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Spontaneous breathing during high-frequency oscillatory ventilation improves regional lung characteristics in experimental lung injury

M. van Heerde[1], K. Roubik[2], V. Kopelent[2], M. C. J. Kneyber[1,3] and D. G. Markhorst[1]
[1]*Department of Pediatric Intensive Care, VU University Medical Center, Amsterdam, The Netherlands;* [2]*Faculty of Biomedical Engineering, Czech Technical University in Prague, Kladno, Czech Republic and* [3]*Department of Pediatric Intensive Care, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, The Netherlands*

Background: Maintenance of spontaneous breathing is advocated in mechanical ventilation. This study evaluates the effect of spontaneous breathing on regional lung characteristics during high-frequency oscillatory (HFO) ventilation in an animal model of mild lung injury.
Methods: Lung injury was induced by lavage with normal saline in eight pigs (weight range 47–64 kg). HFO ventilation was applied, in runs of 30 min on paralyzed animals or on spontaneous breathing animals with a continuous fresh gas flow (CF) or a custom-made demand flow (DF) system. Electrical impedance tomography (EIT) was used to assess lung aeration and ventilation and the occurrence of hyperinflation.
Results: End expiratory lung volume (EELV) decreased in all different HFO modalities. HFO, with spontaneous breathing maintained, showed preservation in lung volume in the dependent lung regions compared with paralyzed conditions. Comparing DF with paralyzed conditions, the center of ventilation was located at 50% and 51% (median, left and right lung) from anterior to posterior and at 45% and 46% respectively, $P < 0.05$. Polynomial coefficients using a continuous flow were -0.02 (range -0.35 to 0.32) and -0.01 (-0.17 to 0.23) for CF and DF, respectively, $P = 0.01$.
Conclusions: This animal study demonstrates that spontaneous breathing during HFO ventilation preserves lung volume, and when combined with DF, improves ventilation of the dependent lung areas. No significant hyperinflation occurred on account of spontaneous breathing. These results underline the importance of maintaining spontaneous breathing during HFO ventilation and support efforts to optimize HFO ventilators to facilitate patients' spontaneous breathing.

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Once Ithe mechanisms responsible for ventilator-induced lung injury (VILI) were elucidated, ventilator strategies were sought that could protect the already injured lung from additional harm.[1,2] Lung-protective ventilation strategies aim at the reversal of atelectasis and avoidance of hyperinflation as well as cyclic opening and closing of lung units during tidal ventilation. High-frequency oscillatory (HFO) ventilation is, at least in theory, a ventilation modality that can achieve optimal lung protection. Several animal studies show that HFO ventilation reduces VILI.[3,4]

Both experimental and clinical studies emphasize the positive effect of spontaneous breathing during mechanical ventilation on the distribution of inflation and ventilation in the diseased lung. Spontaneous breathing improves oxygenation, lowers the need for sedatives, improves hemodynamics and reduces the duration of mechanical ventilation and intensive care stay.[5–8]

In HFO ventilation, more conventional respiratory rates (RR) and tidal volumes, as in spontaneous breathing efforts, are not needed to achieve adequate gas exchange.[9] Vigorous spontaneous breathing during HFO ventilation in large patients may in fact cause swings in set mean airway pressure (mP_{aw}) that activate alarms, interrupt oscillations and produce significant desaturations. Initial adult HFO ventilation trials recommended muscular paralysis for this reason.[10,11] The current HFO ventilators' design (3100 A/B, SensorMedics, Yorba Linda, CA) with a fixed fresh gas rate makes it difficult to breathe during HFO ventilation.[12]

In an earlier paper, we reported on this animal experiment focused on work of breathing during HFO ventilation.[13] We demonstrated that demand flow (DF), instead of a continuous fresh gas flow (CF), facilitated spontaneous breathing. The focus of this part of the experiment was to evaluate the effect of spontaneous breathing during HFO ventilation on lung aeration and ventilation in a porcine model of moderate lung injury with the use of electrical impedance tomography (EIT).

