Imposed Work of Breathing During High-Frequency Oscillatory Ventilation in Spontaneously Breathing Neonatal and Pediatric Models

Alice Bordessoule MD, Lise Piquilloud MD, Aissam Lyazidi PhD, Amelia Moreira MD, and Peter C Rimensberger MD

BACKGROUND: High-frequency oscillatory ventilation (HFOV) is used in cases of neonatal and pediatric acute respiratory failure, sometimes even as the primary ventilatory mode. Allowing patients (at least neonates) on HFOV to breathe spontaneously soon after intubation has been shown to be feasible, and this is becoming a more generally used approach for infants and small children. However, such an approach may increase the imposed work of breathing (WOB), raising the question of whether the imposed WOB varies with the use of newer-generation HFOV devices, which operate according to different functional principles. METHODS: A bench test was designed to compare the pressure-time product (PTP), a surrogate marker of the imposed WOB, produced with the use of 7 HFOV devices. Scenarios corresponding to various age groups (preterm newborn [1 kg], term newborn [3.5 kg], infant [10 kg], and child [25 kg]) and 2 respiratory system conditions (physiologic and pathologic) were tested. RESULTS: The PTP varied between devices and increased with the oscillation frequency for all devices, independent of the respiratory system condition. Furthermore, the PTP increased with age and was higher for physiologic than for pathologic respiratory system conditions. We considered a change of $\geq 20\%$ as being of clinically relevant; the effect of oscillation frequency was the most important parameter influencing imposed WOB during spontaneous breathing. CONCLUSIONS: Variations in imposed WOB, as expressed by PTP values, during spontaneous breathing depend mainly on the oscillator frequency, respiratory system condition, and, though to a lesser extent, on the device itself. *Key words: high-frequency oscillatory ventilation; neonatal intensive care; work of breathing; spontaneous breathing; respiratory insufficiency.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

High-frequency oscillatory ventilation (HFOV) has been used for many years in neonatal and pediatric health care,

mainly as a rescue mode of ventilation in cases of severe hypoxic respiratory failure. More recently, especially in the field of neonatal care, HFOV in the very early phase of acute hypoxic respiratory failure has been suggested.[1-3] This strategy, while allowing for spontaneous breathing during HFOV, has been shown to render direct weaning to CPAP feasible.[4] The maintenance of spontaneous breathing during conventional mechanical ventilation has been shown, at least in adult patients, to enable better ventila-

Drs Bordessoule, Moreira, and Rimensberger are affiliated with the Pediatric and Neonatal Intensive Care Unit, Department of Pediatrics, University Hospital of Geneva, Geneva, Switzerland. Dr Piquilloud is affiliated with the Adult Intensive Care and Burn Unit, University Hospital of Lausanne, Lausanne, Switzerland. Dr Lyazidi is affiliated with the Institut Supérieur des Sciences de la Santé, Laboratoire Rayennement-matière et Instrumentation, Université Hassan I, Settat, Morocco.

Correspondence: Alice Bordessoule MD, Service of Neonatology and Pediatric Intensice Care, Department of Pediatrics, University Hospital of Geneva Rue Willy-Donzé 6 1211 Geneva, Switzerland. E-mail: alice.bordessoule@hcuge.ch.

tion perfusion matching, improve cardiopulmonary function, and shorten ICU length of stay.[5-10] However, allowing for spontaneous breathing during HFOV considerably increases the imposed work of breathing (WOB).[11] In neonates, who have lower maximal inspiratory flow demands, this increase in imposed WOB is less pronounced.[11] Newer-generation HFOV devices use various concepts to build up the mean airway pressure ($\bar{P}_{aw}$) and to generate oscillation waves.[12,13] Therefore, questions arise as to whether the imposed WOB varies with the use of different oscillators and/or settings, and/or in patients with different respiratory system conditions. To investigate these questions, we designed a bench test to compare the imposed WOB that is imposed by HFOV devices while simulating typical breathing patterns of preterm newborns, term newborns, infants, and children with various respiratory system conditions.

Methods

Ventilators

We used 3 piston HFOV devices: Sensormedics 3100A (CareFusion, San Diego, California); Fabian-HFO, with neonatal and pediatric modes, which uses an electromagnetically driven vibrating diaphragm (Acutronic Medical, Hirzel, Switzerland); and HummingX, which is a linear motor piston pump device (Metran, Saitama, Japan). We used 4 contemporary non-piston devices: Babylog VN500, which uses concepts like flow-modulated sine wave generation (Dräger, Lübeck, Germany); SLE 6000, which is a valveless system (SLE, South Croydon, United Kingdom); Stephanie, a 2-valve oscillation pressure-generation device (Stefan, Gackenbach, Germany); and a Servo-n HFOV prototype, which is a newer concept that relies on the inertia of air in the patient circuit when the pressure at airway opening is modified rapidly, combined with very rapidly responding inspiratory valves and high-flow capability (Maquet, Solna, Sweden). The features of the HFOV devices are described in the supplementary materials (see the supplementary materials at http://www.rcjournal.com). The study was conducted in the pediatric and neonatal ICU in the Department of Pediatrics at the University Hospital of Geneva, in Geneva, Switzerland.

