

A Numerical Analysis of Mechanical Ventilation in Newborns

Ira Katz^{1,2*}, Jean-Etienne Bazin³, Sherwin Morgan⁴, Georges Caillibotte⁵

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¹Medical R&D, Air Liquide Santé International, Paris Innovation Campus, France

²Department of Mechanical Engineering, Lafayette College, Easton, USA

³Université Clermont Auvergne, CHU Clermont-Ferrand, Pôle de médecine Périopératoire, Clermont-Ferrand, France

⁴Respiratory Care Services - Pulmonary and Critical Care Medicine; University of Chicago Medicine, Chicago, IL, USA

⁵Healthcare World Business Line, Air Liquide Santé International, Paris Innovation Campus, France

***Corresponding author:** Ira Katz, Medical R&D-ALSI, Paris Innovation Campus, 1 chemin de la Porte des Loges, Les Loges-en-Josas, B.P. 126, 78354 Jouy-en-Josas Cedex, France, Tel: 33 7 72 11 27 93; Email: ira.katz@airliquide.com

Abstract

Background: Mechanical ventilation can be lifesaving procedure but has also been associated with lung injury. In order to better understand the application mechanical ventilation to newborns a numerical study has been performed based on a physiological/physical model. The model consists of the time integration of a quasi-static engineering pressure loss approach to simulate dynamic respiratory parameters during pressure control mode mechanical ventilation. The effects of pressure target, inhalation:exhalation ratio, lung compliance, and endotracheal tube (ETT) size on peak inspiratory and expiratory flow rates, tidal volume and tidal volume retained at the end of exhalation are determined. Also simulations of an ETT obstruction and a comparison of pressure to volume control mode are performed. In an appendix *in vivo* measurements and the results of a numerical analysis of the effects of fluid property variation on dynamic ventilation parameters in pressure control mode during xenon anesthesia are compared, thus providing a validation of the numerical method. The *in vivo* measurements were taken prior to surgery during the wash-in phase of xenon anesthesia in adults. This *in silico* study provides quantitative insight to mechanical ventilation of newborns, a vulnerable patient group where *in vivo* data are often difficult to obtain.

Keywords: Lung morphology; Numerical modeling; Mechanical ventilation; Ventilator; Neonate; Pressure control mode

Abbreviations: NCLD: Neonatal chronic lung disease; BPD: Bronchopulmonary Dysplasia; ETT: Endotracheal

tube; PEEP: Positive end expiratory pressure; CFD: Computational Fluid Dynamics

Introduction

Mechanical ventilation to alleviate the work of breathing or for controlled respiration during anesthesia has been widely used for several decades. In spite of this experience, ventilator design and management can still be challenging and inappropriate ventilation can result in injury to the lungs or respiratory muscles and worsen morbidity and mortality. For intubated patients the challenges include delivering lung-protective ventilation to prevent ventilator-induced lung injury, maintaining adequate gas exchange in severely hypoxaemic patients, avoiding the development of ventilator-induced diaphragm dysfunction, and diagnosing and treating the many pathophysiological mechanisms that impair liberation from mechanical ventilation [1]. The challenges of mechanical ventilation are heightened when treating newborns [2-7]. Early lung injury in the neonatal lung is often provoked due to the immature morphology, inducing defective alveolar septation, impaired angiogenesis and pathologic extracellular matrix remodeling resulting in lung growth impairment. In the long term, these changes result in neonatal chronic lung disease (nCLD), also known as Bronchopulmonary Dysplasia (BPD), frequently complicating the course of preterm or risk term birth. nCLD is one of the most common chronic lung diseases in children, whose incidence is reported to be as high as 77% in neonates born at less than 32 weeks of gestation.

The fundamental mechanisms of injury are complex [8] and follow as a consequence of the physical interaction of gases and the solid but deformable surfaces of the respiratory tract, including the very thin membranes in the alveoli where gas exchange occurs. From the clinicians' point of view, the inputs are the ventilator parameters that must be controlled or monitored to ensure adequate respiration consistent with maintaining lung safety while dealing with major difficulties associated with an unknown complicated morphology and intersubject variability. The use of *in silico*, numerical biomechanics models that consider the fluid mechanics and morphology can add insight through their ability to perform perfectly controlled and parameterized experiments, and to provide more complete ways to view the resulting data; for example, the pressure distribution from the breathing circuit through the endotracheal tube (ETT) into the respiratory tract to the alveoli. Numerical modeling can especially be helpful to understand the mechanical ventilation of neonates because *in vivo* data are difficult to obtain in this vulnerable population (e.g., see Ethical Considerations for Clinical Trials On Medicinal Products

Conducted with The Paediatric Population from the European Medical Agency [9]).

