The effect of airway pressure and oscillation amplitude on ventilation in preterm infants

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Abstract:

We determined the effect of lung recruitment and oscillation amplitude on regional oscillation volume and functional residual capacity (FRC) in high-frequency ventilated (HFV) preterm infants with respiratory distress syndrome (RDS).

Changes in lung volume, oscillation volume and carbon dioxide levels were recorded in 10 infants during a stepwise recruitment procedure and an increase in pressure amplitude of 5 cmH₂O using electrical impedance tomography and transcutaneous monitoring. The pressures at maximal respiratory system compliance, maximal oscillation volume and minimal carbon dioxide levels were determined. Impedance data were analyzed for the chest cross-section and predefined regions of interest.

Despite the fixed pressure amplitude, the oscillation volume changed during the incremental pressure steps following a parabolic pattern, with an inverse relation to the carbon dioxide pressures. The pressures corresponding with maximal compliance, maximal oscillation volume and minimal carbon dioxide were similar and highly correlated. Regional analysis showed similar findings. The increase in pressure amplitude resulted in increased oscillation volumes and decreased carbon dioxide levels, while FRC remained unchanged.

In HFV preterm infants with RDS, oscillation volumes are closely related to the position of ventilation in the pressure-volume envelope and the applied pressure amplitude. Changes in pressure amplitude do not seem to affect FRC.

Keywords: electrical impedance tomography · high-frequency oscillatory ventilation · preterm infant · oscillation volume
Introduction

High frequency oscillatory ventilation (HFOV) is a lung protective ventilation mode frequently used in preterm infants with respiratory failure [1]. It has been suggested that ventilation and oxygenation during HFOV can be controlled independently by adjusting, respectively, the oscillation amplitude or frequency, and the continuous distending pressure (CDP) or the fraction of inspired oxygen (FIO2) [2-6]. An increase in oscillation amplitude at a fixed frequency will increase the oscillatory volume measured at the airway opening and improve carbon dioxide removal [7-9]. An increase in CDP at a fixed FIO2 will increase lung volume by alveolar recruitment in atelectatic lung diseases and improve oxygenation by reducing the intrapulmonary right-to-left shunt [5,10].

From a physiological standpoint it is unlikely that the control of ventilation and oxygenation are truly independent from each other during HFOV [11-13]. Changes in functional residual capacity (FRC) during a recruitment procedure will almost certainly impact lung compliance and oscillation volume, as the position of ventilation changes along the inflation and deflation limbs of the pressure/volume curve [12-15]. Furthermore, adjustments in oscillation amplitude may, in theory, also lead to (small) changes in alveolar pressures, which in turn can affect FRC.

To date, there are no studies exploring the effect of FRC on ventilation and vice versa in high-frequency ventilated preterm infants with respiratory distress syndrome (RDS). An important reason for this knowledge gap is the lack of an easy to use bedside tool for continuous monitoring of lung volume in preterm infants. This has recently changed with the introduction of electrical impedance tomography (EIT). EIT can continuously and non-invasively monitor changes in lung impedance, which are highly correlated to changes in gas volume [16]. EIT provides regional information on lung volume changes in the chest cross-
section, which may be important in case of heterogeneous lung disease or gravitational effects [16-19].

In this study we used EIT to assess the impact of FRC changes during an individualized lung recruitment procedure in preterm infants with RDS on oscillation volume. In addition, we studied the effect of a standardized increase in oscillation amplitude on oscillation volume and FRC. We hypothesized that oscillation volumes change in relation to the position of ventilation on the pressure-volume curve and that changes in oscillation amplitude will impact oscillation volume but not FRC.

**Methods**

**Patients**

The study was performed in the neonatal intensive care unit of the Emma Children’s Hospital, Academic Medical Center (Amsterdam, the Netherlands), where preterm infants (< 37 weeks) with a suspected diagnosis of RDS and failing nasal continuous positive airway pressure are treated with primary open lung HFOV. Infants were included in the study if HFOV was started within 72 hours after birth and written informed consent was obtained from both parents. Exclusion criteria were congenital anomalies, severe circulatory shock or persistent pulmonary hypertension of the newborn. All patients were ventilated in the supine position and were not sedated or paralyzed. The study was approved by Institutional Review Board.

