

The Impact of Imposed Expiratory Resistance in Neonatal Mechanical Ventilation: A Laboratory Evaluation

Robert M DiBlasi RRT-NPS, John W Salyer MBA RRT FAARC, Jay C Zignego, Gregory J Redding MD, and C Peter Richardson PhD

BACKGROUND: Small endotracheal tubes (ETTs) and neonatal ventilators can impact gas exchange, work of breathing, and lung-mechanics measurements in infants, by increasing the expiratory resistance (R_E) to gas flow. **METHODS:** We tested two each of the Babylog 8000plus, Avea, Carestation, and Servo-i ventilators. In the first phase of the study we evaluated (1) the imposed R_E of an ETT and ventilator system during simulated passive breathing at various tidal volume (V_T), positive end-expiratory pressure (PEEP), and frequency settings, and (2) the intrinsic PEEP at various ventilator settings. In the second phase of this study we evaluated the imposed expiratory work of breathing (WOB) of the ETT and ventilator system at various PEEP levels during simulated spontaneous breathing using an infant lung model. Pressure and flow were measured continuously, and we calculated the imposed R_E of the ETT and each ventilator, and the intrinsic PEEP with various PEEP, V_T , and frequency settings. We measured the imposed expiratory WOB with several PEEP levels during a simulated spontaneous breathing pattern. **RESULTS:** The ventilator's contribution to the imposed R_E was greater than that of the ETT with nearly all of the ventilators tested. There were significant differences in ventilator-imposed R_E between the ventilator brands at various PEEP, V_T , and frequency settings. The Babylog 8000plus consistently had the lowest ventilator-imposed R_E in the majority of the test conditions. There was no intrinsic PEEP (> 1 cm H₂O) in any of the test conditions with any ventilator brand. There were also no significant differences in the imposed expiratory WOB between ventilator brands during simulated spontaneous breathing. **CONCLUSIONS:** The major cause of R_E appears to be the ventilator exhalation valve. Neonatal ventilators that use a set constant flow during inhalation and exhalation appear to have less R_E than ventilators that use a variable bias flow during exhalation. Clinical studies are needed to determine whether the imposed R_E of these ventilator designs impacts gas exchange, lung mechanics, or ventilator weaning. *Key words:* airway resistance, respiratory mechanics, work of breathing, positive end-expiratory pressure, PEEP, neonatal intensive care. [Respir Care 2008;53(11):1450–1460. © 2008 Daedalus Enterprises]

Introduction

Elevated resistance of the respiratory system has been implicated as a source of higher risk for the development

of chronic lung disease in premature infants with respiratory distress syndrome (RDS).¹ Premature infants are at higher risk for gas trapping because of the use of high conventional ventilation frequencies and the potential for acute changes in the expiratory time constant of the lung following surfactant-replacement therapy.

Robert M DiBlasi RRT-NPS and John W Salyer MBA RRT FAARC are affiliated with the Respiratory Care Department, Children's Hospital and Regional Medical Center, Seattle, Washington. Robert M DiBlasi RRT-NPS, Jay C Zignego, Gregory J Redding MD, and C Peter Richardson PhD are affiliated with the Center for Developmental Therapeutics, Seattle Children's Hospital Research Institute, Seattle, Washington. Gregory J Redding MD and C Peter Richardson PhD are also affiliated with the School of Medicine, University of Washington, Seattle, Washington.

SEE THE RELATED EDITORIAL ON PAGE 1432

The total respiratory-system expiratory resistance (R_E) during infant mechanical ventilation is impacted by multiple factors, including airway diameter, respiratory mus-

cle activity, gas flow, positive end-expiratory pressure (PEEP), the endotracheal tube (ETT), and the type of ventilator.² Ventilator-imposed R_E limits gas flow during exhalation and is due primarily to the exhalation valve.³

Additive resistance due to the ventilator system, and consequent airflow limitation, can contribute to the resistive load on the patient's respiratory system during exhalation, especially when a preexisting obstructive lung disorder is present.^{4,5} Imposed resistance through any or all of the airways can produce alveolar hyperinflation, uneven regional ventilation, and excessive respiratory-muscle loading that increases work of breathing (WOB), disturbs gas exchange, and prevents ventilator weaning.⁶⁻¹¹

In healthy infants, exhalation is usually passive. However, active exhalation is a common manifestation of a reflex that is present in spontaneously breathing infants with low lung compliance¹² and is associated with increased risk of pneumothorax in ventilated infants.¹³ Imposed resistance within the expiratory path of mechanically ventilated infants is important, especially during the weaning phase, when the patient participates actively in the WOB.¹⁴

Yoder et al found that lung mechanics and gas exchange were affected differently by 2 different brands of neonatal ventilators in preterm baboons with RDS.² In vitro studies of neonatal ventilator exhalation valves found that different designs can result in differences in the mechanical expiratory WOB related to ventilator-imposed R_E .¹⁵⁻¹⁶ There are important R_E differences between different ventilator exhalation valves, which can influence expiratory effort in patients with marked ventilatory demand and/or a short expiratory time (T_E).

One conventional view is that the ETT is the largest contributor to the overall imposed R_E and WOB¹⁷⁻¹⁹ and may therefore impede weaning and contribute to the development of chronic lung disease in the neonate.²⁰ Usually only modest consideration is given to the R_E imposed by the ventilator, and, to our knowledge, concurrent comparison of the ventilator system and the ETT in regard to their overall contribution to the total imposed R_E has not been performed. Furthermore, no investigations of currently available neonatal ventilators have focused on the amount of intrinsic PEEP (PEEPi) and imposed expiratory

WOB caused by the resistive properties of the ETTs, proximal flow sensors, and ventilator exhalation valves.

We hypothesized that there would be no differences in (1) the R_E imposed by the ETT and the ventilator, (2) the ventilator-imposed R_E at various settings and between ventilator brands, (3) the level of PEEPi with higher conventional ventilation frequencies, and (4) the imposed expiratory WOB relative to the ETT and the type of ventilator system used during spontaneous breathing. We tested these hypotheses by conducting in vitro experiments with 2 each of 4 commonly used ventilator designs and a lung model of RDS to simulate the ventilation of an extremely-low-birth-weight infant.

Methods

Lung Model

We modeled lung mechanics with a neonatal test lung (ASL5000, Ingmar Medical, Pittsburgh, Pennsylvania), which has a screw-drive-controlled piston and uses a mathematical model of the equation of motion of the human lung to simulate disease-specific pulmonary mechanics. The inspiratory and expiratory resistances can be set independently. In the first phase of the study we configured the test lung to represent the pulmonary mechanics of an extremely-low-birth-weight infant with RDS: lung compliance 0.5 mL/cm H₂O, inspiratory resistance 100 cm H₂O/L/s, R_E 130 cm H₂O/L/s.²¹

In the second phase of the study we configured the test lung to evaluate the imposed expiratory WOB during spontaneous breathing (active inhalation and exhalation efforts) with a sinusoidal flow profile at a frequency of 50 breaths/min and a V_T of 5 mL.

