New Generation Neonatal High Frequency Ventilators: Effect of Oscillatory Frequency and Working Principles on Performance

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BACKGROUND: Several new generation neonatal ventilators that incorporate conventional as well as high frequency ventilation (HFOV) have appeared on the market. Most of them offer the possibility to use HFOV in a volume-targeted mode, despite absence of any preclinical data. With a bench test, we evaluated the performances of 4 new neonatal HFOV devices and compared them to the SensorMedics HFOV device. METHODS: Expiratory tidal volumes (V_T) were measured for various ventilator settings and lung characteristics (ie, modifications of compliance and resistance of the system), to mimic several clinical conditions of pre-term and term infants. RESULTS: Increasing the frequency proportionally decreased the V_T for all the ventilators, although the magnitude of the decrease was highly variable between ventilators. At 15 Hz and a pressure amplitude of 60 cm H_2O, the delivered V_T ranged from 3.5 to 5.9 mL between devices while simulating pre-term infant conditions and from 2.6 to 6.3 mL while simulating term infant conditions. Activating the volume-targeted mode in the 3 machines that offer this mode allowed the V_T to remain constant over the range of frequencies and with changes of lung mechanical properties, for pre-term infant settings only while targeting a V_T of 1 mL. CONCLUSIONS: These new generation neonatal ventilators were able to deliver adequate V_T under pre-term infant, but not term infant respiratory system conditions. The clinical relevance of these findings will need to be determined by further studies. *Key words: high frequency ventilation; neonatal intensive care; respiratory mechanics; volume-targeted ventilation.* [Respir Care 2015;60(3):363–370. © 2015 Daedalus Enterprises]

Introduction

The clinical use of high frequency oscillatory ventilation (HFOV) in pre-term infants remains controversial, as previous meta-analysis failed to show a significant difference between HFOV and conventional mechanical ventilation in mortality, bronchopulmonary dysplasia, and adverse neurological outcomes.[1,2] However, some studies that initiated HFOV very early in pre-term infants with respiratory distress syndrome have shown that surfactant doses, ventilator days, and chronic lung diseases could be reduced compared with conventional mechanical ventilation.[1,3,4] Therefore, the concept of using HFOV as a primary ventilation mode in infants presenting with respiratory distress syndrome of various origins remains of interest.

Accordingly, several manufacturers have introduced new neonatal HFOV devices on the market. These new devices, including the Babylog VN500 (Dräger Medical, Lübeck, Germany), the Fabian HFO (Acutronic Medical System, Hirzel, Switzerland), the SLE 5000 (SLE, South Croydon, United Kingdom), and the Leoni Plus (Heinen+Löwenstein, Bad Ems, Germany) offer both conventional mechanical ventilation and HFOV as ventilation modes. In addition, a new concept of V_T targeting during HFOV has been introduced in 3 of them (Babylog VN500, Fabian HFO, and Leoni Plus), despite the absence of any clinical data on volume targeting high frequency oscillation. Recently, one experimental study investigated the stability of P_{CO_2} during HFOV using the volume guarantee mode,

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showing that P_{CO_2} remained stable with maintenance of minute ventilation during HFOV before and after surfactant depletion in piglets.[5]

The technical features added to these new ventilators, in particular the choice of the ventilator mode between conventional mechanical ventilation and HFOV, the measurements of V_T, and the volume-targeted mode during HFOV might represent all attractive features for the clinician, but data on volume delivery accuracy and performance of these new generation HFOV devices are lacking. Most of the published data on mechanical performance of oscillatory ventilators dates back more than 10 y,[6-8] and there is only one recent study, which looked into the performance of the Babylog VN500, showing a reduction of its power for generating oscillatory pressure amplitudes at higher operating frequencies.[9] Furthermore, published data on stability of V_T during volume-targeted ventilation are conflicting.[10,11] Our group found, in a bench study[12] on volume-targeted ventilation during conventional mechanical ventilation significant differences between set V_T and delivered V_T among the tested neonatal ventilators under changes in respiratory mechanics. Given these unknowns, we aimed to evaluate the performances of several new neonatal HFOV devices at various oscillations frequencies and in various respiratory system conditions, with and without the volume targeting mode activated.

Therefore, our hypothesis was that the new neonatal HFOV devices would perform similarly to the SensorMedics 3100A (CareFusion, San Diego, California), with and without the volume targeting mode activated, and in various lung conditions.

