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High-frequency oscillatory ventilation guided by transpulmonary pressure in acute respiratory syndrome: an experimental study in pigs

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Abstract

Background: Recent clinical studies have not shown an overall benefit of high-frequency oscillatory ventilation (HFOV), possibly due to injurious or non-individualized HFOV settings. We compared conventional HFOV (HFOV$_{con}$) settings with HFOV settings based on mean transpulmonary pressures (P_{Lmean}) in an animal model of experimental acute respiratory distress syndrome (ARDS).

Methods: ARDS was induced in eight pigs by intrabronchial installation of hydrochloric acid (0.1 N, pH 1.1; 2.5 ml/kg body weight). The animals were initially ventilated in volume-controlled mode with low tidal volumes (6 ml kg^{-1}) at three positive end-expiratory pressure (PEEP) levels (5, 10, 20 cmH$_2$O) followed by HFOV$_{con}$ and then HFOV P_{Lmean} each at PEEP 10 and 20.

The continuous distending pressure (CDP) during HFOV$_{con}$ was set at mean airway pressure plus 5 cmH$_2$O. For HFOV P_{Lmean} it was set at mean P_L plus 5 cmH$_2$O. Baseline measurements were obtained before and after induction of ARDS under volume controlled ventilation with PEEP 5. The same measurements and computer tomography of the thorax were then performed under all ventilatory regimens at PEEP 10 and 20.

Results: Cardiac output, stroke volume, mean arterial pressure and intrathoracic blood volume index were significantly higher during HFOV P_{Lmean} than during HFOV$_{con}$ at PEEP 20. Lung density, total lung volume, and normally and poorly aerated lung areas were significantly greater during HFOV$_{con}$, while there was less over-aerated lung tissue in HFOV P_{Lmean}. The groups did not differ in oxygenation or extravascular lung water index.

Conclusion: HFOV P_{Lmean} is associated with less hemodynamic compromise and less pulmonary overdistension than HFOV$_{con}$. Despite the increase in non-ventilated lung areas, oxygenation improved with both regimens. An individualized approach with HFOV settings based on transpulmonary pressure could be a useful ventilatory strategy in patients with ARDS. Providing alveolar stabilization with HFOV while avoiding harmful distending pressures and pulmonary overdistension might be a key in the context of ventilator-induced lung injury.

Keywords: Volume controlled ventilation, HFOV, Transpulmonary pressure, Aerated lung tissue, Oxygenation, Hemodynamics

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Background

Studies have shown that volume-controlled ventilation (VCV) with small tidal volumes, adequate positive end-expiratory pressure (PEEP) and low driving pressures (<15cmH$_2$0) can improve oxygenation and reduce pulmonary morbidity in patients with acute respiratory distress syndrome (ARDS) [1, 2].

High frequency oscillatory ventilation (HFOV) is another approach to lung-protective ventilation, since it employs very low tidal volumes and very small changes in delta pressure [3] applied with higher continuous distending pressure (CDP). Several earlier studies have demonstrated the efficacy of HFOV in patients with ARDS in whom VCV has failed [4–6]. There is also evidence that outcome is improved when HFOV is initiated at an early stage [7, 8]. However, two recent studies showed either no benefit or even a higher mortality rate with HFOV compared to conventional ventilation [9, 10]. One possible explanation is that inappropriate HFOV ventilator settings had cancelled out the positive effects of HFOV.

Until now, HFOV ventilator settings have been guided by the mean airway pressure (Paw$_{mean}$), and the CDP has been set at Paw$_{mean}$ plus 5 cm H$_2$0 in almost all studies [4, 7, 11]. This approach is more than questionable, because the Paw is not a valid surrogate for transpulmonary pressure (P$_L$). Since only a positive end-exspiratory P$_L$ can prevent cyclic opening and closing and overdistension of the alveolae, P$_L$ has to be > 0 in order to prevent alveolar collapse.

The potential solution thus lies in choosing HFOV settings based on a more exact approach to the distending pressure applied to the lung. Talmor et al. showed that oxygenation and pulmonary compliance improves when PEEP is adjusted according to esophageal pressure (Pes) [12]. In an earlier study we found that we were able to reduce CDP when it was adjusted according to Pes [13]. It is therefore reasonable to hypothesize that it would be of benefit to set CDP according to P$_L$ and not base it on mean airway pressure (Paw$_{mean}$).

The following hypotheses were tested:

(a) Conventional HFOV (HFOV$_{con}$) has a negative effect on cardiac function and hemodynamics at higher CDP levels
(b) There is a difference between the hemodynamic effects of conventional HFOV$_{conv}$ and HFOV guided by transpulmonary pressures (HFOV P$_{Lmean}$)
(c) HFOV P$_{Lmean}$ not only reduces cardiac depression, but also causes less pulmonary overdistension
(d) HFOV P$_{Lmean}$ increases non-ventilated lung areas and will therefore worsen gas exchange

Methods

The study had the approval of our institution's animal study review board. The animals were handled according to the Helsinki convention for the use and care of animals.

Animal preparation

Eight healthy pigs (Göttinger mini-pigs, mean weight 41.7 ± 4.0 kg) were premedicated with 40 mg azaperonium intramuscular (i.m.). After cannulating an ear vein, anesthesia was induced with propofol (2 mg kg^{-1} intravenous (i.v.)) and fentanyl (0.2 μg i.v.), and maintained with infusions of ketamine (10 mg kg^{-1} h^{-1}) and midazolam (1 mg kg^{-1} h^{-1}). Ringer acetate was infused at an average rate of 4–5 ml kg^{-1} h^{-1}.

A cuffed tracheal tube was inserted and the lungs were ventilated in VCV mode (PEEP 5 cmH$_2$O; inspiration: expiration ratio (I:E) = 1:1.5; fraction of inspired oxygen (FiO$_2$) = 1.0; respiratory rate 15 min^{-1}; constant inspiratory flow; tidal volume V$_T$ = 6 ml kg^{-1}). The respiratory rate was adjusted to maintain normocapnia with a maximum rate of 20 min^{-1}. End-tidal CO$_2$ (Datex Capnomac Ultima®, Finland), peripheral oxygen saturation, electrocardiogram (ECG) and non-invasive blood pressure were monitored continuously (Datex – Ohmeda S/3 patient monitor, GE, USA).

A thermistor-tipped fiberoptic catheter (Pulsiocath®, 4F FT PV 2024, Pulsion Medical System, Munich, Germany) was placed in a femoral artery. A pulmonary artery catheter (Volef®, Pulsion Medical System, Munich, Germany) was inserted through an 8.5 French sheath introducer in the right internal jugular vein, and the position of the catheter tip was confirmed by pressure tracing. The catheters were connected to pressure transducers and to an integrated bedside monitor (PiCCO®, Volef, Pulsion Medical Systems).

An esophageal balloon catheter (AVEA ®, Care Fusion, Yorba Linda, CA, USA) was inserted to measure esophageal pressure. The correct placement of the catheter was confirmed as described by Talmor et al. [12].

Experimental protocol

Baseline measurements were performed at 5 cmH$_2$O PEEP after all parameters had been constant for 30 min, first in healthy lungs and then after ARDS had been induced by the intrabronchial installation of hydrochloric acid (0.1 N, pH 1.1; 2.5 ml kg^{-1} body weight) during inspiration. Equal aliquots were instilled through a suction catheter into the right and left main bronchus. The injury was considered stable if partial pressure of arterial oxygen (PaO$_2$) remained constantly lower than 300 mmHg at a FiO$_2$ of 1.0 at 60 min after instillation.