**Ventilation protocol**

The first phase of the study consisted of an oxygenation guided, individualized lung recruitment procedure, aiming to place ventilation on the deflation limb of the pressure-volume curve [20,21]. All patients were ventilated with a Sensormedics 3100A oscillator.
(CareFusion, Yorba Linda, USA), starting at a continuous distending pressure (CDP_{st}) of 6-8 cm H\textsubscript{2}O and pressure amplitude resulting in visible oscillations of the chest with a frequency of 10 Hz and an inspiration time of 33\%. The CDP was increased with steps of 1-2 cm H\textsubscript{2}O every 2 - 3 minutes until oxygenation no longer improved or the FIO\textsubscript{2} was $\leq 0.25$ with a transcutaneous oxygen saturation (SpO\textsubscript{2}) between 86\%-94\% (opening pressure, CDP\textsubscript{o}). Next, CDP was decreased with 1-2 cm H\textsubscript{2}O steps every 2 – 3 minutes, until oxygenation deteriorated, indicating alveolar/saccular collapse (closing pressure, CDP\textsubscript{c}). Finally, the lung was once more recruited with the known CDP\textsubscript{o} and then stabilized with a CDP 2 cm H\textsubscript{2}O above CDP\textsubscript{c} (optimal pressure, CDP\textsubscript{opt}). After confirming the correct endotracheal tube position by chest X-ray, surfactant was administered and following a 10 minutes stabilization period, the postsurfactant CDP\textsubscript{c}, CDP\textsubscript{o} and CDP\textsubscript{opt} were once more determined.

SpO\textsubscript{2} and transcutaneous carbon dioxide pressure (TcPCO\textsubscript{2}) was monitored continuously throughout the recruitment procedure, but only the stabilized values displayed just before each pressure step were used for further analysis. Adjustments in pressure amplitude were only made if the absolute TcPCO\textsubscript{2} value was deemed to be reliable and outside the target range (4.5 – 7.5 kPa) for more than 3 pressure steps during the recruitment procedure.

The second phase of the study started 10 minutes after stabilization at the postsurfactant CDP\textsubscript{opt}. The pressure amplitude was increased by 5 cm H\textsubscript{2}O for 10 minutes and then decreased back to the initial setting.

**EIT examination**

Before intubation sixteen hand-trimmed ECG electrodes (BlueSensor, BRS-50-K, Ambu, Inc., Linthicum) were equidistantly placed on the thorax circumference of the newborn just above the nipple line and connected to the “Goettingen Goe-MF II” EIT system (CareFusion, Hoechberg, Germany). Small electrical currents (5 mA_{rms}, 100 kHz) were
repetitively injected in rotation through adjacent electrodes pairs and voltage changes were measured by all passive electrodes pairs (scan rate 44 Hz). A backprojection image reconstruction algorithm generated a 32 x 32 matrix of local relative impedance changes (ΔZ) compared to a reference state. Changes in lung electrical impedance and airway pressure were continuously recorded during the recruitment procedure and the pressure amplitude trial using the Veit software (CareFusion, Hoechberg, Germany). EIT data were analyzed off-line using AUSPEX version 1.6 (VUMC, Amsterdam, The Netherlands).

Off-line analyses

Lung recruitment and volume changes

Using the absolute pressure steps and the concomitant changes in normalized ΔZ, the inflation and deflation limbs of the recruitment manoeuvre were plotted for all individual patients, as previously described [22]. Next, the inflation limb was fitted according to the model described by Venegas and colleagues, which is formulated as

$$V = a + b/(1+e^{-(P-c)/d})$$

where V is lung volume, P is the pressure at the airway opening, a is the lower asymptote volume, b is the total change in lung volume between the lower and upper asymptote, c corresponds to the pressure at the point of highest compliance and d is proportional to the pressure range within which most of the volume change takes place. Using this formula we determined the pressure at which maximal respiratory system compliance (Crs_{max}) was reached [14].

To assess the effect of CDP changes on oscillation volume a stable 30-s period was selected at each pressure step during the recruitment procedure and referenced to the average ΔZ in that same period. Next, the ΔZ signal was high-pass filtered leaving only ΔZ changes that occurred at a frequency of > 580 per minute (10 Hz). The oscillation amplitudes were calculated using the peaks and troughs of this signal. The averaged oscillation amplitudes of
ΔZ values and the concomitant changes in TcPCO₂ levels were then plotted against the absolute pressure changes for both the inflation and deflation limbs. The derivative of the Venegas equation was used to calculate the pressure corresponding with the maximal oscillation volume and the lowest TcPCO₂ level of the inflation limb [14].

