteriorated (CDPp). Finally, the lung was once more recruited (CDPp) and then stabilized with a CDP of 2 cm H2O above CDPopt. Previous studies have shown that this open lung approach is feasible in the majority of preterm infants with RDS and does not lead to hemodynamic instability (17, 18).

Surfactant was then administered as a bolus via a closed system catheter. After a stabilization period of 10 minutes, the CDPc, CDPp, and CDPopt were once more determined. If CDPc could be successfully reduced to 8 cm H2O without oxygenation compromise, the procedure was stopped and this pressure was designated as CDPopt.

Changes in lung impedance (ΔZ) were continuously recorded during the above-described procedures, using a scan rate of 44 Hz. Relative ΔZ was calculated for each decremental pressure step before and after surfactant treatment using a 30-second reference period at the start of recruitment and just before surfactant administration, respectively. All ΔZ values were normalized setting the ΔZ at presurfactant CDPopt, at 100%. Using the pressure/impedance pairs, individual ventilations were plotted according to Venegas and colleagues, and the upper inflection points (UIPs), maximum compliance of the respiratory system (Crsmax), and pressure at Crsmax were calculated (19). The immediate effect of surfactant on lung volume was assessed by calculating the increase in ΔZ after administration and the stabilization time. The above-described analyses were performed for the whole chest cross-section as well as for the ventral, dorsal, right, and left lung regions. The regional effect of surfactant on lung volume was assessed by calculating the ventral/dorsal and right/left ratios at presurfactant CDPopt, directly after surfactant but before the first decremental pressure step and at postsurfactant CDPopt.

At these same time points the effect of surfactant treatment on oscillation volume was calculated using band-pass filtering (600 ± 15/min). In addition, the ventilator to dorsal and left to right distribution of the normalized oscillatory ΔZ was calculated using functional images (20, 21). The area under the curve ventral = dorsal) were calculated for the ventral, dorsal, left, and right regions.

Nonlinear regression was used to plot the deflation limbs. For comparative analyses the Mann-Whitney or Wilcoxon rank test was used for skewed data and the Student t test for a normal distributed data. A P value less than 0.05 was considered statistically significant.

RESULTS

Fifteen newborn infants were included in the study and completed the recruitment procedure and surfactant administration without complications (Table 1). The mean CDP at the start of lung recruitment (CDPp) was 8.3 ± 1.7 cm H2O with a mean FiO2 of 0.73 ± 0.27. The mean CDPp, CDPc, and CDPopt before surfactant treatment were, respectively, 19.3 ± 1.7, 11.0 ± 1.6, and 13.0 ± 1.6 cm H2O, with a mean FiO2 of 0.26 ± 0.04. Surfactant was administered in a mean dose of 136 ± 27 mg/kg, after which CDP could be decreased in all patients to 8.0 cm H2O, with a mean FiO2 of 0.21.

Surfactant Effect on Lung Volume

Lung volume increased in all patients after surfactant administration with a mean increase of 61 ± 39% expressed as percentage of the presurfactant lung volume at CDPp (Figure 1).

This volume increase was reached after a median time of 241 (interquartile range [IQR], 118–300) seconds. The median ventral to dorsal ratio in lung volume changed significantly from 1.16 (IQR, 0.79–1.89) before to 0.81 (IQR, 0.40–0.96) after surfactant administration, whereas the right to left ratio remained unchanged (Table 2).

The fitting curves of the deflation limbs before and after surfactant could be constructed in all patients with a mean goodness of fit (R²) of 0.98 ± 0.03 and 0.97 ± 0.05, respectively. The UIP after surfactant (10.4 ± 2.4 cm H2O) was significantly lower compared with the UIP before surfactant (16.4 ± 3.1 cm H2O) (P < 0.01) (Table 2). Crsmax increased significantly from a median of 6.9 (IQR, 4.9–8.1) %/cm H2O before to 9.0 (IQR, 8.3–11.8) after surfactant administration. The pressure at which Crsmax was reached also changed from 12.0 (IQR, 8.8–13.2) before to 7.2 (IQR, 4.7–7.8) cm H2O after surfactant treatment (Table 3). These changes were also observed in the different analyzied lung regions.

