Inspiratory Pressure Rise Time, Ventilator Hardware, and Software Influence Regional Ventilation in a Simulated Bronchopulmonary Dysplasia Lung Model

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BACKGROUND: Bronchopulmonary dysplasia (BPD) is a heterogeneous disease that poses a challenge when ventilating premature infants. The purpose of this study was to determine how inspiratory pressure rise time (IRT), different ventilators, and their software updates affect the balance of ventilation among 2 heterogeneous lung units. METHODS: A passive dual-chamber lung model was constructed using the IngMar ASL5000 to approximate moderate BPD. One chamber had a short time constant, and the other had a long time constant. Three ventilators were used to provide pressure control intermittent mandatory ventilation: the Servo-i, an Avea ventilator with the volume guarantee software update, and an Avea ventilator without the volume guarantee software update. Using the same settings for pressure control intermittent mandatory ventilation, the IRT was adjusted between minimum and maximum settings. Data from 100 consecutive breaths/IRT were obtained. Inspiration time to 90% of plateau pressure was used as a surrogate for IRT; this was defined as the time needed to achieve a pressure of 18 cm H_2O at the simulated trachea and was measured in 5 random breaths using ImageJ for each ventilator at each IRT. Outcome variables were tidal volume, peak inspiratory flow, mean inspiratory pressure, and volume balance (%) defined as the difference in chamber tidal volumes divided by total tidal volume. Linear regression was used to assess the impact of the IRT and ventilators on the different variables. RESULTS: In this model, increasing IRT decreased peak inspiratory flow, mean inspiratory pressure, chamber-specific tidal volume, and volume balance. Furthermore, different ventilator hardware and software influenced the waveforms in pressure control intermittent mandatory ventilation, which independently affected the measured variables. CONCLUSIONS: In a lung model of BPD with 2 very heterogeneous lung units, prolonging IRT without any volume balancing measures improved volume balance between the chambers at the expense of total tidal volume. Furthermore, the different ventilators acted as independent factors from the measured inspiration time to 90% of plateau pressure. *Key words: inspiratory rise time; bronchopulmonary dysplasia; regional ventilation; chronic lung disease; prematurity.* [Respir Care 2021;66(5):751–757. © 2021 Daedalus Enterprises]

Introduction

Bronchopulmonary dysplasia (BPD) is a heterogeneous disease affecting mostly very low birthweight premature infants.[1,2] Histologically BPD is characterized by areas of alveolar simplification, vascular pruning with remodeling, and obstructive airway lesions. The heterogeneous nature of this disease often causes difficulties in ventilation due to the propensity of more affected segments to air trap.[3,4] Given the interdependency of pulmonary units, overinflated lung segments in a diseased lung tend to compress healthier segments.

Pressure control ventilation is commonly used in neonatal ICUs to support extremely premature infants.[5] Since the inclusion of microprocessors in modern neonatal ventilators, adjustments to flow and pressure waveforms have become easier than ever, but they are often not addressed clinically or in randomized controlled trials. Flow waveforms in pressure control ventilation can vary to a great degree in neonatal ventilators, from ones with a rapid rise with exponential decay during inspiration to more sinusoidal waveforms mimicking normal breaths in infants.[6] The former tends to generate more square-shaped pressure waveforms, whereas the latter approximates more sine-

shaped pressure waveforms. The setting on most ventilators that governs the transition from one pressure waveform to the other is the inspiratory pressure rise time (IRT). In the adult literature, prolonging IRT is often associated with an increase in respiratory distress and work of breathing as a consequence of insufficient peak inspiratory flow.[7] It is known, however, that premature infants can tolerate lower peak inspiratory flows than adult patients, allowing for the utilization of longer IRT.[3]

Optimal mechanical ventilation settings in infants with established BPD have not been well studied. It is generally accepted that longer inspiratory times are needed to allow for improved gas exchange due to the prolonged respiratory system time constants generated by diseased airways and loss of elastic tissue.[8-12] It is not known how IRT influences regional ventilation in infants with established BPD.