Results from parameterized numerical experiments are presented in this paper based on an engineering pressure loss model [10-12] specifically extrapolated to account for the morphology and breathing characteristics of newborns. Variables considered include ETT size, lung compliance, respiratory rate, pressure control mode target, inspiratory:expiratory ratio, ETT obstruction, all during pressure control mode, the traditionally recommended ventilator mode used for neonates [4]. A comparison between pressure and volume control ventilation modes for a control case is also performed. An appendix provides comparisons of the model to measurements in adults from mechanical ventilation in pressure control mode, thus providing a validation of the numerical method.

Methods

Numerical Model

The numerical model is described in detail in a previous paper [11]. Briefly, a quasi-steady mechanical energy balance on flow and the pressure at any location in the respiratory tract compared to the alveolar pressure is

$$p - p_{alv} = \rho \sum h - \rho \left(\alpha \frac{V^2}{2} \right), \quad (1)$$

where p and V are the pressure and average velocity at each location, ρ is the gas density, and α is a coefficient that modifies the kinetic energy term to account for different flow profiles: $\alpha=1$ for a blunt (turbulent) velocity profile and $\alpha=2$ for a parabolic (laminar) profile. The summation on the right-hand-side of Equation 1 is called the head loss, which represents the sum of all the resistive energy losses per unit mass in the flow path.

In this typical engineering approach, the head losses in all of the straight flow conduits are called "major," and a summation of all the components that change the velocity distribution (acceleration or deceleration of fluid particles), are called "minor." The minor loss occurs in laminar as well as turbulent flow. The summation of head losses is

$$\sum h = \sum_{major} f \frac{L}{D} \frac{V^2}{2} + \sum_{minor} K \frac{V^2}{2}, \quad (2)$$

Where f is called the friction factor for each straight conduit of length L and diameter D , and K is a minor loss coefficient for each component (e.g., the bifurcations in the respiratory tract). For laminar fully developed flow f is analytically determined as

$$f = \frac{64}{Re}, \quad (3)$$

Where Re is the Reynolds number based on D and the density and viscosity of the fluid, ρ and μ , respectively,

$$Re = \frac{\rho VD}{\mu}. \quad (4)$$

After substituting Equations 2-4 into Equation 1 it can be shown that the major loss is independent of density for laminar flow. For turbulent pipe flow f has historically been determined empirically. For smooth tubes the correlation derived by Blasius can be used:

$$f = \frac{0.316}{Re^{0.25}} \quad (5)$$

The criterion used herein for differentiating laminar and turbulent flow was $Re \geq 2000$. The minor loss coefficients representing the effects of airway bifurcations were previously calculated based on computational fluid dynamics (CFD) simulations for inhalation and exhalation. [11]. The minor loss coefficients were calculated on the bases of the local Reynolds number of the flow entering the bifurcation. Thus, the use of CFD provided an estimate of the complex flow fields within the respiratory tract. In the present work the patient interface is broken into two components, the filter and the ETT, and their minor loss coefficients were determined through bench top experiments [10]. Equation 1 was solved over a range of flow rates, for both inhalation and exhalation, and for each gas and ETT combination before fitting to equations of the form

$$\Delta p_{lung} = A Q^2 + B Q. \quad (6)$$

For exhalation it is also necessary to calculate the pressure losses from the Y-piece of the breathing circuit through the ventilator, including the valve to produce positive end expiratory pressure (PEEP). An empirical relationship, excluding PEEP, based on major and minor losses was employed based on the adult ventilator used to obtain the clinical measurements (see Appendix).

$$\Delta p_{vent} = A \rho Q^2 + B \mu Q \quad (7)$$

For pressure in units of N/m^2 , Q in l/min , ρ in kg/m^3 , μ in $kg/s \cdot m (\times 10^5)$, $A=0.25$ and $B=1$. To account for PEEP the recorded value was simply added to the calculated pressure values. Property values at 1 atm and $37^\circ C$ for an enriched nitrogen-oxygen mixture of 50%/50% N_2/O_2 were used in the simulations (density of 1.179 kg/m^3 and viscosity of $1.961 \times 10^{-5} \text{ kg/s.m}$).