Ventilators and Settings

Mechanical ventilation was provided with 8 ventilators: 2 Babylog 8000plus (with software version 5.01, Dräger Medical, Lubeck, Germany), 2 Avea (with software version 3.75, Cardinal/Viasys Healthcare, Yorba Linda, California), 2 Carestation (with software version 4.25, GE Healthcare, Madison, Wisconsin), and 2 Servo-i (with software version 3.01.02, Maquet, Bridgewater, New Jersey).

The Babylog 8000plus is a time-cycled, pressure-limited, constant-flow, microprocessor-controlled ventilator that is specifically designed for use with infants. Flow from the expiratory limb of the patient circuit is controlled by a solenoid-regulated pneumatically powered valve diaphragm. Though the Babylog 8000plus allows the clinician to set separate flow rates during inhalation and exhalation, with the "VIVE" (variable inspiratory, variable expiratory) function, we chose the constant-flow setting, which is commonly used clinically. The constant flow rate

Ventilators and technical support for this study were provided by Maquet, GE Healthcare, Dräger, and Cardinal/Viasys. The authors report no other conflicts of interest related to the content of this paper.

Correspondence: Robert M DiBlasi RRT-NPS, Seattle Children's Hospital Research Institute, Center for Developmental Therapeutics, 1900 Ninth Avenue, Seattle WA 98101. E-mail: robert.dibiasi@seattlechildrens.org.

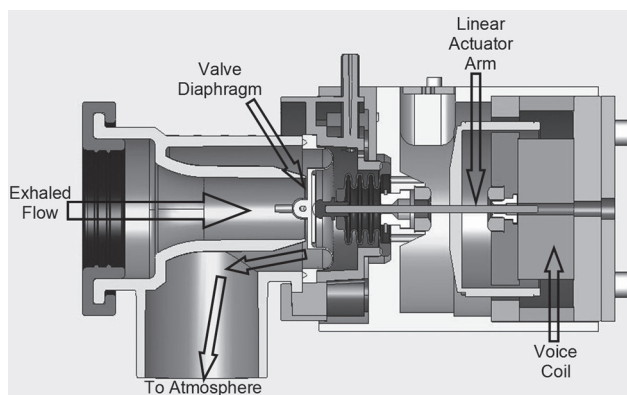


Fig. 1. Voice-coil activated exhalation valve system. (Courtesy of Cardinal/Viasys.)

is set by the operator and provides inspiratory pressure as the valve closes and baseline pressure when the valve cycles to exhalation. A constant flow rate beyond what is necessary to maintain that pressure during the inspiratory phase exits the system through the exhalation valve. An injector valve (reverse Venturi) built into the exhalation valve block produces a negative pressure that is supposed to prevent inadvertent PEEP caused by continuous gas flow during exhalation through the expiratory limb.²²

The Avea, Servo-i, and Carestation are designed for use with infant through adult patients. Gas flow through the expiratory limb is regulated by an electromagnetically powered (proportional solenoid-voice coil) valve diaphragm (Fig. 1). The voice coil activates a linear actuator arm that applies intermittent electromagnetic force to the back side of the exhalation-valve diaphragm. The microprocessor rapidly servo-controls the valve position based on breath phase and pressure measurements from a pressure transducer. Rather than using a constant flow, these ventilators use a variable (or dynamic) gas flow rate, known as bias flow. Bias flow is applied only during exhalation and is primarily intended to provide gas flow for triggering during inhalation; however, when exhaled V_T is small, it can also be beneficial in maintaining PEEP in the ventilator system. During inhalation, the voice coil applies force to the exhalation-valve diaphragm to completely block the outflow of gas and achieve the targeted inspiratory pressure. When the ventilator cycles to exhalation, the valve opens completely and flow from the control valve is zero. Once a minimum T_E has elapsed (approximately 150 ms of exhalation), the flow-control valve restores bias flow back into the circuit and the voice coil's linear actuator arm applies force to the exhalation-valve diaphragm to achieve the set PEEP. If pressure in the circuit exceeds the force applied on the control side of the diaphragm, the exhalation valve opens and excess gas is vented to the atmosphere.²²

Initially, the ventilators were set to deliver baseline settings in adaptive pressure controlled modes (volume-guarantee on the Baby Log 8000plus, machine volume on the Avea, pressure-regulated volume control on the Servo-i, and pressure-control/volume-guarantee on the Carestation) with a frequency of 50 breaths/min, V_T of 5 mL, inspiratory time of 0.25 s, PEEP of 5 cm H_2O , and fraction of inspired oxygen (F_{IO_2}) of 1.0. With the Babylog 8000plus we set a continuous flow of 5 L/min. With the other ventilators we set a bias flow default setting of 0.5–2 L/min.

The Avea can also be used in a continuous-flow mode. However, we did not measure ventilator-imposed R_E in this mode because we were only interested in making measurements with adaptive pressure controlled ventilation, and continuous flow is only available in conventional pressure control on the Avea. Though various inspiratory time settings could have been used, we chose this setting for these tests because it is equivalent to 5 inspiratory time constants of our lung model, satisfies an inspiratory-expiratory ratio of < 1:1 in all of the frequencies tested, and is commonly used with neonatal patients.

Each ventilator was connected to the test lung via a neonatal, disposable, corrugated, heated-wire circuit (Cardinal Health, Dublin, Ohio) and a standard 2.5-mm inner-diameter neonatal ETT (Portex, Smiths Medical, Southington, Connecticut) (Fig. 2). The gas was heated to 37°C with a heater/humidifier (850 series, Fisher Paykel, Auckland, New Zealand). All ventilators were configured to measure delivered V_T with a body-temperature-and-pressure-saturated correction factor. Each of the ventilators has a proprietary proximal flow sensor that is placed between the ventilator circuit Y-piece and the ETT.

After a temperature stabilization period of 20 min and a leak test, the ventilator and ETT were attached to the infant lung model. The V_T setting was adjusted on the ventilator, and delivered V_T was confirmed by independently verified expiratory volume measurements obtained with a separate research pneumotachometer. This method was necessary to measure resistance in all the ventilators tested at comparable exhaled V_T .

Experiments were conducted under 3 sets of conditions. In each series, one of the ventilator settings was varied over a range of values while the other 2 ventilator settings were held constant. The settings were: PEEP of 0, 4, 8, and 12 cm H_2O , V_T of 3, 5, 7, 9, and 12 mL, and frequency of 20, 40, 60, 80, and 100 breaths/min. We recorded data from 20 consecutive breaths at each ventilator setting. The system was evaluated periodically for signs of condensation in the ETT and expiratory limb, and visual accumulate was eliminated.