QUICK LOOK

Current knowledge

The clinical use of high frequency oscillatory ventilation (HFOV) in preterm infants remains controversial as meta-analysis failed to show a significant difference versus conventional ventilation with respect to mortality, bronchopulmonary dysplasia, and adverse neurological outcomes. Despite the unproven utility, a number of conventional ventilators with an HFOV option have been introduced.

What this paper contributes to our knowledge

Neonatal HFOV ventilators deliver adequate oscillation tidal volume (1 mL/kg) under bench test conditions simulating respiratory system mechanics of a pre-term infant and maintain tidal volume constant in the volume-targeted mode. However, not all of the ventilators could deliver adequate oscillation tidal volume (4 mL/kg) for term infant conditions.

Methods

We studied 4 neonatal ventilators offering both HFOV and conventional mechanical ventilation modes: the Babylog VN500, the Fabian HFO, the SLE 5000, and the Leoni Plus (Table 1). As reference device for comparisons, we used the well-established SensorMedics 3100A.

Experimental Set-Up

The ventilators were equipped with the same commercially available standard neonatal respiratory circuit (single-use neonatal respiratory circuit, Fisher & Paykel Healthcare, Auckland, New Zealand) with the exception of the SLE 5000 and the SensorMedics 3100A, which can only operate a unique circuit supplied by the manufacturer. The humidification chamber was kept in line but run dry with no heating. The continuous bias flow was (1) automatically modulated for the Babylog VN500, (2) delivered at a constant flow at 8 L/min for the SLE 5000 and 7 L/min for the Leoni Plus, (3) set at 20 L/min at the maximal value possible for the Fabian HFOV, and (4) set at 20 L/min per our guidelines for the SensorMedics 3100A.

The ventilators were connected to the 8.0-mm internal diameter tube of a neonatal test lung (model 1601, Michigan Instruments, Grand Rapids, Michigan) (Fig. 1). Compliance was adjusted on the test lung, and airway resistance was simulated using different airway resistors, which allowed comparison of the performance of the ventilators in various respiratory system conditions. To simulate the mechanical proprieties of the respiratory systems of a full-term infant (with an assumed body weight of 4 kg), we used a resistance of 70 cm H_2O/L/s with compliance of 4 mL/cm H_2O; to simulate a pre-term infant (with an assumed body weight of 1 kg), we used a resistance of 100 cm H_2O/L/s with compliance of 2 mL/cm H_2O as a baseline settings. The expiratory V_T was measured with the Florian neonatal respiratory monitor (Acutronic Medical System), which has been validated for measurements of very small V_T during HFOV.[13] The Florian's flow sensor was positioned at the Y-piece and was calibrated according to the manufacturer's instructions before each test series. Mean airway pressure ($\bar{P}_{aw}$) and oscillation pressure amplitude (ΔP_{vent}) were measured by the ventilator's transducer inserted between the ventilator and the Y-piece and recorded as displayed by the ventilator. For each of the 5 ventilators, the same operator recorded single measurements manually after the system had reached a steady state, with no more changes in the readout after a minimum of 1 min.

Table 1. Characteristics of Tested Ventilators

	SensorMedics 3100A	Babylog VN500	Fabian HFO	Leoni Plus	SLE 5000
Manufacturer	CareFusion	Dräger	Acutronic	Heinen+Löwenstein	SLE
Technical principles	Oscillations generated by a large loudspeaker	Servo valve controlled pulsed inspiratory flow Expiratory valve oscillation	Membrane oscillation	Membrane oscillation	Opposing flow at the expiratory manifold
Mode	HFOV	Conventional mechanical ventilation and HFOV	Conventional mechanical ventilation and HFOV	Conventional mechanical ventilation and HFOV	Conventional mechanical ventilation and HFOV
Volume-targeted mode	No volume-targeted mode	Volume-targeted mode in HFOV	Volume-targeted mode in HFOV	Volume-targeted mode in HFOV	No volume-targeted mode in HFOV
V_T monitoring	No V_T monitoring	Hot-wire anemometer	Hot-wire anemometer	Hot-wire anemometer	Hot-wire anemometer
Flow	0–40 L/min	2–30 L/min	1–20 L/min	7 L/min	8 L/min
Pressure amplitude setting range	1–90 cm H_2O	1–90 cm H_2O	5–80 cm H_2O	0–100 cm H_2O	4–180 cm H_2O
Mean pressure setting range	3–45 cm H_2O	5–50 cm H_2O	5–50 cm H_2O	0–40 cm H_2O	0–35 cm H_2O
Frequency setting range	3–15 Hz	5–20 Hz	5–20 Hz	5–20 Hz	3–20 Hz
Inspiratory/expiratory ratios	1:1 and 1:2	1:1 to 1:3	1:1 to 1:3	1:1 to 1:3	1:1