Surfactant Effect on Ventilation

Compared with the presurfactant time point (= 100%), the median oscillation volume decreased significantly to 73.6% (IQR, 62.1–80.6) immediately after surfactant treatment followed by an increase to 85.2% (IQR, 75.2–91.4) at optimal postsurfactant inflation (Table 2). Transcutaneous carbon dioxide pressure initially increased after surfactant administration but reached significantly lower values at optimal inflation, despite the fact that the mean oscillation pressure amplitude decreased from 20.4 ± 2.6 cm H2O before to 18.5 ± 3.5 cm H2O after surfactant treatment (Table 3).

In general, oscillatory ventilation showed a slight asymmetrical distribution favoring the ventral lung regions along the vertical axis (Table 2 and Figure 2). Furthermore, oscillatory ventilation was more ventrally located in the right lung compared with the left lung. Surfactant administration did not change this regional distribution (Table 2, Figures 2 and 3).

DISCUSSION

To our knowledge, this is the first study that continuously measured regional lung volume changes during and after surfactant treatment in preterm infants with RDS. Up to now, the effect of exogenous surfactant on lung volume has only been determined...
in conventionally ventilated preterm infants, using different techniques to measure lung volume changes and different time points after administration (5–10, 13). These studies showed that surfactant increased FRC by 20 to 100% (4, 12, 13). In the present study, surfactant was administered during HFOV and after a lung recruitment procedure. The main reason for recruiting the lung before surfactant treatment was to minimize ventilation-induced lung injury as much as possible during the presurfactant ventilation period. Surfactant administration under these conditions is different from the studies using conventional ventilation in which surfactant also plays an important role in lung recruitment. Despite these differences, we found a comparable increase in lung volume (60%) in preterm infants on HFOV. But more importantly, we were able to show that this volume increase was completed in the majority of infants within 5 minutes after surfactant administration. To our knowledge, this observation has not been previously reported.

In addition to measuring the changes in lung volume in the whole chest cross-section after surfactant treatment, EIT also provided regional information on these changes, which ideally should be homogenously distributed. Our study shows that the increase in lung volume was most prominent in the dorsal lung region (i.e., in the dependent lung parts). This finding seems to support previous animal experimental data suggesting that gravity plays an important role in the distribution of exogenous surfactant (22).

The observed increase in lung volume can be caused by either alveolar/saccular distension or recruitment. Considering the fact that the lungs of these preterm infants were already recruited
before surfactant administration, it is most likely that the observed volume increase after surfactant administration was, for the larger part, caused by distension. The fact that we observed only a small improvement in oxygenation after surfactant treatment (FlO₂ from 0.26 to 0.21) supports this assumption, as only alveolar recruitment and not distension will improve oxygenation.

To assess the effect of surfactant on lung mechanics, we mapped the deflation limb of the pressure/impedance curve before and after treatment. As indicated by the significant decrease in the UIP of the deflation limb, surfactant stabilized lung volume at much lower pressures compared with the surfactant-deficient lung. Surfactant treatment also resulted in a significant increase in Crs max and a reduction of the airway pressures. Immediately after surfactant administration, the oscillation volume decreased, probably as a result of airway obstruction. Over time the oscillation volume improved as airway pressures were reduced and surfactant moved into the periphery of the lung. The fact that the oscillation volumes did not return to presurfactant values after completing the postsurfactant recruitment procedure is probably best explained by the reduction in the pressure amplitude. Despite this decrease in pressure amplitude and oscillation volume, transcutaneous carbon dioxide pressure levels were lower after surfactant, indicating improved alveolar ventilation as also shown in previous studies in premature infants (5, 11–13).

