Reflections on Pediatric High-Frequency Oscillatory Ventilation From a Physiologic Perspective

Martin CJ Kneyber MD PhD, Marc van Heerde MD PhD, and Dick G Markhorst MD PhD

Mechanical ventilation using low tidal volumes has become universally accepted to prevent ventilator-induced lung injury. High-frequency oscillatory ventilation (HFOV) allows pulmonary gas exchange using very small tidal volume (1–2 mL/kg) with concomitant decreased risk of atelectrauma. However, its use in pediatric critical care varies between only 3% and 30% of all ventilated children. This might be explained by the fact that the beneficial effect of HFOV on patient outcome has not been ascertained. Alternatively, in contrast with present recommendations, one can ask if HFOV has been employed in its most optimal fashion related especially to the indications for and timing of HFOV, as well as to using the best oscillator settings. The first was addressed in one small randomized study showing that early use of HFOV, instead of rescue use, was associated with improved survival. From a physiologic perspective, the oscillator settings could be refined. Lung volume is the main determinant of oxygenation in diffuse alveolar disease, suggesting using an open-lung strategy by recruitment maneuvers, although this is in practice not custom. Using such an approach, the patient can be oscillated on the deflation limb of the pressure-volume (P-V) curve, allowing less pressure required to maintain a certain amount of lung volume. Gas exchange is determined by the frequency and the oscillatory power setting, controlling the magnitude of the membrane displacement. Experimental work as well as preliminary human data have shown that it is possible to achieve the smallest tidal volume with concomitant adequate gas exchange when oscillating at high frequency and high fixed power setting. Future studies are needed to validate these novel approaches and to evaluate their effect on patient outcome. *Key words: HFOV; ALI/ARDS; obstructive airway disease; oxygenation; ventilation.* [Respir Care 2012;57(9):1496–1504. © 2012 Daedalus Enterprises]

Dr Kneyber is affiliated with the Department of Pediatrics, Division of Pediatric Intensive Care, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, the Netherlands. He is also, along with Drs van Heerde and Markhorst, affiliated with the Department of Pediatrics, Division of Pediatric Intensive Care, VU University Medical Center, Amsterdam, the Netherlands.

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Correspondence: Martin CJ Kneyber MD PhD, Department of Pediatrics, Division of Pediatric Intensive Care, Beatrix Children's Hospital, University Medical Center Groningen, Internal Postal Code CA80, PO Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: m.c.j.kneyber@umcg.nl.

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Introduction

Mechanical ventilation (MV) is intimately linked with the daily care of critically ill children admitted to the pediatric ICU. Indications for MV include diffuse alveolar disease (DAD) including acute lung injury, or ARDS. Although life-saving, MV is also linked with ventilator-induced lung injury (VILI) and the development of multiple system organ failure.[1] This has led to the concept of lung-protective ventilation, which has become standard of care nowadays.[2] High-frequency oscillatory ventilation (HFOV) is, at least theoretically, an ideal tool for lung-protective ventilation, as it allows pulmonary gas exchange using very small tidal volume (V_T) and decreases the risk of atelectrauma.[3–15] Animal studies have pointed out that HFOV might be preferable over conventional MV, given its more beneficial effects on oxygenation, lung compliance, attenuation of the pulmonary inflammation and histologic injury, and better alveolar stability.[16,17] HFOV allows the decoupling of oxygenation and ventilation. Simplified, oxygenation is dependent on lung volume, which is controlled by the continuous distending pressure (CDP). The CDP is depicted by the oscillator as mean airway pressure. CO_2 clearance ($\dot{V}_{CO_2}$) is relatively independent of lung volume, but influenced by oscillatory frequency (f) and the square of V_T ($\dot{V}_{CO_2} = F \times V_T^2$).[18–22]

