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 measurement equipment at the proximal end of the endotracheal tube 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 DFS/PROX, total pressure–time product (PTP) was 66 cm H2O-sec-min⁻¹ (interquartile range 59–74), 64 cm H2O-sec-min⁻¹ (50–72), and 51 cm H2O-sec-min⁻¹ (41–63). Ventilator PTP was 36 cm H2O-sec-min⁻¹ (32–42), 8.6 cm H2O-sec-min⁻¹ (7.4–10), and 1 cm H2O-sec-min⁻¹ (–1.0 to 2.8). Oxygenation, evaluated by PaO₂, was preserved when spontaneous breathing was maintained and deteriorated when pigs were paralyzed. Ventilation, evaluated by Paco₂, improved with demand flow. Paco₂ 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.

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

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 (V₉ 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 work-load 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 best and simplest model 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...
Animal Preparation

Anesthesia. Anesthesia was induced with intramuscular injection of 0.5 mg atropine, 0.5 mg/kg of midazolam, and 10 mg/kg of ketamine. After induction, an ear vein was cannulated and propofol 3 mg/kg was injected before endotracheal intubation with a cuffed tube (inner diameter 8 mm). Anesthesia was maintained with continuous infusion of propofol 4 mg/kg/hr and remifentanil 0.4 μg/kg min⁻¹ during instrumentation and lung lavage. To allow spontaneous breathing, propofol dosage was lowered to 2 mg/kg/hr, and that of remifentanil to 0.05–0.1 μg/kg 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 (Paco₂ 38–45 mm Hg): RR 20 min⁻¹, inspiratory pause time 0.6 seconds, positive end-expiratory pressure 5 cm H₂O, inspired to expiration ratio 1:2, Fio₂ 1.0, initial Vt 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 pressure 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 H₂O 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 (mPaw) 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 mPaw. The changes in mPaw 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 mPaw 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 1A. 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 (PTP), 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 (SensorMedics, Yorba Linda, CA) was placed in the stomach to measure the approximate pleural pressure. An esophageal catheter was inserted into the superior vena cava to infuse fluids and anesthetics.

Syringe, Hans Rudolph, Kansas City, MO). 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 (PTP), 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 (SensorMedics, Yorba Linda, CA) was placed in the stomach to measure the approximate pleural pressure. An esophageal catheter was inserted into the superior vena cava to infuse fluids and anesthetics.

Hemodynamic and Respiratory Variables. Arterial and mixed venous blood samples were analyzed with ABL505 and OSM3 blood-gas analyzers (Radiometer, Copenhagen, Denmark). Continuous arterial blood gas analysis was conducted by the Paratrend 7. Physiologic shunt fraction (Qs/Qt) 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:
the start of each HFO ventilation mode, a
In a fourth step, all animals studied were to-
evaluate the influence of the measuring equip-
pressure pick-up points were necessary to
cheal tube (DFSPROX). The two different
sampled at the proximal end of the endotra-
flow, where pressure to regulate the DFS was
(DFS); and 3) HFO ventilation with demand
directly at the Y-piece of the ventilator circuit
2) HFO ventilation with demand flow, where
HFO ventilation with a CF of 20 L
ous breathing was randomly determined: 1)
three different HFO modalities with spontane-
try and RR is highest in the CF mo-
ponent of PTP per cycle were highest
were maintained. When pigs were paralyzed,
creased significantly using CF or during
A–C
mPaw 20 cm H2O, proximal pressure amplitu-
ed ([Delta]P) was set to maintain normocap-
(a3–a5 mm Hg), oscillatory frequency 5
Hz, inspiration/expiration ratio 1:2, fresh gas
flow 40 L min–1, and Pao2 1.0. The order of the
three different HFO modalities with spontane-
ous 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
(DF); and 3) HFO ventilation with demand
flow, where pressure to regulate the DFS was
sampled at the proximal end of the endotra-
cheal tube (DFSPROX). The two different
pressure pick-up points were necessary to
evaluate the influence of the measuring equip-
ment (Fig. 1) on the performance of the DFS.
In a fourth step, all animals studied were to-
tally paralyzed. To standardize lung volume
at the start of each HFO ventilation mode, a
recruitment maneuver was performed (6, 21).
Initially, mPaw on HFO ventilation was in-
creased to 30 cm H2O for 5 minutes. mPaw
was lowered to 25 cm H2O when heart rate or
blood pressure was unstable for >2 minutes.
mPaw was then lowered until the animals
started breathing in a regular pattern. Mea-
surements were done in the last 5 minutes of
each 30 minutes of different HFO ventilation
modalities.