Analysis of the regional distribution of the oscillatory volume showed that ventilation was more prominent in the right and ventral lung region. This (novel) finding is probably best explained by the anatomical position of the heart, resulting in less lung

### TABLE 2. CHANGES IN LUNG VOLUME, OSCILLATION VOLUME DISTRIBUTION, AND FRACTIONAL VENTILATION DISTRIBUTION DIRECTLY AFTER SURFACTANT INSTILLATION AND AT THE OPTIMAL PRESSURE POSTSURFACTANT

<table>
<thead>
<tr>
<th></th>
<th>Optimal Pressure</th>
<th>Postsurfactant before the First Decremental Pressure Step</th>
<th>Optimal Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Presurfactant</td>
<td></td>
<td>Postsurfactant</td>
</tr>
<tr>
<td>Ventral to dorsal</td>
<td>1.6 (0.79–1.89)</td>
<td>0.84 (0.60–1.49)</td>
<td>0.81 (0.40–0.96)</td>
</tr>
<tr>
<td>Right to left ratio</td>
<td>1.07 (0.73–1.39)</td>
<td>0.94 (0.86–1.17)</td>
<td>0.97 (0.83–1.21)</td>
</tr>
<tr>
<td>$\Delta Z_{\text{osc}}$, %</td>
<td>6.9 (5.7–8.0)</td>
<td>7.3 (6.3–8.1)†</td>
<td>6.3 (5.7–7.9)†</td>
</tr>
<tr>
<td>T $\text{P}_{\text{CO}_2}$, kPa</td>
<td>53.8 ± 9.0</td>
<td>54.0 ± 7.8</td>
<td>53.5 ± 7.4</td>
</tr>
<tr>
<td>AUC$\text{ven}$, total matrix, %</td>
<td>57.7 ± 8.7</td>
<td>56.7 ± 6.8</td>
<td>56.0 ± 7.3</td>
</tr>
<tr>
<td>AUC$\text{ven}$, right half, %</td>
<td>49.3 ± 9.9†</td>
<td>51.1 ± 9.9†</td>
<td>50.5 ± 8.5</td>
</tr>
<tr>
<td>Geometric center, whole matrix, %</td>
<td>48.1 ± 4.2</td>
<td>47.9 ± 3.7</td>
<td>48.3 ± 3.5</td>
</tr>
<tr>
<td>Geometric center, right half, %</td>
<td>46.0 ± 4.1</td>
<td>46.4 ± 3.3</td>
<td>46.8 ± 3.7</td>
</tr>
<tr>
<td>Geometric center, left half, %</td>
<td>50.5 ± 4.7</td>
<td>49.4 ± 4.8*</td>
<td>49.8 ± 3.8†</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AUC$\text{ven}$ = area under the curve of the ventral lung region; $\Delta Z_{\text{osc}}$ = relative oscillation impedance change; T $\text{P}_{\text{CO}_2}$ = transcutaneous carbon dioxide pressure.

Values are shown as mean ± SD or median (IQR, 25–75).

* Indicates a significant change in contrast to optimal pressure before surfactant, $P < 0.05$.

† Indicates a significant change in contrast to directly after surfactant treatment, $P < 0.01$.

‡ Indicates a significant change in contrast to directly after surfactant treatment, $P < 0.05$.

### TABLE 3. CHANGES IN THE DEFLATION LIMB CHARACTERISTICS BEFORE AND AFTER SURFACTANT TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>Deflation Limb before Surfactant</th>
<th>Deflation Limb after Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global</td>
<td>Ventral</td>
</tr>
<tr>
<td>UIP, cm H₂O</td>
<td>16.4 ± 3.1</td>
<td>15.7 ± 2.8</td>
</tr>
<tr>
<td>Crs max, %/cm H₂O</td>
<td>6.4 (4.9–8.1)</td>
<td>3.6 (2.7–4.4)</td>
</tr>
<tr>
<td>Pressure at Crs max, cm H₂O</td>
<td>12.0 (9.3–12.9)</td>
<td>10.0 (8.6–12.2)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: Crs max = maximal compliance of the respiratory system; UIP = upper inflection point.

