The effect of airway pressure and oscillation amplitude on ventilation in pre-term 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 oscillatory ventilation (HFOV) used in pre-term 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 cmH_2O was measured 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 analysed 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 relationship 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 pre-term 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, oscillation volume, pre-term infant

High-frequency oscillatory ventilation (HFOV) is a lung protective ventilation mode frequently used in pre-term 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 (F_{I,O_2}) [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 F_{I,O_2} 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 on lung compliance and oscillation volume (V_{osc}), as the position of ventilation changes along the inflation and deflation limbs of the pressure–volume curve [12–15]. Furthermore, adjustments in oscillation amplitude also may, in theory, 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 pre-term 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 pre-term infants. This has recently changed with the introduction of electrical impedance tomography (EIT). EIT can continuously

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and noninvasively monitor changes in lung impedance, which are highly correlated with 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 our study, we used EIT to assess the impact of FRC changes during an individualised lung recruitment procedure in pre-term infants with RDS on V_{osc}. In addition, we studied the effect of a standardised increase in oscillation amplitude on V_{osc} and FRC. We hypothesised that V_{osc} changes in relation to the position of ventilation on the pressure–volume curve and that changes in oscillation amplitude will impact on V_{osc} 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 pre-term 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 h 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 paralysed. The study was approved by the Institutional Review Board of the Academic Medical Centre of Amsterdam (Amsterdam, the Netherlands).

Ventilation protocol
The first phase of the study consisted of an oxygenation-guided, individualised lung recruitment procedure, aiming to place ventilation on the deflation limb of the pressure–volume curve [20, 21]. All patients were ventilated with a Sensor-medics 3100A oscillator (CareFusion, Yorba Linda, CA, USA), starting at a continuous distending pressure (CDP_{st}) of 6–8 cmH_2O 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 cmH_2O every 2–3 min until either oxygenation no longer improved or the F_{I,O_2} was ≤0.25 with an arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) of 86–94% (opening pressure (CDP_o)). Next, CDP was decreased with 1–2 cmH_2O steps every 2–3 min until oxygenation deteriorated, indicating alveolar/saccular collapse (closing pressure (CDP_c)). Finally, the lung was once more recruited with the known CDP_o and then stabilised with a CDP 2 cmH_2O above CDP_c (optimal pressure (CDP_{opt})). After confirming the correct endotracheal tube position by chest radiograph, surfactant was administered and, following a 10-min stabilisation period, the post-surfactant CDP_c, CDP_o and CDP_{opt} were once more determined.

S_{p,O_2} and transcutaneous carbon dioxide pressure (P_{tc,CO_2}) were monitored continuously throughout the recruitment procedure, but only the stabilised values that were displayed just before each pressure step were used for further analysis. Adjustments in pressure amplitude were made only if the absolute P_{tc,CO_2} value was deemed to be reliable and outside the target range (4.5–7.5 kPa) for more than three pressure steps during the recruitment procedure.

The second phase of the study started 10 min after stabilisation at the post-surfactant CDP_{opt}. The pressure amplitude was increased by 5 cmH_2O for 10 min and then decreased back to the initial setting.

EIT examination
Before intubation, 16 hand-trimmed ECG electrodes (BlueSensor, BRS-50-K; Ambu Inc., Linthicum, MD, USA) 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 electrode pairs, and voltage changes were measured by all passive electrodes pairs (scan rate 44 Hz). A backprojection image reconstruction algorithm generated a 32×32 matrix of local relative impedance changes (ΔZ) compared with 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). EIT data were analysed 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 normalised 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 *et al.* [14], 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 ($C_{rs,max}$) was reached [14].

To assess the effect of CDP changes on V_{osc}, 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 min (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 P_{tc,CO_2} 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 V_{osc} and the lowest P_{tc,CO_2} level of the inflation limb [14].

The analyses described above were also performed for the V_{osc} 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 V_{osc}, 30-s periods were selected at the end of each 10-min period

before, during and after the increase in pressure amplitude and referenced to the average ΔZ in that same period. For each of these three periods, the EIT signal was band-pass filtered in the spontaneous breathing domain (5–90 per min) and the spontaneous tidal breathing frequency was determined. In addition, the signal was high-pass filtered (>580 per min), focussing only on the oscillation frequency and its higher harmonics to determine the change in V_{osc}, 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 (Graph-Pad Software Inc., San Diego, CA, USA) and SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Depending on their distribution, data were expressed as mean $\pm$ SD or as median with inter-quartile range (IQR). For comparative analyses, a Mann–Whitney or Wilcoxon rank test were used for skewed data and a paired t-test for normal distributed data. Bivariate nonpara-metric correlations (Spearman's rank correlation coefficient, ρ) were calculated for V_{osc} versus P_{tc,CO_2} and between pressure at $C_{rs,max}$, maximal V_{osc} and minimal P_{tc,CO_2}. A p-value of <0.05 was considered statistically significant.