The 3100 A/B HFO ventilator (SensorMedics, Yorba Linda, California) is the most commonly used HFOV device in pediatrics. With this system, pressure oscillations with a frequency of 3–15 Hz are superimposed upon a CDP in a square-wave manner. The CDP is generated by a fixed fresh gas flow/bias flow leaving the ventilator circuit by an expiratory balloon valve. A membrane superimposes high-frequency pressure oscillations around the CDP. The oscillatory pressure amplitude is highly attenuated over the ETT and the airways, and results in the delivery of a very small V_T, usually lower than anatomical dead space.[23] Because of this small V_T, there is a decreased risk of entering the so-called non-safe zones within the pressure-volume loop of the diseased lung.[22]

The use of HFOV in pediatric critical care varies between 3% and 30% of all ventilated children.[23–27] This relatively low use may be explained by several factors. First, lack of equipment or disbelief of the attending physician because of the absence of sound evidence of effect. Second, and perhaps even more importantly, many aspects of pediatric HFOV remain to be explored, including among others the identification of patients who are most likely to benefit from HFOV, timing of HFOV (early vs rescue), optimal oscillator settings, and monitoring during HFOV.

The purpose of this paper is to review published clinical experiences with HFOV and to reflect on how its use might be improved in light of the physiological properties of specific lung diseases and data from animal as well as bench studies.

Clinical Experiences

The effect of HFOV on mortality was compared with conventional MV in 2 randomized controlled trials (RCTs) (Table).[28–42] The largest of the 2 was performed 15 years ago, in 5 centers, during a 3.5 year period.[28] In this cross-over study, 58 patients with acute respiratory failure or pulmonary barotrauma, and an oxygenation index (OI) > 13, demonstrated by 2 consecutive measurements over a 6 hour period, were randomized to either HFOV ($n = 29$) using a strategy of aggressive increase in CDP targeted at $S_{pO_2} \geq 90\%$ with $F_{IO_2} \leq 0.6$, or conventional mechanical ventilation ($n = 29$), using a strategy utilizing PEEP and limited inspiratory pressures. Patients with obstructive airway disease (OAD), intractable septic or cardiogenic shock, or non-pulmonary terminal diagnosis were excluded. Targeted blood gas values were equal for each group. The main finding was that HFOV did not improve survival (HFOV 66% vs 59%) or total ventilator days (HFOV 20 ± 27 vs 22 ± 17), compared with conventional mechanical ventilation, when the data were analyzed by initial assignment. However, the percentage of survivors requiring supplemental oxygen at 30 days was significantly lower in the HFOV group (21% vs 59%, $P = .039$). Furthermore, mortality was only 6% ($n = 1/17$) in patients who were exclusively managed on HFOV, whereas it was 42% ($n = 8/19$) for patients who failed conventional mechanical ventilation and were transitioned to HFOV. Yet, mortality in patients who were exclusively managed with conventional mechanical ventilation was 40% ($n = 4/10$). Samransamruajkit et al reported the results of a small single-center study comparing HFOV ($n = 7$ patients) with conventional mechanical ventilation ($n = 9$ patients) with ARDS in a 2-year study period.[29] Survival was higher with HFOV (71%), compared with conventional mechanical ventilation (44%), and predicted by plasma levels of soluble intercellular adhesion molecule 1.

Both RCTs have not been repeated so far, but various institutions have described their (limited) experiences with HFOV (see the Table).[30–43] Overall survival varied between 40% and 90%. The largest cohort study came from a collaborative of 10 pediatric centers reporting 232 patients.[35] Duration of conventional mechanical ventilation prior to HFOV was between 2.2 ± 4.2 to 4.5 ± 3.1 days, whereas patients with preexisting lung injury were managed for up to 11.4 ± 45.5 days before transfer to HFOV. Thirty-day mortality ranged from 30% for patients with respiratory syncytial virus lower respiratory tract disease, to 59% for patients with congenital heart disease. Mortality was independently predicted by the OI 24 hours after start of HFOV and the presence of immunocompromise. The ap-