Each ventilator was then set to the pressure-support mode (pressure support 5 cm H_2O , PEEP 5 cm H_2O , cycling at 15% of the inspiratory peak flow, and F_{IO_2} 1.0), and the lung model was configured to breathe spontaneously while

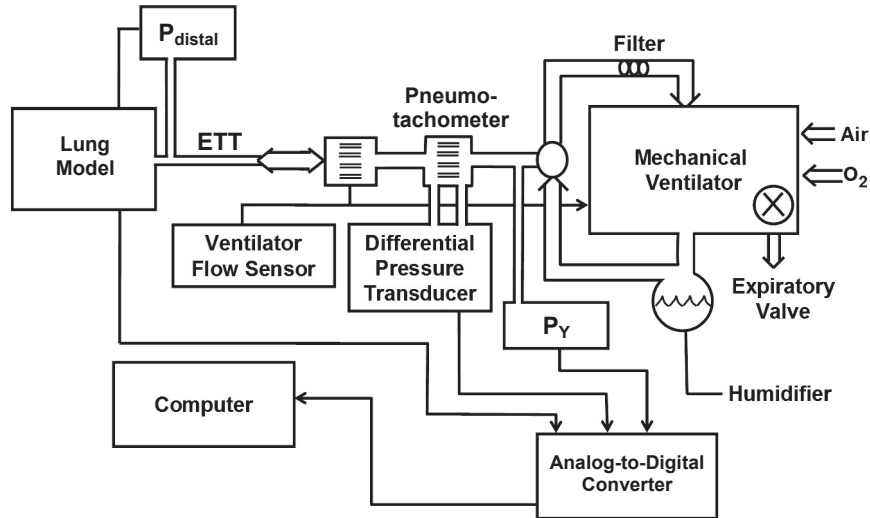


Fig. 2. Experiment setup. ETT = endotracheal tube. P_{distal} = pressure at the interface between the ETT and the lung model. P_Y = pressure at the Y-piece (interface of the ventilator circuit and the ETT).

we measured the imposed expiratory WOB at PEEP of 0, 4, 8, and 12 cm H₂O.

Measurement of Pressure, Flow, and Tidal Volume

We measured pressure (relative to atmospheric pressure) at the interface between the ETT and the lung model (P_{distal}), and at the Y-piece (ie, the interface of the ventilator circuit and the ETT) (P_Y) (see Fig. 2). This allowed us to isolate the resistance of the lung model, the ETT (including the flow sensor), and the expiratory side of the ventilator circuit, including the expiratory valve.

Airway pressure was measured continuously with pressure transducers (XRA515GN, Honeywell, Morristown, New Jersey), which were calibrated with a digital manometer (calibrated by the manufacturer, Digitron PM-23, Topac, Cohasset, Massachusetts). Expiratory flow (\dot{V}) was measured with a pneumotachometer (8431 series, Hans Rudolph, Shawnee, Kansas) connected to a differential pressure transducer (XCAL5004DN, Honeywell, Morristown, New Jersey). The pneumotachometer was calibrated with heated (39°C) humidified gas and an F_{IO_2} of 1.0. We drew 100 mL of heated, humidified oxygen into a glass calibration syringe and then emptied the syringe at a flow rate within the calibration range suggested by the pneumotachometer manufacturer. The digital signals were integrated and set equal to the 100-mL volume, which yielded calibration factors for the inhalation and exhalation flows. Analog signals from the pressure and flow transducers were sampled at 1 kHz for 20 breaths, with a 16-bit analog-to-digital converter (DT BNC Box USB 9800 series, Data Translation, Waltham, Massachusetts) and recorded on a laptop computer. Pressure and flow signals were dig-

itally processed with a 4th-order Butterworth filter that had a cut-off frequency of 50 Hz. V_T values were obtained by integrating flow with the trapezoid rule to estimate areas.

Calculations

Ventilator-Imposed R_E . The exhalation valve in each ventilator acts as a variable resistor during exhalation, so ventilator-imposed R_E was calculated as an average. This method first calculates resistance in time:

$$R(t) = \Delta P(t) / \dot{V}(t)$$

where

$$\Delta P(t) = P_Y(t) - PEEP$$

and $\dot{V}(t)$ is the flow of exhalation gas through the system.

$P_Y(t) - PEEP$ is the driving force that causes gas to flow through the ventilator. PEEP is determined as the average airway pressure during the last 5% of exhaled gas volume. Ventilator-imposed R_E is calculated as the integrated average resistance during exhalation, averaged in volume (as opposed to over time). The instantaneous $R(t)$ is integrated over 95% of the exhaled volume, and that integral is divided by V_T to obtain ventilator-imposed R_E :

$$\text{Ventilator-imposed } R_E = \frac{\int_{V_{e0}}^{V_{e95}} R dV}{\int_{V_{e0}}^{V_{e95}} dV}$$

where V = volume, $Ve0$ = exhaled volume at the start of exhalation, and $Ve95$ = exhaled volume at 95% of exhalation.

Expiratory filters were placed at the terminus of the patient circuit and proximal to the exhalation valve. The pressure drop across these filters was independently verified in the flow range 1–10 L/min prior to and after the experiments. The range of resistance was 0.004–0.005 cm H₂O/L/s with all the filter brands tested. In addition, there was no measurable change in pressure versus flow across the patient circuit, so neither the patient circuit nor the exhalation filters were important sources of imposed resistance when calculating the ventilator-imposed R_E or imposed expiratory WOB.

Endotracheal Tube Resistance

ETT resistance was calculated at each set of conditions via a linear regression equation with the pressure drop across the ETT ($P_Y - P_{\text{distal}}$), which included the ventilator flow sensor and research pneumotachometer, and the flow that was measured throughout the exhalation time. We calculated the slopes of the linear fits and correlation coefficients for 20 breaths and set resistance equal to the slope. The resistance of the research pneumotachometer was subtracted from these measurements, but the ventilator flow sensor, which is a resistive element that can add to the imposed R_E , was included in the ETT resistance measurement. The mean and standard deviation of the resistance and correlation coefficients were calculated for the 20 breaths.

PEEPi

PEEPi was measured, at various frequencies, as the P_{distal} when flow equaled zero at the beginning of inhalation, via interpolation between points measured at 1 kHz. An end-expiratory occlusion test was not used with such high frequencies, because that method would not allow sufficient time for pressure to equilibrate in the system.