The animals were then ventilated in the study modes at consecutive PEEP levels of 10 and 20 cmH$_2$O. Measurements were performed after 10 min ventilation at each PEEP level. Mean airway (Paw$_{mean}$) and esophageal pressures (Pes) were recorded. End-expiratory esophageal

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pressure was measured during an end-expiratory hold (PEEP) and the inspiratory esophageal pressure was measured during an inspiratory hold (plateau pressure). The end-expiratory and the end-inspiratory esophageal pressure were then added and divided through the arithmetic mean, in order to calculate the mean esophageal pressure (Pes_{mean}). The transpulmonary pressures (P_L) were then calculated (Fig. 1):

$$P_{L\ mean} = Paw_{mean} - Pes_{mean}.$$

At the end of the measurements at each PEEP level the lungs were allowed to collapse by disconnecting the tracheal tube from the respirator for 30 s. A recruitment maneuver was then performed by inflating the lungs to a pressure of 40 cmH_2O for 40 s after which ventilation was started at the next PEEP level.

VCV was performed as described above. HFOV was performed with a SensorMedics®-Ventilator 3100B (Care Fusion, Yorba Linda, CA, USA). For $HFOV_{con}$ the CDP was set at 5 cmH_2O above the Paw_{mean}. For HFOV P_{Lmean} the CDP was set at 5 cmH_2O over the mean P_L measured during VCV at the corresponding PEEP level as described by Talmor et al. [12] (Fig. 1). The initial ventilator settings were bias flow 20 l min^{-1}, power 70%, inspiration time 44%, and frequency 5 Hz. It was not

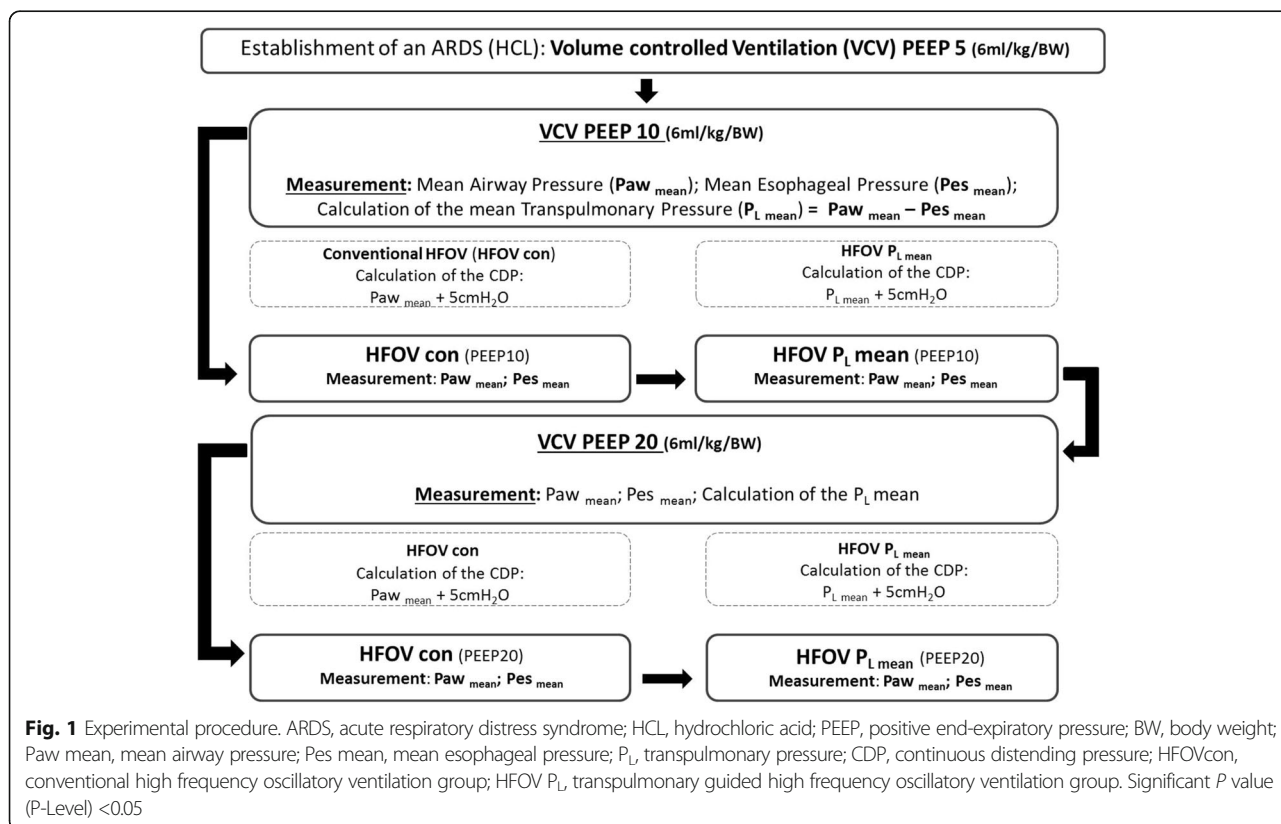possible to randomize the order of these measurements due to the nature of the study design.

Lung imaging and analysis

Computed tomography (CT) scans of the lungs were obtained from apex to base during an end-expiratory hold at a PEEP of 5 cmH_2O (GE Light Speed VCT, GE Medical Systems, thickness 5 mm, interval 0.5 mm, 100 mA, 100 kV). The method used for quantitative image analysis has been described previously [14]. Quantitative analysis of the entire lung was performed to assess lung density (Hounsfield units, HU), total lung volume, and extent of lung tissue aeration (none, poor, normal, or over-aerated).

Pulmonary parenchyma with a CT density ranging from – 1000 to – 900 HU was classified as overinflated, – 900 to – 500 HU as normal, – 500 to – 100 HU as poorly aerated, and – 100 to + 300 HU as non-aerated (atelectatic).

Measurements

Cardiac output (CO), stroke volume, right end-diastolic volumes, pulmonary artery pressures, central venous pressures, extravascular lung water index (ELWI), and intrathoracic blood volume index (ITBI) were measured. Cardiac output measurements were performed in triplicate by the same investigator using bolus injections of

Fig. 1 Experimental procedure. ARDS, acute respiratory distress syndrome; HCL, hydrochloric acid; PEEP, positive end-expiratory pressure; BW, body weight; Paw mean, mean airway pressure; Pes mean, mean esophageal pressure; P_L, transpulmonary pressure; CDP, continuous distending pressure; HFOVcon, conventional high frequency oscillatory ventilation group; HFOV P_L, transpulmonary guided high frequency oscillatory ventilation group. Significant *P* value (P-Level) <0.05

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20 ml ice-cold 0.9% saline. Arterial samples were collected and blood gases were analyzed immediately (ABL 510, Radiometer, Copenhagen, Denmark).

Data acquisition

Data recording and analysis was performed using the Modular Intensive Care Data Acquisition System (MIDAS) developed by P. Herrmann and P. Nguyen (Institut für Biomedizinische Technik, Hochschule Mannheim, Germany).

Statistical analysis

The data were analyzed and the figures created with the statistical software R (www.r-project.org). Data are presented as median and interquartile range (IQR). Changes from baseline in each individual series were assessed using the Wilcoxon test for paired samples.

Results

Lung

Gas exchange and continuous distending pressures (CDP)

PaO_2 decreased and $paCO_2$ increased after induction of ARDS. $PaCO_2$ was significantly lower in both HFOV groups than in the volume-controlled ventilation groups (VCV), except at a PEEP level of 10 cm H_2O in the transpulmonary pressure (P_L)-guided group (Table 1). There was no difference in paO_2 between $HFOV_{con}$ and HFOV P_{Lmean} at any PEEP level. The CDP based on mean P_L was approximately 40% lower than that based on mean airway pressures (Fig. 2).

