Demand flow facilitates spontaneous breathing during high-frequency oscillatory ventilation in a pig model

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Objective: **Maintenance breathing is advocated in mechanical ventilation, which is difficult for the high-frequency oscillatory (HFO) ventilation. To facilitate spontaneous breathing during HFO ventilation, a demand flow system (DFS) was designed. The aim of the present study was to evaluate the system.**

Design: **Animal experiment.**

Setting: **University animal laboratory.**

Subjects: **Eight pigs (47–64 kg).**

Interventions: **Lung injury was induced by lung lavage with normal saline. After spontaneous breathing was restored HFO ventilation was applied, in runs of 30 minutes, with continuous fresh gas flow (CF) or the DFS operated in two different setups. Pressure to regulate the DFS was sampled directly at the Y-piece of the ventilator circuit (DFS) or between the endotracheal tube and measurement equipment at the proximal end of the endotracheal tube. In the end, animals were paralyzed. Breathing pattern, work of breathing, and gas exchange were evaluated.**

Measurements and Main Results: **HFO ventilation with demand flow decreased breathing frequency and increased tidal volume compared with CF. Comparing HFO modes CF, DFS, and DFSPROX, total pressure–time product (PTP) was 66 cm $H_2O \cdot sec \cdot min^{-1}$ (interquartile range 59–74), 64 cm $H_2O \cdot sec \cdot min^{-1}$ (50–72), and 51 cm $H_2O \cdot sec \cdot min^{-1}$ (41–63). Ventilator PTP was 36 cm $H_2O \cdot sec \cdot min^{-1}$ (32–42), 8.6 cm $H_2O \cdot sec \cdot min^{-1}$ (7.4–10), and 1 cm $H_2O \cdot sec \cdot min^{-1}$ (−1.0 to 2.8). Oxygenation, evaluated by Pao_2, was preserved when spontaneous breathing was maintained and deteriorated when pigs were paralyzed. Ventilation, evaluated by $Paco_2$, improved with demand flow. $Paco_2$ increased when using continuous flow and during muscular paralysis.**

Conclusions: **In moderately lung-injured anesthetized pigs during HFO ventilation, demand flow facilitated spontaneous breathing and augmented gas exchange. Demand flow decreased total breathing effort as quantified by PTP. Imposed work caused by the HFO ventilator appeared totally reduced by demand flow. (Crit Care Med 2009; 37:1068–1073)**

KEY WORDS: high-frequency ventilation; work of breathing; respiratory mechanics; mechanical ventilators

Acute lung injury and acute respiratory distress syndrome affect the lung heterogeneously. Both experimental models and clinical studies emphasize the positive effect of spontaneous breathing during mechanical ventilation (MV) on distribution of inflation and ventilation in the diseased lung. Spontaneous breathing improves oxygenation, lowers need for sedatives, improves hemodynamics, and reduces duration of MV and intensive care stay (1–4).

An open lung approach, as described by Froese (5) and Lachmann (6), reverses atelectasis, avoids overdistension of open lung units, and protects the injured lung from further harm. High-frequency oscillatory (HFO) ventilation, with an open lung strategy, is, in theory, a modality that can achieve optimal lung protection. Early application of HFO ventilation seems to give the optimal lung protection (7–9).

In HFO ventilation, more conventional respiratory rates (RRs) and tidal volumes (V_t values) are not needed to achieve adequate gas exchange (10). Preservation of spontaneous breathing during MV was not yet an issue during the development of the HFO ventilator (SensorMedics, 3100 A/B, Yorba Linda, CA) in the 1970s and 1980s. To have patients spontaneously breathe was, therefore, not the focus of the design of the HFO ventilator. As a result, spontaneous breathing during HFO ventilation is not well tolerated in large pediatric and adult patients, which is caused by a high imposed workload added by the HFO ventilator (11). The use of HFO ventilation for life-sustaining gas exchange is counterbalanced by the need for heavy sedation and possible muscular paralysis (11, 12). Furthermore, weaning from the HFO ventilator may be prolonged due to sedative and paralytic use. In an HFO ventilator, the fixed continuous fresh gas flow (CF) is the most important factor defining the imposed work of breathing (WOB). A demand flow system (DFS) was developed to advance to better HFO ventilation strategies that incorporate spontaneous breathing of a patient. In a bench study, we already demonstrated that the imposed WOB decreased considerably when demand flow was used instead of CF (13).