Imposed Expiratory WOB

The imposed expiratory WOB measures the amount of energy required to move gas through the series of resistive features caused by the ETT, flow sensor, and ventilator system during exhalation. In a spontaneously breathing patient the imposed expiratory WOB is an additional flow-resistive work load that is superimposed on the physiologic WOB and thus increases the total WOB.^{9,10,23} Imposed expiratory WOB was calculated from measurements made during simulated spontaneous breathing with pressure support of 5 cm H₂O and PEEP of 0, 4, 8, and

12 cm H₂O, with the P_{distal} , PEEP, and expiratory change in volume (dV) of 20 breaths:

$$\text{Imposed expiratory WOB} = \frac{1}{V_{\text{TE}}} \int (P_{\text{distal}} - \text{PEEP}) dV$$

where V_{TE} = exhaled tidal volume.

Statistical Methods

With statistics software (Stata, StataCorp, College Station, Texas) we organized the data into 3 series. In each series, one ventilator setting was varied over a range of values while the other 2 ventilator settings were held constant. Each experiment series had a balanced, 2-way design with one fixed factor (for brand, 4 levels) and repeated measures in the second factor. For example, in the PEEP experiment series we collected data from each of 2 ventilators of each of the 4 brands, at PEEP settings of 0, 4, 8, and 12 cm H₂O. In this series, PEEP was the repeated-measures factor because two of each brand of ventilator were tested at every PEEP.

The ventilator-imposed R_E and imposed expiratory WOB data were analyzed with 2-way analysis of variance, with brand as a fixed factor and settings as the repeated factor. The Greenhouse-Geisser correction for correlation among the measurements from a given ventilator is used in statistical tests of the effect of the repeated factor and interactions that involve the repeated factor. Heteroscedasticity (non-constant variance) was apparent across brands. Post hoc comparisons between specific pairs of factor levels are sensitive to heteroscedasticity. Because of this, and the small number of ventilators tested at each combination of settings, post hoc comparisons were not feasible. Statistical significance was established a priori as $P \leq .05$.

Results

Overall, the ventilator-imposed R_E was larger than the imposed R_E of the ETT and flow sensors, with all 4 ventilator brands (Fig. 3). There were 52 possible combinations of ventilator brand and test conditions. The ventilator-imposed R_E was greater than the ETT-imposed R_E in 47 of the 52 combinations. The 5 instances where the average ventilator-imposed R_E was slightly lower than the ETT-imposed R_E were with the Babylog 8000plus ventilators. Figure 4 shows the contributions to the total respiratory-system resistance from the lung model and ETT. The imposed resistance of some ventilators not only exceeded the resistance of the infant lung model but also made large contributions to the R_E of the entire system.

There were statistically significant differences in ventilator-imposed R_E between the ventilator brands in all the

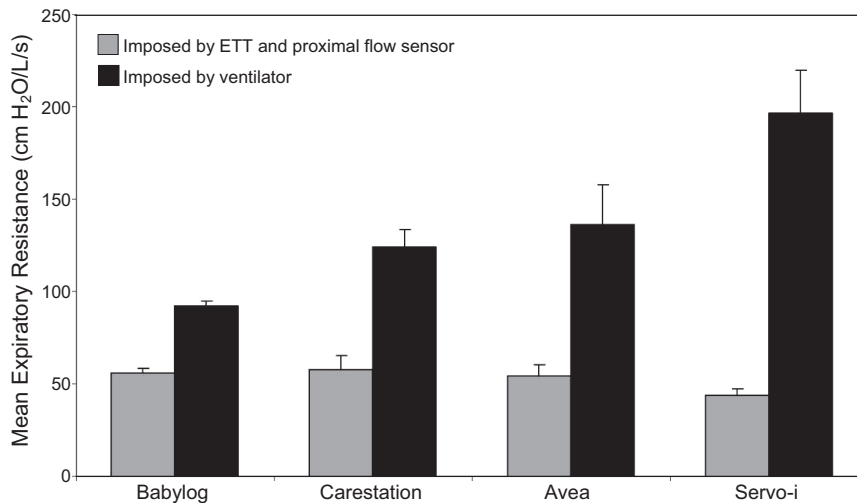


Fig. 3. Expiratory resistance imposed by the ventilator versus that imposed by the endotracheal tube (ETT) and proximal flow sensor. The error bars indicate the standard deviations of the 2 ventilators, averaged by brand. The measurements were taken during adaptive pressure controlled ventilation with tidal volume of 5 mL, frequency of 50 breaths/min, positive end-expiratory pressure of 4 cm H₂O, and 100% oxygen. ETT resistance includes the resistance of a 2.5-cm inner-diameter ETT and the proprietary neonatal proximal flow sensor. The resistance of the research pneumotachometer was subtracted from the ETT resistance value.

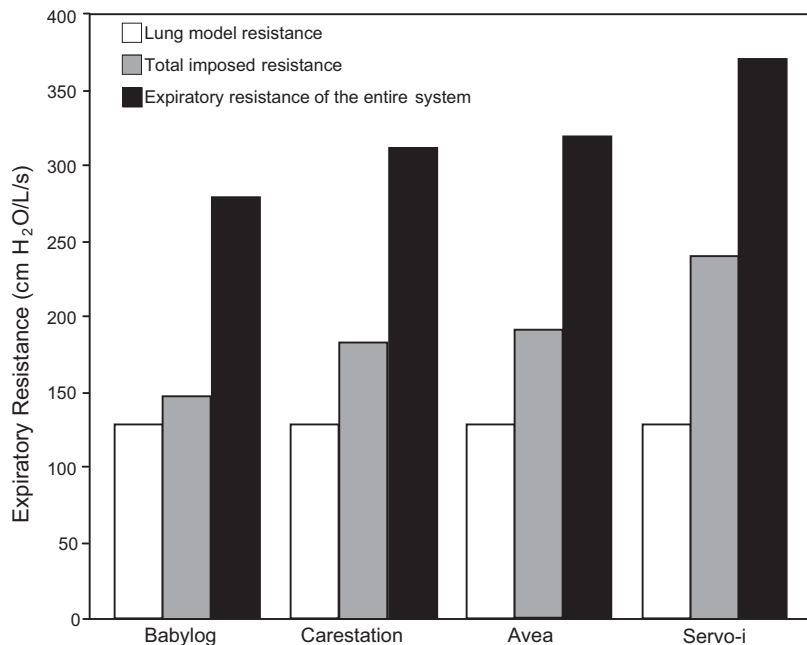


Fig. 4. Components of expiratory resistance of the entire system. The expiratory-resistance of the entire system measurement includes the sum of the physiologic lung resistance (lung model) plus the total imposed resistance (endotracheal tube, flow sensor, ventilator-imposed expiratory resistance). The measurements were taken during adaptive pressure controlled ventilation with tidal volume of 5 mL, frequency of 50 breaths/min, positive end-expiratory pressure of 4 cm H₂O, and 100% oxygen.

experiments. First we measured ventilator-imposed R_E at PEEP of 0, 4, 8, and 12 cm H₂O while holding V_T at 5 mL and frequency at 50 breaths/min (Fig. 5). The impact of brand in this experiment series was statistically significant ($P = .002$). PEEP had no statistically significant impact on

ventilator-imposed R_E , nor were there significant interactions between PEEP and brand.