Lung density and total lung volume and aeration

Total lung density expressed in mean HU, total lung volume and percentage of normally, poorly, non-aerated and over-aerated lung tissue is shown in Table 2. Lung density increased significantly during HFOV P_{Lmean} while it stayed the same during $HFOV_{con}$ compared to VCV at PEEP 10 ($p < 0.05$) (Fig. 3). Furthermore there was a significant increase in density during HFOV P_{Lmean} compared to $HFOV_{con}$ at PEEP 10. At PEEP 20, lung density decreased during $HFOV_{con}$ and increased during HFOV P_{Lmean} compared to VCV. There was also a significant difference in lung density between $HFOV_{con}$ and HFOV P_{Lmean} ($p < 0.05$) (Fig. 3).

Total lung volume was greater with $HFOV_{con}$ than with HFOV P_{Lmean}. Roughly summarized, there was significantly more normally and poorly aerated lung tissue with $HFOV_{con}$, while less over-aerated and more non-aerated lung tissue was observed with HFOV P_{Lmean} (Figs. 4 and 5).

Extravascular lung water

The extravascular lung water index (ELWI) increased after induction of ARDS ($p < 0.05$), but there was no difference between HFOV P_{Lmean} and $HFOV_{con}$.

Hemodynamics and cardiac function

Heart rate (HR), MAP, central venous pressue (CVP), mean pulmonary arterial pressure (mPAP), CO, stroke volume (SV), intrathoracic blood volume index (ITBI) and ELWI are shown in Table 3. Mean PAP, right ventricular end-diastolic volume index (RVEDI), and ELWI increased significantly after induction of ARDS.

During volume-controlled ventilation, HR, CVP, mPAP, MAP, and ELWI increased after the change from PEEP 10 to PEEP 20, while SV decreased ($p < 0.05$). SV was larger during HFOV P_{Lmean} than during $HFOV_{con}$ at PEEP 10. At PEEP 20, SV and MAP, CO, and ITBI were greater during $HFOVP_{Lmean}$ than during $HFOV_{con}$ ($p < 0.05$) (Table 3; Fig. 6).

Discussion

To our knowledge this is the first study in animals that compares the effects of two HFOV regimens on systemic hemodynamics, gas exchange, and lung aeration; one in which the continuous distending pressure (CDP) was adjusted according to mean airway pressure ($HFOV_{con}$), and one adjusted to the corresponding mean transpulmonary pressure (HFOV P_{Lmean}).

The main finding of the present study is that transpulmonary pressure-guided HFOV with high PEEP values has less impact on systemic hemodynamics than conventional HFOV and does not compromise oxygenation. The reduction in distending pressures (CDP) associated with transpulmonary pressure-guided HFOV resulted in less pulmonary overdistension, but increased the percentage of non-aerated lung tissue (Figs. 3, 4 and 5). Furthermore on comparison between VCV and transpulmonary pressure-guided HFOV there was higher MAP and ITBI and a lower percentage of normal and poor ventilated lung tissue, but less pulmonary overdistension at high PEEP levels in HFOV P_{Lmean}.

In previous studies of conventional HFOV, the CDP was based on the mean airway pressure at each PEEP level [4, 7, 8, 11, 15]. This universally established procedure of setting CDP as airway pressure + 5cmH_2O is merely an empirical convention that is not underpinned by experimental evidence. It is known that one cannot equate mean airway pressure and transpulmonary pressure, particularly not in patients with ARDS, because of the changes in chest wall and lung elastance. Using Paw or plateau pressure as the reference point would most likely yield a CDP that was too high and could cause overdistension of the lung and, in the end, ventilator-induced lung injury (VILI).

Table 1 Pulmonary gas exchange, serum lactate and airway pressures

	T_0 PEEP 5			ARDS PEEP 5			ARDS PEEP 10			ARDS PEEP 20		
pHa	Median	25%	75%	Median	25%	75%	Median	25%	75%	Median	25%	75%
VCV	7.47	7.46	7.50	7.36	7.35	7.39	7.34^	7.32	7.42	7.31	7.28	7.34
ARDS HFOV con	–	–	–	–	–	–	7.54	7.49	7.58	7.51	7.47	7.52
ARDS HFOV $P_{L\ mean}$	–	–	–	–	–	–	7.46	7.36	7.52	7.58	7.51	7.59
$PaCO_2$, mmHg												
VCV	41.5	38.3	42.8	45.0#	43.0	46.5	50.5^	46.3	52.0	51.0©	48.3	55.3
ARDS HFOV con	–	–	–	–	–	–	28.0	27.0	30.3	29.5	27.0	33.3
ARDS HFOV $P_{L\ mean}$	–	–	–	–	–	–	40.5	32.8	47.5	28.0	25	29.3
PaO_2, mmHg												
VCV	666.0*	647.8	675.8	71.0	65.3	80.8	54.0	50.8	71.8	88.0	46.0	121.8
ARDS HFOV con	–	–	–	–	–	–	51.0	39.8	71.8	67.5	39.0	105.8
ARDS HFOV $P_{L\ mean}$	–	–	–	–	–	–	43.5	40.5	52.8	63.0	53.0	131.1
Lactate, mmol/l												
VCV	1.9*	1.5	2.4	2.4	1.6	3.1	2.4	2.0	2.8	2.8	2.4	3.3
ARDS HFOV con	–	–	–	–	–	–	2.7	2.5	3.2	2.6	2.5	3.0
ARDS HFOV $P_{L\ mean}$	–	–	–	–	–	–	2.6	2.1	3.0	2.8	2.6	3.4
Airway pressures												
Plateau airway pressure VCV	14.5	14.0	16.0	24.5	23.8	26.0	29.5	28.0	30.3	38.5	37.8	39.0
Mean air pressure												
VCV	8.0	8.0	8.7	11.5	11.3	12.0	16.5	16.0	16.8	26.1	25.9	26.3
HFOV con	–	–	–	–	–	–	20.5	19.5	21.0	30.0	30.0	30.0
HFOV $P_{L\ mean}$	–	–	–	–	–	–	11.0	11.0	16.3	20.5	17.0	22.8
Mean esophageal pressure												
VCV	4.5	1.2	8.4	4.5	3.7	9.2	10.0	7.1	12.3	12.2	10.2	14.3
HFOV con	–	–	–	–	–	–	10.0	7.1	12.3	11.5	9.3	14.3
HFOV $P_{L\ mean}$	–	–	–	–	–	–	8.5	7.0	9.3	9.0	7.0	11.5
$P_{L\ mean}$												
VCV	3.8	0.0	6.8	6.7	3.4	7.3	6.3	4.1	9.7	13.5	11.9	15.5
HFOV con	–	–	–	–	–	–	9.5	6.5	13.3	18.5	15.8	20.8
HFOV $P_{L\ mean}$	–	–	–	–	–	–	3.0	1.5	9.0	11.5	7.8	15.8

Values are medians (25th and 75th quartiles) in eight animals

T_0 *PEEP 5* start of the experiment without acute respiratory distress syndrome (ARDS) and positive end-expiratory pressure (PEEP = 5 cmH$_2$O), *ARDS PEEP 5/10/20* ARDS with PEEP of 5, 10, and 20 cm H$_2$O, *VCV* conventional volume controlled ventilation, *HFOV* high frequency oscillatory ventilation, *HFOV con* conventional high frequency oscillatory ventilation, *HFOV P_L mean* HFOV guided by mean transpulmonary pressure, *pHa* pH in arterial blood, *PaCO$_2$* arterial carbon dioxide tension, *PaO$_2$* arterial oxygen tension, *Paw* mean airway pressure, *P_L* transpulmonary pressure (P_L = Paw-esophageal pressure)