The objective of this study was to explore how changing IRT influences regional ventilation in a simulated lung model of BPD, and to establish whether ventilators of different makes and software revisions operate similarly at similar IRTs.

QUICK LOOK

Current knowledge

Bronchopulmonary dysplasia is a heterogeneous lung disease that affects premature infants. This heterogeneity predisposes some segments to overinflation, which in turn can compromise others. This renders affected infants difficult to ventilate.

What this paper contributes to our knowledge

Using a simulated 2-chamber lung model to mimic the regional differences in bronchopulmonary dysplasia, our results indicate that prolonging the inspiratory rise time can improve regional ventilation balance at the cost of a reduced tidal volume delivered. Our results also demonstrate the inherent differences between ventilators from different manufacturers and between different software versions for the same ventilator.

Methods

Equipment, BPD Model, and Ventilator Settings

To simulate moderate BPD, an ASL5000 breathing simulator was used (software version 3.6.3, IngMar Medical, Pittsburgh, Pennsylvania). An infant circuit (Fisher & Paykel, Auckland, New Zealand) was used to connect the simulator to each of the tested ventilators. Three ventilators were evaluated: the Servo-i (Maquet, Rastatt, Germany, software version 7.00.04), and 2 Avea ventilators (CareFusion, San Diego, California). Both Avea ventilators were of the same model and were running software version 4.6b, but one had an optional "volume guarantee" (VG) software module installed. Throughout this study, volume targeting was not enabled for the Servo-i and for the Avea with VG.

To build the BPD model, previously published data were used to approximate a dual-lung chamber model of established BPD in a term-corrected infant;[13-19] one lung chamber had a short time constant due to lower airway resistance and lower compliance, and the other lung chamber had a long time constant due to higher airway resistance and higher compliance (Table 1). A passive lung model was chosento focus on the effects of different lung mechanics independent of effects due to arbitrary values of simulated inspiratory efforts, for which there are little data in the literature.

The ventilators were placed in pressure control intermittent mandatory ventilation mode with set-point targeting[20] at a breathing frequency = 40 breaths/min, inspiratory pressure = 15 cm H_2O above PEEP, PEEP = 5 cm H_2O, pressure support = 0, inspiratory time = 0.4 s, and F_{IO_2} = 0.21 (Table 2). The IRT on the Servo-i ventilator was adjusted from its lowest setting of 0 ms to its longest setting of 200 ms in increments of 40 ms. For the Avea ventilators, they were adjusted from their lowest setting of 1 to their longest setting of 9 in increments of 2.

Experimental Procedure

At least 250 breaths were captured using the ASL5000 at each designated IRT point for each ventilator. The lung simulator recorded flows, pressure waveforms, and volume changes at a sampling rate of 512 Hz. For breath analysis, 100 consecutive breaths were used after allowing for at least 10 initial breaths to equilibrate the ventilator and simulator at each IRT setting. Data were extracted using the accompanying ASL5000 software. Conditions for analysis were set to "as measured," with a moving average pressure filter and volume threshold of 5 mL to identify inspiration and expiration.

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Table 1. Details of Dual-Chamber Model

Uncompensated residual capacity, L	0.1
Tracheal inspiratory resistance, cm H_2O/L/s	24
Tracheal expiratory resistance, cm H_2O/L/s	24
Short time constant	
Inspiratory resistance, cm H_2O/L/s	90
Expiratory resistance, cm H_2O/L/s	135
Linear compliance, L/cm H_2O	0.001
Long time constant	
Inspiratory resistance, cm H_2O/L/s	135
Expiratory resistance, cm H_2O/L/s	202
Linear compliance, L/cm H_2O	0.0015

Table 2. Settings Used With All 3 Ventilators

Patient type	Neonatal
Mode	PC-IMV
Breathing frequency, breaths/min	40
Pressure control, cm H_2O above PEEP	15
PEEP, cm H_2O	5
Pressure support, cm H_2O	0
Compliance compensation	On
Inspiratory time, s	0.4

PC-IMV = pressure control intermittent mandatory ventilation

Ventilation balance was calculated as $\frac{V_{T_{LTC}} - V_{T_{STC}}}{V_{T_{Total}}} \times 100$, where LTC is the long time constant and STC is the short time constant. For example, if both chambers have the same V_T, then the ventilation balance is 0%.