Next we measured ventilator-imposed R_E at V_T of 3, 6, 9, and 12 mL, while holding PEEP at 5 cm H₂O and frequency at 50 breaths/min (Fig. 6). Brand was a statis-

IMPOSED EXPIRATORY RESISTANCE IN NEONATAL MECHANICAL VENTILATION

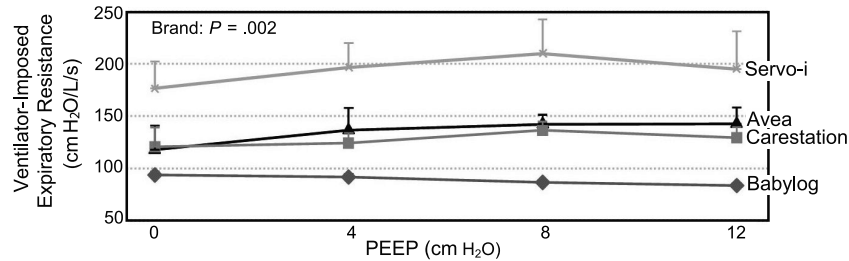


Fig. 5. Effect of positive end-expiratory pressure (PEEP) on ventilator-imposed expiratory resistance. The values are mean \pm SD from 2 ventilators per brand.

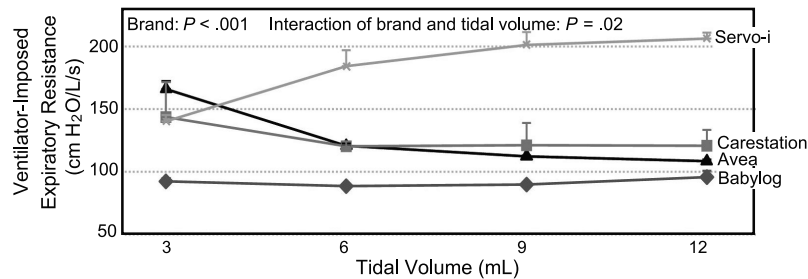


Fig. 6. Effect of tidal volume (V_T) on ventilator-imposed expiratory resistance. The values are mean \pm SD from 2 ventilators per brand.

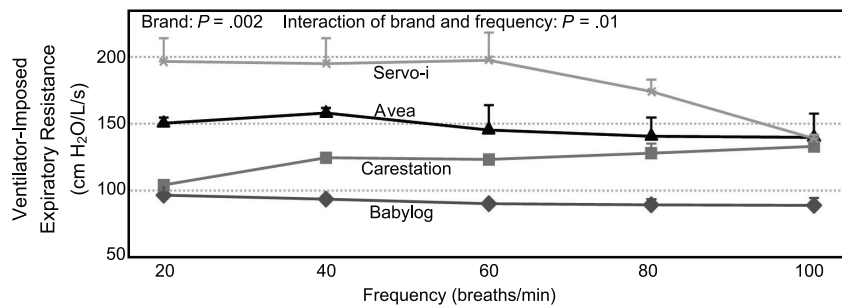


Fig. 7. Effect of frequency on ventilator-imposed expiratory resistance. The values are mean \pm SD from 2 ventilators per brand.

tically significant factor in this experiment series ($P < .001$), and there was a significant interaction between V_T and brand ($P = .02$), illustrated by the crossing lines in Figure 6. With the Servo-i, the ventilator-imposed R_E increased between V_T of 3 mL and 6 mL. With the Carestation and Avea, ventilator-imposed R_E decreased when V_T was increased from 3 mL to 6 mL. In most cases there did not appear to be a linear increase in resistance as the V_T was increased. In contrast, the Babylog 8000plus had very little variation in ventilator-imposed R_E across all the V_T settings.

In the final series we used frequencies of 20, 40, 60, 80, and 100 breaths/min with PEEP of 5 cm H₂O and V_T of 5 mL (Fig. 7). Again, brand was a statistically significant factor ($P = .002$), and the effect of frequency on ventilator-imposed R_E differed from brand to brand ($P = .01$ for the interaction term). However, PEEPi, which was mea-

sured concurrently at all the frequencies, never increased above 1 cm H₂O because of the differences in imposed resistance by the ventilators' exhalation valves, even at frequencies of 100 breaths/min.

Of interest, the ventilator-imposed R_E of the Servo-i decreased as the frequency was increased to > 60 breaths/min. On further inspection, we measured the flow from the flow-control valves at the inspiratory outlets of these ventilators at frequencies of 60, 80, and 100 breaths/min and found that there were differences in the slope of the bias flow when it was introduced into the system at around 150 ms after the beginning of exhalation.

For the reasons described above, we did not conduct post hoc statistical comparisons between specific brands at specific ventilator settings, but the Babylog 8000plus consistently produced the lowest ventilator-imposed R_E measurements, with every combination of PEEP, V_T , and fre-

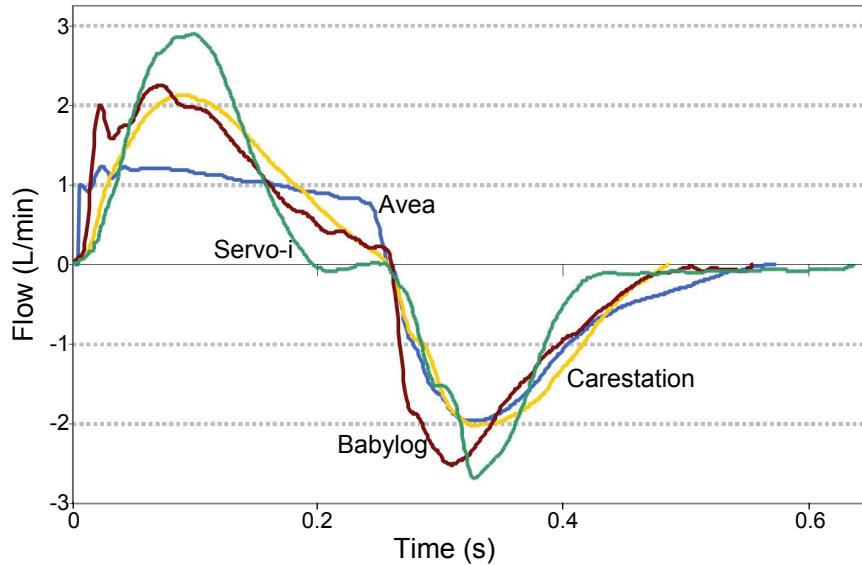


Fig. 8. Flow-time waveforms of inspiratory and expiratory flow (negative and positive flow, respectively), at identical settings and lung mechanics.