Neonate Morphology Model

There is very little neonate morphological data (e.g., airway dimensions) in the literature. For the analysis performed herein we adopted the morphology model previously used to study unsteady surfactant-laden liquid plug propagation in neonatal airways [13]. Based on the Weibel representation of the lung as a symmetric dichotomous tree, [14] the neonate model assumes that the trachea has the same dimensions as the 7th generation of the adult model and continues the adult sub-tree to its conclusion at generation 23 resulting in a neonate model from generations 0-16. Furthermore, the minor loss coefficients for each of the generations for the adult model are used for the neonate model. As the adult model assumes no minor losses in the pulmonary region (below generation 16) minor losses are assumed to be negligible after generation 9 in the neonate model. The dimensions of the neonate morphology model are given in Table 1.

Generation	Diameter (mm)	Length (mm)
0-Trachea	3.57	23.81
1	2.83	18.90
2	2.25	15.00
3	1.78	11.91
4	1.42	9.45
5	1.12	7.50
6	0.89	5.95
7	0.71	4.72
8	0.56	3.75
9	0.45	2.98
10	0.35	2.36
11	0.28	1.88
12	0.22	1.49
13	0.18	1.18
14	0.14	0.94
15	0.11	0.74
16	0.09	0.59

Table 1: Neonate morphology model dimensions.

Numerical Integration

For inhalation, equation 6 was evaluated in time using Excel (Microsoft, USA). At each new time step (2000 steps per ventilation cycle) the alveolar pressure was calculated based on the compliance and volume at the previous time step. With the boundary condition of applied pressure at the ventilator Y-Piece, equation 6 can be solved for Q . Similarly, for exhalation at each new time step equation 6, with the outflow pressure at the ventilator determined using equation 7, is solved for Q based on the alveolar pressure calculated using the lung compliance and lung volume from the previous time step.

Numerical Experiments

The parametric variables considered were respiratory rate (RR), pressure target during pressure control mode ventilation, ratio of inhalation/exhalation time, lung compliance, and ETT diameter. The numerical test cases are listed in Table 2, where the control case is specifically identified. The PEEP for all of the cases is 5 cm H₂O. The rise time for the pressure to reach the target was chosen as 0.25 s. The output variables used to compare the different cases are defined in the schematics based on an adult case shown in Figure 1 and listed on Table 2. The example of an obstruction in the ETT was based on a numerical representation of the Rp50 resistor [15] which is the smallest resistance value provided for use with an infant test lung (Michigan Instruments, USA) [16].