Table. Summary of Clinical Experiences With High-Frequency Oscillatory Ventilation in Critically Ill Children

First Author	Study Period	*n*	Inclusion Criteria	Initial HFOV Settings	Recruitment Maneuver	Survival (%)	Outcome Predictor(s)
Randomized Clinical Trials							
Arnold[28]	3.5 years	58	OI > 13 or pulmonary barotrauma > grade 1	Frequency: 5–10 Hz Amplitude: chest wall wiggle	No	66 HFOV vs 59	OI at 24 hours
Samransamruajkit[29]	1 month	16	ARDS	Frequency: weight-dependent Amplitude: 10 > peak pressure on conventional mechanical ventilation	No	71 HFOV vs 44	Soluble intercellular adhesion molecule 1 (sICAM-1)
Cohort Studies							
Slee-Wijffels[30]	6 years	53	Patients with diffuse alveolar disease and small airway disease	Frequency: weight-dependent Amplitude: chest wall wiggle	Yes	64	Not reported
Lochindarat[31]	3 years	21	Patients with ARDS with OI > 10 and P_{aO_2}/F_{IO_2} < 200 mm Hg	Unknown	Unknown	52.4	Survival predicted by OI at 24 hours
Watkins[32]	5.5 years	100	Not reported	Unknown	Unknown	45*	Not reported
Sarnaik[33]	45 months	31†	Severe acute respiratory failure (P_{aO_2}/F_{IO_2} < 150 mm Hg) with PEEP ≥ 8 cm H_2O, and/or P_{aCO_2} ≥ 60 mm Hg	Frequency: 8–10 Hz Amplitude: 40 cm H_2O	No	74	Death predicted by pre-HFOV OI ≥ 20 and failure to decrease by 20% at 6 hours of HFOV
Berner[34]	10 years	13	Confirmed respiratory syncytial virus bronchiolitis	Frequency: 8–12 Hz Amplitude: chest wiggle	Yes	100	Not reported
Arnold[35]	1.5 years	232	Not reported	Frequency: 5–10 Hz Amplitude: chest wall wiggle	Yes	53.4‡	Death independently predicted by immunodeficiency and OI at 24 hours of HFOV. Chronic lung disease independently predicted by presence of sepsis and OI at 24 hours of HFOV
Brogan[36]	5 years	66	Not reported	Frequency: weight-dependent Amplitude: chest wall wiggle	No	39.4	Presence of non-pulmonary organ failure associated with death
Martinon Torres[37]	3 months	6	OI > 13	Frequency: weight-dependent Power: 40	Yes	40	Not reported
Ben Jaballah[38]	4 years	20	Weight ≤ 35 kg, F_{IO_2} > 0.6	Frequency: weight-dependent Amplitude: chest wall wiggle	Yes	75	Not reported
Duval[39]	4 years	35	Diffuse alveolar disease and small airway disease	Frequency: weight-dependent Amplitude: chest wall wiggle	Yes	88.6	Not reported
Anton[40]	1.5 years	19	Patients with ARDS with P_{aO_2}/F_{IO_2} < 200 mm Hg	Not reported	Unknown	73.7	Initial OI > 20 and failure to decrease by 20% at 6 hours predicted death
Rosenberg[41]	Unknown	12§	OI > 13, gross air leak, weight < 35 kg	Frequency: weight-dependent Amplitude: chest wall wiggle	No	41.7	In non-survivors OI increased after 24 hours of HFOV
Fedora[42]	Unknown	26	ARDS, stratification by duration of conventional ventilation	Frequency: weight-dependent Amplitude: chest wall wiggle	Yes	42	Early HFOV (≤ 24 hours) associated with significant improvement in mortality

* Authors reported a decrease in mortality over time.

† 20 patients were managed with high-frequency oscillatory ventilation (HFOV), the remaining with high-frequency jet ventilation.

‡ Overall survival is shown. Authors reported differences in survival rate depending upon the underlying cause of the acute respiratory failure.