Lung Model

To simulate spontaneous breathing and to test different lung-compliance scenarios, a lung simulator (ASL 5000, Ing-Mar Medical, Pittsburgh, Pennsylvania) was used. In this simulator, flow is generated by a motor-driven piston. System compliance was set directly, and resistance was determined and modified using associations of various resistive tubes. The endotracheal tube and the resistance system were then placed between the lung model and the tested ventilator

QUICK LOOK

Current knowledge

The imposed work of breathing during high-frequency oscillatory ventilation (HFOV) while allowing the patient to breathe spontaneously is greater for pediatric and adult patients than for newborns and infants. Therefore, heavy sedation and even muscle paralysis are often required in older patients, whereas these are usually not needed in newborns and infants, in whom it is furthermore feasible to extubate directly from HFOV.

What this paper contributes to our knowledge

Imposed work of breathing varies mainly with the oscillator frequency and respiratory system condition. Therefore, although it is recommended to use high oscillation frequencies in restrictive lung disease, it might be reasonable to lower these during the weaning phase from HFOV, when lung function has improved and the patient has to take over more spontaneous breathing efforts, since this will allow to reduce iWOB.

(Fig. 1). Data were acquired online from the ASL 5000 and stored in a laptop computer for subsequent analysis.

Scenarios

Scenarios corresponding to various age groups (a preterm newborn weighing 1 kg, a term newborn weighing 3.5 kg, an infant weighing 10 kg, and a child weighing 25 kg) and physiologic and pathologic respiratory system conditions were tested. Scenario details are provided in Table 1. The scenarios were developed in accordance with previous publications.[14-18] The pathologic conditions were characterized for each age group by poor compliance and normal resistance to simulate restrictive pulmonary disease, corresponding to the most frequent alteration of respiratory mechanics encountered in neonatal and pediatric patients (see the supplementary materials at http://www.rcjournal.com).

Ventilator Settings

HFOV settings were selected according to current clinical practice (Table 2) using:

- one continuous distending pressure level set at 12 cm H_2O;

- 2 bias gas flows (10 and 20 L/min), when the device permitted modification of this parameter;

- 2 oscillation frequencies (10 Hz and 15 Hz for the preterm scenario, 8 Hz and 12 Hz for the term scenario, 5 Hz and
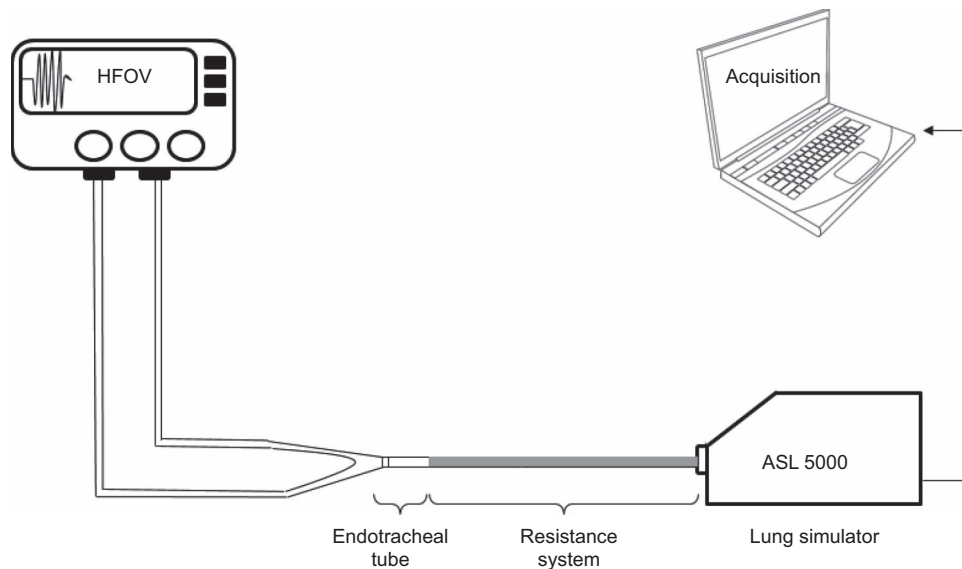
Fig. 1. Experimental setup. The endotracheal tube and the resistance system were placed between the mechanical lung model (ASL 5000) and the tested ventilator. Resistance was set using associations of different resistive tubes.