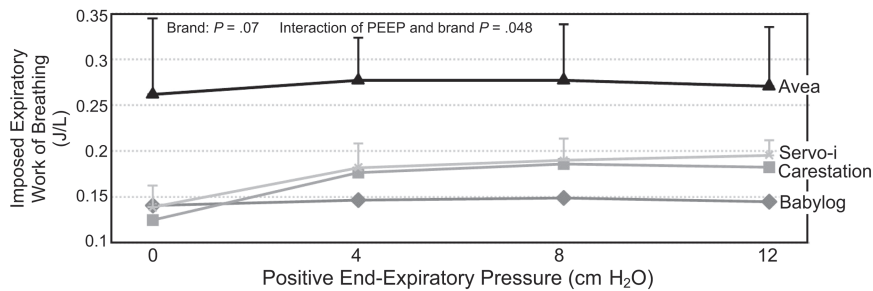


Fig. 9. Effect of positive end-expiratory pressure (PEEP) on imposed work of breathing. The values are mean \pm SD from 2 ventilators per brand.

quency. Figure 8 shows that the flow-time waveform of the initial release of the exhalation valve and acceleration of expiratory gas flow was quickest with the Babylog 8000plus.

Figure 9 describes the expiratory WOB during spontaneous breathing. Ventilator brand was not a statistically significant factor in this experiment series ($P = .07$), but there was a significant interaction between PEEP and imposed WOB within the ventilator brands ($P = .048$). The Babylog 8000plus appeared to have the lowest imposed expiratory WOB in the majority of test situations, especially when PEEP was ≥ 4 cm H₂O.

Discussion

The ETT has long been considered the single largest component of imposed resistance in the patient circuit. The ETT retards inspiratory and expiratory flow and increases WOB.²⁴⁻²⁶ LeSouf et al found that respiratory-system resistance decreased by 44% immediately after ex-

tubation in a series of neonates with ETTs of 2.5–3.5 mm inner diameter.²⁷ They attributed the reduction in resistance to the removal of the ETT. However, in that study, prior to extubation, the patients breathed through an ETT and received continuous positive airway pressure. That report²⁷ does not describe the ventilator they used to deliver the continuous positive airway pressure, but the ventilator could have contributed significantly to the imposed R_E.

Our study indicates that the R_E imposed by the circuits and exhalation valves of the 4 neonatal ventilator brands we tested were generally higher than the R_E imposed by the ETT and flow sensor. As part of our analysis we combined the resistances from the ETT and proximal flow sensor, to simulate the growing use of proximal flow sensors in neonatal intensive care units. Figure 3 shows that the Servo-i had the greatest difference between ventilator-imposed R_E and the R_E imposed by the ETT plus flow sensor, whereas the Babylog 8000plus had the smallest difference. This is related to the fact that the proximal flow

sensor of the Servo-i had the lowest resistance of the brands tested. Figure 4 shows that under some test conditions the total expiratory respiratory-system resistance appears to be affected more by the ventilator than by any other factor. This may be an important consideration when measuring respiratory-system resistance in intubated, mechanically ventilated infants.

Our ETT R_E values agree with those reported by Fontán et al²⁶ for a 2.5-mm inner-diameter ETT (58 cm $H_2O/L/s$), but are lower than those presented by Manczur et al²⁸ (81–139 cm $H_2O/L/s$) and Oca et al²⁰ (426–500 cm $H_2O/L/s$). The much higher R_E values in the latter 2 studies may have been due to those researchers' use of higher flows. Because of turbulence, the resistance of a small ETT increases as gas flow increases.

In nearly all of our test conditions, the ventilator-imposed R_E was lowest with the Babylog 8000plus (see Figs. 5–7). This finding is consistent with that of Yoder et al,² who evaluated lung mechanics in an extremely-low-birth-weight baboon model of RDS and compared physiologic responses to ventilation with 2 brands of neonatal ventilator. The baboons on the later-generation ventilator required higher settings than those on the older-generation ventilators. There were significant differences in expiratory respiratory-system resistance and indices of impaired ventilation between the ventilator brands during long-term, low- V_T ventilation. The animals ventilated with the newer-generation ventilator had 62% higher expiratory respiratory-system resistance, higher settings, and worse gas exchange than the animals ventilated with the older-generation ventilators. Yoder et al speculated that the differences between the ventilator brands were related to ventilator-imposed R_E , but they did not test that hypothesis.

The design and functioning of the various ventilator exhalation systems is a major contributor to the differences between the above-mentioned studies. A detailed analysis of the complex functional properties of the exhalation valves in these ventilators is beyond the scope of the present paper. All of the exhalation valves we tested are classified as variable threshold resistors, which allow gas to pass freely through a wide-open orifice without causing any resistance to gas flow.⁶ However, our findings are consistent with Hirsch et al, who described threshold resistors as also being partial flow resistors.²⁹ None of the ventilator exhalation valves performed like total threshold resistors. In most cases, the ventilator-imposed R_E either decreased or remained constant when V_T was increased. The Servo-i, however, functioned mainly as a flow resistor, because as the set V_T and, hence, expiratory flow was increased, the ventilator-imposed R_E also increased (see Fig. 6).

Exhalation-valve resistance significantly affects airway pressure during exhalation, which can lead to expiratory flow retardation and gas trapping.⁶ The rate of decay from

end-inspiratory to baseline pressure is directly related to exhalation-valve resistance. As we stated above, the instantaneous $R(t)$ is $\Delta P(t)/\dot{V}(t)$ (the quotient of the pressure difference driving gas through the ventilator and gas flow). The perfect ventilator, in terms of ventilator-imposed R_E , would reduce the airway pressure to PEEP immediately at the start of exhalation and hold that pressure, so the pressure difference and ventilator-imposed R_E would be zero. Our results show that even at zero PEEP there is still considerable resistance to gas flow and imposed expiratory WOB with these systems.

We speculate that the lower ventilator-imposed R_E and resulting lower expiratory flow retardation with the Babylog 8000plus may not be related solely to this particular ventilator design, but to several factors that are exclusive to neonatal ventilators that use a constant-flow setting. In these time-cycled, pressure-limited, constant-flow ventilators, the set flow typically exceeds the delivered flow required to maintain pressure in the system during inhalation and exhalation. During inhalation the exhalation valve is usually slightly open to allow excess flow to vent to the atmosphere, and therefore has a theoretical advantage when cycling to exhalation, because the valve takes less time to completely open, so there is less resistance to exhalation. This can be seen in Figure 8, where exhaled flow of the Babylog 8000plus drops off precipitously at the onset of exhalation.