V_T = tidal volume
HFOV = high frequency oscillatory ventilation

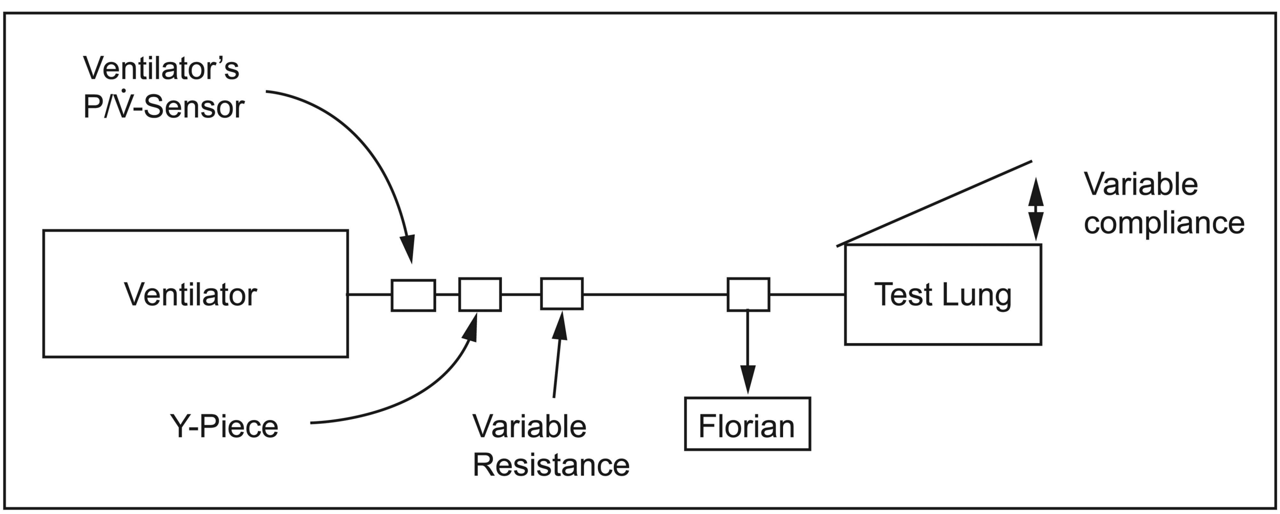

Fig. 1. Diagram of the experimental setup of the test lung. P/V̇-sensor = pressure/flow sensor.

Study Protocol

We compared the expiratory V_T at different oscillatory frequencies (5, 10, and 15 Hz) and at increasing ΔP_{vent} (30, 45, 60 cm H_2O and maximal ΔP_{vent} offered by the ventilator) in full-term and pre-term infant settings. The $\bar{P}_{aw}$ was set at 15 cm H_2O, and the I-E ratio was set at 1:1. To simulate restrictive lung disease, the compliance was modified from 4 to 2 mL/cm H_2O (full-term) and from 2 to 1 mL/cm H_2O (pre-term). To simulate obstructive disease, resistance was modified from 70 to 200 cm H_2O/L/s (full-term) and from 100 to 200 cm H_2O/L/s (pre-term). To evaluate the effectiveness of the volume-targeted mode in maintaining the desired V_T, the test series was repeated with the volume-targeted mode activated in 3 of the ventilators offering this option. We used a targeted V_T of 4 mL under full-term settings and 1 mL under pre-term infant settings. These target tidal volumes during oscillation have been chosen based on our own clinical observations (with most often observed V_T, which resulted in normocapnia, in the range 0.5–1.5 mL/kg body weight at an oscillation frequency of 15 Hz) over the years with the use of the SensorMedics 3100A device in combination with a neonatal respiratory monitor (Florian). The Florian has been validated for V_T measurements during HFOV by Scalfaro et al.[13]

Results

Influence of the Ventilator Properties on Delivered V_T (Volume-Targeted Mode Inactivated)