*$p < 0.05$ VCV T_0 PEEP 5 vs. VCV ARDS PEEP 5; ^$p < 0.05$ VCV ARDS PEEP 10 vs. HFOV con "PEEP 10"; $^{\mho}p < 0.05$ VCV ARDS PEEP 10 vs. HFOV P_L mean "PEEP 10"; $p < 0.05$ HFOV con ARDS "PEEP 10" vs. HFOV P_L mean ARDS "PEEP 10"; ©$p < 0.05$ VCV ARDS PEEP 20 vs. HFOV con "PEEP 20"; $^{\text{E}}p < 0.05$ VCV ARDS PEEP 20 vs. HFOV P_L mean "PEEP 20"; $^{\Omega}p < 0.05$ HFOV con ARDS "PEEP 20" vs. HFOV P_L mean ARDS "PEEP 20"; $p < 0.05$ (p values were determined using the Wilcoxon test for paired samples)
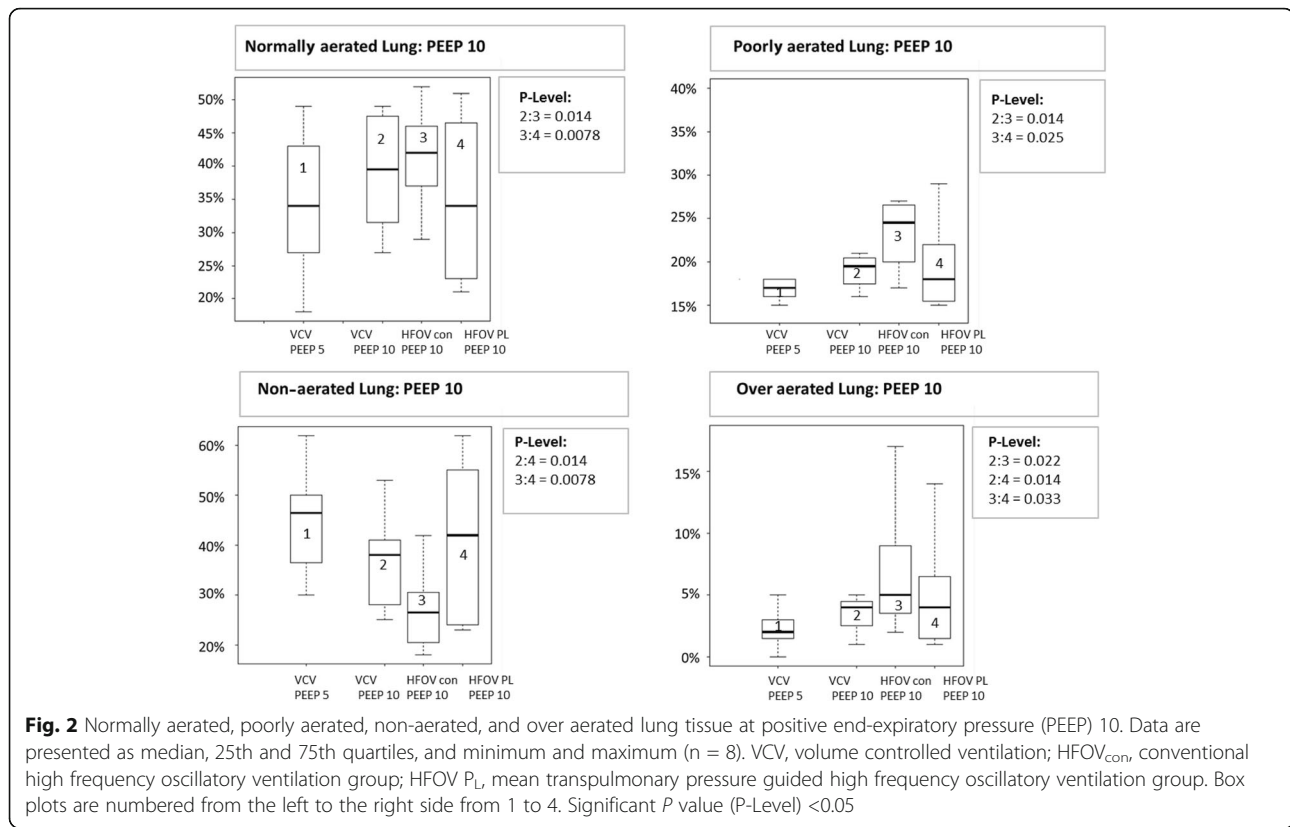
For the sake of comparison in the present study, CDP was set at 5 cmH$_2$O above the mean transpulmonary pressure at each corresponding PEEP level. This is also an empirical approach, albeit it an approach that induces only one modification and not the additional factor of a different pressure increment over the reference point.

Talmor et al. [12] have already shown that H$_L$-guided ventilation is superior to conventional mechanical ventilation. In this study the CDP levels based on P_{Lmean} were approximately 40% than those based on mean airway pressures at both employed PEEP levels.

The lesser degree of adverse circulatory effects compared to those observed in the conventionally ventilated animals or described in recently published studies on HFOV is possibly due to the lower CDP used in HFOV P_{Lmean} [15, 16]. These circulatory effects are probably caused by an intrathoracic pressure-related preload reduction or by direct impairment of right ventricular

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Fig. 2 Normally aerated, poorly aerated, non-aerated, and over aerated lung tissue at positive end-expiratory pressure (PEEP) 10. Data are presented as median, 25th and 75th quartiles, and minimum and maximum (n = 8). VCV, volume controlled ventilation; HFOV$_{con}$, conventional high frequency oscillatory ventilation group; HFOV P$_L$, mean transpulmonary pressure guided high frequency oscillatory ventilation group. Box plots are numbered from the left to the right side from 1 to 4. Significant *P* value (P-Level) <0.05

function [15, 17]. Most HFOV studies in the past did not take the hemodynamic instability of patients with ARDS into account, which was the consequence of the strict fluid reduction in ARDS therapy [18]. HFOV employed under conditions of hypovolemia will reduce pulmonary perfusion and affect oxygenation. This was confirmed in a study by Ursulet et al. [19], who showed that HFOV indeed caused a significant reduction in cardiac index, but not in arterial blood pressure in hypovolemic patients. Echocardiography or hemodynamic evaluation should therefore be performed before HFOV is started in order to reduce the potential negative circulatory effects. An animal study by Songqiao and coworkers [20] demonstrated that almost no hemodynamic depression actually occurs if the CDP is carefully titrated.

The lower CDP in our study resulted in a higher percentage of non-aerated lung tissue because the higher distending pressures in conventional HFOV are comparable to high PEEP levels. High PEEP levels and a correspondingly high CDP can recruit lung tissue but on the other hand it can also lead to lung overdistension [21]. Fu et al. showed that lung overdistension triggered by an increase in transpulmonary pressure produced a significant increase in the number of epithelial and endothelial breaks [22], which can cause pulmonary edema. Parker et al. are confident that microvascular permeability might be actively modulated by a cellular response due

to overdistension [23]. The authors assumed that this cellular response might be initiated by stretch-activated cation channels. The 3.7-fold increase in the capillary filtration coefficient found in their study is a strong argument for avoiding overdistension. It is noteworthy that there was no difference in oxygenation between the two groups, although the animals in the P$_{Lmean}$ group had a greater percentage of non-ventilated lung tissue. This might be explained by the fact that the young animals had a more robust hypoxic pulmonary vasoconstriction (HPV) reflex [24] so that perfusion was reduced in the lung areas that were no longer ventilated. The situation in patients in intensive care might be a different one.