The above described analyses were also performed for the oscillation volumes in the ventral, dorsal, right and left halves of the cross-section.

**Pressure amplitude and volume changes**

To establish the effect of pressure amplitude changes on oscillation volume, 30-s periods were selected at the end of each 10 minute period before, during and after the increase in pressure amplitude and referenced to the average ΔZ in that same period. For each of these 3 periods, the EIT signal was band-pass filtered in the spontaneous breathing domain (5-90 per minute) and the spontaneous tidal breathing frequency was determined. In addition, the signal was high-pass filtered (>580 per minute) focusing only on the oscillation frequency and its higher harmonics to determine the change in oscillation volume, expressed as a percentage of the starting value.

Using the same 30-s periods, we also assessed the effect of changed pressure amplitude on lung volume, by using a fixed reference period selected at the start of the intervention.

**Statistical analysis**

For statistical analysis we used GraphPad Prism 5.0 (Graphpad Software Inc., San Diego, USA) and SPSS version 16.0 (SPSS Inc., Chicago, USA). Depending on their distribution, data were expressed as mean ± standard deviation (SD) or as median with interquartile ranges (IQR). For comparative analyses a Mann-Whitney or Wilcoxon rank test were used for skewed data and a student t-test for normal distributed data. Bivariate non
parametric correlations (Spearman’s rank correlation coefficient = $\rho$) were calculated for oscillation volume versus $TcPCO_2$ and between pressure at $Crs_{\text{max}}$, maximal oscillation volume and minimal $TcPCO_2$. A $p$ value less than 0.05 was considered statistically significant.

Results

Ten newborn infants were included in the study and completed the recruitment procedure and the change in pressure amplitude without complications (Table 1). The mean $CDP_{\text{st}}$ was 7.6 ± 1.3 cm H$_2$O with a $FIO_2$ of 0.73 ± 0.24. The recruitment procedure resulted in a mean $CDP_o$, $CDP_c$ and $CDP_{\text{opt}}$ of, respectively, 19.2 ± 2.1, 10.1 ± 1.5 and 12.1 ± 1.5 cm H$_2$O with a reduction in mean $FIO_2$ to 0.24 ± 0.03. The mean pressure amplitude at the start of recruitment was 20.6 ± 2.3 cm H$_2$O and it was maintained during the presurfactant recruitment procedure. The change in pressure amplitude in the second phase of the study after surfactant administration was performed at a mean $CDP_{\text{opt}}$ of 7.2 ± 1.0 cm H$_2$O and resulted in a mean increase from 18.2 ± 2.3 cm H$_2$O to 23.2 ± 2.3 cm H$_2$O.

Lung recruitment and volume changes

All individual pressure/impedance curves showed clear lung hysteresis (Figure 1). Modelling of the inflation limb according to the Venegas equation was possible in all patients with a mean goodness of the fit ($R^2$) of 0.99 ± 0.00 resulting in a median pressure at $Crs_{\text{max}}$ of 12.9 (IQR 12.1 – 16.7) cm H$_2$O. The changes in oscillation volume and $TcPCO_2$ showed a significant, inverse correlation in all patients during the recruitment procedure (Figure E1A and E1B). As expected, the pressure/oscillation volume and pressure/$TcPCO_2$ relationship during inflation showed a parabolic shape in almost all infants (Figure 1). The derivative of the Venegas equation could be fitted for the oscillation volume in 10 patients ($R^2 = 0.92$ ±
0.06) and for the TcPCO₂ data in 8 patients (R² = 0.95 ± 0.03). The median pressure at maximal oscillation volume determined from these fitted curves during inflation was 14.0 (IQR 13.0 – 14.5) cm H₂O. For the minimal TcPCO₂, it was 13.7 (IQR 11.8 – 14.8) cm H₂O. Both pressures were significantly correlated with the Crs max pressure (Figure 2). During the decremental pressure steps, the pressure/oscillation volume and pressure/TcPCO₂ relationships could not be fitted due to insufficient number of data points, but in all patients CDP reduction from CDP₀ resulted in an (initial) increase in oscillation volume (Figure 1 and Figure E1A and E1B).

Regional analysis of the data from the ventral versus dorsal and right versus left cross-section halves of the oscillation volume showed similar results in pressure at Crs max, maximal oscillation volume and minimal TcPCO₂, with no significant differences between the different regions of interest.