While simulating full-term infant conditions, all ventilators demonstrated a linear increase of the V_T at 5 and 10 Hz following ΔP_{vent} increase (Fig. 2A). However, at 15 Hz and a ΔP_{vent} set at 60 cm H_2O, we observed heterogeneity in the delivered V_T, which ranged from 2.6 to 6.3 mL. In particular, the Babylog VN500 was unable to increase the V_T because ΔP_{vent} could not be increased beyond 36 cm H_2O at this oscillation frequency. While simulating pre-term infant conditions, we observed larger variability in the delivered V_T between devices (Fig. 2B), in particular at 15 Hz, with V_T ranging from 3.5 to 5.9 mL with a pressure amplitude set at 60 cm H_2O. Again, the Babylog VN500 delivered lower V_T at 5 Hz and 15 Hz than the other ventilators and was unable to increase its maximal ΔP_{vent} beyond 55 cm H_2O at a frequency of 10 Hz and beyond 33 cm H_2O at a frequency of 15 Hz. Notably, the performance of the Babylog VN500 was unaffected by the type of the ventilator circuit used: Fisher Paykel Healthcare or Hyrtel (Dräger Medical), the latter being the only one recommended by the manufacturer.

Effect of Lung Mechanical Proprieties on Delivered V_T

When compliance was changed from 4 to 2 mL/cm H_2O in full-term infant setting (Table 2), delivered V_T remained similar in all the ventilators and for all the frequencies tested, except for 15 Hz. At 15 Hz, the Babylog VN500 and the Leoni Plus responded to a decrease in compliance by an increase of the delivered V_T. In pre-term infant settings (Table 3), a compliance change from 2 to 1 mL/cm H_2O at 5 Hz resulted in a decrease in V_T, whereas at 15 Hz, the V_T remained similar for all the ventilators with the exception of the Fabian HFO (which increased its V_T). The increase in resistance both in pre-term and full-term infant settings resulted in a decrease of the delivered V_T for all the ventilators, regardless of compliance.

Influence of Volume-Targeted Mode on V_T After Modification of Lung Mechanical Properties

While simulating a full-term infant at 5 and 10 Hz and with a volume target set at 4 mL, all 3 ventilators compensated for changes in compliance and resistance and kept the targeted volume constant (Fig. 3A). However, at 15 Hz, none of the ventilators could fully compensate for the increase in resistance, resulting in a substantial loss of V_T. While simulating a pre-term infant, with a targeted