Not only overdistension, but also high oxygen concentrations can cause lung injury. HFOV initiated late in the course of ARDS will require a high FiO$_2$, and high oxygen concentrations in combination with low distending pressures tend to promote airway closure with consequent atelectasis in dependent regions [25]. Derosa et al. showed in a porcine model of ARDS that no alveolar collapse occurred with low FiO$_2$ and low distending pressures. One can therefore safely conclude that the FiO$_2$ of 1.0 in our study increased the amount of non-ventilated lung tissue. High distending pressures can prevent lung collapse but they also cause the cyclical alveolar opening and closing that increases lung injury. HFOV should therefore not be simply regarded as a

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Table 2 Lung density, total lung volume, normally aerated, poorly aerated, non-aerated and over aerated lung tissue

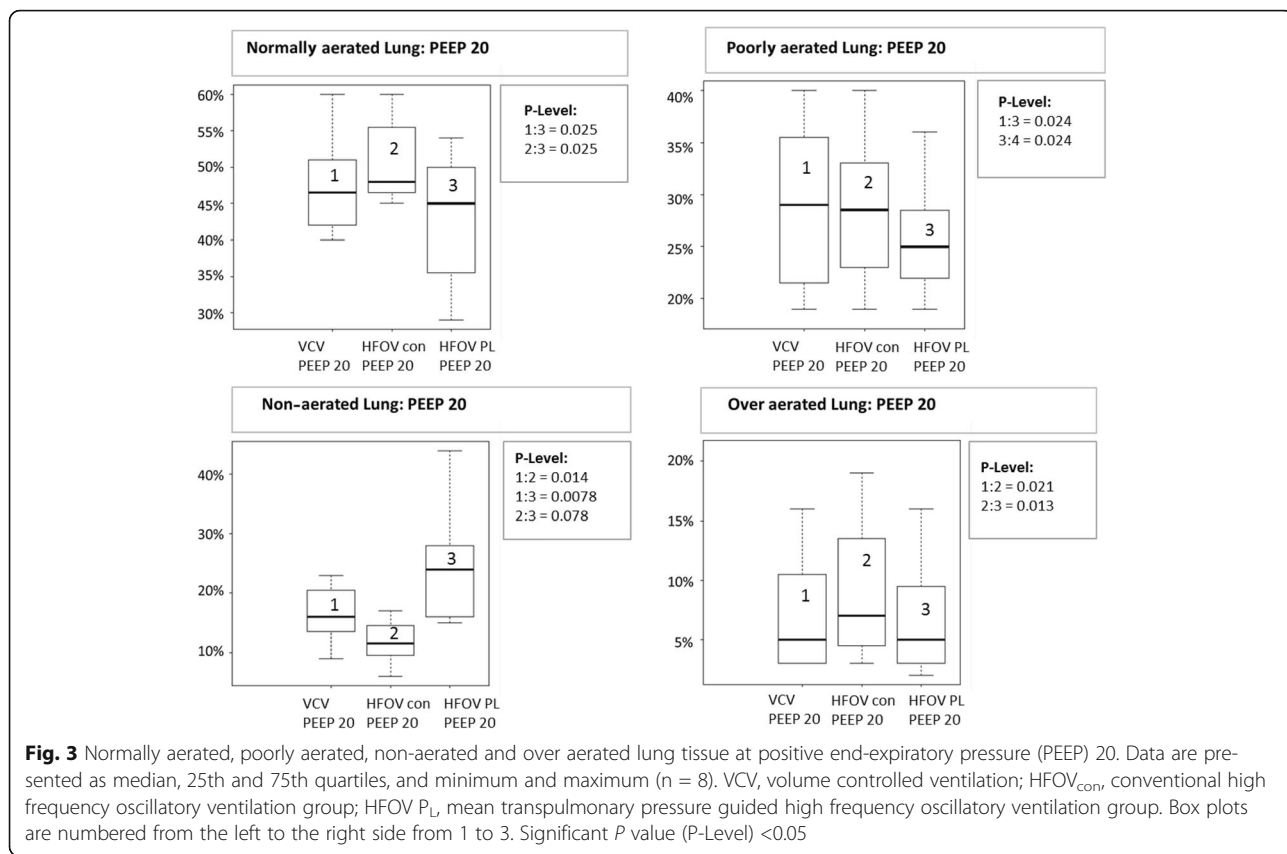|		ARDS PEEP 5			ARDS PEEP 10			ARDS PEEP 20		
Hounsfield units	HU	Median	25%	75%	Median	25%	75%	Median	25%	75%
VCV expiration		− 313.6	− 379.0	− 266.0	−379.2♀	− 452.6	− 331.1	− 479.5©£	− 554.7	− 439.5
ARDS HFOV $_{con}$		–	–	–	− 418.1	−517.5	− 398.9	− 535.4 $^{\Omega}$	− 580.3	− 484.6
ARDS HFOV $P_{L\ mean}$		–	–	–	−338.6	− 477.2	− 238.9	− 447.1	− 549.4	− 399.0
Total lung volume	ml									
VCV		1351.6	1197.8	1480.9	1619.3^	1553.5	1765.6	2349.2©	2230.8	2435.9
ARDS HFOV $_{con}$		–	–	–	1976.6	1870.1	2249.7	2582.1 $^{\Omega}$	2468.3	2734.3
ARDS HFOV $P_{L\ mean}$		–	–	–	1817.4	1464.8	1955.6	2256.0	2159.2	2388.3
Normally aerated tissue	ml									
VCV expiration		484.3	387.5	509.9	647.9♀	591.8	725.6	1112.9£	1016.3	1157.6
ARDS HFOV $_{con}$		–	–	–	855.4	812.7	937.7	1292.6 $^{\Omega}$	1196.9	1424.4
ARDS HFOV $P_{L\ mean}$		–	–	–	593.3	418.5	881.7	979.0	885.3	1166.5
Poorly aerated tissue	ml									
VCV expiration		225.1	217.2	246.3	306.1^	283.7	341.6	621.6£	509.5	818.3
ARDS HFOV $_{con}$		–	–	–	447.9	390.5	507.2	685.9 $^{\Omega}$	596.9	776.6
ARDS HFOV $P_{L\ mean}$		–	–	–	336.1	221.4	413.1	557.2	500.1	614.5
Non-aerated tissue	ml									
VCV expiration		628.3	447.0	725.3	608.4♀	448.8	705.6	409.3©£	325.5	459.0
ARDS HFOV $_{con}$		–	–	–	567.9	450.5	610.9	350.2 $^{\Omega}$	250.6	367.5
ARDS HFOV $P_{L\ mean}$		–	–	–	736.5	484.1	775.7	518.6	391.6	642.4
Over aerated tissue	ml									
VCV expiration		26.3	19.3	32.2	59.5^♀	47.2	68.0	124.8©	71.1	218.0
ARDS HFOV $_{con}$		–	–	–	106.1	72.1	167.7	180.7 $^{\Omega}$	113.7	390.7
ARDS HFOV $P_{L\ mean}$		–	–	–	72.9	23.6	107.4	121.0	63.6	208.4

Values are medians (25th and 75th quartiles) in eight animals. See text or Table 1 for description of groups

ARDS acute respiratory distress syndrome, *VCV* volume controlled ventilation, *HFOV con* conventional high frequency oscillatory ventilation, *HFOV P_L mean* HFOV guided by mean transpulmonary pressure, *PEEP* positive end-expiratory pressure

^$p < 0.05$ VCV ARDS PEEP 10 expiration vs. HFOV con "PEEP 10"; ♀$p < 0.05$ VCV ARDS PEEP 10 expiration vs. HFOV P_L mean "PEEP 10"; $p < 0.05$ HFOV con ARDS "PEEP 10" vs. HFOV P_L mean ARDS "PEEP 10"; ©$p < 0.05$ VCV ARDS PEEP 20 expiration vs. HFOV con "PEEP 20"; £$p < 0.05$ VCV ARDS PEEP 20 expiration vs. HFOV P_L mean "PEEP 20"; $^{\Omega}p < 0.05$ HFOV con ARDS "PEEP 20" vs. HFOV P_L mean ARDS "PEEP 20"; $p < 0.05$ (p values were determined using the Wilcoxon test for paired samples)

rescue therapy but rather as an early therapeutic option, because in the early stage of ARDS a low FiO_2 and low distending pressures will be sufficient therapy.