**Pressure amplitude and volume changes**

Increasing the pressure amplitude by 5 cm H₂O, resulted in a significant increase in the median oscillation volume and a concomitant decrease in TcPCO₂ (Figure 3). This increase in oscillation volume was evenly distributed over the ventral and dorsal lung regions. Comparing the right and left lung revealed that the volume increase was significantly higher in the right lung (data not shown). The increase in pressure amplitude resulted in a significant (p < 0.01) decrease in the median spontaneous breathing frequency from 36 (IQR 20 – 76) per minute to 18 (IQR 10 – 30) per minute. Functional residual capacity showed no significant change in response to the increase in pressure amplitude.

**Discussion**
HFOV is a lung protective ventilation mode that is used in 15-25% of the preterm infants [1,23]. It has been suggested that oxygenation and ventilation during HFOV can be controlled independently by adjusting, respectively, lung volume via the CDP and the oscillation volume via the pressure amplitude [3-6]. This study shows, for the first time, that this assumption is not correct for preterm infants with RDS during lung volume recruitment following the initiation of HFOV.

The most important finding of this study is that pulmonary ventilation and gas exchange, expressed as both the oscillation volumes and TcPCO₂ levels, changes during a lung recruitment procedure on HFOV, despite the fact that the pressure amplitude remains constant. The changes in oscillation volume and TcPCO₂ were inversely correlated in all patients, strengthening the validity of our findings. The pattern of these changes during inflation was similar in most of the patients, showing an increase in oscillation volume and a decrease in TcPCO₂ during the first part of recruitment, followed by a decrease in oscillation volume and an increase in TcPCO₂ towards the end of the incremental pressure steps. The fact that the airway pressures resulting in the maximal compliance, the highest oscillation volume and lowest TcPCO₂ were almost identical and highly correlated, strongly suggests that the observed ventilation pattern is best explained by the changes in lung compliance as ventilation moves up the inflation limb of the pressure-volume curve. Despite of only few data points available during deflation, the increase in oscillation volume with a concomitant decrease in TcPCO₂ seem to support the association between lung volume and ventilation. Our findings are in line with the study of van Genderingen and colleagues, showing a similar relationship between FRC and ventilation, expressed as the oscillatory pressure ratio, in high frequency ventilated surfactant deficient pigs [24]. The fact that the association between FRC and (tidal) ventilation was also found in animal experiments using pressure-controlled ventilation indicates that these physiological principles are independent of the ventilation mode [15,18].
In an in vitro study, Pillow and colleagues also found a clear association between changes in lung compliance and tidal volumes during HFOV [25]. However, this association disappeared when compliance exceeded a certain threshold, indicating that the findings of our study may have specific relevance to recruitment from atelactasis and are less important when lung volume is maintained at optimal CDP.

An important advantage of EIT is its ability to assess the regional changes in lung aeration. Our study shows that the changes in oscillation volume during lung recruitment are evenly distributed across the ventral and dorsal lung regions, supporting previous findings that RDS is a relatively homogenous lung disease [21,22].

Previous studies have shown that an increase in pressure amplitude increases the oscillation volume measured at the airway opening [6-8]. This study shows that this increase in oscillation volume can also be detected at the regional pulmonary level using EIT. Furthermore we were able to show that this increase in oscillation volume also resulted in a decrease in TcPCO$_2$ and the spontaneous breathing frequency, strengthening the validity of our EIT finding. Again, the increase in oscillation volume was evenly distributed across the ventral and dorsal lung regions. We did, however, find a significantly higher increase in oscillation volume in the right lung compared with the left lung. This right-sided predominance is probably best explained by the presence of the heart in the left hemi-thorax [21,26].

The increase in pressure amplitude did not seem to impact FRC, but this finding needs to be interpreted with some caution because the variation in pressure amplitude was relatively modest and only applied at one point in time during HFOV when the lung was already at optimal CDP. Further, the pressure amplitude change was confined to a short interval. The results may be different if the change in pressure amplitude was more substantial or applied at different stages of lung recruitment, lung disease and at different ventilator settings. To our
knowledge, only one study varied the pressure amplitude repeatedly in preterm infants on HFOV, but unfortunately this study did not measure FRC [9]. However, the authors did report a modest but significant increase in arterial O₂ pressure (1.1 kPa), which may have reflected an increase in lung volume.