The aim of this study was to evaluate the influence of our DFS with HFO ventilation on different components of breathing effort, on respiratory variables, and on gas exchange in a pig model of acute lung injury.

MATERIALS AND METHODS

The study was approved by the Animal Welfare Committee of the VU University Medical

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Center. Eight Dalland pigs (body weight range, 47–64 kg) were used.

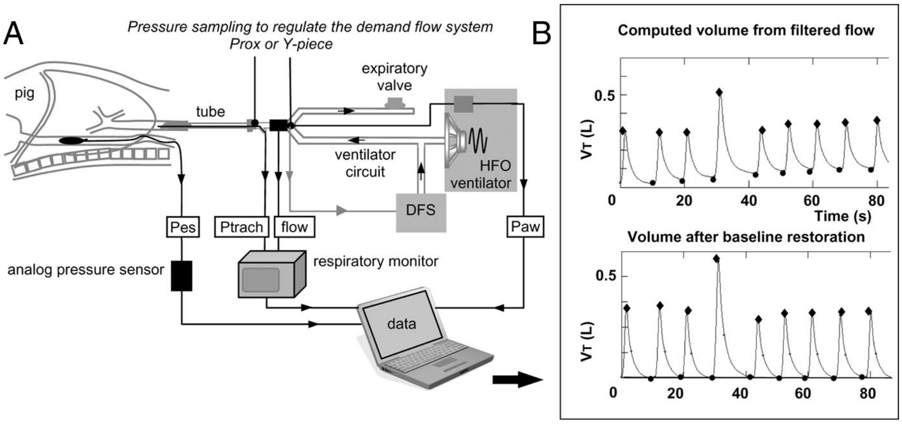

Figure 1. Experimental setup and signal processing. *A*, Pressure to regulate the demand flow system (*DFS*) is sampled at two different sites: *Prox*, between the endotracheal tube and measuring equipment proximal end of the endotracheal tube or *Y-piece*, between ventilator circuit and measuring equipment. P_{es}, esophageal pressure; P_{trach}, tracheal pressure; P_{aw}, pressure at Y-piece; *HFO*, high-frequency oscillatory; V_t, tidal volume. *B*, Top: computed tidal volume of spontaneous breathing. ●, start of inspiration; ◆, end of inspiration. Bottom: restoration of tidal breathing to same start volume.

Animal Preparation

Anesthesia. Anesthesia was induced with intramuscular injection of 0.5 mg atropine, 0.5 mg·kg^{-1} midazolam, and 10 mg·kg^{-1} ketamine. After induction, an ear vein was cannulated and propofol 3 mg·kg^{-1} was injected before endotracheal intubation with a cuffed tube (inner diameter 8 mm). Anesthesia was maintained with continuous infusion of propofol 4 mg·kg^{-1}·hr^{-1} and remifentanil 0.4 μg·kg^{-1}·min^{-1} during instrumentation and lung lavage. To allow spontaneous breathing, propofol dosage was lowered to 2 mg·kg^{-1}·hr^{-1}, and that of remifentanil to 0.05–0.1 μg·kg^{-1}·min^{-1}. When necessary according to the experimental protocol, spontaneous breathing was suppressed using pancuronium bromide 0.3 mg·kg^{-1}·hr^{-1}. At the end, animals were killed using sodium pentobarbital.

Surgical Preparation. During instrumentation, lung lavage, and the stabilization period, animals were ventilated with a Servo 900C ventilator (Maquet Critical Care AB, Solna, Sweden) in a volume-controlled mode with the following settings and then adjusted to maintain normocapnia (Paco$_2$ 38–45 mm Hg): RR 20 min^{-1}, inspiratory pause time 0.6 seconds, positive end-expiratory pressure 5 cm H_2O, inspiration to expiration ratio 1:2, FIO$_2$ 1.0, initial V_t 10 mL·kg^{-1}. Animals were placed in supine position on a heated table. Temperature was kept in the normal range (38–39°C) using a heating pad.