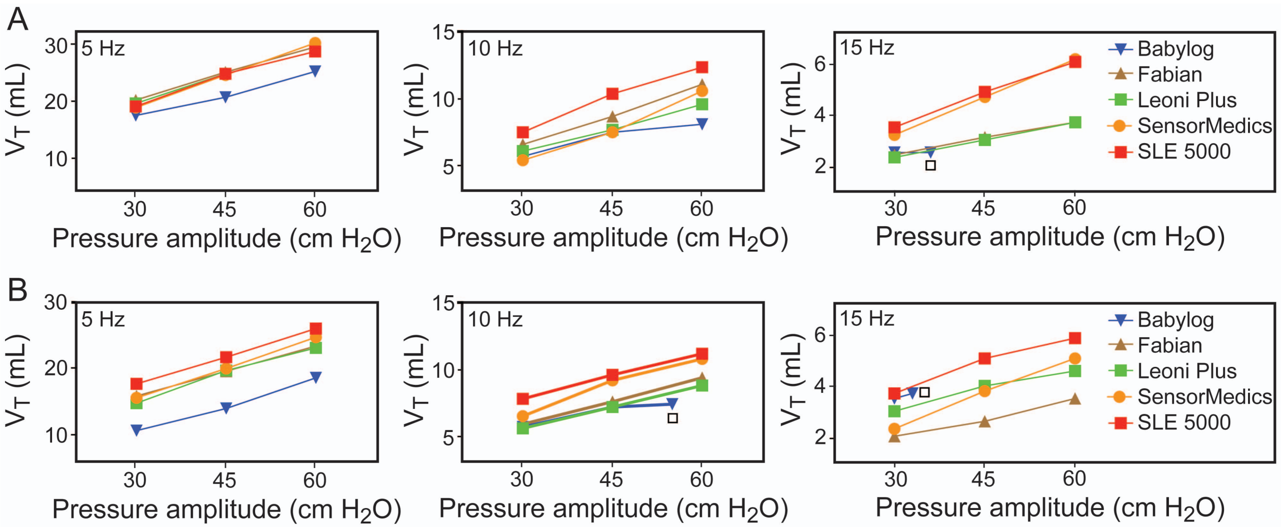

Fig. 2. Delivered tidal volume (V_T) with various pressure amplitudes and oscillation frequencies in A: full-term infant settings and B: pre-term infant settings. Five ventilators were compared: Babylog VN500, Fabian HFO, Leoni Plus, SensorMedics, and SLE 5000, using the same mean airway pressure setting of 15 cm H_2O and I:E of 1:1. Note that, at a frequency of 15 Hz under full-term infant settings, the Babylog VN500 was not able to increase the pressure amplitude beyond 36 cm H_2O (white marker); under pre-term infant settings, the maximal pressure amplitudes delivered by the Babylog VN500 at 10 Hz and 15 Hz were 55 cm H_2O and 33 cm H_2O, respectively (white markers).

Table 2. Tidal Volume Variation After Change in Lung Condition Under Full-Term Infant Settings

Ventilator	Frequency Rates (Hz)	Compliance Decrease (% V_T change)	Resistance Increase (% V_T change)	Combined (% V_T change)
Babylog VN500				
	5	−5.5	−66.5	–68.1
	10	0.0	−62.1	−63.2
	15	80.0	−48.0	−32.0
SensorMedics				
	5	1.1	−72.8	−73.5
	10	2.5	−70.4	−70.4
	15	3.6	−66.7	−64.3
Leoni Plus				
	5	−4.4	−66.7	−67.3
	10	0.0	−64.0	−65.8
	15	52.3	−59.1	−52.3
Fabian HFO				
	5	−1.4	−69.2	−69.9
	10	3.8	−66.3	−66.3
	15	5.9	−55.9	−64.7
SLE 5000				
	5	2.3	−69.1	−69.5
	10	−2.4	−61.8	−62.9
	15	6.7	−61.3	−58.7

Results are presented as percentage of variation in tidal volume (V_T) when the test lung compliance was decreased from 4 to 2 ml/cm H_2O, the resistance increased from 70 to 200 cm H_2O/L/s, or when both compliance and resistance were changed. Mean airway pressure was set at 15 cm H_2O with an I:E of 1:1 and maximal pressure amplitude.

Table 3. Tidal Volume Variation After Change in Lung Condition Under Preterm Infant Settings

Ventilator	Frequency rates (Hz)	Compliance decrease (% V_T change)	Resistance increase (% V_T change)	Combined (% V_T change)
Babylog VN500				
	5	−12.0	−60.6	−61.0
	10	1.3	−57.3	−58.7
	15	5.4	−54.1	−56.8
SensorMedics				
	5	−17.0	−66.0	−66.9
	10	2.8	−66.0	−61.7
	15	8.1	−59.5	−59.5
Leoni Plus				
	5	−9.0	−61.3	−62.4
	10	0.0	−62.1	−61.2
	15	1.9	−61.1	−61.1
Fabian HFO				
	5	−13.3	−65.5	−63.1
	10	−1.0	−65.3	−61.4
	15	57.1	−57.1	−35.7
SLE 5000				
	5	−4.7	−58.5	−60.1
	10	−0.7	−56.6	−57.9
	15	5.9	−54.4	−54.4

Results are presented as percentage of variation in tidal volume (V_T) when the test lung compliance was decreased from 2 to 1 ml/cm H_2O, when the resistance was increased from 100 to 200 cm H_2O/L/s, or when both compliance and resistance were changed. Mean airway pressure was set at 15 cm H_2O with an I:E of 1:1 and maximal pressure amplitude.

volume of 1 mL, all 3 ventilators compensated for changes in lung compliance and resistance and delivered the targeted V_T when the frequency was set at 15 Hz (Fig. 3B). However, below 15 Hz, all the ventilators delivered a V_T that was higher than the pre-set 1 mL.

Discussion

We observed large variability in performance between the ventilators, in particular at high oscillatory frequency (ie, 15 Hz). The activation of the volume-targeted mode in pre-term infant settings allowed the V_T to remain constant, although not always matching the set V_T, during changes of the respiratory system mechanical properties.

As shown previously,[6-8,14] the principal factors influencing the mechanical performance of HFOV ventilators are frequency, inspiratory time, and load charge. Although all ventilators delivered lower V_T with increasing frequencies, there were marked differences in the extent of V_T decrease between ventilators at an oscillatory frequency of 15 Hz. Indeed, the new generation of neonatal HFOV ventilators (Babylog VN500, Fabian HFO, and Leoni Plus) delivered lower V_T than the 3100A and SLE 5000 with the same pressure amplitude settings, both under pre-term infant and full term infant settings. As the CO_2 elimination during HFOV is proportional to $f{\cdot}V_T$,[2,15,16] the difference in performance observed under our test conditions may be even more significant in clinical settings.