EIT is a noninvasive technique for pulmonary imaging. EIT provides meaningful dynamic information on pulmonary conditions. EIT is able to accurately describe both global and regional lung volume changes over time during mechanical ventilation.[14] Compared with electron beam computed tomography, as an established method to assess changes in local air content, simultaneous EIT measurements correlate quite closely.[14–16]

Materials and methods

Animal model preparation

The study was approved by the local Animal Welfare Committee. Eight Dalland pigs 53 ± 6.5 kg (mean $\pm$ SD) were used. Anesthesia was induced with an intramuscular injection of 0.5 mg atropine, 0.5 mg/kg midazolam and 10 mg/kg ketamine. After induction, propofol 3 mg/kg was injected intravenously before endotracheal intubation with a cuffed tube (inner diameter 8 mm). Anesthesia was maintained with continuous infusions of propofol 4 mg/kg/h and remifentanil 0.4 μg/kg/min during instrumentation and lung lavage. To allow spontaneous breathing, propofol dosage was reduced to 2 mg/kg/h, and that of remifentanil to 0.05–0.1 μg/kg/min. Spontaneous breathing was suppressed using pancuronium bromide 0.3 mg/kg/h during instrumentation, lung lavage and when necessary according to the experimental protocol. At the end, animals were euthanized using sodium pentobarbital.

During instrumentation, lung lavage and the stabilization period, animals were ventilated using a Servo 900C ventilator (Maquet Critical Care AB, Solna, Sweden) in the volume-controlled mode: RR 20/min, inspiratory pause time 0.6 s, positive end-expiratory pressure 5 cmH_2O, inspiration to expiration ratio 1 : 2, FiO_2 1.0, initial tidal volume (V_T) 10 ml/kg and then adjusted to maintain normocapnia ($PaCO_2$ 38–45 mmHg). Animals were placed in a supine position on a heated table. Temperature was maintained in the normal range (38–39 °C) using a heating pad.

The left femoral artery was cannulated to measure blood pressure and sample blood. A pulmonary arterial catheter was inserted to sample mixed venous blood. A separate catheter was inserted into the superior vena cava to infuse fluids and anesthetics.

Flow was measured at the proximal end of the endotracheal tube using a hot-wire anemometer (Florian, Acutronic Medical Systems AG, Hirzel, Switzerland). The pressure at the Y-piece in the ventilator circuit (P_{aw}) was sampled using the electronic signal from the internal pressure sensor of the HFO ventilator. The pressure sensor signal was calibrated using a water column. Flow and pressure signals were recorded at 100 Hz and stored on a laptop computer for off-line analysis.

Surfactant deficiency was induced by repeated whole lung lavage. Normal saline 30–40 ml/kg of 37 °C was instilled in the lungs at a pressure of 50 cmH_2O and then directly removed by drainage. The lavage was repeated after one hour.[17,18]

HFO ventilator

HFO ventilation was applied using the 3100B HFO ventilator (SensorMedics). The HFO ventilator was used in a standard configuration with a CF. In order to facilitate spontaneous breathing, the HFO ventilator was equipped with a custom-made DF system. The DF system is able to respond to fluctuations in mP_{aw} on account of spontaneous breathing. The DF system is programmed to maintain a stable mP_{aw}. During inspiration, fresh gas flow is increased, and during expiration, decreased. The DF system is capable of delivering fresh gas flow from 0 to 160 l/min. A more detailed description of the system is given elsewhere.[19]

Study protocol

The study design is depicted in Fig. 1. After 30 min of stabilization on conventional ventilation (CMV) after the last lung lavage, HFO ventilation was initiated. Initial settings: mP_{aw} 20 cmH_2O, proximal pressure amplitude (ΔP) was set to attain normocapnia (38–45 mmHg) and thereafter remained unchanged, oscillatory frequency 5 Hz, inspiration/expiration ratio 1 : 2, fresh gas flow 20 l/min and FiO_2 1.0. HFO ventilation was then applied for 30 min in three different modes: (1) continuous fresh gas flow of 20 l/min and spontaneous breathing