Table 1.   Respiratory System Mechanics for Various Scenarios in Pathologic and Physiologic Conditions

	Endotracheal Tube Size, mm	Physiologic Condition				Pathologic Condition			
		Resistance, cm H_2O/L/s	Compliance, mL/cm H_2O	Breaths/min	Muscle Pressure, cm H_2O	Resistance, cm H_2O/L/s	Compliance, mL/cm H_2O	Breaths/min	Muscle Pressure, cm H_2O
Premature (1 kg)	3.0	120	1.6	50	−12	120	0.5	70	−17
Term (3.5 kg)	3.5	29	4	30	−8	29	2	40	−10
Infant (10 kg)	4.0	13	20	25	−8	13	9	50	−12
Child (25 kg)	6.0	6	71	18	−5	6	24	30	−8

Table 2.   Settings for the HFOV Devices Tested

	Mean Airway Pressure, cm H_2O	Targeted Tidal Volume, mL/kg	Frequency, Hz	Bias Flow, L/min
Premature (1 kg)	12	1.5	10/15	10/20*
Term (3.5 kg)	12	1.5	8/12	10/20*
Infant (10 kg)	12	1.5	5/9	10/20*
Child (25 kg)	12	1.5	5/8	10/20*

HFOV = high-frequency oscillatory ventilation
* When the device permitted modification of this parameter.

9 Hz for the infant scenario, and 5 Hz and 8 Hz for the child scenario);

- an inspiratory-expiratory ratio of 1:1;

- an amplitude pressure (ΔP) set to obtain a target tidal volume (V_T) of 1.5 mL/kg, measured with an external hot wire anemometer (Florian, Acutronic Medical).[19]
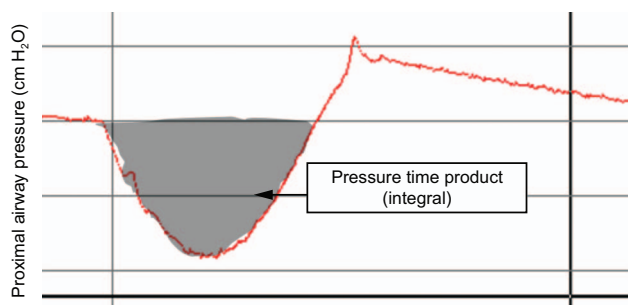
Because oscillation power varies among oscillators, we chose a clinically relevant V_T to enable comparison of similar conditions by targeting HFOV efficiency. To facilitate comparison of ΔP values among devices for the same scenario, ΔP was expressed as a percentage of the maximum amplitude for each oscillator. For this, the scenario was used without spontaneous breathing, and the ΔP was set to the required value up to the maximum permitted by the oscillator.

Parameters Measured

For each experimental condition, a 1-min period was recorded. The final 3 breaths were then analyzed. The modified Campbell diagram[20] is recognized as the accepted standard for imposed WOB measures in patients. Unfortunately, we could not obtain reliable Campbell diagram graphics in our bench setting because the high oscillation frequencies created too many artifacts. We therefore used the pressure-time product (PTP) measure as a surrogate

Fig. 2. The PTP was analyzed as the integral of $\bar{P}_{aw}$ as a function of time (expressed in cm $H_2O \times$ s), which corresponds to the area under the curve between the start of the negative deflection of the P_{aw} signal and the return to P_{aw} baseline. PTP = pressure-time product; $\bar{P}_{aw}$ = mean airway pressure.

marker of the imposed WOB of the simulated patient breaths, after filtering out the high-frequency oscillation pressure waves with a low-pass filter (set at 2 Hz). The PTP was analyzed as the integral of $\bar{P}_{aw}$ as a function of time (expressed in cm $H_2O \times$ s), which corresponds to the area under the curve between the start of the negative deflection of the P_{aw} signal and the return to P_{aw} baseline (Fig. 2).

The second parameter analyzed was the oscillator ΔP, expressed as a percentage of the maximum amplitude for each oscillator corresponding to the power of each ventilator. For this study, we defined an oscillator as sufficiently powerful when the amplitude needed to generate the target V_T was $< 50\%$ of the maximum ΔP setting, reflecting the capacity to increase the ΔP if disease worsens further.

Statistical Analysis

Data are presented as mean $\pm$ SD. We used analysis of variance for multiple comparisons with a post hoc Tukey test for pairwise comparisons between ventilators to examine differences in PTP between ventilators under equivalent test conditions. We used t tests to compare the 2 various bias flow of the Sensormedics 3100A and the Fabian-HFO, the only devices able to modify the bias flow. We considered differences in PTP values of $\geq 20\%$ as potentially clinically relevant. Data were analyzed using Acqknowledge software (version 3.7.3, Biopac Systems, Goleta, California). P values $< .05$ were considered to be significant.