RESULTS

10 newborn infants were included in the study and completed the recruitment procedure and the change in pressure amp-litude without complications (table 1). The mean $\pm$ SD CDPst was 7.6 ± 1.3 cmH$_2$O with a F_{I,O_2} of 0.73 ± 0.24. The recruitment procedure resulted in CDPo, CDPc and CDPopt of 19.2 ± 2.1, 10.1 ± 1.5 and 12.1 ± 1.5 cm H$_2$O, respectively, with a reduction in F_{I,O_2} to 0.24 ± 0.03. The pressure amplitude at the start of recruitment was 20.6 ± 2.3 cm H$_2$O and it was maintained during the pre-surfactant recruitment procedure. The change in pressure amplitude in the second phase of the study after surfactant administration was performed at a CDPopt of

7.2 ± 1.0 cmH$_2$O and resulted in an increase from 18.2 ± 2.3 cmH$_2$O to 23.2 ± 2.3 cmH$_2$O.

Lung recruitment and volume changes

All individual pressure–impedance curves showed clear lung hysteresis (fig. 1). Modelling of the inflation limb according to the Venegas equation was possible in all patients with a goodness of fit (R^2) of 0.99 ± 0.00 resulting in a median (IQR) pressure at $C_{rs,max}$ of 12.9 (12.1–16.7) cmH$_2$O. The changes in V_{osc} and P_{tc,CO_2} showed a significant, inverse correlation in all patients during the recruitment procedure (figs S1A and S1B). As expected, the pressure–V_{osc} and pressure–P_{tc,CO_2} relation-ships during inflation showed a parabolic shape in almost all infants (fig. 1). The derivative of the Venegas equation could be fitted for the V_{osc} in 10 patients (R^2=0.92 ± 0.06) and for the P_{tc,CO_2} data in eight patients (R^2=0.95 ± 0.03). The pressure at maximal V_{osc} determined from these fitted curves during inflation was 14.0 (13.0–14.5) cmH$_2$O. For the minimal P_{tc,CO_2}, it was 13.7 (11.8–14.8) cmH$_2$O. Both pressures were significantly correlated with $C_{rs,max}$ pressure (fig. 2). During the decremental pressure steps, the pressure–V_{osc} and pressure–P_{tc,CO_2} relation-ships could not be fitted due to insufficient number of data points, but in all patients, CDP reduction from CDPo resulted in an (initial) increase in V_{osc} (figs 1, S1A and S1B).

Regional analysis of the data from the ventral versus dorsal and right versus left cross-section halves of the V_{osc} showed similar results in pressure at $C_{rs,max}$, maximal V_{osc} and minimal P_{tc,CO_2}, with no significant differences between the different regions of interest.

Pressure amplitude and volume changes

Increasing the pressure amplitude by 5 cmH$_2$O resulted in a significant increase in the median V_{osc} and a concomitant decrease in P_{tc,CO_2} (fig. 3). This increase in V_{osc} was evenly distributed over the ventral and dorsal lung regions. Comparing the right and left lungs 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 spontaneous breathing frequency from 36 (20–76) to 18 (10–30) per min. 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 pre-term 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 V_{osc} via the pressure amplitude [3–6]. This study shows, for the first time, that this assumption is not correct for pre-term 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 V_{osc} and P_{tc,CO_2} levels, changes during a lung recruitment procedure on HFOV, despite the fact that the pressure amplitude remains constant. The changes in V_{osc} and P_{tc,CO_2} were inversely cor-related 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 V_{osc} and a decrease

TABLE 1	Patient characteristics				
Subject no.	GA weeks	Weight g	5' Apgar score	Age at intubation h	mOI
1	25.3	750	6	3	4.5
2	28.1	760	9	4	4.5
3	25.6	790	7	1	12.0
4	29.3	1095	8	2	3.1
5	28.7	880	8	24	6.7
6	29.6	1000	4	10	5.3
7	26.3	1020	9	2	11.4
8	28.0	840	9	3	4.3
9	27.0	610	8	3	8.8
10	28.6	775	9	4	4.7
Median	27.1	815	8	3	5.0