The left femoral artery was cannulated to measure arterial blood pressure and to sample blood. A Paratrend 7 continuous intravascular blood gas monitor (Biomedical Sensors, High Wycombe, United Kingdom) was inserted at the left femoral artery. A triple lumen pulmonary arterial catheter was inserted to monitor pulmonary arterial and central venous pressures and to sample mixed venous blood. A separate catheter was inserted into the superior vena cava to infuse fluids and anesthetics.

Surfactant Depletion. Surfactant deficiency was induced by a repeated whole lung lavage. Normal saline 30–40 mL·kg^{-1} of 37°C was instilled in the lungs at a pressure of 50 cm H_2O and then directly removed by drainage. The lavage was repeated after 1 hour (14, 15).

HFO Ventilator

A SensorMedics 3100B HFO ventilator (SensorMedics, Yorba Linda, CA) was used. In the HFO ventilator, mean airway pressure (mP_{aw}) is maintained by two mechanisms: setting of a CF and setting of the resistance of the expiratory balloon valve. A patient's spontaneous breathing during HFO ventilation generates changes in mP_{aw}. The changes in mP_{aw} determine directly the workload for the patient; the higher the changes, the higher the workload (16). The standard HFO ventilator cannot compensate for changes in mP_{aw} caused by spontaneous breathing. To solve the problem, the 3100B HFO ventilator was equipped with a custom-made DFS. A detailed description of the DFS is given elsewhere (13).

Measurements and Samples

Data Acquisition. The experimental setup is depicted in Figure 1*A*. Flow was measured at the proximal end of the endotracheal tube using a hot-wire anemometer (Florian, Acutronic Medical Systems AG, Hirzel, Switzerland). For measurement of the tracheal pressure (P_{trach}) with the respiratory monitor, an air-filled 5F catheter was introduced into the endotracheal tube, its tip located at the distal end of the tube. An esophageal balloon catheter (SmartCath Catheter 8F, Viasys Healthcare, Palm Springs, CA) was placed for measurement of esophageal pressure (P_{es}) to approximate pleural pressure. P_{es} was sampled using an analog pressure sensor (40PC, Honeywell, Morristown, NJ). Validation of proper placement of the esophageal catheter was done using the occlusion test (17). The pressure at the Y-piece in the ventilator circuit (P_{aw}) was sampled using the unfiltered electronic signal from the internal pressure sensor of the HFO ventilator. Pressure sensors were calibrated using a water column. Flow and pressure signals were recorded at 100 Hz and stored on a laptop computer for off-line analysis.

Data Processing. A MATLAB environment was used for data processing (The Mathworks, Natick, MA). In each animal, 5-minute segments of air flow and pressure signals were recorded for different HFO ventilation modes. For evaluation, 2-minute segments with a regular breathing pattern were studied from the 5-minute recordings.

To eliminate HFO ventilator oscillations, the recorded 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 flow changes caused by spontaneous breathing of the pigs. The initial volume at the start of each breath changed in time (Fig. 1*B*, top). Using linear interpolation, a zero baseline was created (Fig. 1*B*, bottom).

Data Evaluation. From the integrated filtered flow signals, breathing pattern and minute ventilation were determined for each individual breath and averaged over a 2-minute period. To evaluate the influence of the DFS with HFO ventilation on different components of breathing effort, inspiratory pressure–time product (PTP) was evaluated (18, 19). Total PTP was calculated as the area between elastic recoil pressure of the chest wall (P_{escw}) and P_{es} (19). Static chest wall compliance (C_{cw}) was measured to calculate P_{escw}. C_{cw} was determined during muscular paralysis, after the second lung lavage, by inflating the lungs with a volume of 1.5 L with a syringe (3.0 L Calibrated Syringe, Hans Rudolph, Kansas City, MO). C_{cw} was calculated as the V_t divided by the difference in inspiratory and expiratory P_{es} at points of zero flow. Total imposed and ventilator PTP were computed as the area between set mP_{aw} and P_{trach} and P_{aw}, respectively.