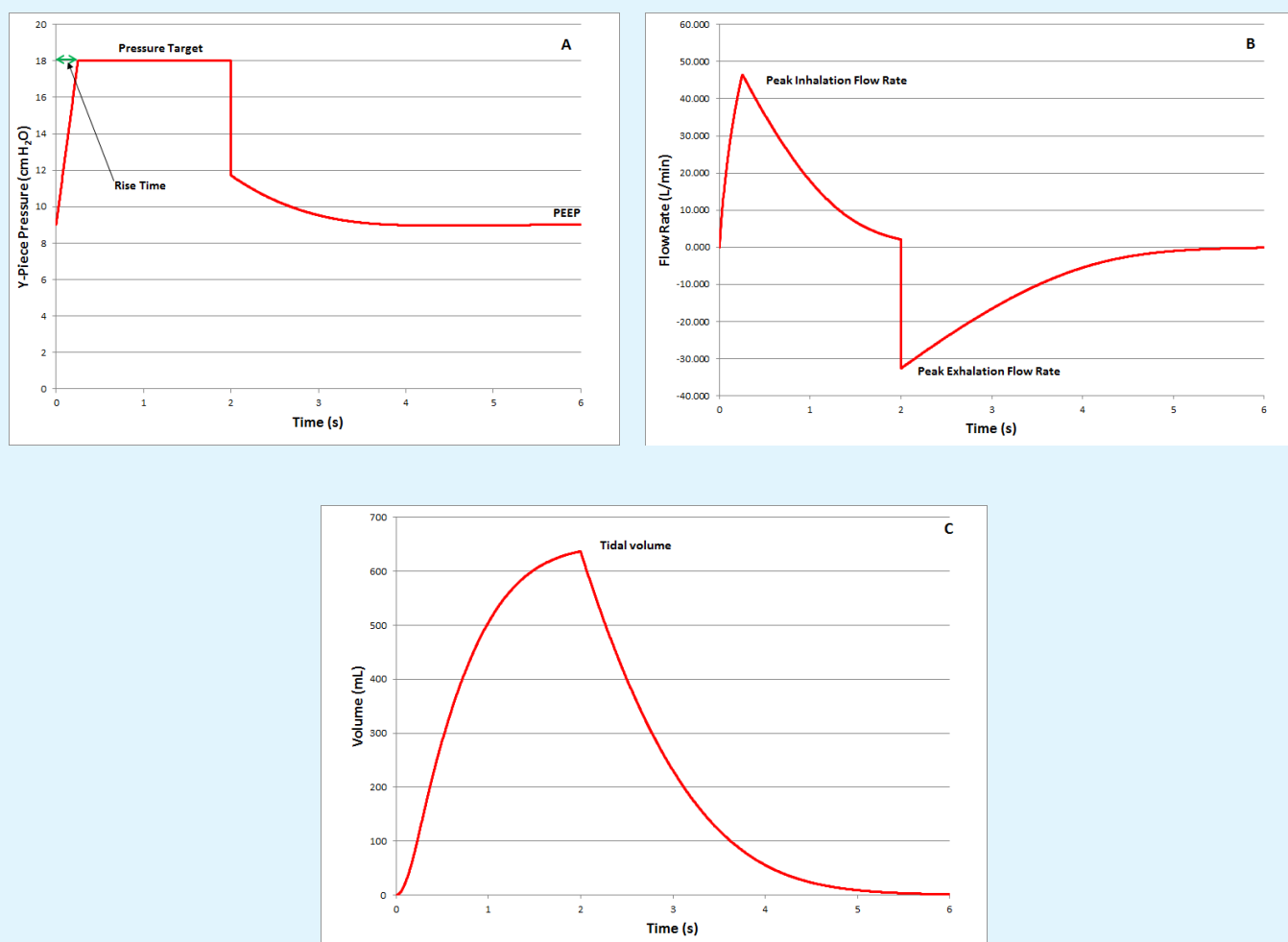


Figure 1: Pressure Control Mode patterns based on an adult case for Y-piece pressure (A), flow rate (B) and volume (C) as would be seen on a ventilator control screen. Input and output variables used in the simulations also are defined on the graphs. The rise time was fixed at 0.25 s for all of the simulations.

Variable Modified	RR (bpm)	Pressure Target (cmH2O)	Inhalation: Exhalation ratio	Lung Compliance (ml/cmH2O)	ETT Size (mm)	Peak Inspiratory Flow (l/min)	Peak Expiratory Flow (l/min)	Tidal Volume (ml)	Tidal Volume Retained (ml)
RR	20	15	1:1	3	3	4.0	6.6	29.8	0.01
Control	30	15	1:1	3	3	4.0	6.4	28.5	0.19
RR	40	15	1:1	3	3	4.0	6.0	26.3	0.67
RR	50	15	1:1	3	3	4.0	5.6	23.8	1.32
Pressure	30	10	1:1	3	3	2.1	3.7	14.3	0.07
Pressure	30	20	1:1	3	3	5.8	8.5	42.6	0.35
Ratio	30	15	1:2	3	3	4.0	5.8	25.1	0.02
Compliance	30	15	1:1	2	3	3.4	6.6	19.8	0.01
Compliance	30	15	1:1	4	3	4.3	6.1	35.7	0.91
Compliance	30	15	1:1	6	3	4.7	5.4	46.0	4.33
ETT	30	15	1:1	3	2.5	3.3	5.1	27.8	0.31
ETT	30	15	1:1	3	3.5	4.5	7.5	29.2	0.07
ETT	30	15	1:1	3	4	5.0	8.4	29.5	0.03
Obstruction	30	15	1:1	3	3	1.0	0.9	13.5	3.01
Vol Control Mode	30	NA	1:1	3	3	1.7*	6.4	28.5**	0.00

Table 2: Test cases and results. The shaded case represents the control for the parametric numerical experiments.

*Constant inhalation flow rate, **Volume target chosen to match the PC mode control case.