During exhalation, constant flow plays a vital role in reducing resistive factors that oppose exhalation in the Babylog 8000plus, by increasing inertial forces on the patient side of the valve diaphragm. This attenuates the "spring-like" tension of the exhalation-valve diaphragm from returning to the resting (closed) position throughout the entire exhalation phase.³⁰

In contrast, the exhalation valves in the other ventilators we tested are usually completely closed at the onset of exhalation. The initial acceleration of exhaled gas and capacitance of the patient circuit are low, because flow from the control valve has ceased until the bias flow is later introduced into the circuit. Higher expiratory-limb resistance is related to the inability of exhaled gas flow to create enough force to oppose the resistance of the exhalation-valve diaphragm. Once bias flow is restored into the circuit, the exhalation valve applies force to the valve diaphragm to close the valve, which increases system resistance. The rise in resistance is greater in ventilators that have lower bias-flow settings or aggressive gas-delivery systems, which result in a slower decay from end-inspiratory pressure to the preset PEEP during passive exhalation. This explains why resistance to flow is higher when ventilating neonates than when ventilating larger pediatric patients and adults with ventilators designed to ventilate all patient sizes.

Inadvertent PEEP can occur with a long expiratory time constant and inadequate T_E .³¹ The time constant of the respiratory system is defined by the time it takes the alveoli (capacitor) to discharge 63% of its V_T through the airways, ETT, and ventilator system (resistors).³² Usually the lung empties to 95% within 3 expiratory time constants. In theory, as long as the exhalation valve remains open for at least 3 expiratory time constants, then there will be enough time for the peripheral air spaces to empty without PEEPi. Roithmaier et al³¹ found that extremely-low-birth-weight infants ventilated with a $T_E < 4$ times the expiratory time constant were more likely to develop PEEPi in the range 1–4.5 cm H₂O. They also found that infants ventilated with a $T_E > 4$ –5 times the expiratory time constant had no detectable PEEPi.

Based on our assessment, there were important differences in the respiratory-system resistance that were specifically related to the ventilator-imposed R_E of the various ventilators (see Fig. 4), which could affect the expiratory time constant. However, in our experiments PEEPi was never > 1 cm H₂O, even with high frequencies. This relationship may be very different, however, in patients with obstructive diseases.

Emeriaud et al³³ recently confirmed that in intubated, spontaneously breathing, mechanically ventilated infants receiving PEEP, the diaphragm remains partially active during expiration, to adjust end-expiratory lung volume and to prevent lung derecruitment. During exhalation, the patient exerts WOB to overcome inertia, airflow, tissue resistance, and the resistance imposed by the ETT and ventilator system.¹⁵ The increase in respiratory-muscle loading secondary to imposed expiratory WOB increases the magnitude and duration of diaphragm contraction, increases oxygen consumption, and can lead to respiratory-muscle fatigue that can exacerbate causal distress and delay ventilator weaning.

Moomjian et al³⁴ found that increasing expiratory load with an external expiratory resistor (30 cm H₂O/L/s) may help recruit alveoli after extubation, in spontaneously breathing neonates. However, expiratory loading of the respiratory system significantly increased inspiratory WOB. Kirton et al⁹ evaluated spontaneously breathing adult patients with normal pulmonary mechanics and gas exchange who were weaning from ventilation, and found that the WOB imposed by the ETT and ventilator was as much as 80% of the total WOB. However, they did not separate the resistance caused by the ETT from the resistance caused by the expiratory limb of the ventilator circuit.

Our findings show that during active breathing the imposed expiratory WOB varied significantly at different PEEP settings within the ventilator brands tested, but there were no statistical differences between the ventilator brands. It is also evident that the ventilators that had higher R_E during passive breathing did not necessarily have higher

imposed expiratory WOB during the second phase of this study. This can be explained by functional differences in the performance of these valves during passive versus active exhalation (when a higher external force is being applied) and by the response times and software in the ventilator systems, which control the tension placed on the expiratory valve diaphragm. The resistance imposed by these ventilators' proprietary flow sensors may also help explain why the imposed expiratory WOB was higher with some of the ventilators during active breathing.

We were concerned about the presence of imposed expiratory WOB with all of the ventilators we tested. In infants, expiratory WOB is not typically recorded in the literature, because exhalation is commonly perceived as passive. However, we compared our imposed expiratory WOB measurements to previously reported inspiratory WOB values from premature infants, and our values were, on average, 150–250% higher.³⁵ We speculate that the additional R_E and expiratory WOB created by the exhalation valve, rather than the ETT alone, explains why some patients appear to breathe more comfortably once they are extubated and removed from the mechanical ventilator.

Our study has several limitations. We only tested 2 of each ventilator brand. There was inter-ventilator variability, which makes it difficult to draw inferences about the performance differences between the ventilator brands.

Another limitation, which applies to all lung-modeling studies, is that there are uncertainties about the validity of the test-lung model. In this case this issue seems less pressing because we predominantly tested portions of the ventilator-patient system external to the test lung, the characterization of which should not be affected by the performance of the test lung. We did not test the VIVE function of the Babylog 8000plus, nor did we examine the effect of different expiratory flow settings, which may have impacted ventilator-imposed R_E and expiratory WOB.

We also did not explore the entire range of lung mechanics or ventilator settings that might be encountered clinically. Notably, we did not evaluate ventilator-imposed R_E at higher frequencies combined with an acute increase in pulmonary compliance, which could increase after administration of artificial surfactant, and could increase the expiratory time constant and thus increase PEEPi.

Since we found no PEEPi during our testing, it appears that, under these conditions, all of these ventilators operate safely and are unaffected by R_E related to the exhalation valve, as long as the patient is passive and the T_E is > 3 times the respiratory-system time constant. However, with some of these ventilators, with a higher frequency or longer inspiratory time the combination of shorter T_E and relatively prolonged time to exhale to zero flow might have the undesirable clinical effect of increasing PEEPi.

Conclusions

With these limited data it would be difficult to make any clinically related assumptions about the performance of these ventilators or ventilator brands, based solely on these experiments. Additional ventilator testing should be done to evaluate various aspects of performance in infants with ventilators designed exclusively for infants and ventilators intended to ventilate all patient sizes. Future investigations should also study clinically important impacts of exhalation valve performance on pulmonary mechanics, gas exchange, and WOB.

ACKNOWLEDGMENTS

Thanks to two of our colleagues at Seattle Children’s Research Institute: Kristy Seidel MSc for statistical analysis; and Stewart Carlson for data analysis.