Hemodynamic and Respiratory Variables. Arterial and mixed venous blood samples were analyzed with ABL505 and OSM3 hemoximeters (Radiometer, Copenhagen, Denmark). Continuous arterial blood gas analysis was conducted by the Paratrend 7. Physiologic shunt fraction (Q_s/Q_t) and respiratory indices were calculated according to standard formulas (20).

Experimental Protocol

Study Design. Figure 2 shows the study design. After a 30-minute stabilization period on conventional ventilation, HFO ventilation was initiated. Initial settings were as follows:

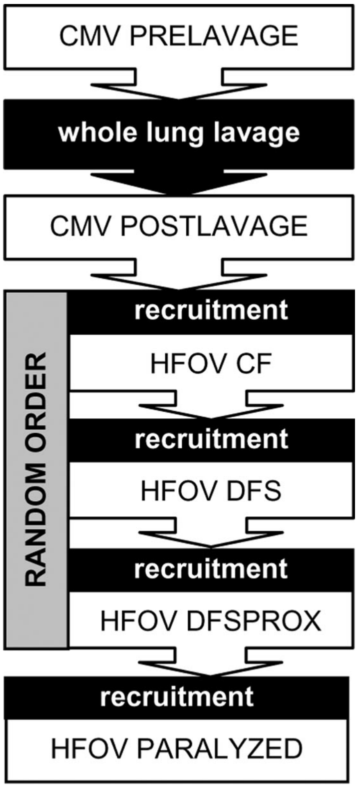

Figure 2. Study design. *CMV*, conventional mechanical ventilation; *HFOV*, high-frequency oscillatory ventilation; *CF*, continuous flow; *DFS*, demand flow system; *DFSPROX*, DFS were pressure to regulate the system is sampled at the proximal end of the endotracheal tube.

mP_{aw} 20 cm H_2O, proximal pressure amplitude ([Delta]P) was set to maintain normocapnia (38–45 mm Hg), oscillatory frequency 5 Hz, inspiration/expiration ratio 1:2, fresh gas flow 40 L·min^{-1}, and F_{IO_2} 1.0. The order of the three different HFO modalities with spontaneous breathing was randomly determined: 1) HFO ventilation with a CF of 20 L·min^{-1} (CF); 2) HFO ventilation with demand flow, where pressure to regulate the DFS was sampled directly at the Y-piece of the ventilator circuit (DFS); and 3) HFO ventilation with demand flow, where pressure to regulate the DFS was sampled at the proximal end of the endotracheal tube (DFSPROX). The two different pressure pick-up points were necessary to evaluate the influence of the measuring equipment (Fig. 1) on the performance of the DFS. In a fourth step, all animals studied were totally paralyzed. To standardize lung volume at the start of each HFO ventilation mode, a recruitment maneuver was performed (6, 21). Initially, mP_{aw} on HFO ventilation was increased to 30 cm H_2O for 5 minutes. mP_{aw} was lowered to 25 cm H_2O when heart rate or blood pressure was unstable for >2 minutes. mP_{aw} was then lowered until the animals started breathing in a regular pattern. Measurements were done in the last 5 minutes of every 30 minutes of different HFO ventilation modalities.

Table 1. Respiratory variables during different high-frequency oscillatory ventilation modes

	CF	DFS	DFSPROX
RR (min^{-1})	8.5 (7.8–9.4)	7.6 (6.4–9.9)^{a}	5.0 (4.1–5.8)^{a,b}
V_t (L)	0.23 (0.22–0.25)	0.28 (0.22–0.34)^{a}	0.43 (0.36–0.48)^{a,b}
V_t (mL·kg^{-1})	4.3 (4.2–4.7)	5.1 (4.2–6.4)^{a}	8.1 (6.8–9.1)^{a,b}
MV (L·min^{-1})	2.1 (1.9–2.2)	2.2 (1.9–2.4)	1.9 (1.7–2.4)
T_i (sec)	1.5 (1.5–1.8)	1.7 (1.4–2.0)^{a}	2.1 (1.9–2.2)^{a,b}
Pressure (time product per minute, cm H_2O·s·min^{-1})			
Total	66 (59–74)	64 (50–72)	51 (41–63)^{a,b}
Total imposed	67 (58–78)	51 (41–57)^{a}	36 (28–43)^{a,b}
Ventilator	36 (32–42)	8.6 (7.4–10)^{a}	1.0 (−1.0–2.8)^{a,b}