Due to the differences in how the ventilators assigned IRT, a more objective measure was needed. The time to 90% of plateau pressure (T90) was used as a standard measure (ie, 18 cm H_2O, at the "trachea" of the simulator). To assess T90, 5 individual pressure waveforms for each IRT point were extracted from the ASL5000 software as pressure data points sampled at 512 Hz for each of the 3 ventilators. While the ASL5000 software is capable of measuring T90 automatically and accurately for the Servo-i and the Avea with VG, measurements obtained for the Avea without VG were haphazard due to the software's inability to define plateau pressure with a sine-shaped pressure waveform. Due to these limitations, the waveforms were reconstructed in Microsoft Excel using exported data points to allow the resulting waveforms to be standardized and enlarged. The waveforms were then exported into high dot-per-inch images for analysis in ImageJ 1.51m9 (Available at: https://imagej.nih.gov/ij, *Accessed January 20, 2021*). The scale for each image was calibrated using ImageJ's built-in scale tool. T90 was calculated using the built-in measuring tool.[21] T90 was used thereafter as a surrogate for IRT to allow for direct comparison of the ventilators.

Statistical Analysis

Linear regression analysis was used to compare the impact of changes in T90 with different ventilators on peak inspiratory flow, mean inspiratory pressure, short time constant, and long time constant chamber-specific tidal volumes (V_T; Minitab 19, Penn State University, State College, Pennsylvania). To ascertain differences between the ventilators, a single linear equation to describe each variable was used, but the separate equations are presented for each ventilator. A $P < .05$ was deemed significant.

Results

Different Ventilators Have Different T90 Ranges

T90 was measured for each of the 3 ventilators at each IRT point; the Servo-i with IRT ranging from 0 ms to 200 ms, the Avea without the VG update (Avea without VG) with IRT set incrementally from 1 through 9, and the Avea with the VG update (Avea with VG) with IRT set incrementally from 1 through 9. The 2 Avea ventilators had completely different T90 ranges that did not overlap. The T90 range for the Avea without VG had the longest times. The Servo-i T90 range was the widest. As T90 got longer, the pressure waveforms shifted from a square-shaped wave to a more sine-shaped wave. To achieve these pressure waveforms, the ventilator shifted from a rapid onset with exponential decline flow waveform to a more sine-shaped flow waveform. (Fig. 1).

Prolonging T90 was associated with a decrease in peak inspiratory flow for all 3 ventilators. The Avea without VG, with its longer T90 range, experienced the lowest values of all 3 ventilators. Although the T90 range of the Avea with VG overlapped that of the Servo-i, there was a statistically significant difference between the 2 ventilators (Fig. 2).

As pressure waveforms shifted from a square-shaped waveform to a more sine-shaped waveform by prolonging T90, mean inspiratory pressure decreased. Mean inspiratory pressure values were lowest with the Avea without VG, which had the longest T90 range. Despite the Avea with VG and the Servo-i having an overlapping T90 range, differences persisted in mean inspiratory pressures that were independent of the T90 values between the 2 ventilators (Fig. 2).