Although spontaneous ventilation is a cornerstone of ARDS therapy, muscle relaxation in the early phase can reduce lung injury [26]. Muscle relaxation facilitates ventilator synchronization and thus helps to limit alveolar pressure peaks with overdistension and consecutive pulmonary or systemic inflammation [26]. But it also increases the percentage of non-ventilated tissue. In view of our results, transpulmonary pressure-guided HFOV probably has a similar effect because it reduces overdistension. The results of the OSCILLATE and the OSCAR trials called the safety of HFOV into question [9, 10]. The OSCILLATE trial was terminated before completion because the interim analysis had shown that the use of HFOV resulted in a 12% increase in in-hospital mortality. 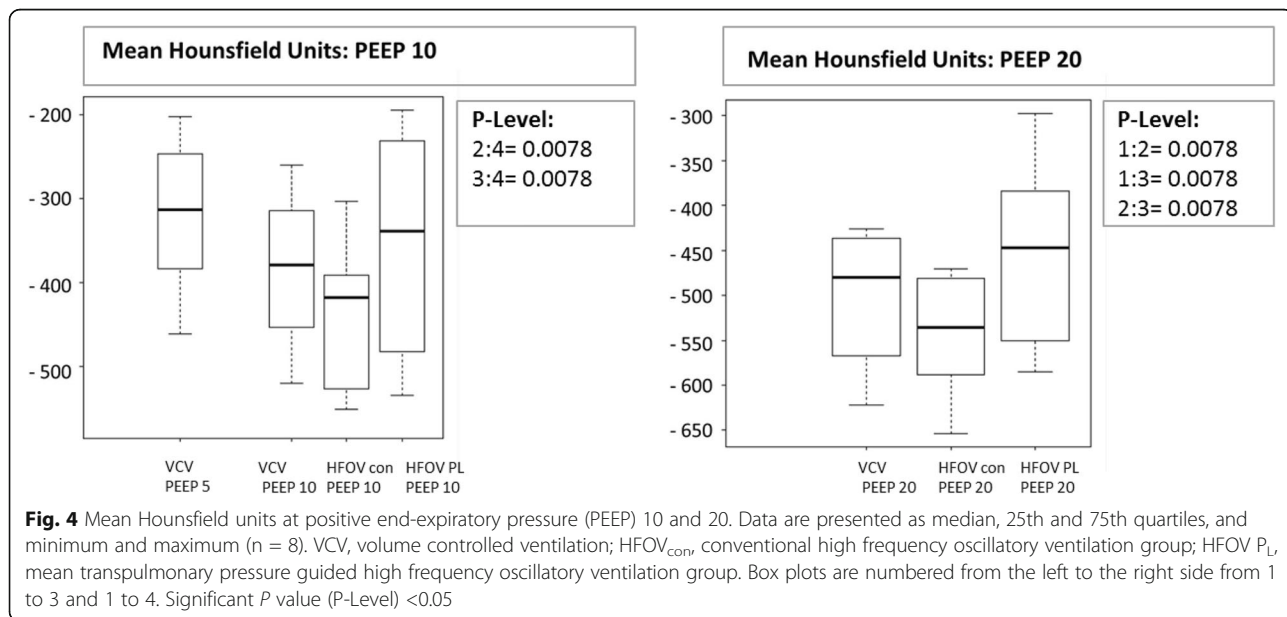The patients in the HFOV group had required more vasopressor support, perhaps due to the high intrathoracic pressures used in the OSCILLATE trial. High intrathoracic pressures cause hemodynamic compromise and increased right ventricular afterload. Employing transpulmonary pressure-guided HFOV would have resulted in lower mean airway pressures and hemodynamic compromise would have been less severe. It is also important to select suitable patients because HFOV is probably only a superior method in patients with homogenously damaged lungs [27], which are potentially recruitable for gas exchange. It should also be emphasized that centers with little or no experience in the use of HFOV participated in both trials, so the question arises whether suitable patients had been selected, and if HFOV had been correctly implemented.

The high airway pressures used in conventional ventilation or conventional HFOV induce regional overdistension in healthy lung units, which is probably the

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Fig. 3 Normally aerated, poorly aerated, non-aerated and over aerated lung tissue at positive end-expiratory pressure (PEEP) 20. Data are presented as median, 25th and 75th quartiles, and minimum and maximum (n = 8). VCV, volume controlled ventilation; HFOV$_{con}$, conventional high frequency oscillatory ventilation group; HFOV P$_L$, mean transpulmonary pressure guided high frequency oscillatory ventilation group. Box plots are numbered from the left to the right side from 1 to 3. Significant *P* value (P-Level) <0.05
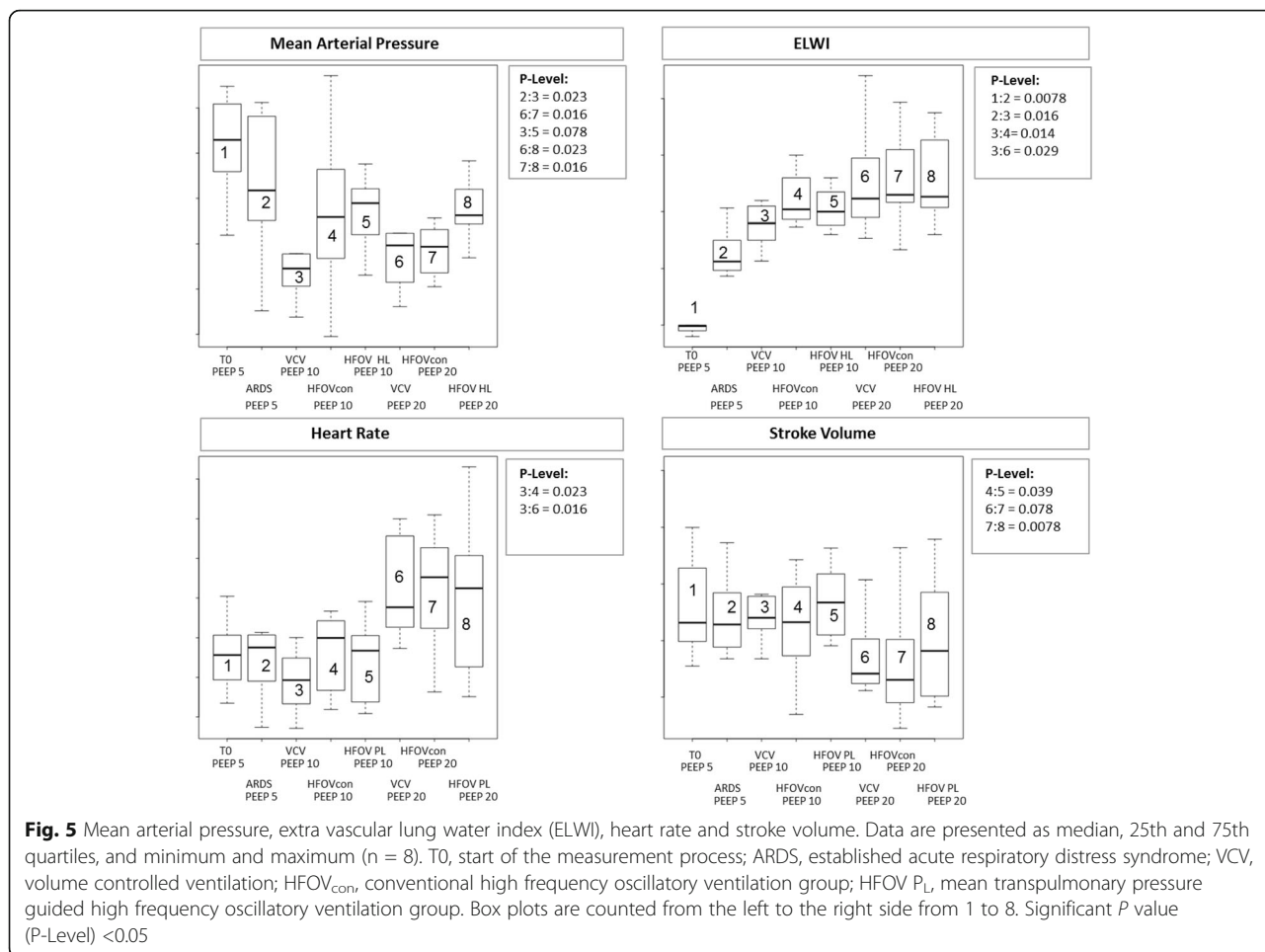
reason why the open-lung concept has failed to reduce mortality in ARDS in the past. One should note that the OSCAR trial, in which there was no difference in mortality between HFOV and conventional ventilation, used lower airway pressures than the OSCILLATE trial.