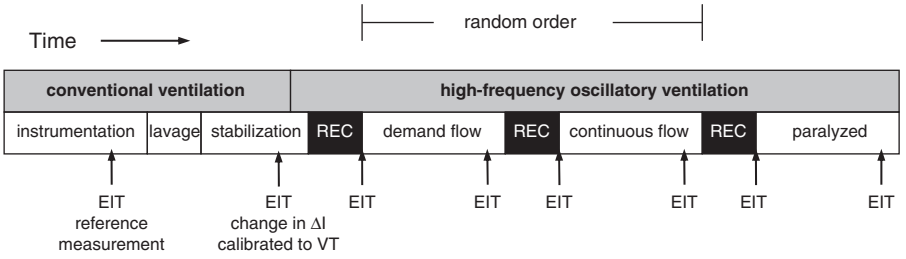

Fig. 1. Study design and electrical impedance tomography analysis. EIT, electrical impedance tomography measurement; rec, recruitment maneuver; ΔI, relative impedance change; V_T, tidal volume of spontaneous breathing.

maintained (CF), (2) DF and spontaneous breathing maintained (DF), both in random order, and in a last step (3) during muscular paralysis (PAR). EIT and physiologic measurements were performed during the last 5 min of every HFO ventilation modality. To avoid the occurrence of lung collapse on account of the preceding HFO ventilation run, a recruitment maneuver was performed preceding each HFO ventilation modality.[20,21] At the start of the recruitment maneuver, mP_{aw} was increased to 30 cmH_2O for five minutes. mP_{aw} was then reduced in steps of 3 cmH_2O each 3 min until the animals started breathing in a regular pattern.

EIT measurements

EIT measurements were performed using the Göttingen Goe-MF II EIT system (Cardinal Health, Yorba Linda, CA). Sixteen electrodes (Blue Sensor BR-50-K, Ambu, Denmark) were circumferentially applied around the chest at the xyphoid level. A 30-s reference measurement was recorded before lung lavage (Fig. 1). All further measurements were referenced to this measurement. Measurements were performed at a scan rate of 44 Hz for 2 min. A 5 mA peak-to-peak, 50 kHz electrical current was injected at one adjacent electrode pair and the resultant potential differences were measured at the remaining adjacent electrode pairs. Subsequently, all adjacent electrode pairs were used for current injection, thus completing one data cycle. A back-projection algorithm calculated the changes in impedance in time and reconstructed topographic EIT images of 912 pixels representing local impedance changes in a circular plane.[22]

EIT data analysis

Both the respiratory and the cardiac components of the EIT signal were identified in the frequency spectra generated from all EIT measurements (Fourier transformation). To eliminate the cardiac signal from the impedance measurements, the cut-off frequency of the low-pass filter was set below the heart rate, 0.67 Hz, 40 beats/min.[23] Figure 2A depicts the method used for assessing the region of interest of the lungs before lung lavage.[24] For comparison of changes in expiratory lung volumes (EELV), the changes in impedance (ΔI) were calibrated to V_T during CMV after the last lung lavage (Fig. 1). For comparison of EELV, the change in EELV at the end of each HFO ventilation modality was referenced to the EELV at completion of the preceding recruitment maneuver. The EIT data were analyzed over three regions of interest, comprising the total area of the lungs and the upper and lower halves of the lungs (Fig. 2B).[25]

The center of ventilation was determined in order to compare shifts in the distribution of ventilation between the three HFO ventilation modes. The center of ventilation was the point where the sum of fractional ventilation was 50% of the summed fractional ventilation (Fig. 2C).[26]

To assess the occurrence of regional hyperinflation or recruitment on account of spontaneous breathing, regional filling characteristics of the lungs were calculated as depicted in Fig. 3.[27,28] To do this, the local relative impedance change was compared with the total relative impedance change of all pixels during inspiration and then fitted to a polynomial function of the second degree: $y = ax^2+bx+c$. See Fig. 3 for a detailed explanation.