As T90 is prolonged and mean inspiratory pressure decreases, the chamber-specific and total V_T delivered decreased in all 3 ventilators. Again, the Avea without VG exhibited the lowest delivered total and chamber-specific V_T due to its longer T90 range; at its shortest T90, this ventilator delivered a total V_T of 29.5 ± 0.1 mL versus 26.9 ± 0.1 mL at its longest T90, an 8.7% drop. Chamber-specific

A

Settings on Avea Ventilators		1	3	5	7	9
Measured T90 (ms)	Avea Without VG	245 ± 2	258 ± 3	271 ± 2	282 ± 3	293 ± 2
	Avea With VG	103 ± 1	109 ± 1	117 ± 2	126 ± 2	133 ± 2
Settings on Servo-i	0	40	80	120	160	200
Measured T90 (ms)	58 ± 2	71 ± 3	97 ± 2	131 ± 4	165 ± 1	199 ± 2

B

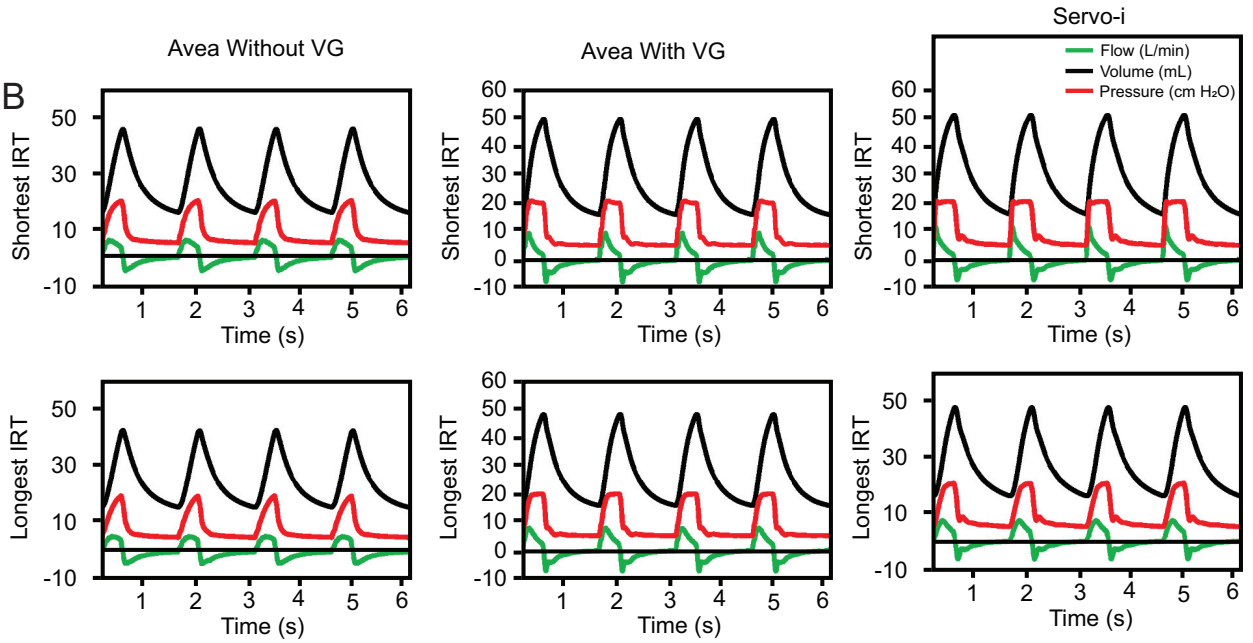


Fig. 1. A: Measured T90 values at each IRT settings for each of the ventilators. B: Flow, volume, and pressure waveforms at the limits of IRT for each of the 3 ventilators tested. IRT = inspiratory pressure rise time; T90 = time to 90% of plateau pressure.