There is no consensus about the ideal V_T for HFOV, but studies in animals[17,18] and pre-term neonates[19] have shown that a V_T of 2–3 mL/kg allows optimal gas exchange during HFOV. Although the use of these new generation neonatal ventilators is intended for the neonatal population unlike the 3100A (a ventilator that can be used with patients larger than neonates), some of them might not have sufficient power to deliver required V_T for adequate gas exchange, especially when used in full-term infants at high oscillatory frequencies.

Differences in the new HFOV ventilator design limiting maximal oscillatory flows may account for the variability in performance observed in conditions characterized by reduced flows toward the patient (ie, at higher frequencies and lower inspiratory time). The SLE 5000, whose operating principle includes a continuous bias flow with 3 opposing jet flows, was the most powerful neonatal ventilator in term of volume delivery, with a performance

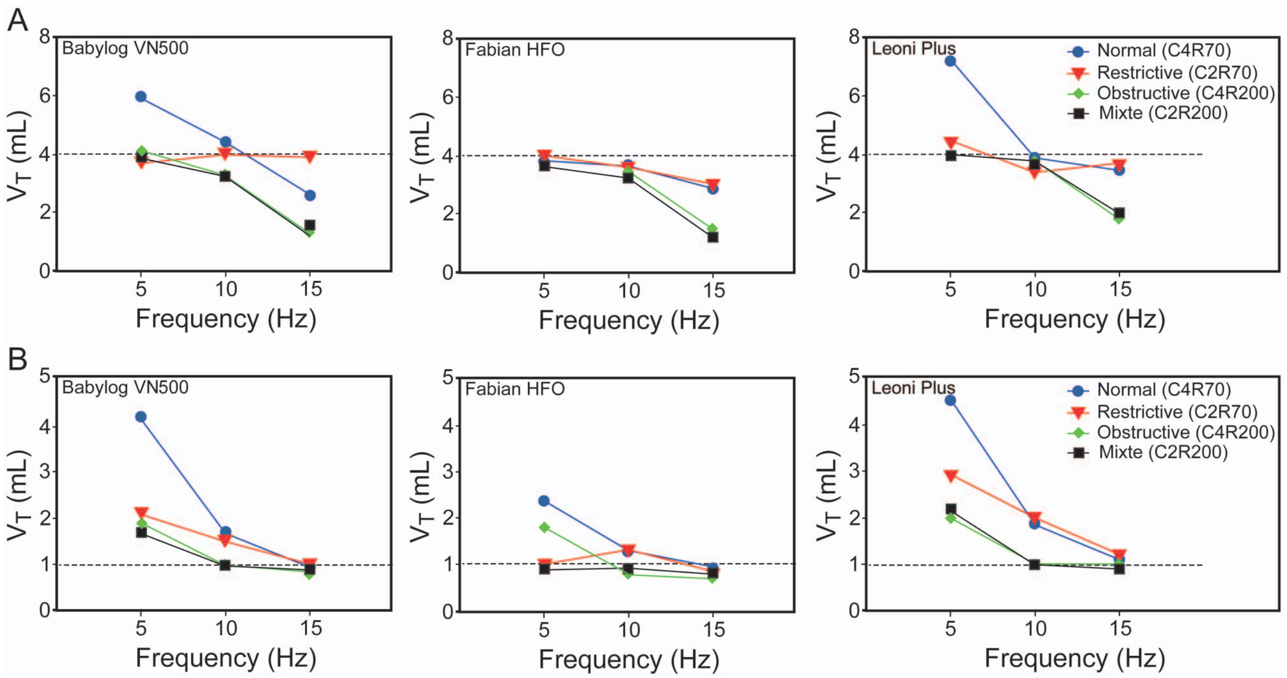

Fig. 3. Tidal volume (V_T) responses to change in oscillation frequencies, lung compliance, and resistance after activation of the volume-targeted mode in A: full-term and B: pre-term infant settings. Three ventilators were compared: Babylog VN500, Fabian HFO, and the Leoni Plus, using the same mean airway pressure setting of 15 cm H_2O, I:E of 1:1, and the maximal setting for oscillatory pressure limitation. The V_T target was set at 4 mL under full-term infant settings and 1 mL under pre-term infant settings. C = compliance; R = resistance