Results

PTP

PTP values are presented as mean $\pm$ SD in Table 3. Statistics for PTP values obtained with the 7 ventilators under 16 conditions are presented in Supplementary Table

2 (see the supplementary materials at http://www.rcjournal.com). PTP values for the premature newborn and term newborn scenarios are illustrated in Figure 3 and 4. Values for the infant and child scenarios are not represented because we chose to illustrate only differences that might be relevant in the clinical setting (ie, $\geq 20\%$).

Influence of Bias Flow. The 3100A and Fabian devices permitted testing with bias flows of 10 L/min and 20 L/min. No difference in PTP was observed between bias flows, except for the 3100A device in the physiologic term scenario (-2.3 cm $H_2O \times$ s for 10 L/min, -1.9 cm $H_2O \times$ s for 20 L/min) ($P = .007$).

Influence of Frequency. No oscillator could deliver the V_T at 8 Hz for the child scenario. The PTP increased with frequency independent of the respiratory condition and oscillator in all conditions (Table 3, Fig. 3). This increase was less pronounced for the infant conditions.

Influence of Patient Type and Respiratory System Condition. Under pathologic and physiologic premature and pathologic term conditions, no ventilator was superior to any other in terms of imposed WOB as measured by PTP (Fig. 4). Under the physiologic term condition, the HummingX produced the highest PTP values (-3.88 cm $H_2O \times$ s at 8 Hz, -4.04 cm $H_2O \times$ s at 12 Hz), which were approximately double the values obtained with the other oscillators (Table 3, Fig. 3). The infant and child conditions were not tested with the Babylog VN500, which is cleared only for neonatal use. For the other devices, PTP values were similar under the pathologic and physiologic infant and child conditions. In general, measured PTP values were age-dependent, with higher values in older-patient scenarios.

Device Power

For the premature newborn and term newborn scenarios, all but 1 of the tested ventilators were able to deliver the target V_T via HFOV; the Babylog VN500 failed to do so under the physiologic premature and pathologic and physiologic term conditions at 15 Hz and 12 Hz, respectively (Supplementary Table 3; see the supplementary materials at http://www.rcjournal.com). For the infant and child scenarios, the tested ventilators were able to deliver the target V_T, with 2 exceptions: the Fabian-HFO (even when used in the pediatric mode), and the Servo-n prototype at 9 Hz in the infant scenarios. The 3 most powerful ventilators were the 3100A, the HummingX, and the SLE 6000, independent of the clinical condition tested and the frequency chosen.

Table 3. Factors Affecting Imposed Work of Breathing During HFOV for Spontaneously Breathing Neonatal and Pediatric Models

	3100A	Babylog VN500	Fabian Neonate Mode	Fabian Pediatric Mode	HummingX	Servo-n Prototype	SLE 6000	Stephanie
Premature (1 kg)								
Pathologic								
10 Hz	−0.34 ± 0.00	−0.23 ± 0.02	−0.32 ± 0.03		−0.29 ± 0.00	−0.34 ± 0.01	−0.28 ± 0.02	−0.47 ± 0.06
15 Hz	−0.36 ± 0.00	−0.42 ± 0.01	−0.58 ± 0.03		−0.47 ± 0.02	−0.45 ± 0.01	−0.50 ± 0.04	−0.53 ± 0.02
Physiologic								
10 Hz	−0.97 ± 0.34	−1.51 ± 0.00	−1.06 ± 0.02		−1.50 ± 0.00	−1.31 ± 0.01	−1.49 ± 0.01	−1.32 ± 0.00
15 Hz	−1.09 ± 0.35	*	−1.40 ± 0.03		−1.91 ± 0.01	−1.67 ± 0.02	−2.15 ± 0.10	−2.10 ± 0.01
Term (3.5 kg)								
Pathologic								
8 Hz	−1.32 ± 0.01	−1.61 ± 0.08	−1.22 ± 0.03		−1.30 ± 0.00	−0.65 ± 0.01	−1.45 ± 0.02	−0.92 ± 0.01
12 Hz	−1.34 ± 0.00	*	−1.81 ± 0.02		−1.41 ± 0.03	−1.21 ± 0.02	−1.71 ± 0.10	−1.49 ± 0.02
Physiologic								
8 Hz	−1.81 ± 0.00	−2.22 ± 0.01	−2.85 ± 0.02		−3.88 ± 0.00	−1.80 ± 0.01	−2.11 ± 0.05	−1.33 ± 0.01
12 Hz	−1.99 ± 0.00	*	−3.02 ± 0.02		−4.04 ± 0.01	−2.17 ± 0.00	−2.61 ± 0.03	−2.11 ± 0.01
Infant (10 kg)								
Pathologic								
5 Hz	−1.11 ± 0.01			−1.28 ± 0.01	−1.27 ± 0.01	−1.35 ± 0.01	−1.27 ± 0.00	−1.02 ± 0.01
9 Hz	−1.26 ± 0.01			*	−1.53 ± 0.02	*	−1.30 ± 0.05	−1.45 ± 0.02
Physiologic								
5 Hz	−2.58 ± 0.01			−2.76 ± 0.02	−2.77 ± 0.01	−2.61 ± 0.00	−2.79 ± 0.02	−2.57 ± 0.01
9 Hz	−2.72 ± 0.01			*	−2.90 ± 0.02	*	−3.04 ± 0.02	−2.71 ± 0.01
Child (25 kg)								
Pathologic								
5 Hz	−2.07 ± 0.01			−2.03 ± 0.13	−2.29 ± 0.01	−1.95 ± 0.01	−2.30 ± 0.05	−2.31 ± 0.03
8 Hz	*			*	*	*	*	*
Physiologic								
5 Hz	−2.57 ± 0.00			−2.87 ± 0.03	−2.78 ± 0.01	−2.44 ± 0.00	−2.80 ± 0.04	−2.69 ± 0.02
8 Hz	*			*	*	*	*	*