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

<table>
<thead>
<tr>
<th></th>
<th>CF</th>
<th>DFS</th>
<th>DFSPROX</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (min–1)</td>
<td>8.5 (7.8–9.4)</td>
<td>7.6 (6.4–9.9)</td>
<td>5.0 (4.1–5.8)</td>
</tr>
<tr>
<td>Vt (L)</td>
<td>0.23 (0.22–0.25)</td>
<td>0.28 (0.22–0.34)</td>
<td>0.43 (0.36–0.48)</td>
</tr>
<tr>
<td>Vt (mL kg–1)</td>
<td>4.3 (4.2–4.7)</td>
<td>5.1 (4.2–6.4)</td>
<td>8.1 (6.8–9.1)</td>
</tr>
<tr>
<td>MV (L min–1)</td>
<td>2.1 (1.9–2.2)</td>
<td>2.2 (1.9–2.4)</td>
<td>1.9 (1.7–2.4)</td>
</tr>
<tr>
<td>T0 (sec)</td>
<td>1.5 (1.5–1.8)</td>
<td>1.7 (1.4–2.0)</td>
<td>2.1 (1.9–2.2)</td>
</tr>
<tr>
<td>Pressure (time product per minute, cm H2O s–1)</td>
<td>Total</td>
<td>66 (59–74)</td>
<td>64 (50–72)</td>
</tr>
<tr>
<td></td>
<td>Total imposed</td>
<td>67 (58–78)</td>
<td>51 (41–57)</td>
</tr>
<tr>
<td>Ventilator</td>
<td>36 (32–42)</td>
<td>8.6 (7.4–10)</td>
<td>1.0 (1–2.8)</td>
</tr>
</tbody>
</table>

RR, respiratory rate; Vt, tidal volume at airway opening; MV, minute ventilation; T0, inspiratory time; CF, continuous fresh gas flow; DFS, demand flow system; DFSPROX, demand flow with pressure sampled at proximal end of endotracheal tube.

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 ani-
mals completed the entire experimental
protocol. The respiratory variables ob-
tained during different HFO modalities
are summarized in Table 1. Minute ven-
tilation of spontaneous breathing (MV)
was equal in all three HFO ventilation
modalities, Vt and RR significantly differed
between HFO ventilation modes. Vt is
lowest and RR is highest in the CF mo-
dality; in the DFSPROX mode, this was
reversed. Paco2 increased significantly
using CF or during DFS and DFSPROX.

Gas Exchange. Results for gas ex-
change are shown in Table 2. Oxygen-
ation improved in all HFO ventilation
modes when spontaneous breathing was
maintained. When pigs were paralyzed,
Pao2 decreased remarkably during the 30-
minute period. Paco2 decreased in the
DFS and DFSPROX mode. Paco2 in-
creased significantly using CF or during
muscular paralysis.

DISCUSSION

Our animal study demonstrates that
demand flow facilitates spontaneous
breathing during HFO ventilation by lower-
ning WOB. The DFS was able to effect-
ively minimize work imposed by the ven-
tilator. The amount of support during
spontaneous breathing can be influenced
by changing the pressure sampling site
to regulate the DFS. Even additional pres-
sure support can be generated to over-
come WOB imposed by the endotracheal
tube.
Respiratory Variables. The spontaneous breathing pattern changed when different modalities of HFO ventilation were compared. In HFO ventilation with CPAP, \( V_t \) 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\(^{-1}\)·min\(^{-1}\). 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. \( \text{Pao}_2 \) improved in all HFO ventilation modes when spontaneous breathing was maintained. Muscular paralysis had a deteriorating effect on \( \text{Paco}_2 \). 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 \( \text{Paco}_2 \) in the DFS and DFSPROX mode. \( \text{Paco}_2 \) 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 \( \text{mPaw} \). 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 \( \text{mPaw} \) 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 \( \text{mPaw} \). Furthermore, the DFS algorithm is adaptive over time. The response time of the DFS, to react on changes in \( \text{mPaw} \), 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 \( \text{mPaw} \) to keep oxygenation in acceptable ranges; high \( \text{mPaw} \), 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 \( \text{mPaw} \) 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
The 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 \( m_{\text{ Paw}} \) and higher RRs seen in clinical use of HFO ventilation. Furthermore, patient and DFS synchrony needs to be evaluated.

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