RR, respiratory rate; V_t, tidal volume at airway opening; MV, minute ventilation; T_i, inspiratory time; CF, continuous fresh gas flow; DFS, demand flow system; DFSPROX, demand flow with pressure sampled at proximal end of endotracheal tube.

$^{a}p < 0.05$; CF vs. DFS or DFSPROX; $^{b}p < 0.05$; DFS vs. DFSPROX.

Statistical Analysis

Data are expressed as median and 25th to 75th interquartile range. Parameter comparison for different HFO ventilation modes was performed using repeated-measures analysis of variance with Bonferroni *post hoc* testing. In all analysis, a p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 15 for Windows (SPSS, Chicago, IL).

RESULTS

Respiratory Variables. All eight animals completed the entire experimental protocol. The respiratory variables obtained during different HFO modalities are summarized in Table 1. Minute ventilation of spontaneous breathing (MV) was equal in all three HFO ventilation modes. V_t and RR significantly differed between HFO ventilation modes. V_t is lowest and RR is highest in the CF modality; in the DFSPROX mode, this was the reverse. V_t per kg increased from 4.3 (4.2–4.7) in the CF mode to 8.1 mL·kg^{-1} (6.8–9.1) in the DFSPROX mode. RR was inversely related to V_t. An increase of V_t was paralleled by an increase of inspiratory time (T_i).

Breathing Effort. PTP per minute was significantly lower for all different components in the DFSPROX mode compared with the CF and DFS mode. Total imposed and ventilator PTP per minute in the DFS mode were lower compared with the CF mode. No active expiration was observed. The effectiveness of the DFS system to lower breathing effort for different V_t values of spontaneous breathing is depicted in Figure 3*A*–*C*. For a given V_t, different components of PTP per cycle were highest when CF mode was used. Compared with CF total PTP per cycle decreased 10% to 39% using DFS, and decreased 39% to 48% using DFSPROX.

In Figure 4, the effect of the DFS on P_{aw} and V_t is illustrated. The DFS is able to reduce changes in P_{aw} on account of spontaneous breathing. When pressure to regulate the DFS was sampled directly at the proximal end of the endotracheal tube, pressure support was added during inspiration in the example. During expiration, P_{aw} is lower than set mP_{aw}. The fact that demand flow generates a higher V_t is also demonstrated. All three different breaths have approximately equal inspiratory PTP per cycle. With increase in support of the DFS, the flow and thus V_t increases clearly.

Gas Exchange. Results for gas exchange are shown in Table 2. Oxygenation improved in all HFO ventilation modes when spontaneous breathing was maintained. When pigs were paralyzed, P_{AO_2} decreased remarkably during the 30-minute period. Pa_{CO_2} decreased in the DFS and DFSPROX mode. Pa_{CO_2} increased significantly using CF or during muscular paralysis.

DISCUSSION

Our animal study demonstrates that demand flow facilitates spontaneous breathing during HFO ventilation by lowering WOB. The DFS was able to effectively minimize work imposed by the ventilator. The amount of support during spontaneous breathing can be influenced by changing the pressure sampling site to regulate the DFS. Even additional pressure support can be generated to overcome WOB imposed by the endotracheal tube.