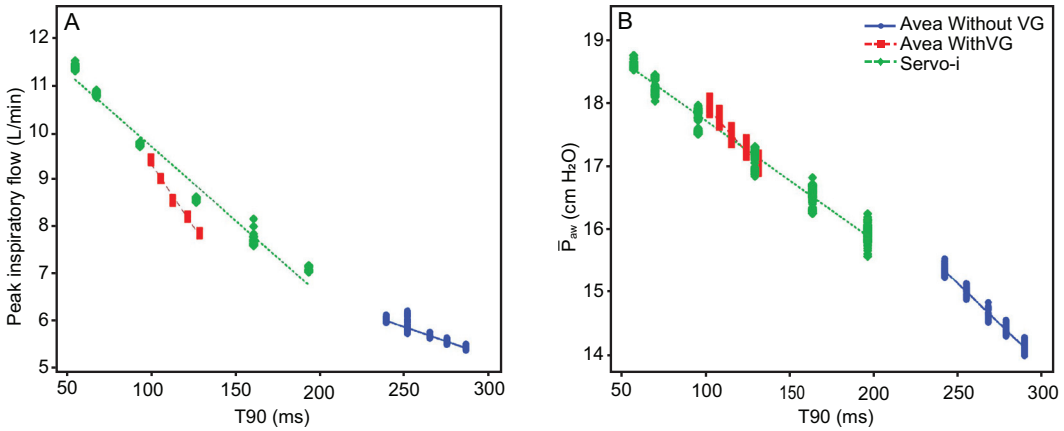
and total V_T continued to differ between the Avea with VG and the Servo-i despite their overlapping T90 ranges. The Avea with VG managed to deliver a total V_T of 33.7 ± 0.02 mL versus 32.5 ± 0.02 mL when T90 was adjusted between its shortest and longest setting, a 3.7% drop; the Servo-i managed to deliver 34.8 ± 0.02 mL at its shortest T90 compared to 31.1 ± 0.03 mL at its longest T90, a 10.6% drop (Fig. 3).

Interestingly, the degree of change in chamber-specific V_T in response to prolonging T90 was also chamber-specific, with the long time constant chamber experiencing a greater decline in V_T compared to the short time constant chamber. This resulted in an increase in the proportion of V_T attributed to the short time constant chamber with increasing IRT. These changes occurred in all 3 ventilators. The Avea without VG was associated with the lowest ventilation balance due to its generally longer T90 range (ie, ventilation balance changed from 5.29 ± 0.04% to 3.95 ± 0.05% as T90 went from its shortest to its longest value). The ventilation balance for the Avea with VG went from 8.15 ± 0.02% to 7.11 ± 0.03% as T90 was prolonged. For the Servo-I, ventilation balance values went from 8.65 ± 0.03% to 5.29 ± 0.05% as T90 was prolonged through its range (Fig. 3).

Discussion

This study examines the effect of changing IRT in a dual-chamber model of a heterogeneous lung with significantly different time constants. IRT is used to modify the slope of a pressure controlled breath from a more square-shaped waveform to one that is more sine-shaped. Prolonging IRT using different ventilators consistently decreased peak inspiratory flow, mean inspiratory pressure, and lead to the delivery of smaller V_T, as expected. These results demonstrate that the reduction in V_T preferentially impacts the chamber with the longer time constant, which in turn improves ventilation balance.

These findings are in keeping with what would be predicted by the equations of gas motion and its derivatives: $P_{vent} = \dot{V} \times R + V \times E + PEEP$, where P_{vent} is the ventilator peak pressure, $\dot{V}$ is flow, R is resistance, V is volume, and E is elastance; and $\Delta V = C_{STAT} \times \Delta P \times \left(1 - e^{\left(-\frac{I_{Time}}{\tau}\right)}\right)$, where ΔV is delivered V_T, C_{STAT} is static compliance, ΔP is pressure differential applied over PEEP, e is Euler's number, I_{Time} is inspiratory time, and τ is the time constant. The larger V_T delivered at baseline in the long time constant chamber is due to its higher compliance compared to the short time



PIF	(L/min)	Intercept	Slope	(ms)
Avea Without VG	=	8.942	-0.012	T90
Avea With VG	=	14.784	-0.053	T90
Servo-i	=	12.98	-0.032	T90
	S	R^2	R^2 (adjusted)	
	0.0147	99.37%	99.37%	

$\bar{P}_{aw}$	(cm H_2O)	Intercept	Slope	(ms)
Avea Without VG	=	21.682	-0.026	T90
Avea With VG	=	21.088	-0.030	T90
Servo-i	=	19.715	-0.019	T90
	S	R^2	R^2 (adjusted)	
	0.098	99.54%	99.53%	

Fig. 2. A: Prolonging T90 decreases peak inspiratory flow (PIF) in all the ventilators tested. B: Prolonging T90 decreased mean inspiratory pressure ($\bar{P}_{aw}$) in all of the ventilators tested. T90 = time to 90% of plateau pressure.