§ 7 patients were managed with HFOV, the remaining with high-frequency jet ventilation.

OI = oxygenation index

plicability of the OI as a predictor for patient outcome during HFOV has been confirmed by others.[31,41] Some have linked failure of the OI to improve by at least 20% 6 hours after transition to HFOV with adverse outcome.[33,40]

The use of HFOV in pulmonary conditions with increased airway resistance and prolonged time constants, such as virus-induced OAD, remains a subject of debate because of the assumed risk of dynamic air-trapping resulting from inadequate egress of air during expiration, as seen in high-frequency jet ventilation. However, the SensorMedics 3100 A/B oscillator has an active expiratory phase. Nevertheless, several institutions have reported safe and beneficial use of HFOV in this patient population.[30,34,35,37,39,44]

It can thus be concluded that at present a beneficial effect of HFOV on mortality has not been established. This may be explained by various factors. First, the knowledge on lung-protective ventilation has significantly increased over the past years. It is now universally accepted that a low V_T should be applied. However, the study by Arnold and colleagues[28] was conducted in the era prior to the ARDS Network trial. In their study, the authors did not specify the V_T used on conventional mechanical ventilation. Similar criticisms can be made toward the study by Samransamruajkit et al,[29] so that it is not unthinkable that patients on conventional mechanical ventilation were subjected to high V_T. Second, both RCTs were not powered to detect statistically significant differences in mortality.

Critical Appraisal of the HFOV Strategy Employed

Alternatively, the question could also be raised whether HFOV was applied in its most optimal fashion. These issues (among others) include identification of the patient who will benefit the most from HFOV, the timing of crossover from conventional mechanical ventilation to HFOV, as well as determining the best oscillator settings.

Indications for and Timing of HFOV

The indications for HFOV are ill-defined and usually depend upon the personal preference of the attending physician. In general, HFOV is considered only as a rescue approach when conventional mechanical ventilation fails. One group of investigators have evaluated the early use of HFOV instead of using it as rescue therapy.[42] In their small observational study of 26 patients, it was found that the group of patients who was transitioned to HFOV within 24 hours of conventional mechanical ventilation had a significantly higher 30-day survival rate (58.8 vs 12.5%). We suggest that HFOV should be considered if oxygenation remains severely impaired (in our institution defined by $S_{pO_2} < 88\%$ and/or $P_{aO_2} < 50$ mm Hg with $F_{IO_2} > 0.6$) despite the application of maximal lung-protective conventional mechanical ventilation (ie, limiting peak inspiratory pressures to 30–35 cm H_2O and sufficient level of PEEP) in children with acute lung injury/ARDS. Alternatively, the OI can be used, although a specific threshold needs to determined. For patients with OAD no guideline is available for when to consider HFOV. Based upon our own experiences we consider HFOV when refractory respiratory acidosis persists despite maximum conservative measures such as nebulization or intravenous administration of bronchodilators, use of heliox, or use of external PEEP to stent occluded airways.

In our opinion there are no known contraindications for HFOV, although its safety has been questioned in patients with severe traumatic brain injury, based upon the assumption that the high intrathoracic pressures are propagated toward the brain and impede the cerebral circulation. However, this has been refuted by both animal and clinical data.[45,46]

Best HFOV Approach and Oscillator Settings for Oxygenation

Lung volume is the main determinant of oxygenation in DAD during HFOV. Simplified, the P_{aO_2} increases linearly with lung volume up to a certain point when alveoli become overdistended.[47] This suggests that an open-lung strategy (ie, opening up the lung and keeping it open) in DAD by (repeated) recruitment maneuvers (RM) should be considered when switching to HFOV. Furthermore, pressure oscillations are less dampened in lungs with ongoing atelectasis, thus exposing the conducting airways to higher injurious pressure swings.[48] Animal work has indeed shown improved lung compliance and less hyaline membrane formation when such strategies were applied.[15,49,50] However, in both pediatric RCTs, as well as in nearly half of all observational cohort studies, there is no mention of RMs being performed.[28,29,31–33,36,40,41] Also, there is much ongoing scientific debate related to use and efficacy of RMs. Not all lung diseases are recruitable, and in general the potential for lung recruitability is highly variable.[51] Furthermore, there are so far no clinical studies establishing the beneficial effects of RMs during HFOV, let alone determining the best RM.