Hemodynamic and respiratory variables

A MATLAB environment was used for data processing (MATLAB 7.04, The Mathworks, Natick, USA). The data processing is described elsewhere.[13] In short, in order to eliminate HFO ventilator oscillations, the recorded flow and pressure signals were low-pass filtered using a seventh-order Butterworth filter with a cut-off frequency of 2.5 Hz. The filtered flow signal represented the flow change caused by spontaneous breathing of the pigs. From the integrated filtered flow signals, breathing pattern and minute ventilation were determined for each individual breath and averaged over a two-minute period. Arterial and mixed venous blood samples were analyzed using ABL505 and OSM3 hemoximeters

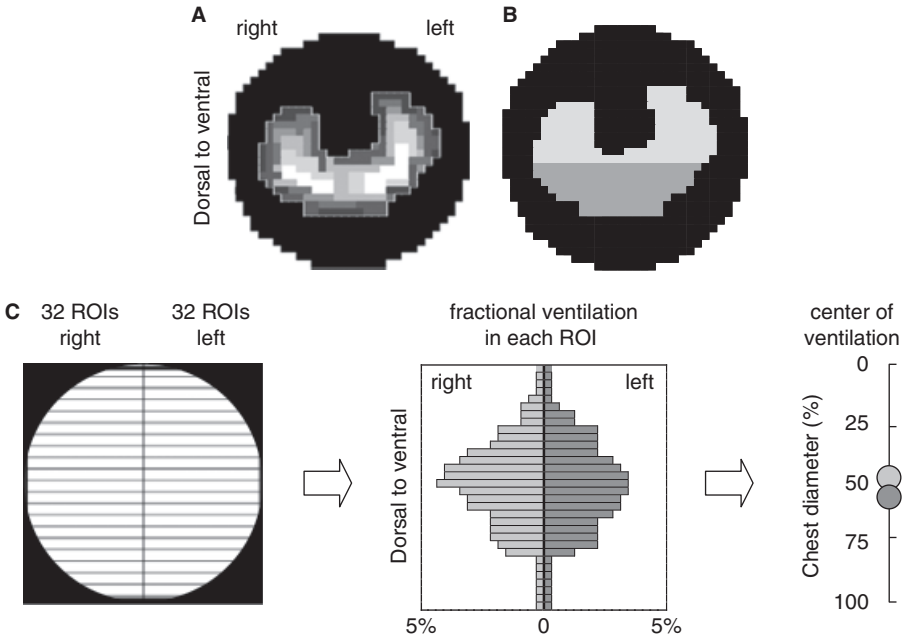

Fig. 2. Electrical impedance tomography analysis. (A) Example of an electrical impedance tomography (EIT) image. Gray areas, within the white line, represent those pixels where the impedance variation exceeded 20% of the maximum pixel variation in the image, corresponding with the lung. (B) EIT image showing the tree regions of interest (ROIs) used for the evaluation of end expiratory lung volume (EELV). The total lung, total gray area. The ventral and dorsal lung regions, the light and dark gray areas, respectively. (C) Example of determination of fractional regional lung ventilation. Each half of the scan is analyzed in 32 ROIs. The 64 values represent the ventral to dorsal profiles of local ventilation in the chest as a percentage of the total ventilation of each half of the EIT image. The center of ventilation was defined as the point where the sum of fractional ventilation was 50% of the summed fractional ventilation.