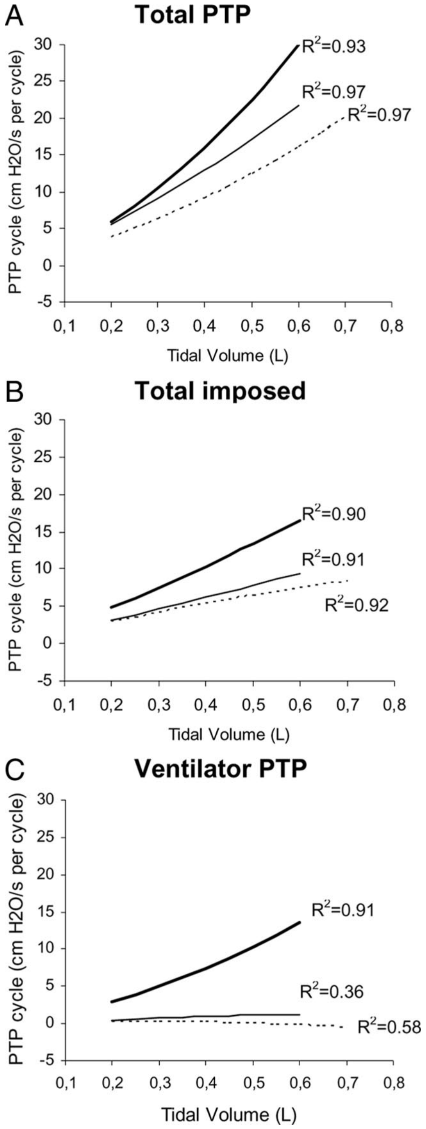

Figure 3. Correlation between tidal volume and (*A*) total, (*B*) total imposed, and (*C*) ventilator pressure–time product (*PTP*) per breathing cycle. Continuous flow (**—**) and demand flow with pressure sampled at the Y-piece (—) and at the proximal end of the endotracheal tube (- -). *Lines* represent second-order polynomial regression curves.

Respiratory Variables. The spontaneous breathing pattern changed when different modalities of HFO ventilation were compared. In HFO ventilation with CF, V_t was lowest and breathing frequency highest. In the DFSPROX mode, V_t was highest and breathing frequency lowest. These results are consistent with the theory of minimal work. The breathing frequency adopted by the animal to achieve a target minute ventilation represents a strategy to minimize inspiratory effort (22). The lower RRs observed with the DFS in use was caused by the effective reduction in WOB by the DFS. The V_t in the DFSPROX mode increased to 8.1 mL·kg^{-1} (6.8–9.1). These V_t values are not exceptionally high and are not expected to cause additional lung injury (23). The lung lavage model used did not cause widespread atelectasis and consolidation in the animal lungs, as concluded from the data on gas exchange. Whether an increase in V_t also improved the distribution of ventilation is impossible to say based on the results and is an area of further research.

Breathing Effort. Total, total imposed, and ventilator PTP per minute were lowest in the DFSPROX mode. The DFS is effective in reducing PTP per cycle for different V_t values (Fig. 3). Comparison of the results with earlier bench tests show differences in the amount of imposed PTP (11, 13). In the animal study, the amount of imposed workload was substantially lower compared with earlier bench test results. The difference in imposed breathing work can be explained by a lower breathing frequency of the animals compared with the breathing frequencies simulated in the bench tests.

Gas Exchange. The results for gas exchange show a benefit of spontaneous breathing during HFO ventilation. Pao_2 improved in all HFO ventilation modes when spontaneous breathing was maintained. Muscular paralysis had a deteriorating effect on Pao_2. Accordingly, there is a trend of worsening of physiologic shunt fraction when animals were paralyzed. The trend did not reach statistical significance. Use of the demand flow during HFO ventilation improved ventilation as is illustrated by a decrease in Paco_2 in the DFS and DFSPROX mode. Paco_2 increased significantly using CF or during muscular paralysis.

To observe the effect of spontaneous breathing and muscular paralysis on gas exchange, HFO ventilator settings were not changed during the 30 minutes of each HFO mode. The pigs only had mild lung injury. Therefore by adjustment of HFO ventilator settings, the derangement in gas exchange would have been easily corrected. The results on gas exchange, however, indicate that, when spontaneous breathing is maintained, adequate gas exchange may be achieved at a lower mP_{aw}.