The latter has been addressed in one study in which 4 different RM approaches were compared: a step-wise pressure increase over 6 min; a 20 s sustained dynamic inflation (either one or repeated 6 times); and a standard approach (setting mean airway pressure direct at start).[52] This study showed that a step-wise pressure increase produced the greatest increase in lung volume and resolution of atelectasis. Thus, this study suggests that the stepwise increase pressure approach might be considered for optimizing lung volume during HFOV, as it incorporates not

only pressure but also adequate duration of the RM. The clinical benefits of RMs during HFOV have been addressed in a recently completed phase II trial in critically ill adults comparing HFOV with and without RMs (www.clinicaltrials.gov NCT00399581). Unfortunately, a pediatric counterpart is lacking, but the adult results are eagerly awaited.

Another, at least theoretical, benefit of RMs is that it allows oscillating the patient on the deflation limb of the P-V curve, thereby (partially) avoiding injurious hyperinflation and atelectasis.[22,53–59] By doing so, less CDP is needed to maintain a certain lung volume on the inflation limb, because of the hysteresis of the respiratory system. In our view and practice, this can be achieved in clinical practice in patients with DAD by initially setting the CDP 3–5 cm H_2O above the mean airway pressure on conventional mechanical ventilation, as the distal CDP is lower than the set proximal CDP.[60,61] Then the CDP should be increased stepwise over a certain period of time until the point where oxygenation (either the S_{pO_2} or the P_{aO_2}) does not improve at a fixed F_{IO_2} (suggestive of approximating total lung capacity). Also, with increasing compliance the ΔP depicted by the oscillator may decrease; hence, it may be indicative for approximating total lung capacity when ΔP increases again.[62] The next step would be to reduce the CDP to the point where oxygenation starts to decrease after initial improvement (suggestive of derecruitment). The ΔP depicted by the oscillator may initially decrease, but may increase again when derecruitment on the deflation limb occurs. Ultimately, the CDP will finally set 2–4 cm H_2O above this point. We have adopted such an approach in our clinical practice. A positive effect of sustained inflations prior to the stepwise increase in CDP has not been demonstrated.[52,63]

HFOV may also be considered in patients with refractory OAD. However, in these patients the purpose of the stepwise increase in CDP is to splint open and stent the airways to a certain point when the P_{aCO_2} starts to drop, in order to prevent relatively healthy alveoli being exposed to high pressures once the airways are open.[64] Importantly, the novel approach toward optimizing oxygenation as discussed needs to be studied for safety and effectiveness.

Best HFOV Approach and Oscillator Settings for Ventilation

The $\dot{V}_{CO_2}$ is determined by patient-related characteristics and oscillator settings. The first include compliance and resistance of the respiratory system.[62,65] With reduced compliance in unresolved atelectasis there is a marked increase in transmission of the peak-to-trough ΔP to the alveoli and bronchi. Increased resistance decreases the transmission of the peak-to-trough ΔP over the airways to the alveoli.[62] Oscillator settings include oscillatory power setting (magnitude of membrane displacement), frequency (f), in Hertz (Hz), inspiratory to expiratory ratio, position of the membrane, endotracheal tube (ETT) length and diameter, and the presence of ETT leakage.[20,66,67]

The ETT constitutes the major work load to the oscillator and is an important determinant of V_T.[68,69] V_T is proportional to the ETT inner cross-sectional area, because the impedance of the ETT exceeds the impedance of the lung.[70,71] Increasing diameter (inner diameter 2.5–4.0 mm) of the ETT increases pressure transmission.[62]