Pressure-time product expressed in cm $H_2O \times$ s as mean ± SD for the 7 tested ventilators under 16 conditions.

* Indicates the conditions when the oscillator was not able to deliver the target tidal volume of 1.5 mL/kg.

HFOV = high-frequency oscillatory ventilation

Discussion

The main result of this study is that variations in the imposed WOB (as expressed by PTP values) during spontaneous breathing depend on the oscillator frequency, respiratory system condition, and, less importantly, the HFOV device. The second finding is that the power of the tested oscillator, as reflected by the ΔP required to obtain the target V_T, varied notably among devices.

Influence of Bias Flow

The shift from 10 L/min to 20 L/min only marginally reduced the PTP obtained with the 3100A. This finding is in part consistent with the results reported by van Heerde et al,[11] but that group increased the bias flow from 20 L/min to 60 L/min.

Influence of Frequency

The increase of oscillation frequency raised the PTP specifically for premature and term scenarios. These results can be explained by the rapid back-and-forth flows in the tubing system against which the patient must breathe. This dependence of the imposed WOB on oscillation frequency seems to call for the use of low-oscillation frequencies when allowing for spontaneous breathing. However, the use of higher frequencies with unchanged amplitude settings not only results in lower V_T, but also decreases the magnitude of pressure swings and flow spikes transmitted downstream to the proximal and distal lung compartments,[21,22] thereby reducing the risk of barotrauma and/or rheotrauma. Pressure-wave damping is known to be least pronounced in the stiff, poorly compliant lung, and most pronounced in the compliant lung.[23-25] Despite this knowledge, frequencies as low as 8 Hz in newborns and
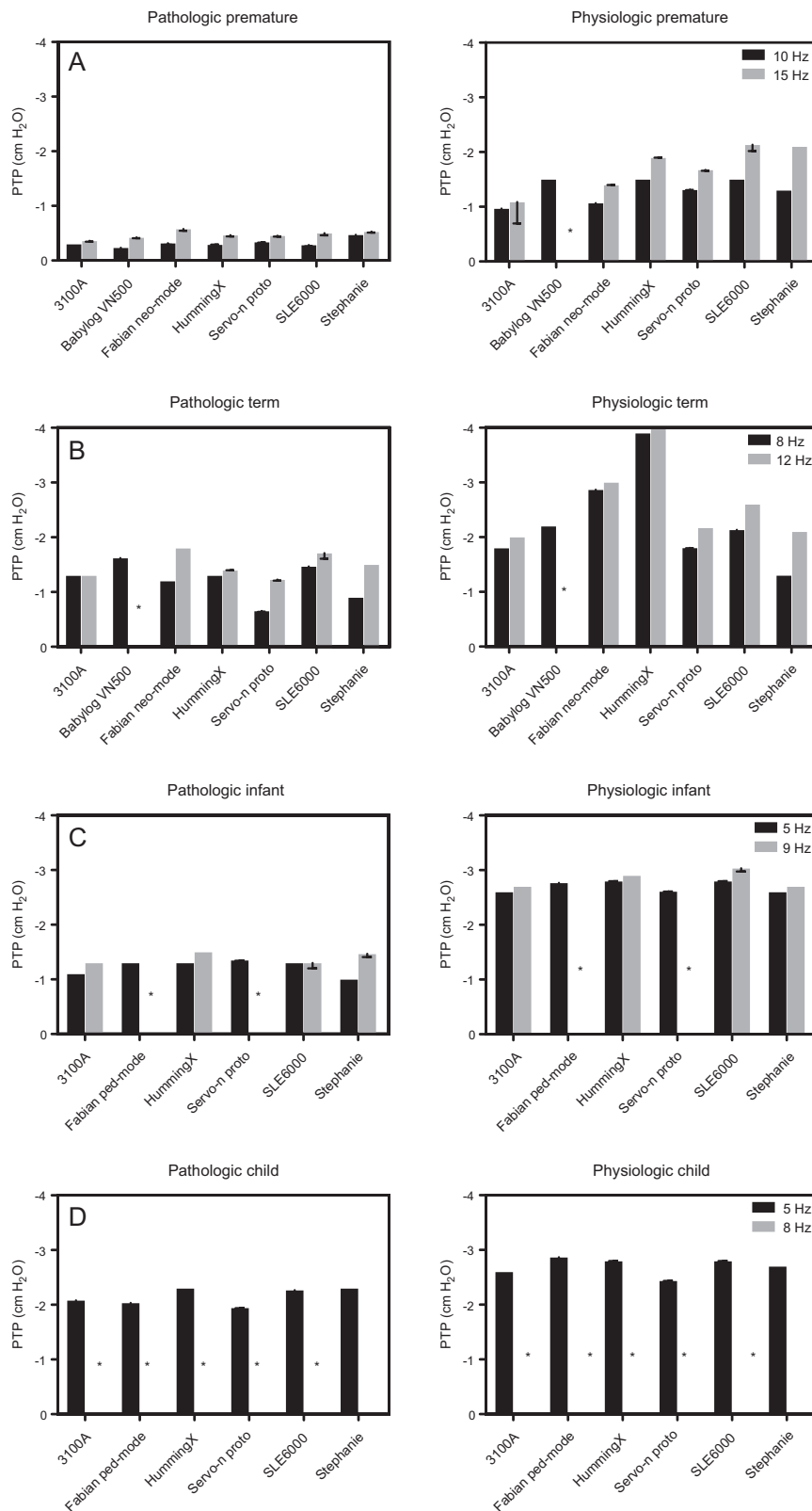
WOB$_{IMP}$ DURING HFOV