Synchronization. MV assumes the WOB, improves gas exchange, and unloads the respiratory muscles, all of which require good synchronization between the patient and the ventilator (24). In conventional MV, synchrony is evaluated by analysis of triggering and flow and pressure recordings. The DFS has no flow or pressure trigger comparable with conventional mechanical ventilators. Simplified, the DFS responds to changes in mP_{aw} caused by spontaneous breathing with the following approach: The DFS algorithm predicts an oscillatory P_{aw} signal. Because of spontaneous breathing, the actual P_{aw} signal will change. When the DFS detects a difference between the predicted and actual P_{aw}, it adjusts the fresh gas flow to maintain a stable mP_{aw}. Furthermore, the DFS algorithm is adaptive over time. The response time of the DFS, to react on changes in mP_{aw}, will therefore change in time. During the experiment flow over time generated by the DFS was not recorded. Therefore synchrony between the DFS and animal's spontaneous breathing pattern could not be evaluated. The animals at least showed no signs of air hunger but were, of course, sedated.

Limitations. Our study has some limitations. In a clinical setting, HFO ventilation is applied in severe acute lung injury/acute respiratory distress syndrome. We initially thought of using a model of severe lung injury, which necessitates high mP_{aw} to keep oxygenation in acceptable ranges; high mP_{aw}, however, induces apnea in pigs (Wrigge H, Department of Anesthesiology and Intensive Care Medicine of the University of Bonn, personal communication). Therefore, to test our DFS we could apply only mild lung injury. Our results are, thus, restricted to low mP_{aw} and to mild lung injury. Additionally, we could not test high RR, which is regrettable, as our DFS was less effective at higher than at lower RR in bench tests (13). Flow and pressure sensors, necessary for data acquisition added considerable resistance to the ventilator circuit. The additional resistance has a negative effect on the DFS performance. By regulating the DFS at different pressure sampling sites, the additional resistance was partly overcome.

CONCLUSIONS

During HFO ventilation in surfactant-depleted pigs, DFS facilitates spontaneous breathing, reduces breathing effort, and improves gas exchange. Demand flow may prove to be a valuable tool in reducing the threshold for early application of HFO ventilation. In addition, demand flow may augment weaning during HFO ventilation. The development of a flow demand system for a