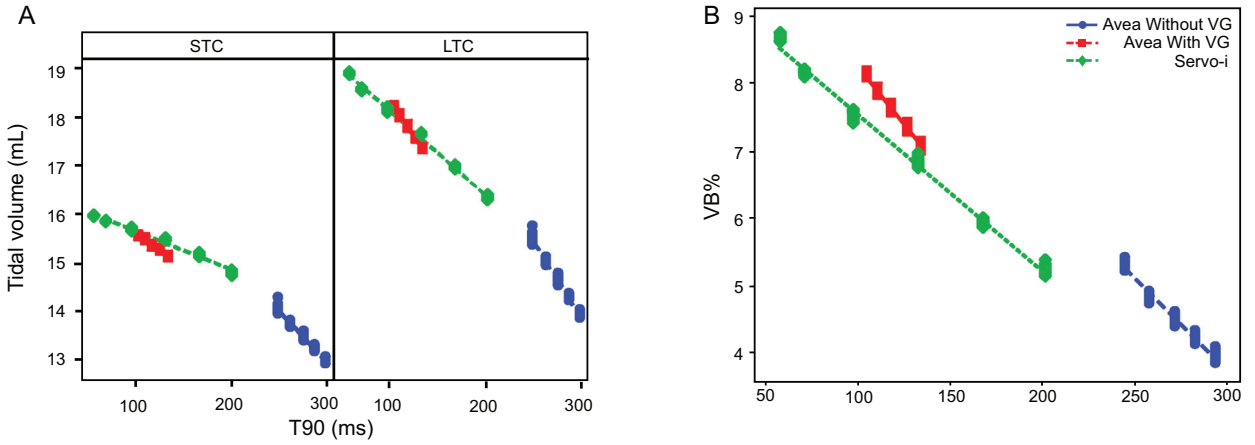
constant chamber. The changes observed in V_T delivery and balance as IRT is prolonged, can be explained by changes in effective inspiratory time to τ ratio at peak pressure, or alternatively by reductions in mean inspiratory pressure.

IRT is an often-neglected mechanical ventilator setting in the neonatal ICU unit, with its setup often relegated to either the default setting or to the whim of the individual setting up the ventilator, with little attention paid to the pulmonary disease process being supported. The adult literature suggests that IRT needs to be shortened to increase peak inspiratory flow in order to reduce air hunger and work of breathing in this patient group.[7,22,23] However, pulmonary mechanics of premature infants and term newborns are significantly different from those of adults. In spontaneously breathing premature and term newborns, peak inspiratory flow averages 5.7 L/min and 8.0 L/min, respectively.[24] These lower flows are related to the significantly lower V_T and shorter time constants of newborn lungs compared to those of adults.[25,26] Expert opinion on ventilating infants with BPD also suggests that these infants can be effectively supported with more sine-shaped pressure waveforms[27] and peak inspiratory flow of 5–10 L/min; these flows are much lower than what many modern ventilators generate at their shortest IRT.[3,8] While there is limited exploration of the impact of IRT in neonatal respiratory disease, animal models of neonatal ventilator-induced lung injury indicate that shortening the IRT through increasing the bias flow will lead to more pronounced lung injury.[28]

Unlike previous definitions of BPD in which fibrosis and a decrease in lung compliance are prominent features, the current concept of "new BPD" is that of a multifactorial, heterogeneous lung disease characterized by areas of alveolar septal loss with destruction of recoiling lung parenchyma and formation of airway lesions that increase airway resistance.[12,29-32] This heterogeneity of the disease within a single patient causes different segments of the lung to possess different time constants. This variation in time constants and the propensity of airway lesions to cause air trapping causes overinflation of more diseased lung segments at the expense of healthier lung segments within the chest cavity.