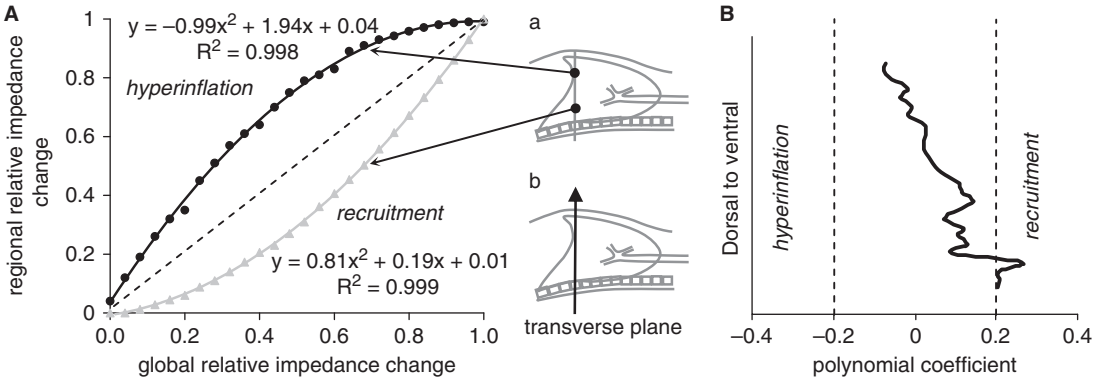

Fig. 3. Determination of regional filling characteristics. (A) Examples of relative impedance change in two individual pixels compared with the relative impedance change of all selected pixels representing the lungs. Both regional and global relative impedance change were calculated as a fraction of 1. Filling characteristics were calculated for every single spontaneous breath beginning at inspiration and ending at end-inspiration and averaged over the 2-min electrical impedance tomography (EIT) recording. • and ▲ represent the measured data points of one single spontaneous inspiration in two different pixels. The plots were fitted to a polynomial of the second degree, $y = ax^2+bx+c$, the black and gray lines. The polynomial coefficient of the second degree, a, describes the curve linearity of the plot. A polynomial coefficient a near zero (-0.2 to 0.2), near the dotted line, suggests a homogeneous regional tidal volume change on account of spontaneous breathing. A negative polynomial coefficient a (< -0.2) indicates low late regional filling and suggests local hyperinflation. A positive a (>0.2) indicates low initial filling and suggests local recruitment. (B) Example of regional filling characteristics in the transverse plane in one animal. Polynomial coefficients of each individual pixel were averaged in each horizontal level in order to evaluate regional filling in the dorsal to ventral direction.

(Radiometer, Copenhagen, Denmark). Continuous arterial blood gas analysis was conducted by the Paratrend 7 (Biomedical Sensors, High Wycombe, UK). Respiratory indices were calculated according to standard formulas.[29]

Statistical analysis

Data are expressed as median and 25th to 75th interquartile range (IQR) unless otherwise stated. Parameter comparison for different HFO ventilation modes was performed using repeated measures analysis of variance with Bonferroni's *post hoc* testing. Parameter comparison for the polynomial coefficient was performed using the Wilcoxon signed rank test. In all analyses, a $P<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 15 for Windows (SPSS, Chicago, IL).

Results

All animals completed the entire study protocol. Respiratory variables and data on gas exchange are summarized in Table 1. V_T of spontaneous breathing during HFO ventilation with DF was significantly higher, 5.1 ml/kg, compared with the V_T with continuous fresh gas flow, 4.3 ml/kg. Oxygenation improved in all HFO ventilation modes when spontaneous breathing was maintained. When pigs were paralyzed, PaO_2 decreased remarkably during the 30-min experimental period. $PaCO_2$ decreased using DF. $PaCO_2$ increased significantly using a continuous fresh gas flow and during muscular paralysis.

Figure 4 depicts the changes in EELV referenced to EELV after the completion of each preceding recruitment maneuver. In all HFO ventilation modalities, a decrease in lung volume was observed. Lung volume was significantly better preserved when spontaneous breathing was maintained. When ventral and dorsal lung regions were considered separately, changes in lung volume were most markedly in the dorsal lung areas.

In Fig. 5, the center of lung ventilation, determined from functional EIT measurements for all HFO ventilation modalities, is shown for the right and the left lung separately. When the animals were breathing spontaneously on HFO ventilation and DF was used, the center of ventilation significantly shifted towards the dependent dorsal parts of both lungs compared with the measurements during muscular paralysis.

Figure 6 summarizes the regional filling characteristics of all animals for both CF and DF. Summarizing all individual results, the polynomial coefficient calculated using HFO ventilation and continuous flow was -0.02 (IQR -0.05 to 0.14, range -0.35 to 0.32). For measurements using DF, polynomial coefficients were significantly different -0.01 (IQR -0.006 to 0.11, range -0.17 to 0.23), $P = 0.01$.

Discussion

The present study is the first to investigate the effect of spontaneous breathing during HFO ventilation on lung aeration and the distribution of ventilation. The main results of the animal experiment were that (1) lung volume was best preserved when spontaneous breathing was maintained during HFO ventilation, predominantly in the dorsal-dependent lung zones. (2) The use of DF during HFO ventilation shifted the center of ventilation to the dependent lung zones when compared with HFO ventilation during muscular paralysis. (3) There was no indication that spontaneous breaths during HFO ventilation resulted in regional hyperinflation.