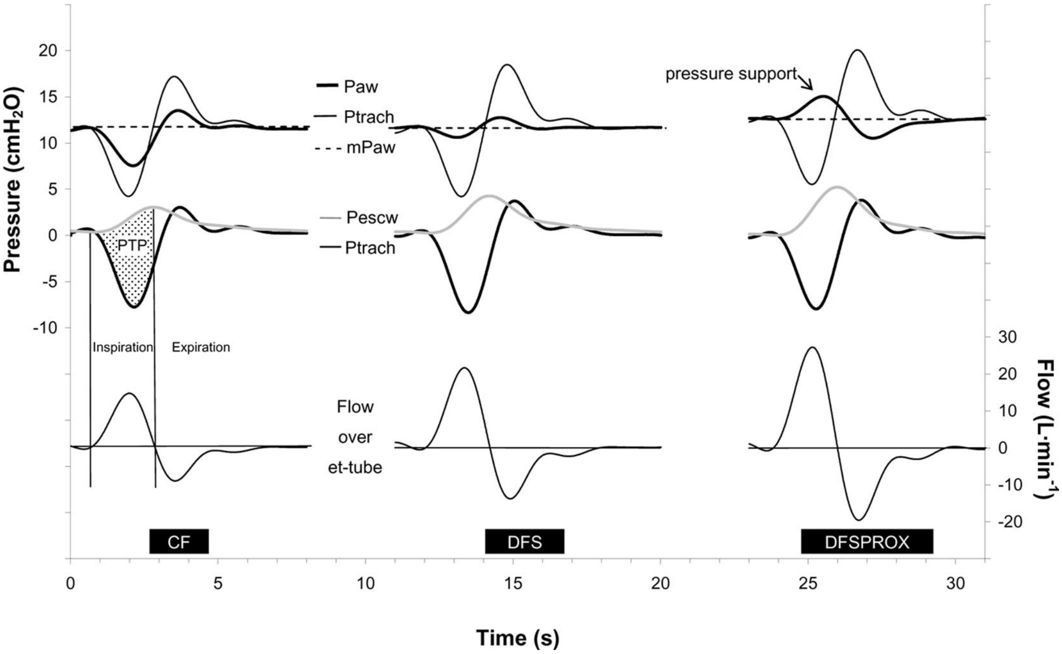

Figure 4. Illustration of pressures and flow during different high-frequency ventilation modes. P_{aw}, airway pressure; P_{trach}, tracheal pressure; mP_{aw}, set mean airway pressure on the high-frequency oscillatory ventilator; P_{escw}, elastic recoil pressure of the chest wall; P_{es}, esophageal pressure; and *et-tube*, endotracheal tube. Depicted are three different breaths: 1) left with continuous fresh gas flow (*CF*), 2) middle with demand flow where pressure was sampled at the Y piece (demand flow system [*DFS*]) and 3) right with demand flow and pressure sampled at the proximal end of the endotracheal tube (*DFSPROX*). Note that due to the demand flow system, the swings in P_{aw} decrease comparing CF and DFS. When pressure was sampled at the proximal end of the endotracheal tube, during inspiration there was some pressure support, as P_{aw} becomes higher than set mP_{aw}. There was no pressure overshoot as P_{trach} is lower than mP_{aw} during inspiration. During expiration, P_{aw} is lower than set mP_{aw} to facilitate expiration. The *dotted area* represents the total inspiratory pressure–time product (*PTP*). Note that with almost equal PTP for all three breaths, the DFSPROX generates the highest flow and thus the highest V_{t}.

Table 2. Physiologic variables during different high-frequency oscillatory ventilation modes

	Spontaneously Breathing			Paralyzed
	CF	DFS	DFSPROX	PAR
Pao$_2$ (mm Hg)	493 (455–502)	473 (420–502)	501 (493–554)	451 (420–489)
ΔPao$_2$ (mm Hg)	19.9 (19.6–37)	31 (−5.5 to 84)	19.3 (5.5–34)	−140 (−225 to −53)^a
Paco$_2$ (mm Hg)	53 (52–54)	49 (46–52)	52 (48–53)	70 (63–72)
ΔPaCO$_2$ (mm Hg)	6.3 (−3.0–18)	−5.7 (−4.3 to −7.4)^b	−4.9 (−3.8 to −7.0)^b	9.9 (3.6–22)^c
Aa-DO$_2$ (mm Hg)	150 (145–192)	174 (145–198)	136 (95–148)	168 (125–216)
Q_s/Q_t	0.06 (0.04–0.08)	0.1 (0.06–0.3)	0.01 (0.002–0.3)	0.3 (0.29–0.3)
mP_{aw} (cm H$_2$O)	10 (9.9–11)	10 (8.7–11)	10 (9.9–11)	10 (9.9–11)
OI	2.1 (2.0–2.2)	2.0 (1.9–2.1)	2.0 (1.8–2.1)	2.1 (2.0–2.5)

CF, continuous fresh gas flow; DFS, demand-flow system; DFSPROX, demand flow with pressure sampled at proximal end of endotracheal tube; PAR, muscular paralysis; ΔPao$_2$ and ΔPaco$_2$, difference in Pao$_2$ and Paco$_2$ at the beginning and end of 30-min HFO ventilation; Aa-DO$_2$, alveolar-arterial Po$_2$ difference; Q_s/Q_t, physiologic shunt fraction; mP_{aw}, mean airway pressure; OI, oxygenation index.

$^a p < 0.05$; PAR vs. CF, DFS and DFSPROX; ^{b}CF vs. DFS and DFSPROX; ^{c}PAR vs. DFS and DFSPOX.

HFO ventilator is an important step toward further improvement of HFO ventilation strategies that incorporate spontaneous breathing of a patient.

Further studies are needed to elucidate DFS performance at higher mP_{aw} and higher RRs seen in clinical use of HFO ventilation. Furthermore, patient and DFS synchrony needs to be evaluated.

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