The manufacturer's manual recommends setting f and power according to the patient's age, ventilator settings, and observation of chest wiggle. This recommendation has been adopted into clinical practice, using the f and power in a weight and age-dependent manner in both RCTs, as well as in the observational cohort studies.[28–30,33–39,41,42]

We propose that these recommendations may be refined. From a physiological perspective it seems more appropriate to use the highest possible f in DAD. First, f determines the rate of oscillations and directly influences the V_T. Hence, the higher the f, the smaller the V_T, because changes in f are inversely proportional to the distal oscillatory pressure amplitude. Consequently, it becomes easier to stay within the limits of the safe zone (ie, the zone with the smallest risk of injurious hyperinflation or atelectasis) of the P-V loop. Second, collapsed lung regions are more easily opened at higher f.[72] Third, the delivered V_T is more equally distributed, as it becomes less dependent on regional compliance at higher f.[73] Lastly, the square block waveform is better preserved, allowing a more constant V_T.[74,75] Needless to say, it is necessary to maintain an appropriate CDP when setting the f.

The next question, then, is what could be considered as optimal f. Venegas and Fredberg have proposed that how f needs to be set depends upon the so-called corner frequency (F_c) of the lung, $F_c = 1/(2\pi RC)$, where R is resistance and C compliance.[59] F_c defines the optimal frequency at which there is adequate gas transport during HFOV in combination with the least injurious pressures, and is influenced by the underlying disease (Figure). It is increased in lung diseases characterized by short time constants and low compliance, such as in DAD. This implies that at higher f, alveoli are ventilated at a lower pressure cost of ventilation, as opposed to lung diseases characterized by prolonged time constants (for example OAD).

Importantly, f is intimately linked with ΔP. Basically, the higher the ΔP, the larger the V_T. Yet, we (unpublished data) and others have observed in bench test studies that V_T was smaller when combining high f (15 Hz) and high power (set to achieve a ΔP of 90), compared with low f (5 Hz) and low power settings, as the distal pressure amplitude was much lower but still associated with a sufficient $\dot{V}_{CO_2}$.[76] These findings were in agreement with the work from Hager and co-workers. They have measured V_T in adult patients with ARDS managed on HFOV and found

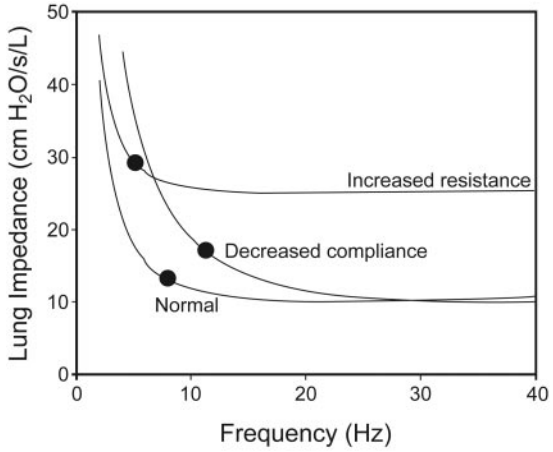

Figure. Corner frequency (F_c) of the lung in patients with decreased compliance, such as acute lung injury/ARDS and increased resistance, such as obstructive airway disease. F_c (graphically depicted by the dot) defines the optimal frequency at which there is adequate gas transport during HFOV in combination with the least injurious pressures. It is defined by $1/2\pi RC$, where R is resistance and C compliance. (From Reference 59, with permission.)

smaller V_T with the combination high f and high power setting.[69] The use of these higher f did not impair gas exchange.[77]

Importantly, how are these theoretical benefits translated into clinical practice? At present it is impossible to detect the F_c and thus impossible to identify the optimal f. Furthermore, what ΔP should be targeted? Based upon our own experiences, we propose using the highest f in combination with a fixed power setting that is associated with acceptable CO_2 elimination (in our view pH $>$ 7.25) in patients with DAD. For patients with OAD the initial f should theoretically be between 5 and 7 Hz. The ΔP should not exceed 70–90, because higher pressures may theoretically expose the proximal airways to injurious pressures. Again, this novel approach toward optimizing ventilation during HFOV requires further evaluation for its safety and efficacy. For instance, it has been suggested that the use of high amplitudes might lead to gas trapping due to the development of so-called choke points causing expiratory flow limitation, especially at low CDP.[78] However, the occurrence of choke points has never been demonstrated.