When lung aeration was considered, a positive effect of spontaneous breathing during HFO ventilation was observed. Lung volume at the end of expiration of spontaneous breathing during HFO ventilation, both for CF and DF, was significantly higher compared with the measurements during

Table 1

Respiratory and physiologic variables during different high-frequency oscillatory ventilation modes.

	Spontaneously breathing		
	Continuous flow	Demand flow	Paralyzed
RR (min)	8.5 (7.8–9.4)	7.6 (6.4–9.9)*	
V_T (ml/kg)	4.3 (4.2–4.7)	5.1 (4.2–6.4)*	
MV (l/min)	2.1 (1.9–2.2)	2.2 (1.9–2.4)	
mP_{aw} (cmH_2O)	10 (9.9–11)	10 (8.7–11)	10 (9.9–11)
PaO_2 start (mmHg)	460 (454–498)	458 (421–509)	590 (536–611)*
PaO_2 end (mmHg)	493 (455–502)	473 (420–502)	451 (420–489)
ΔPaO_2 (mmHg)	19.9 (19.6–37)	31 (-5.5–84)	-140 (-225 to -53)*
$PaCO_2$ start (mmHg)	54 (47–58)	55 (51–56)	56 (48–62)
$PaCO_2$ end (mmHg)	53 (52–54)	49 (46–52)	70 (63–72)*
$\Delta PaCO_2$ (mmHg)	6.3 (-3.0–18)	-5.7 (-4.3 to -7.4)*	9.9 (3.6–22)*,†

Data are expressed as median (IQR), $P < 0.05$;
*vs. continuous flow,
†vs. demand flow.
RR, respiratory rate; V_T, tidal volume of spontaneous breathing; MV, minute ventilation; mP_{aw}, mean airway pressure; PaO_2 start and PaO_2 end, PaO_2 at the start and at the end of the HFO ventilation modality; $PaCO_2$ start and $PaCO_2$ end, $PaCO_2$ at the start and at the end of the HFO ventilation modality; ΔPaO_2 and $\Delta PaCO_2$, difference in PaO_2 and $PaCO_2$ at the start and at the end of the HFO ventilation modality.

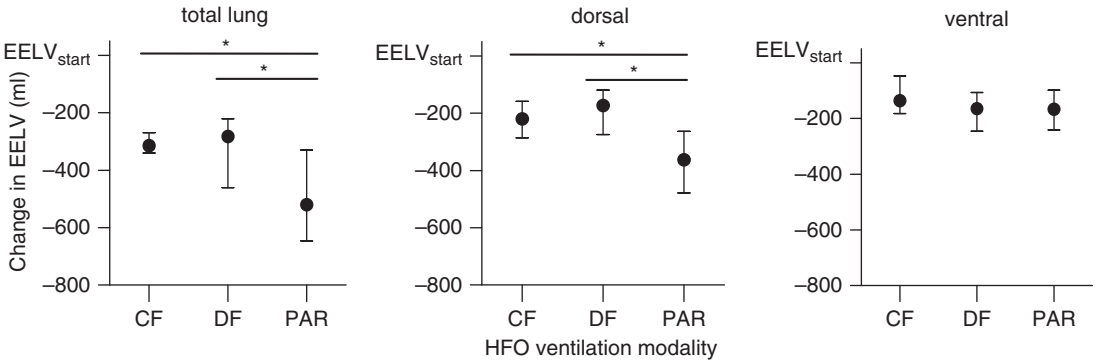

*Fig. 4. Change in the end expiratory lung volume (EELV) determined from electrical impedance tomography (EIT) measurements for all high-frequency oscillatory (HFO) ventilation modalities. Data are expressed as median (IQR), *P < 0.05. The EELV at the end of each HFO ventilation modality is referenced to the EELV at the start (EELV$_{start}$) of the same 30-min experimental run. A comparison of change in EELV was performed for the total lung EIT measurement and for the ventral and dorsal lung zones separately. CF, continuous fresh gas flow; DF, demand flow; PAR, paralyzed.*