similar to the 3100A. On the other hand, the Babylog VN500 presented important oscillatory flow limitations at high frequency settings as has also been reported in a recent bench study by John et al,[9] and these were similar to those seen in the older Babylog 8000.[6,7] This feature may be explained by the specific design of the Babylog VN500 that incorporates some of the technical concepts of the Babylog 8000 (ie, a Venturi multi-valve system on the expiratory side) combined with a new pulsed inspiratory flow. Because the flow is set automatically based on the frequency and the $\bar{P}_{aw}$, an insufficient bias flow may explain the power limitation of this ventilator seen in our study.

The use of volume target modes during conventional mechanical ventilation is well documented in neonates and has been shown to reduce the incidence of death, bronchopulmonary dysplasia, and severe intraventricular hemorrhage compared with pressure limited ventilation.[20] Despite those obvious benefits, several reports demonstrated inaccuracies in the delivered V_T during volume target ventilation with conventional mechanical ventilation with volume overshooting upon rapid change in respiratory mechanics.[10,12]

During HFOV, V_T represents the principal determinant for CO_2 removal and several reports found important fluctuation in the delivered V_T during HFOV.[21] In absence of direct V_T monitoring on the old generation HFOV such as the SensorMedics 3100A, the clinician had to rely on the clinical exam as well as on repeated blood gas measurements to make changes in the ventilator settings which exposed the patients at risk for variation in P_{aCO_2}.

In this perspective, the incorporation of a flow sensor to measure V_T into these new generation of neonatal HFOV represents a potentially useful improvement for the clinician although some inaccuracies in the measurements of V_T has been reported.[22] In addition, the possibility to combine HFOV with a volume-targeted mode on these ventilators will keep V_T constant after change in lung mechanics as demonstrated recently in an animal model of surfactant deficiency.[5]

The activation of the volume-targeted mode under high resistance conditions allowed the ventilators to maintain constant small targeted V_T (1 mL) but failed to maintain larger targeted V_T (4 mL) at 15 Hz. Furthermore, at lower frequencies with a lower target V_T of 1 mL, all 3 ventilators delivered a higher-than-set V_T. Although there might theoretically be some potential advantages of using a guaranteed volume during HFOV, especially for small pre-term neonates, some precautions must be taken when this option is activated at a low frequency with a small V_T setting, as it may result in undesired overventilation for very small pre-term babies. Therefore, experimental studies are needed to rule out our concerns before clinical studies can be conducted to determine the real utility of this new mode.

The primary limitation of our study is the experimental setup, which differs from the previous bench evaluation of neonatal HFOV ventilators.[6,8,23] First, we used a test lung with airway resistance simulated using different sized airway resistors. This system allowed us to test different changes in respiratory mechanics but cannot completely reproduce the complexity of the neonatal respiratory system. Second, the delivered V_T was directly measured using a hot-wire flow sensor, which may have added further resistance and could have attenuated the V_T delivered by the ventilators. Although this might have induced a measurement bias, it could only be very small, because the resistance of the Florian anemometer is only 0.55 Pa/mL with a $\dot{V}$ of 100 mL/s, which would result theoretically in an additional reduction in V_T of only 0.3 mL.[13]

The record of single manual measurements on single ventilators constitutes another limitation, which may have affected the accuracy of the results. However, the record of measurements after 1 min steady state and the use of functional ventilators provided by their respective manufacturer and tested as per manufacturers' protocol before each test series helped to reduce the impact of these limitations on the different ventilators' characteristics described in this study. Because of these limitations, our results might not be directly applied to the clinical setting but emphasize the need for further clinical and animal studies to evaluate the performance and ventilation efficiency of the new generation neonatal HFOV ventilators.

In summary, all of the new generation neonatal HFOV ventilators can deliver adequate oscillation V_T (1 mL/kg) under bench test conditions simulating various respiratory system mechanics of a pre-term infant, and do keep the V_T constant in various respiratory system conditions upon activation of the volume-targeted mode. However, not all of the ventilators could deliver adequate oscillation V_T (4 mL/kg) for term infant conditions. Furthermore, there was heterogeneity between devices in the V_T delivery at higher frequencies. Therefore, further studies are needed to determine the clinical importance of our findings from the bench.

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