Results

The results of the parametric study are given in Table 2. The characteristics of pressure control mode ventilation can be observed in Figure 1. First, a rise in pressure occurs, during a rise time, to a pressure target that is maintained until the exhalation period begins. Exhalation is passive, as flow is driven by the elasticity of the lungs through the breathing circuit to eventually reach ambient pressure, though an elevated PEEP pressure can be maintained by the ventilator. Two quantitative values that characterize the ventilation are the peak inhalation and exhalation flow rates. Another important characteristic of the ventilation is the tidal volume inhaled and the extent of exhalation, specifically recorded as the retained tidal volume.

The effect of increase in RR, a reduction in the time for inhalation and exhalation, is to reduce tidal volume and increase the retained tidal volume at the end of exhalation. Increasing the pressure target increases tidal volume and flow rates. There are negligible differences in flow rates, tidal volume, or tidal volume retained between the control case with a 1:1 ratio and a 1:2 ratio. The important effect due to lung compliance is to reduce the tidal volume when using the same pressure target in

pressure control mode. Furthermore, for very compliant lungs the tidal volume retained becomes significant. Decreasing ETT diameter increases airway resistance. The result can be seen in the reduced magnitude of peak flow rates. The increased resistance could become problematic if for other reasons ventilation or oxygenation is restricted, such as the obstruction considered next. For the Rp50 ETT obstruction modeled there is a major reduction in peak flow rates and the tidal volume, while there is a tremendous volume retained. This level of obstruction would certainly require corrective action. A comparison of pressure control mode to the equivalent volume control mode; i.e., that results in the same tidal volume, indicates that the peak inhalation flow rate is almost three times greater. Exhalation is essentially the same in both cases. The pressure distribution curves shown in Figure 2 from the ETT through the respiratory tract indicate that almost half of the drop occurs in the ETT for both ventilation modes. Figure 3 provides similar Re distribution curves. In the ETT Re almost reaches 1500 for peak inhalation flow in pressure control mode. This is below the critical value for the onset of turbulence in straight tubes, and by further investigation in the literature specifically for ETTs, [17] turbulence is not expected for clean tubes.

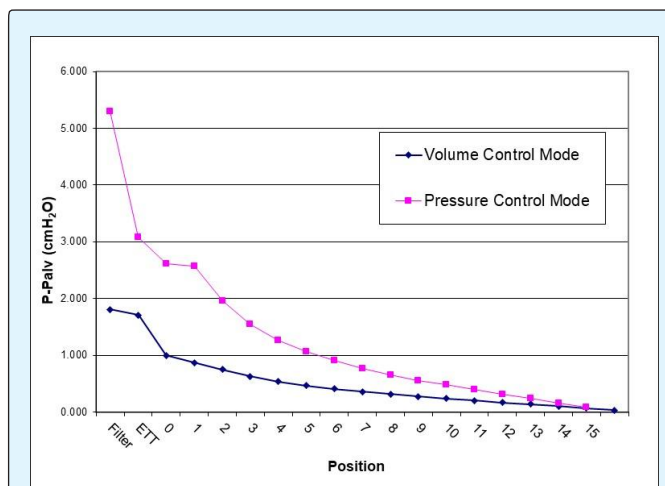


Figure 2: A comparison of the pressure distributions through the respiratory tract during pressure and ventilation control modes. The pressure control mode curve only occurs at the peak inhalation flow rate.

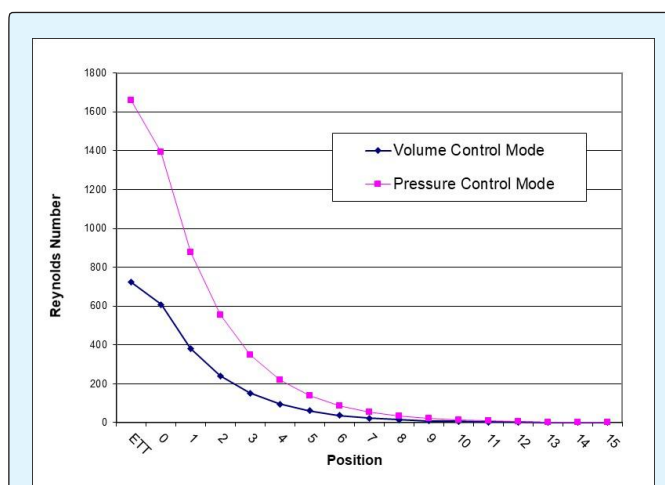


Figure 3: Comparison of Reynolds number through the respiratory tract comparing pressure and ventilation control modes. The pressure control mode curve only occurs at the peak inhalation flow rate.