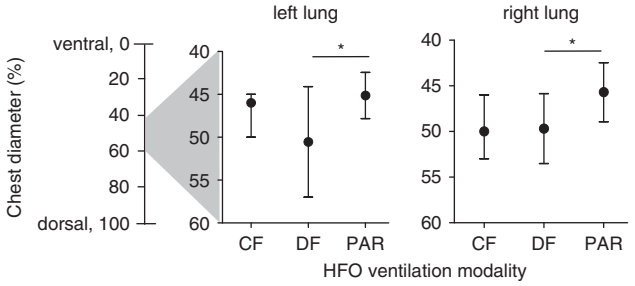

*Fig. 5. Ventral to dorsal distribution of lung ventilation. Data are expressed as median (IQR), *P < 0.05. Ventral to dorsal distribution of lung ventilation determined from EIT measurements for all high-frequency oscillatory (HFO) ventilation modalities. The center of ventilation is depicted for the left and right lung separately. EIT, electrical impedance tomography; CF, continuous fresh gas flow; DF, demand flow; PAR, paralyzed.*

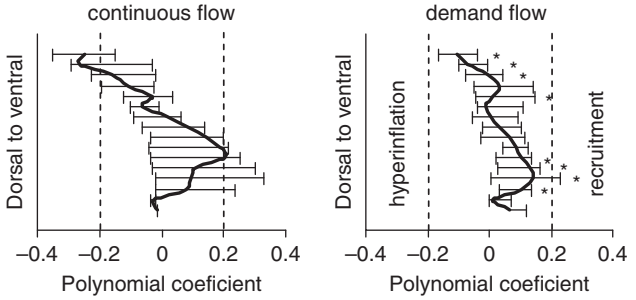

*Fig. 6. Polynomial coefficients of regional versus global filling characteristics. Data are expressed as median (range), *P < 0.05. Polynomial coefficients of regional vs. global filling, on account of spontaneous breathing, in the dorsal to ventral direction. Results determined from electrical impedance tomography measurements during high-frequency oscillatory ventilation with continuous flow or demand flow.*

muscular paralysis. The maintenance of EELV was most markedly in the dependent dorsal lung areas.

An explanation for the results on lung aeration is that ventilation and aeration are distributed differently when comparing spontaneous breathing and controlled mechanical ventilation.[6,30] The most important factor responsible is the diaphragm. The diaphragm consists of an anterior tendon plate and a posterior muscle section. An active diaphragm lowers pleural pressure. As a result, transpulmonary pressure increases, enabling better aeration of dependent lung regions close to the diaphragm. In addition, during spontaneous breathing, the active dorsal muscle section of the diaphragm shifts the ventilation to the dorsal lung areas. A positive effect on lung aeration was already observed in several animal and clinical studies, when during mechanical ventilation, spontaneous breathing contributed only 10–30% to the total minute ventilation.[6,30–32]

After lung recruitment, a decrease in the lung volume was observed in all HFO ventilation modalities (Fig. 4). The decrease in the lung volume can be explained by the low mP_{aw} that could be applied. Higher mP_{aw} would have prevented lung collapse. However, high mP_{aw} is known to induce apnea in pigs, representing a limitation of the study (personal communication H. Wrigge from the department of Anesthesiology and Intensive Care Medicine of the University of Bonn). The decrease in the lung volume only coincided with a decrease in PaO_2 when pigs were paralyzed. When spontaneous breathing was maintained, the decrease in the lung volume did not lead to a decrease in PaO_2. Considering the mechanisms of gas exchange during HFO ventilation spontaneous

breathing is not necessary.[9] The results indicate, however, that a lower mP_{aw} may be required to achieve adequate gas exchange when spontaneous breathing is maintained.

We observed a significant shift in the center of ventilation to the dependent lung zones in favor of HFO ventilation with DF compared with HFO ventilation during muscular paralysis. This observation is in agreement with other studies that investigated the effect of lung recruitment on lung mechanics and the distribution of ventilation.[26] Thus, in the HFO ventilation with DF, the spontaneous breathing not only resulted in a better preservation of EELV, it also directed ventilation towards the dependent lung zones. The redirection of ventilation favored gas exchange, indicated by the increase in PaO_2 and decrease in $PaCO_2$ during HFO ventilation with DF.