Fig. 3. Influence of the frequency, patient type, and respiratory system condition on the PTP. * Conditions under which the oscillator could not deliver the target tidal volume of 1.5 mL/kg. PTP = pressure-time product.
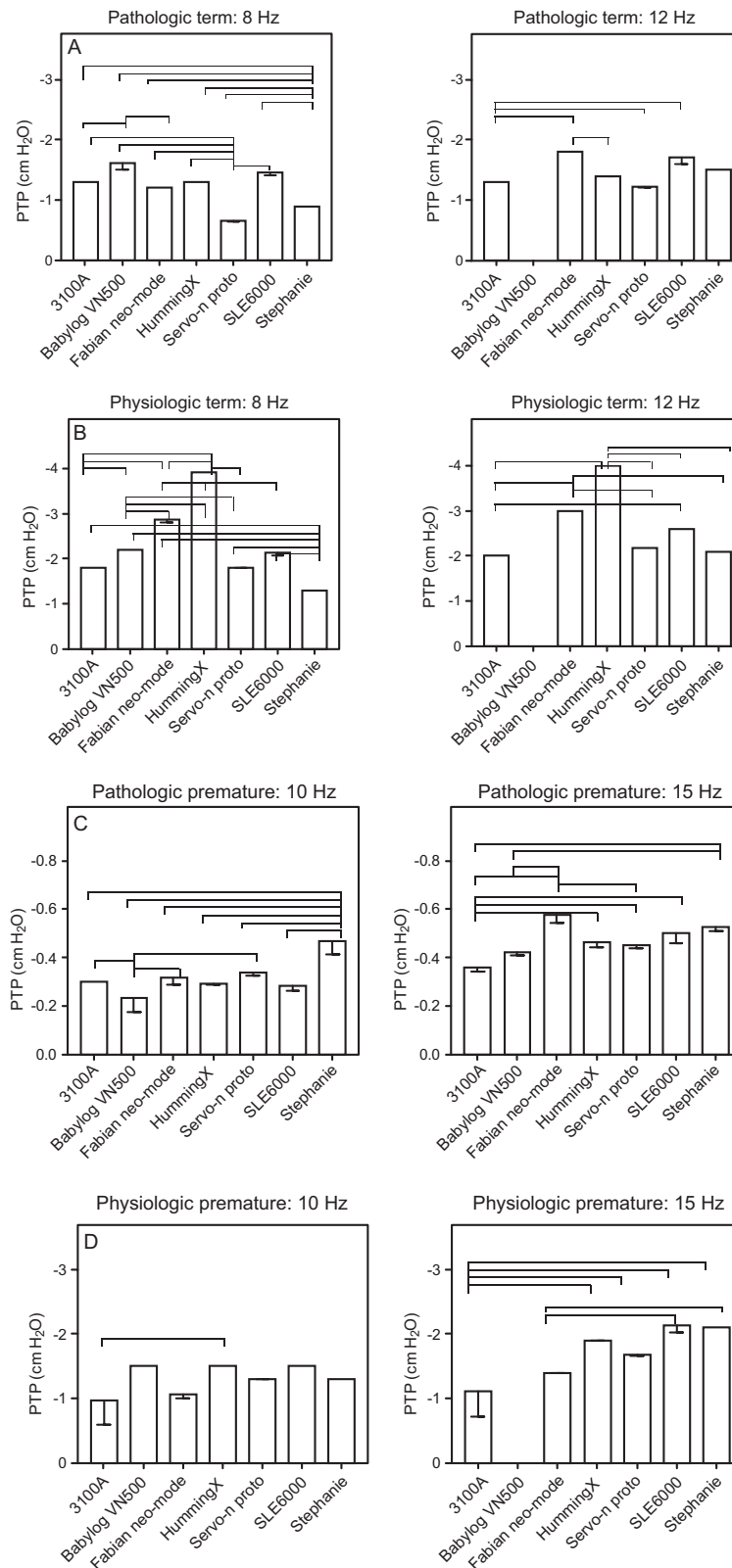
Fig. 4. PTP values for premature and term settings. Brackets between devices indicate significant differences ($P < .05$). Only differences that might be relevant in the clinical setting ($\geq 20\%$) are shown. PTP = pressure-time product.