This study has several limitations that need to be addressed. First, EIT only provides information on a transverse “slice” of the lung. Considering the fact that RDS is a relatively homogeneous lung disease, it is very likely that the EIT findings as described in this study are representative for the entire lung. The close association between the cross-sectional changes in oscillation volume and TcPCO₂ seem to support this assumption. Second, this study only included preterm infants with RDS and the findings may be different in other causes of respiratory failure. Finally, although not essential, this study did not provide information on the absolute changes in oscillation volume. Unfortunately, calibration of the electrical impedance tomography signal to tidal volumes measured at the airway opening is not yet feasible.

Despite these limitations and the fact that EIT remains a research tool, our study has important implications for clinicians using HFOV in preterm infants. First, this study shows that, in addition to oxygenation, changes in oscillation volumes and TcPCO₂ can also assist the clinician in optimizing the lung volume during HFOV. Transcutaneous monitoring is nowadays increasingly used in clinical practice and many of the newer ventilators display (a measure of) tidal volumes during HFOV. Especially during the incremental pressure steps, falling oscillation volumes or an increase in pressure amplitude in case of volume guarantee and an increase in TcPCO₂ can alert the clinician that he or she is approaching the flat part of the inflation limb, i.e. optimal recruitment. Second, clinicians should closely monitor TcPCO₂ during lung recruitment and if necessary adjust the pressure amplitude in order to minimize the risk of hypo- and hypercapnia. Finally, in those infants that are not heavily sedated during
HFOV, changes in spontaneous breathing activity seem to be associated with oscillatory volume and TcPCO₂. This finding suggests that spontaneous breathing activity can be used in a clinical strategy that aims to preserve normal breathing during HFOV, thereby reducing the risk of overventilation and diaphragmatic dysfunction.

In conclusion, this study shows that the oscillatory volumes during HFOV in preterm infants with RDS are closely related to the position of ventilation on the inflation and deflation limb of the pressure volume relationship of the lung, and the applied pressure amplitude. Changes in pressure amplitude do not seem to impact the FRC. This information can help the clinician in optimizing lung volume and ventilation during HFOV.
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*Definition of abbreviations: GA = gestational age, mOI = modified oxygenation index (CDP x FIO₂/SpO₂; FiO₂ in percentage)*
Figure 1

Representative global pressure/impedance (left panel; inflation limb: open diamonds; deflation limb: closed diamonds), oscillation volume/pressure (open circles) and transcutaneous carbon dioxide pressure/pressure (closed circles) relationships during the inflation (middle panel) and deflation limb (right panel) of an open lung high-frequency ventilated preterm infant. The X-axis of the deflation limb is shown in the reversed order from high to low continuous distending pressures. The Spearman’s rank correlation coefficients between oscillation volume and transcutaneous carbon dioxide pressure are given in the right upper corner of each individual patient (* $p < 0.05$, ** $p < 0.01$).

Definition of abbreviations: AU = arbitrary unit, CDP = continuous distending pressure, kPa = kilopascal, P-V = pressure-volume, TcPCO$_2$ = transcutaneous carbon dioxide pressure level, Vosc = oscillation volume

Figure 2

Continuous distending pressures corresponding with maximal respiratory system compliance (empty box), maximal oscillation volume (light grey box) and minimal transcutaneous pressure of carbon dioxide (dark grey box) during lung inflation. The Spearman’s rank correlation coefficients between these three variables are shown above the box plots (* $p <
0.05, ** $p < 0.01$). The median, the 25th and the 75th percentile, minimum and maximum values of 10 infants are shown.

Definition of abbreviations: CDP = continuous distending pressure, Crs$_{max}$ = maximal compliance of the respiratory system, Vosc$_{max}$ = maximal oscillation volume, TcPCO$_2$$_{min}$ = minimal transcutaneous carbon dioxide pressure level, (* $p < 0.05$, ** $p < 0.01$)
**Figure 3**

Oscillation volumes (empty boxes) and transcutaneous carbon dioxide pressure levels (grey boxes) before, during, and after a 5 cm H$_2$O increase in pressure amplitude in high-frequency ventilated preterm infants. The initial oscillation volume before the pressure amplitude increase was set at 100%. The median, the 25$^{th}$ and the 75$^{th}$ percentile, minimum and maximum values of 10 infants are shown.

** p < 0.01 during vs before the increase in pressure amplitude
++ p < 0.01 after vs during the increase in pressure amplitude
* p < 0.05 after vs before the increase in pressure amplitude
+ p < 0.05 after vs during the increase in pressure amplitude

*Definition of abbreviations:* Vosc = oscillation volume, TcPCO$_2$ = transcutaneous carbon dioxide pressure level