Overdistension, and to some degree even recruitment, causes local and systemic inflammation, which leads to the question whether a larger percentage of non-aerated lung tissue, as found in our study, might actually be an advantage. It should be noted that on comparison

Fig. 4 Mean Hounsfield units at positive end-expiratory pressure (PEEP) 10 and 20. Data are presented as median, 25th and 75th quartiles, and minimum and maximum (n = 8). VCV, volume controlled ventilation; HFOV$_{con}$, conventional high frequency oscillatory ventilation group; HFOV P$_L$, mean transpulmonary pressure guided high frequency oscillatory ventilation group. Box plots are numbered from the left to the right side from 1 to 3 and 1 to 4. Significant *P* value (P-Level) <0.05

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Fig. 5 Mean arterial pressure, extra vascular lung water index (ELWI), heart rate and stroke volume. Data are presented as median, 25th and 75th quartiles, and minimum and maximum (n = 8). T0, start of the measurement process; ARDS, established acute respiratory distress syndrome; VCV, volume controlled ventilation; HFOV$_{con}$, conventional high frequency oscillatory ventilation group; HFOV P$_L$, mean transpulmonary pressure guided high frequency oscillatory ventilation group. Box plots are counted from the left to right side from 1 to 8. Significant *P* value (P-Level) <0.05

between VCV and HFOV P$_{Lmean}$ there were fewer differences in hemodynamics than on comparison between HFOV$_{con}$ and HFOV P$_{Lmean}$. Only the MAP and the ITBI were higher in HFOV P$_{Lmean}$ compared to VCV, but SV and CO stayed the same at high PEEP levels in comparison to HFOV$_{con}$ and HFOV P$_{Lmean}$. CT examinations of HFOV P$_{Lmean}$ and VCV were comparable to HFOV P$_{Lmean}$ versus HFOV$_{con}$, because a higher percentage of non ventilated and poorly ventilated lung tissue was observed, but there was less over distended lung tissue in HFOV P$_{Lmean}$.

We propose that HFOV guided by transpulmonary pressure monitoring can be an alternative therapeutic option in the early stage of ARDS because it reduces the amount of overdistension and thereby limits escalation of lung injury.

Limitations

The primary limitation of the study was that it was not possible to randomize the order in which the ventilatory modes were applied, since the transpulmonary pressures used for the HFOV settings were determined during the preceding phase with conventional ventilation. There is

the possibility, albeit a small one, that using each animal for both ventilator modes might have induced factors relating to the history of the lung, which as a consequence might have influenced subsequent measurements. However, performing all measurements in a single animal has the major advantage of reducing inter-individual variability and allows the use of paired-data analysis that gives greater statistical power and reduces the risk of type II error. Statistical analysis was exploratory and differences in median and interquartile ranges were reported. Significance was assessed using the paired Wilcoxon test, but was not adjusted for multiple testing in order to avoid false negatives.

Another limitation is the fact that the hemodynamic advantages of HFOV P$_{Lmean}$ over HFOV$_{con}$ were only detectable at a very high PEEP level of 20 cmH$_2$O. The plateau pressures of more than 30 cmH$_2$O associated with this PEEP level would not have been tolerated in a clinical setting. The lower, clinically acceptable Paw would have resulted in a lower CDP during HFOV$_{con}$ and there might have been no difference detectable at this pressure.
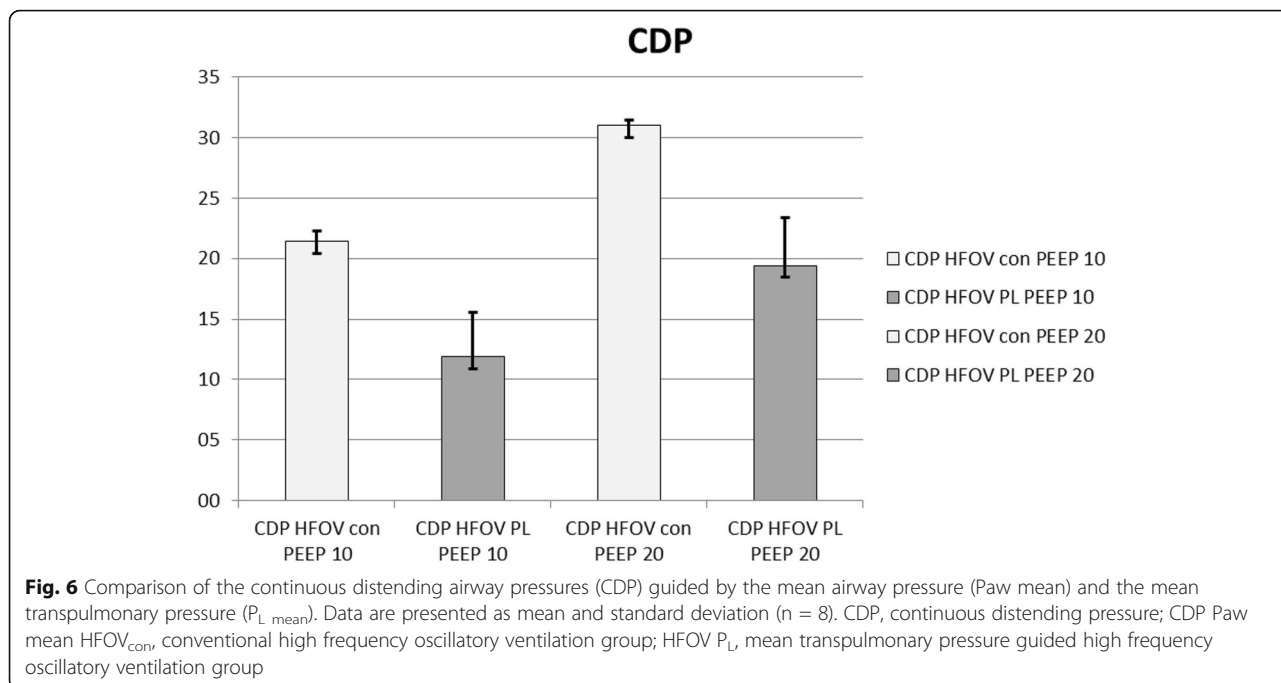
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Table 3 Hemodynamic parameters