One of the basic principles of a lung-protective HFO strategy is the application of small tidal volumes, usually below the anatomical dead space.[9] Spontaneous breathing during HFO ventilation caused considerably larger volumes in our animal model. To assess the occurrence of regional hyperinflation and recruitment, regional filling characteristics of the lungs on account of spontaneous breathing were analyzed (Fig. 6). Regional filling characteristics of the lungs were more homogeneous when DF was used instead of continuous flow. The more homogeneous distribution can be derived from the fact that polynomial coefficients were closer to 0 throughout the lungs when the DF was used.

The cut-off values for the polynomial coefficients to indicate hyperinflation, recruitment or homogeneous filling are arbitrary. In a study describing the regional filling characteristics in mechanically ventilated adults with acute respiratory failure, $PaO_2/FiO_2 < 300$ mmHg, a much broader heterogeneity of regional filling was found.[28] In that study, minimal regional polynomial coefficients varied from -2.8 to -0.56 (median -1.16), and maximum coefficients varied from 0.58 to 3.65 (median 1.41). In comparison with these data, the regional filling characteristics we observed were more homogeneous.

Despite the fact that the tidal volumes of spontaneous breathing were higher using DF, there was no indication that this caused hyperinflation. It is an important observation with respect to the earlier discussed shift of the center of ventilation towards the dorsal lung regions when DF was used. This shift is explained by enhanced ventilation of the dorsal lung regions, rather than hyperinflation of the anterior lung parts during the use of DF.

The interaction between spontaneous breathing and mechanical ventilation differs in various ventilation modes. Modes like airway pressure release ventilation (APRV) or biphasic positive pressure (BIPAP) ventilation allow unrestricted spontaneous breathing. In assist-control ventilation, only some breathing effort is necessary to trigger the ventilation and assist a breath. The presented modification of the HFO ventilator with a DF system allows unrestricted spontaneous breathing. The optimal mode for delivering partial ventilatory support is much discussed.[33] A recent prospective observational study, however, did not demonstrate a difference in outcome when APRV/BIPAP and assist/control ventilation were compared.[34]

Not all research is in favor of the preservation of spontaneous breathing during mechanical ventilation. Some studies suggest that the use of neuromuscular blocking agents in the early phase of ALI/ARDS may improve oxygenation and reduce inflammation. Gentle spontaneous breathing may be beneficial; it can be argued that vigorous spontaneous respirations are contraindicated for the injured lung. Forceful respiration efforts can impose stress on the lungs and aggravate VILI.[35,36] During our experiments with only mild lung injury, we observed calm spontaneous respirations with a limited tidal volume of spontaneous breaths. The effects of the HFO ventilator with DF on spontaneous breathing pattern and effort in severe lung injury need further study.

The animal study has limitations. As the application of high mP_{aw} prevented the animals from breathing spontaneously, only mild lung injury could be induced. Therefore, only two single lung lavages with no specific target for lung injury could be performed. With the limited lung lavage experimental conditions are not completely stable.[17] The PaO_2 at the start of HFO ventilation during paralysis indicate that lungs improved during the experiment. Whether similar results would be observed during spontaneous in severe human ARDS, using an open lung strategy with higher mP_{aw}, will require further research.

Conclusions

This animal study demonstrates that spontaneous breathing during HFO ventilation preserves lung volume and when DF was used improves ventila-

tion of the dependent lung areas. No significant hyperinflation occurred on account of spontaneous breathing. These results underline the importance of maintaining spontaneous breathing during HFO ventilation and support efforts to optimize HFO ventilators to facilitate patients' spontaneous breathing.

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Conflict of interest: None.

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Address:
Dr *Marc van Heerde*
Department of Pediatric Intensive Care
VU University Medical Center
Room 8D12
PO Box 7057
1007 MB Amsterdam
The Netherlands
e-mail: m.vanheerde@vumc.nl