Our results indicate that different ventilator brands and software revisions affect the IRT range available, as demonstrated by the differences in the range of observed T90 values. This in turn affects the overall pressure and flow waveforms that the ventilator can generate. Furthermore, by comparing the 2 Avea ventilators with different software packages, we noted a significant difference in pressure waveforms, with one showing a more sine-wave shape while the other showing a mostly square-wave shape. This drastic change in pressure waveforms causes an increase in maximum peak inspiratory flow of $\sim$ 60% under the same pressure control settings with volume targeting turned off, despite the same equipment being used.

While this study demonstrates improved balance in ventilation by prolonging IRT, this improvement in distribution comes at the cost of decreased overall V_T



STC V_T	(mL)	Intercept	Slope	(ms)
Avea Without VG	=	19.266	-0.021	T90
Avea With VG	=	16.938	-0.014	T90
Servo-i	=	16.385	-0.008	T90

S	R^2	R^2 (adjusted)
0.038	99.83%	99.83%

LTC V_T	(mL)	Intercept	Slope	(ms)
Avea Without VG	=	23.305	-0.032	T90
Avea With VG	=	21.184	-0.029	T90
Servo-i	=	19.884	-0.017	T90

S	R^2	R^2 (adjusted)
0.045	99.92%	99.92%

VB	%	Intercept	Slope	(ms)
Avea Without VG	=	11.920	-0.027	T90
Avea With VG	=	11.666	-0.034	T90
Servo-i	=	9.899	-0.023	T90

S	R^2	R^2 (adjusted)
0.066	99.81%	99.81%

Fig. 3. A: Prolonging T90 decreases tidal volumes in both the short time constant (STC) and long time constant (LTC) chambers. B: Prolonging T90 decreases the difference in tidal volumes between both chambers as denoted by a decrease in ventilation balance (VB) percentage. T90 = time to 90% of plateau pressure; V_T = tidal volume.

delivery. Although this may be potentially helpful in reducing overinflation of diseased lung segments, the reduced peak inspiratory flow may be associated with increased work of breathing, and the reduction in V_T delivery may need to be compensated for by other means, either by balancing the inspiratory time, which could render any improvement in ventilation balance null, or by increasing the peak inspiratory pressure manually or through volume-targeting schemes. More importantly, this examination of various ventilators demonstrates the need for practitioners to be familiar with the features and limitations of various machines in clinical use.

The strengths of this study are the proof of concept for how changing IRT impacts ventilation balance in heterogeneous pulmonary disorders using a number of different ventilators, the high degree of reproducibility and precision allowed by a lung simulator, and the use of published human data to build the model of our test lungs. The lack of published regional ventilation measurements for validation in human neonates with BPD is a limitation of the model used. Furthermore, human lungs are confined to a limited space within the thoracic cavity, causing lung segments to be interdependent. This interdependence of lung segments cannot be reproduced by a lung simulator, which means our model likely underestimates the impact of an overinflated lung segment on neighboring structures. Furthermore, while the differences in observed ventilation balance are relatively small in this study, this reflects the somewhat moderate differences in compliance and resistance chosen. Another limitation of using such a high-fidelity lung simulator is that only 2 extremes can be examined at the same time. This contrasts with the biological intermediates that will occur in nature.

Conclusions

We therefore conclude that prolonging IRT improves ventilation balance at the expense of total delivered V_T. Further study in a clinical setting is needed to ascertain the clinical impact of this conclusion, with additional consideration for V_T balancing measures such as adjusting inspiratory time and peak pressures, either manually or through volume-targeting control schemes.

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