Discussion

In this paper a numerical engineering pressure loss model has been used with a neonate lung morphology model to analyze mechanical ventilation in newborns. The development of such a model, simple to implement in Excel, with the ability to change parameters including properties for the inhaled gas, provides a tool for easier understanding of potential hazards; especially for

researchers in the development phase of new gas therapies. For example, if the use of xenon anaesthesia were ever extended to newborns this model could be easily adapted to provide insight before actually administering the gas.

In terms of accuracy, calculations of airway resistance, including the endotracheal tube, for the control case is 50.5 to 78.6 cm H₂O/L/s for 0.3 to 5 L/min, respectively. This range of values compares well to a published range of 50-150 cmH₂O/L/s for a normal 3 kg infant [2].

In a previous paper the engineering pressure loss model was compared to *in vivo* data during mechanical ventilation in volume control mode in adult patients [18]. In an appendix model results are compared to *in vivo* data specifically to assess its capabilities to account for the dynamics of the respiratory cycle during mechanical ventilation in pressure control mode. The direct comparisons of model and experimental time histories of Y-piece pressure and flow rate indicate that with knowledge of the gas composition, ETT size, and lung compliance the dynamic ventilatory parameters can be predicted.

The safety concerns related to mechanical ventilation can be organized into two broad categories, 1) lung injury and 2) adequate respiration. Regarding 1) lung injury, a detailed discussion of the anatomical and physiologic causes is beyond the scope of this paper, but the reader is directed to a reference that addresses the concept of lung stress/strain as applied to the whole lung or specific pulmonary regions in context of mechanical ventilation [19]. The current paper has presented data expressed by parameters such as flow rate, pressure, and volume that are intended to guide researchers and clinicians specifically for the difficult cases of newborns by providing parametric results covering several variables. It is noted that pressure control mode can normally avoid barotraumas by limiting the alveolar pressure. However, the higher peak inhalation flow rate compared to volume control mode could pose problems because the strain rate due to high inspiratory flow has also been shown to cause lung injury in piglets [20] while a reduction of inspiratory flow has been shown to provide lung protection in sheep [21]. Regarding 2) adequate respiration, a key factor is to obtain adequate tidal volume. Variables such as RR, lung compliance, and the ETT size can affect the tidal volume, but of the simulations performed in this study, the development of an obstruction in the ETT would pose the greatest challenge to providing adequate tidal volume and respiration. Occlusion is a recognized hazard of prolonged endotracheal intubation resulting from deposition of

secretions on the inner surface of the ETT. When volume-controlled ventilation is used, progressive ETT occlusion may be detected by monitoring the difference between peak and plateau airway pressures. In pressure-controlled modes, however, inspiratory airway pressures are preset and thus cannot act as a warning indicator. Instead, changes in delivered tidal volumes may aid in the identification of ETT occlusion [22]. Furthermore, the high tidal volume retained would eventually result in a less compliant lung. With a partial occlusion it is much more likely that turbulent flow would occur in the ETT that would be convected downstream, thus also affecting airway resistance in the lung.

There are several limitations to this study. There exists very limited morphological data for neonate lungs in the literature. Thus, the morphology model is somewhat speculative. The lung morphology is considered to be perfectly rigid, an assumption that is shown to cause errors as lung compliance increases (see appendix), so it is expected that peak inhalation flow rates calculated in this study are higher than would be seen on the ventilator. The ventilator model utilized is based on the adult experiments described in the appendix. The exhalation pressure drop, rise time, and general ventilator performance will depend on the make and model. The parametric study has considered a representative range of parameters but not all possible combinations. The Rp50 resistance modeled for the obstruction is a purely inertial resistance such that pressure drop increases with the square of flow rate (thus termed a parabolic resistance) and proportionally to the density. Obstructions might also occur that in effect reduce the lumen of the ETT, resulting in increased pressure loss proportional to the flow rate and the viscosity. The response to a linear resistance increase can be inferred from the results on the smaller caliber ETTs.

In conclusion, this paper has presented a numerical study of mechanical ventilation in newborns with the goal of providing insight to this potentially dangerous clinical procedure in a vulnerable patient group where *in vivo* data are difficult to obtain. In addition, results of the adult version of the model are compared with data from downloaded ventilator data of the administration of xenon anesthesia.

Competing Interests

The authors have no competing interests to declare.

Data Availability

The data presented in this study is available from the corresponding author upon request.

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