	T$_0$ PEEP 5			ARDS PEEP 5			ARDS PEEP 10			ARDS PEEP 20		
HR, min^{-1}	Median	25%	75%	Median	25%	75%	Median	25%	75%	Median	25%	75%
VCV	55.7	50.2	59.9	57.6	49.7	60.4	49.3#^	44.6	53.9	67.6	63.6	84.2
ARDS HFOV $_{con}$	–	–	–	–	–	–	60.0	48.5	63.8	75.2	66.1	79.5
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	56.7	43.9	60.5	72.5	54.4	77.4
MAP, mmHg												
VCV	82.9	76.2	89.2	71.8	65.4	86.7	54.6#♀	50.9	57.7	59.7©£	52.5	62.3
ARDS HFOV $_{con}$	–	–	–	–	–	–	65.9	57.3	74.6	59.4 ^{Ω}	54.4	62.8
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	68.9	62.2	70.7	66.3	64.6	70.8
CVP, mmHg												
VCV	12.5	11.0	14.5	11.5	8.5	12.3	7.0#^♀	6.0	9.5	10.0	7.8	11.5
ARDS HFOV $_{con}$	–	–	–	–	–	–	9.5	7.8	10.5	10.5	9.0	12.3
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	8.0	7.0	10.5	10.0	8.0	12.3
mPAP, mmHg												
VCV	19.3*	17.6	21.3	25.4	23.3	28.1	22.1#	18.7	25.1	26.6	21.8	27.7
ARDS HFOV $_{con}$	–	–	–	–	–	–	21.9	19.1	31.3	25.6	21.2	31.4
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	21.2	17.1	26.1	24.0	21.7	26.7
CO, l.min^{-1}												
VCV	2.2	2.1	2.5	2.6	2.4	3.1	2.4	2.2	2.6	2.4©	2.1	2.6
ARDS HFOV $_{con}$	–	–	–	–	–	–	2.5	2.3	2.8	2.1 ^{Ω}	1.8	2.5
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	2.4	2.2	3.0	2.5	2.2	2.9
SV, ml												
VCV	46.4	41.1	63.9	45.7	38.2	55.2	48.1#	45.0	55.3	28.3©	25.5	39.9
ARDS HFOV $_{con}$	–	–	–	–	–	–	46.5	38.0	58.4	26.1 ^{Ω}	18.9	37.2
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	53.4	42.2	59.0	36.4	20.9	54.2
RVEDI, ml m^{-2}												
VCV	90.3*	86.2	97.5	104.0	97.7	127.6	103.9	96.1	110.5	102.2	90.6	120.6
ARDS HFOV $_{con}$	–	–	–	–	–	–	102.8	101.1	115.9	86.6	71.3	101.3
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	119.5	99.3	133.6	98.5	94.1	100.4
ITBI; ml m^2												
VCV	550.0	514.4	603.1	637.2	586.5	718.8	638.5	604.8	708.9	575.8©£	513.5	651.8
ARDS HFOV $_{con}$	–	–	–	–	–	–	651.7	611.3	706.1	560.7 ^{Ω}	506.8	665.9
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	660.6	639.6	733.0	621.0	573.0	675.7
ELWI, ml kg^{-1}												
VCV	4.9*	4.6	5.0	10.6	9.9	12.4	14.0#^	12.8	15.3	16.2	14.5	19.1
ARDS HFOV $_{con}$	–	–	–	–	–	–	15.2	14.3	17.0	16.5	15.9	20.3
ARDS HFOV P$_{L\ mean}$	–	–	–	–	–	–	15.0	14.1	16.1	16.3	15.7	20.5

Values are medians (25th and 75th quartiles) in eight animals. See text or Table 1 for description of groups

HR heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *mPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *CO* cardiac output, *SV* stroke volume, *SVV* stroke volume variation, *ITBI* intrathoracic blood volume index, *ELWI* extravascular lung water index, *ARDS* acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure

*$p < 0.05$ VCV T$_0$ PEEP 5 vs. VCV ARDS PEEP 5; #$p < 0.05$ VCV ARDS PEEP 10 vs. VCV ARDS PEEP 20; ^$p < 0.05$ VCV ARDS PEEP 10 vs. HFOV con "PEEP 10"; ♀$p < 0.05$ VCV ARDS PEEP 10 vs. HFOV P$_L$ mean "PEEP 10"; $p < 0.05$ HFOV con ARDS "PEEP 10" vs. HFOV P$_L$ mean ARDS "PEEP 10"; ©$p < 0.05$ VCV ARDS PEEP 20 vs. HFOV con "PEEP 20"; £$p < 0.05$ VCV ARDS PEEP 20 vs. HFOV P$_L$ mean "PEEP 20"; ^{Ω}$p < 0.05$ HFOV con ARDS "PEEP 20" vs. HFOV P$_L$ mean ARDS "PEEP 20"; $p < 0.05$ (p values were determined using the Wilcoxon test for paired samples)

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Fig. 6 Comparison of the continuous distending airway pressures (CDP) guided by the mean airway pressure (Paw mean) and the mean transpulmonary pressure ($P_{L\ mean}$). Data are presented as mean and standard deviation (n = 8). CDP, continuous distending pressure; CDP Paw mean $HFOV_{con}$, conventional high frequency oscillatory ventilation group; HFOV P_L, mean transpulmonary pressure guided high frequency oscillatory ventilation group

Last, the CDP used for HFOV P_{Lmean} was obtained by a method analogous to that used for $HFOV_{con}$, i.e. by adding 5 cmH_2O to the reference pressure, in this case P_L. This is also an empirical approach and has no experimental basis.

Conclusions

When treating ARDS, the ventilator settings demand meticulous adjustments and are a compromise between recruiting and stabilizing non-aerated lung tissue while avoiding overdistention and hemodynamic compromise. Our study results showed that HFOV guided by transpulmonary pressure is equal or superior to conventional HFOV with regard to systemic hemodynamics, oxygenation, and lung overdistension in animals. It might therefore be useful as a prophylactic approach to prevent worsening of lung injury in the early phase of ARDS. The promising results of transpulmonary pressure-guided HFOV would justify a clinical trial in which HFOV is initiated immediately after the onset of ARDS.

Abbreviations
ARDS: Acute respiratory distress syndrome; BW: Body weight; CDP: Continuous distending pressure; cmH_2O: Centimeter of water; CO: Cardiac output; CO_2: Carbon dioxide; CT: Computer tomography; CVP: Central venous pressure; ELWI: Extravascular water index; F: French; FiO_2: Fraction of inspired oxygen; HCl: Hydrochloric acid; HFOV $P_{L\ mean}$: High frequency oscillatory ventilation; mean transpulmonary pressure-guided; HFOV: High frequency oscillatory ventilation; $HFOV_{con}$: High frequency oscillatory ventilation; conventional mode; HR: Heart rate; HU: Hounsfield units; i.v.: Intravenous; I:E: Inspiratory: expiratory ratio (I: inspiration; E: expiration); ITBI: Intrathoracic blood volume index; Kg: Kilogram; MAP: Mean arterial pressure; mg: Milligram; MIDAS: Modular Intensive Care Data Acquisition System; ml: Milliliter; mPAP: Mean pulmonary arterial pressure;

n: Number; p: P level; PaO_2: Partial arterial oxygen pressure; $PaCO_2$: Partial arterial CO_2 pressure; Paw mean: Mean airway pressure; PEEP: Positive end-expiratory pressure; Pes $_{mean}$: Mean esophageal pressure; P_L: Transpulmonary pressure; P_{pl}: Pleural pressure; SV: Stroke volume; VCV: Volume controlled ventilation; VT: Tidal volume

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