even lower in adults with poorly compliant lungs are often used to increase ventilation efficiency. In the acute stage of restrictive lung disease, preference is often given to the reduction of frequency because of the fear of using "high" pressure amplitudes, as measured at the airway opening. In contrast, in the weaning phase frequencies are often increased, which will result in the need for higher amplitude levels for a relative short time period. Both concepts seem to be incompletely thought out. The approach of using low frequencies in patients with restrictive respiratory-system conditions may increase the risk of barotrauma and/or rheotrauma, due to poor downstream oscillation pressure-wave damping.[26,27] In the more compliant lung (eg, during weaning from HFOV, when more effective spontaneous breathing efforts by the patient can be allowed), oscillation pressure-wave damping becomes much more important because it reduces the risk of barotrauma. Therefore, lower frequencies can be used, and oscillation pressure amplitudes at the airway opening can be further reduced while maintaining the same ventilation efficiency. This approach also reduces the risk of rheotrauma as a result of high peak airway flows. Thus, the reduction of frequency and oscillation amplitude might be suggested when lung conditions (ie, lung compliance) improve. This approach would help reduce the imposed WOB in spontaneously breathing patients during the weaning phase. When introducing the concept of the corner frequency during HFOV, Venegas and Fredberg[26] addressed the selection of the optimal protective oscillation frequency according to the mechanical conditions of the lung in much more detail.

Influence of the Respiratory System Condition and Patient Age

The imposed WOB, as measured by PTP, increased with simulated age. This can be explained by the higher inspiratory flows older patients will generate during spontaneous breathing efforts. These results are consistent with those reported in a previous publication[11] and with the observation that neonatal patients not only tolerate spontaneous breathing during HFOV more than do older children and adults, without requiring deep sedation or neuromuscular blockade,[28] but also can be more easily be weaned directly from HFOV.[4]

Power

Regardless of simulated condition or oscillation frequency, the 3 most potent ventilators were the 3100A, the HummingX, and the SLE 6000. These findings are in agreement with previous reports[29] and should render the user attentive to the fact that not all HFOV devices are equally powerful or can be used over the same range of patient age and/or body weight. Furthermore, all devices showed less power reserve at higher frequencies, which was a major limitation for some devices in some of the clinical scenarios tested.

Conclusions

The main result of this neonatal and pediatric oscillator bench test study was that the PTP, a surrogate marker of the imposed WOB, depended on the oscillator frequency, respiratory system condition, and, though to a much lesser extent, on the HFOV device used. Our observations might have a major impact on the development of recommendations for the selection of optimal oscillation parameters, such as the oscillation frequencies in the acute phase of restrictive lung disease and later, in the weaning phase, when lung function improves and spontaneous breathing efforts are permitted.

REFERENCES

1. Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev 2015;(3): CD000104.
2. Rimensberger PC, Beghetti M, Hanquinet S, Berner M. First intention high-frequency oscillation with early lung volume optimization improves pulmonary outcome in very low birth weight infants with respiratory distress syndrome. Pediatrics 2000;105(6):1202-1208.
3. De Jaegere A, van Veenendaal MB, Michiels A, van Kaam AH. Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. Am J Respir Crit Care Med 2006; 174(6):639-645.
4. van Velzen A, De Jaegere A, van der Lee J, van Kaam A. Feasibility of weaning and direct extubation from open lung high-frequency ventilation in preterm infants. Pediatr Crit Care Med 2009;10(1):71-75.
5. Cereda M, Foti G, Marcora B, Gili M, Giacomini M, Sparacino ME, et al. Pressure support ventilation in patients with acute lung injury. Crit Care Med 2000;28(5):1269-1275.
6. Hering R, Peters D, Zinserling J, Wrigge H, von Spiegel T, Putensen C. Effects of spontaneous breathing during airway pressure release ventilation on renal perfusion and function in patients with acute lung injury. Intensive Care Med 2002;28(10):1426-1433.
7. Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier TA. Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med 1994;149(6):1550-1556.
8. Neumann P, Wrigge H, Zinserling J, Hinz J, Maripuu E, Andersson LG, et al. Spontaneous breathing affects the spatial ventilation and perfusion distribution during mechanical ventilatory support. Crit Care Med 2005;33(5):1090-1095.
9. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J. Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;159(4 Pt 1):1241-1248.
10. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, et al. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 2001;164(1):43-49.