GA: gestational age; mOI: modified oxygenation index (continuous distending pressure × fraction of inspired oxygen (%)/oxygen saturation).
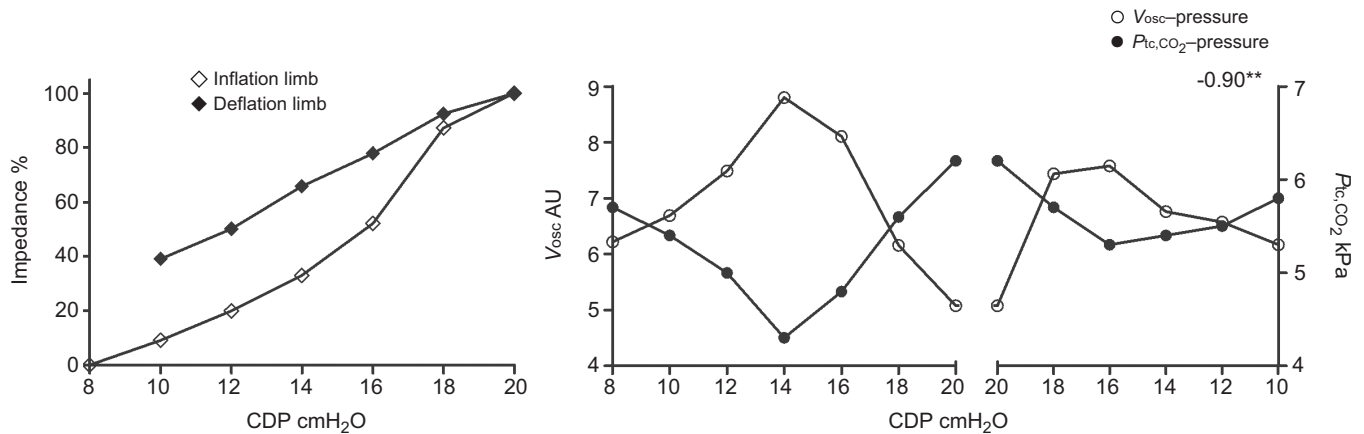
FIGURE 1. Representative global pressure–impedance (left panel), oscillation volume (V_{osc})–pressure and transcutaneous carbon dioxide pressure (P_{tc,CO_2})–pressure relationships during the inflation (middle panel) and deflation limb (right panel) of an open lung high-frequency ventilated pre-term infant. The X-axis of the deflation limb is shown in the reverse order from high to low continuous distending pressures (CDP). The Spearman's rank correlation coefficients between V_{osc} and P_{tc,CO_2} is given in the right upper corner. **: $p < 0.01$.

in P_{tc,CO_2} during the first part of recruitment, followed by a decrease in V_{osc} and an increase in P_{tc,CO_2} towards the end of the incremental pressure steps. The fact that the airway pressures resulting in the maximal compliance, the highest V_{osc} and the lowest P_{tc,CO_2} 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 only few data points being available during deflation, the increase in V_{osc} with a concomitant decrease in P_{tc,CO_2} seems to support the association between lung volume and ventilation. Our findings are in line with the study of VAN GENDERINGEN *et al.* [24], showing a similar relationship between FRC and ventilation, expressed as the oscillatory pressure ratio, in high-frequency ventilated surfactant-deficient pigs. 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 *et al.* [25] also found a clear association between changes in lung compliance and tidal volumes during HFOV. 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 V_{osc} during lung recruitment are evenly distributed
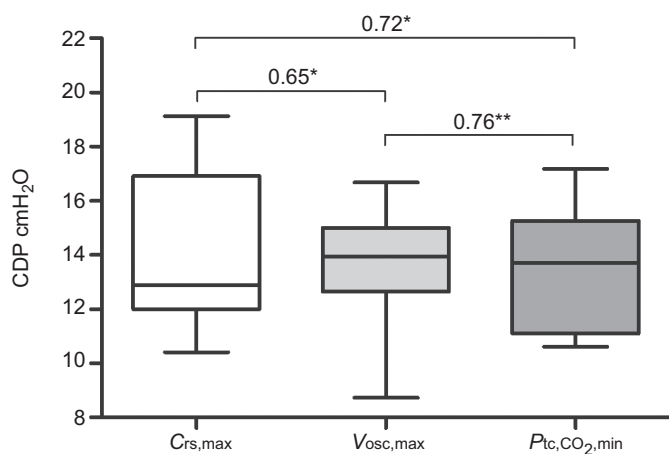