Monitoring During HFOV

At present, physicians have the S_{pO_2}, blood gas analysis, ΔP, and chest radiography at their disposal for evaluating the response of a patient to HFOV. It is often advised to obtain chest radiographs to evaluate the optimal lung inflation. However, such an approach has never been validated, and we therefore do not routinely obtain chest radiographs. Repeated daily blood gas analyses may be informative to assess if targets of ventilation (ie, permissive hypercapnia [pH $>$ 7.15–7.25]) are being met. Transcutaneous CO_2 (P_{tCO_2}) monitoring may be used as a noninvasive alternative.[79] Developments are being made with respect to electrical impedance tomography and respiratory inductance plethysmography incorporated in the Bicore II as tools for the determination of the optimal CDP.[80,81]

We have recently begun to explore the use of respiratory inductance plethysmography in guiding the stepwise increase in CDP. Alternatively, the optimal CDP may be recognized when both lung compliance and OI (calculated by CDP $\times$ F_{IO_2} $\times$ 100/P_{aO_2}) are optimal.[82] The benefit of the OI over the P_{aO_2}/F_{IO_2} ratio is that it takes the degree of ventilator settings (as summarized by the mean airway pressure) into account. Van Genderingen and co-workers found that the lowest OI during the RM indicated at which CDP the oxygenation was considered to be optimal; this also indicated the point on the deflation limb of the P-V curve where physiologic shunt fraction was the lowest.[83]

The oscillatory pressure ratio (OPR) may also aid in the identification.[65] OPR is defined as the ratio of the distal and proximal ETT pressure swings. To calculate the OPR it is necessary to measure the tracheal pressure. In a 3.0 mm ETT neonatal respiratory distress syndrome simulated model, OPR decreased when the CDP was increased (suggestive of lung recruitment) but increased when the CDP was increased further. This suggested hyperinflation. The OPR was the lowest at maximum compliance. The OPR was also affected by frequency, ΔP, and ETT inner diameter. The OPR was further evaluated in an animal model of acute lung injury.[84] One of the main findings of this study was that, after lung recruitment, similar oxygenation with smaller pressure swings could be achieved with a lower CDP set by the deflation limb of the P-V curve rather than the inflation limb. The clinical use of these potential aids, however, needs to be established.

Spontaneous Breathing During HFOV

Maintaining spontaneous breathing during HFOV improves oxygenation and regional ventilation.[85,86] Spontaneous breathing during HFOV is feasible for small children but becomes more difficult when the patient demands high inspiratory flows. The maximal possible bias flow delivered by the oscillator may be well below the needs of the patient. This will lead to increased work of imposed breathing, as shown by our group in a bench test model.[87] Because of this, many older children on the oscillator are likely to need sedatives and neuromuscular blockade during their illness, prohibiting spontaneous breathing.

Conclusions

The beneficial effect of HFOV on outcome in critically ill children remains unclear. However, based upon the physiologic properties of the oscillator, one can ask if HFOV has been employed in its most optimal fashion. We suggest that in patients with diffuse alveolar disease, convert to HFOV early in the disease course; employ an open-lung strategy using (repeated) RMs; and use the highest frequency and high fixed power setting, providing that adequate gas exchange is maintained. For patients with OAD, HFOV may be considered to open up and stent the airways. Importantly, future studies are needed to validate these novel approaches and to evaluate their effect on patient outcome.

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