11. van Heerde M, van Genderingen HR, Leenhoven T, Roubik K, Plotz FB, Markhorst DG. Imposed work of breathing during high-frequency oscillatory ventilation: a bench study. Crit Care 2006;10(1): R23.

12. Harcourt ER, John J, Dargaville PA, Zannin E, Davis PG, Tingay DG. Pressure and flow waveform characteristics of eight high-frequency oscillators. Pediatr Crit Care Med 2014;15(5):e234-e240.

13. Tingay DG, John J, Harcourt ER, Black D, Dargaville PA, Mills JF, et al. Are all oscillators created equal? In vitro performance characteristics of eight high-frequency oscillatory ventilators. Neonatology 2015;108(3):220-228.

14. Cook SE, Fedor KL, Chatburn RL. Effects of imposed resistance on tidal volume with 5 neonatal nasal continuous positive airway pressure systems. Respir Care 2010;55(5):544-548.

15. Essouri S, Durand P, Chevret L, Haas V, Perot C, Clement A, et al. Physiological effects of noninvasive positive ventilation during acute moderate hypercapnic respiratory insufficiency in children. Intensive Care Med 2008;34(12):2248-2255.

16. Carteaux G, Lyazidi A, Cordoba-Izquierdo A, Vignaux L, Jolliet P, Thille AW, et al. Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest 2012;142(2):367-376.

17. Cambonie G, Milesi C, Jaber S, Amsallem F, Barbotte E, Picaud JC, et al. Nasal continuous positive airway pressure decreases respiratory muscles overload in young infants with severe acute viral bronchiolitis. Intensive Care Med 2008;34(10):1865-1872.

18. Vitacca M, Clini E, Pagani M, Bianchi L, Rossi A, Ambrosino N. Physiologic effects of early administered mask proportional assist ventilation in patients with chronic obstructive pulmonary disease and acute respiratory failure. Crit Care Med 2000;28(6):1791-1797.

19. Scalfaro P, Pillow JJ, Sly PD, Cotting J. Reliable tidal volume estimates at the airway opening with an infant monitor during high-frequency oscillatory ventilation. Crit Care Med 2001;29(10):1925-1930.

20. Cabello B, Mancebo J. Work of breathing. Intensive Care Med 2006; 32(9):1311-1114.

21. Rossing TH, Slutsky AS, Lehr JL, Drinker PA, Kamm R, Drazen JM. Tidal volume and frequency dependence of carbon dioxide elimination by high-frequency ventilation. N Engl J Med 1981;305(23): 1375-1379.

22. Slutsky AS, Kamm RD, Rossing TH, Loring SH, Lehr J, Shapiro AH, et al. Effects of frequency, tidal volume, and lung volume on CO2 elimination in dogs by high frequency (2-30 Hz), low tidal volume ventilation. J Clin Invest 1981;68(6):1475-1484.

23. Pillow JJ, Sly PD, Hantos Z, Bates JH. Dependence of intrapulmonary pressure amplitudes on respiratory mechanics during high-frequency oscillatory ventilation in preterm lambs. Pediatr Res 2002; 52(4):538-544.

24. Pillow JJ, Wilkinson MH, Neil HL, Ramsden CA. In vitro performance characteristics of high-frequency oscillatory ventilators. Am J Respir Crit Care Med 2001;164(6):1019-1024.

25. Pillow JJ, Sly PD, Hantos Z. Monitoring of lung volume recruitment and derecruitment using oscillatory mechanics during high-frequency oscillatory ventilation in the preterm lamb. Pediatr Crit Care Med 2004;5(2):172-180.

26. Venegas JG, Fredberg JJ. Understanding the pressure cost of ventilation: why does high-frequency ventilation work? Crit Care Med 1994;22(9 Suppl):S49-S57.

27. Marini JJ. Does high-pressure, high-frequency oscillation shake the foundations of lung protection? Intensive Care Med 2015;41(12): 2210-2212.

28. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013;368(9):795-805.

29. Grazioli S, Karam O, Rimensberger PC. New generation neonatal high frequency ventilators: effect of oscillatory frequency and working principles on performance. Respir Care 2015;60(3):363-370.