Values are shown as mean ± SD or median (IQR, 25–75).

* Indicates a significant change in contrast to the deflation limb before surfactant, $P < 0.01$.

† Indicates a significant change in contrast to the deflation limb before surfactant, $P < 0.05$. 

‡ Indicates a significant change in contrast to optimal pressure before surfactant, $P < 0.05$. 

§ Indicates a significant change in contrast to optimal pressure before surfactant, $P < 0.01$. 

||
This finding seems to support the validity of the presented EIT data. It was interesting to observe that surfactant treatment did not change the distribution of oscillatory ventilation. Although this finding might suggest a homogenous surfactant distribution, other explanations should also be considered. First, surfactant treatment in an already recruited, and thus homogeneously aerated lung might not impact ventilation distribution even if surfactant distribution is heterogeneous. Second, the oscillatory volumes may be too small to pick up more subtle changes in ventilation distribution. This might be different during conventional mechanical ventilation, although a recent animal study does not seem to support this explanation (2).

This study has several limitations that need to be addressed. First, EIT only monitored lung volume changes in one transversal “slice” of the lung. RDS is suggested to be a homogenous lung disease, making it highly likely that the presented findings are representative for the entire lung. Second, although not essential, this study did not provide information on the absolute changes in lung volume as the calibration of the EIT signal has, so far, not been feasible. Third, all the patients in this study were treated with open lung HFOV. The results may be different during conventional (tidal) ventilation, during which surfactant also plays an important role in lung recruitment. However, the similar findings on FRC and compliance in animal and human studies using conventional ventilation seem to be reassuring (2, 7). Finally, surfactant was administered relatively late (⩾ 2 h) after birth, which may have reduced its efficacy. This delay is probably best explained by the fact that all patients in our unit are started on nCPAP (1). The fact that many clinicians have adopted the use of early nCPAP makes our study results clinically relevant.

Despite these limitations, our study has important implications for clinical practice. First, this study shows that surfactant treatment during high-frequency ventilation increases lung volume comparable to treatment during conventional (tidal) ventilation. Second, based on the stabilizing effect of surfactant on lung volume, clinicians should reduce the airway pressures after treatment to avoid possible overdistension and to profit from the increased compliance. Third, this reduction in pressure should be started within 5 minutes after surfactant therapy. Finally, rescue surfactant treatment in a recruited lung seems to result in a relatively homogenous distribution, although there is a possible gravity-dependent tendency for surfactant to move to the more dependent lung parts. This latter finding suggests that body positioning might be an effective way to augment regional surfactant deposition in heterogeneous lung disease.

In conclusion, this study shows that rescue surfactant treatment in open lung high-frequency ventilated preterm infants with RDS causes a rapid increase (minutes) and subsequent stabilization of lung volume, which is most prominent in dependent lung regions. In addition, surfactant treatment increases maximal compliance, but at lower airway pressures. Ventilation distribution is relatively homogeneous and not affected by surfactant.

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**Figure 2.** Distribution of the normalized oscillation amplitude (ΔZ in percentage) in 32 anterior to posterior slices at optimal pressure before (left panel), after (middle panel), and at the optimal pressure after surfactant administration (right panel). The slices were denoted by setting the most anterior part to 0% and the most posterior part to 100%. Data are presented as mean values ± SD.

**Figure 3.** Summarized fractional regional oscillation distribution in 32 anterior to posterior slices of the right and left halves of the chest determined at optimal pressure before (left panel), after (middle panel), and at optimal pressure after surfactant administration (right panel). The numbers in the left and right corners of these diagrams specify the fractional ventilation in the right and left thoracic cross-sections, respectively. Data are presented as mean values ± SD. D = dorsal; L = left; R = right; V = ventral.
References