FIGURE 2. Continuous distending pressures (CDPs) corresponding with maximal respiratory system compliance ($C_{rs,max}$), maximal oscillation volume ($V_{osc,max}$) and minimal transcutaneous pressure of carbon dioxide ($P_{tc,CO_2,min}$) during lung inflation. The Spearman's rank correlation coefficients between these three variables are shown above the box plots. The median, 25th and 75th percentiles, and the minimum and maximum values of 10 infants are shown. *: $p < 0.05$; **: $p < 0.01$.
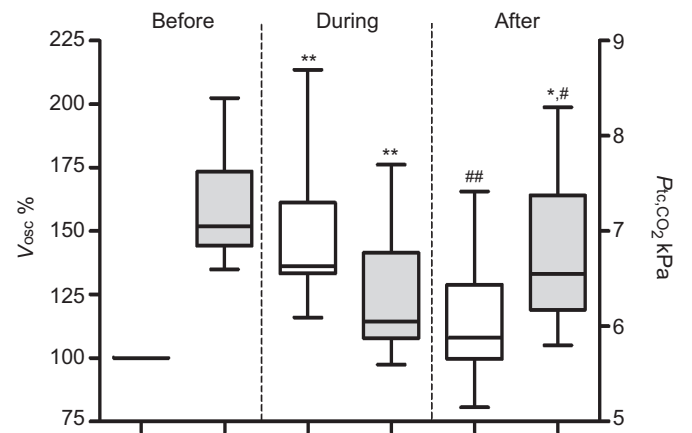

FIGURE 3. Oscillation volumes (V_{osc}; white box) and transcutaneous carbon dioxide pressure (P_{tc,CO_2}; grey box) levels before, during and after a 5-cmH_2O increase in pressure amplitude with high-frequency oscillatory ventilation in pre-term infants. The initial V_{osc} before the pressure amplitude increase was set at 100%. The median, 25th and 75th percentile, and the minimum and maximum values of 10 infants are shown. *: $p < 0.05$ after *versus* before the increase in pressure amplitude; **: $p < 0.01$ during *versus* before the increase in pressure amplitude; #: $p < 0.05$ after *versus* during the increase in pressure amplitude; ##: $p < 0.01$ after *versus* during the increase in pressure amplitude.

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 V_{osc} measured at the airway opening [6–8]. This study shows that this increase in V_{osc} can also be detected at the regional pulmonary level using EIT. Furthermore, we were able to show that this increase in V_{osc} also resulted in a decrease in P_{tc,CO_2} and the spontaneous breathing frequency, strengthening the validity of our EIT finding. Again, the increase in V_{osc} was evenly distributed across the ventral and dorsal lung regions. We did, however, find a significantly higher increase in V_{osc} 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 hemithorax [21, 26].

The increase in pressure amplitude did not seem to impact on 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. Furthermore, 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 pre-term infants on HFOV, but unfortunately this study did not measure FRC [9]. However, the authors did report a modest but significant increase in arterial oxygen 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 of the entire lung. The close association between the cross-sectional changes in V_{osc} and P_{tc,CO_2} seem to support this assumption. Secondly, this study only included pre-term 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 V_{osc}. 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 pre-term infants. First, this study shows that, in addition to oxygenation, changes in V_{osc} and P_{tc,CO_2} can also assist the clinician in optimising 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. During the incremental pressure steps in particular, falling V_{osc} or an increase in pressure amplitude in case of volume guarantee and an increase in P_{tc,CO_2}, can alert the clinician that he or she is approaching the flat part of the inflation limb, *i.e.* optimal recruitment. Secondly, clinicians should closely monitor P_{tc,CO_2} during lung recruitment and if necessary, adjust the pressure amplitude in order to minimise 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 P_{tc,CO_2}. 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 pre-term infants with RDS is 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 optimising lung volume and ventilation during HFOV.

STATEMENT OF INTEREST

A statement of interest for this study can be found at www.erj. ersjournals.com/site/misc/statements.xhtml

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