REFERENCES

1. Goldman SL, Gerhardt T, Sonni R, Feller R, Hehre D, Tapia JL, Bancalari E. Early prediction of chronic lung disease by pulmonary function testing. *J Pediatr* 1983;102(4):613-617.
2. Yoder BA, Martin H, McCurin DA. Lung function measurements in a preterm animal model of respiratory failure: comparison of two different neonatal ventilators. *Pediatr Pulmonol* 2006;41(11):1069-1076.
3. Lofaso F, Aslanian P, Richard JC, Isabey D, Hang T, Corrigier E, et al. Expiratory valves used for home devices: experimental and clinical comparison. *Eur Respir J* 1998;11(6):1382-1388.
4. Lumb AB. Anaesthesia. In: Lumb AB, Nunn’s applied respiratory physiology, 6th edition. Philadelphia: Elsevier; 2006: 297-326.
5. Desautels DA, Blanch PB. Mechanical ventilation. In: Burton BG, Hodgkin JE, Ward JJ, editors. *Respiratory care: a guide to clinical practice*. Philadelphia: JB Lipincott; 1991: 505-598.
6. Banner MJ, Downs JB, Kirby RR, Smith RA, Boysen PG, Lampotang S. Effects of expiratory flow resistance on inspiratory work of breathing. *Chest* 1988;93(4):795-799.
7. Dubois, AB. Resistance to breathing. In: Fenn WO, Rahn H. *Handbook of physiology: respiration*. Section 3. Volume 1. Washington DC: American Physiological Society; 1964: 451-461.
8. Isono S, Nishino T, Sugimori K, Mizuguchi T. Respiratory effects of expiratory flow-resistive loading in conscious and anesthetized humans. *Anesth Analg* 1990;70(6):594-599.
9. Kirton OC, DeHaven CB, Morgan JP, Windsor J, Civetta JM. Elevated imposed work of breathing masquerading as ventilator weaning intolerance. *Chest* 1995;108(4):1021-1025.
10. Kirton OC, Banner MJ, Axlerod A, Drugas G. Detection of unsuspected imposed work of breathing: case reports. *Crit Care Med* 1993; 21(5):790-795.
11. Morganroth ML, Morganroth JL, Nett LM, Petty TL. Criteria for weaning from prolonged mechanical ventilation. *Arch Intern Med* 1984;144(5):1012-1018.
12. Greenough A. Update on modalities of mechanical ventilators. *Arch Dis Child Fetal Neonatal Ed* 2002;87(1):F3-F6.
13. Greenough A, Sharma A. Optimal strategies for newborn ventilation: a synthesis of the evidence. *Early Hum Dev* 2005;81(12):957-964.
14. Marini JJ, Culver BH, Krik W. Flow resistance of exhalation valves and positive end-expiratory pressure. *Am Rev Respir Disease* 1985; 131(6):850-854.
15. Kopotic RJ, Mannino FL. Effects of infant ventilator design on spontaneous breathing. *J Perinatol* 1987;7(4):298-300.

16. Calzia E, Linder KH, Stahl W, Martin A, Radermacher P, Georgieff M. Work of breathing, inspiratory flow response, and expiratory resistance during continuous positive airway pressure with the ventilators Evita-2, Evita-4, and SV 300. *Intensive Care Med* 1998; 24(9):931-938.
17. Kacmarek RM, Chipman D. Basic principles of ventilator machinery. In: Tobin MJ. *Principles and practice of mechanical ventilation*. New York: McGraw-Hill; 2006: 53-95.
18. Shapiro M, Wilson RK, Casar G, Bloom K, Teague RB. Work of breathing through different sized endotracheal tubes. *Crit Care Med* 1986;14(12):1028-1031.
19. Bersten AD, Rutten AJ, Vedig AE, Skowronski GA. Additional work of breathing imposed by endotracheal tubes, breathing circuits, and intensive care ventilators. *Crit Care Med* 1989;17(7):671-677.
20. Oca MJ, Becker MA, Dechert RE, Donn SM. Relationship of neonatal endotracheal tube size and airway resistance. *Respir Care* 2002; 47(9):994-997.
21. Durand M, Sardesai S, McEvoy C. Effects of early dexamethasone therapy on pulmonary mechanics and chronic lung disease in very low birth weight infants: a randomized, controlled trial. *Pediatrics* 1995;95(4):584-590.
22. Grenier B. Mechanical ventilators. In: Czervinske MP, Barnhart SL. *Perinatal and pediatric respiratory care*. St. Louis: Saunders; 2003: 248-293.
23. Banner MJ, Kirby RR, Blanch PB. Differentiating the work of breathing into its component parts: essential for appropriate interpretation. *Chest* 1996;109(5):1141-1143.
24. Branson RD. The patient-ventilator interface: ventilator circuit, airway care, and suctioning. In: MacIntyre NR, Branson RD, editors. *Mechanical ventilation*. Philadelphia: WB Saunders; 2001: 85-101.
25. Farstad T, Bratlid D. Effects of endotracheal tube size and ventilator settings on the mechanics of a test system during intermittent flow ventilation. *Pediatr Pulmonol* 1991;11(1):15-21.
26. Fontán JP, Heldt GP, Gregory G. Resistance and inertia of endotracheal tubes used in infants during periodic flow. *Crit Care Med* 1985;13(12):1052-1055.
27. LeSouef PN, England SJ, Bryan AC. Total resistance of the respiratory system in preterm infants with and without an endotracheal tube. *J Pediatr* 1984;104(1):108-111.
28. Manczur T, Greenough A, Nicholson GP, Rafferty GF. Resistance of pediatric and neonatal endotracheal tubes: influence of flow rate, size, and shape. *Crit Care Med* 2000;28(5):1595-1598.
29. Hirsch C, Kacmarek RM, Stanek K. Work of breathing during CPAP and PSV imposed by the new generation mechanical ventilators: a lung model study. *Respir Care* 1991;36(8):815-826.
30. Kayaleh RA, Wilson AF. Mechanisms of expiratory valves resistance. *Am Rev Respir Dis* 1988;137(6):1390-1394.
31. Roithmaier A, Hultsch W, Lipowsky G, Reinhardt D. Airway pressure measurements during high-frequency positive pressure ventilation in extremely low birth weight neonates. *Crit Care Med* 1994; 22(9 Suppl):S71-S76.
32. Wood BR. Physiologic principles. In: Goldsmith JP, Karotkin EH, editors. *Assisted ventilation of the neonate*. 4th edition. Philadelphia: Saunders; 2003: 15-40.
33. Emeriaud G, Beck J, Tucci M, Lacroix J, Sinderby C. Diaphragm electrical activity during expiration in mechanically ventilated infants. *Pediatr Res* 2006; 59(5):705-710.
34. Moomjian AS, Schwartz JG, Wagaman MJ, Shutack JG, Shaffer TH, Fox WW. The effect of external expiratory resistance on lung and pulmonary function in the neonate. *J Pediatr* 1980;96(5):908-911.
35. Liptsen E, Aghai ZH, Pyon KH, Saslow JG, Nakla T, Long J, et al. Work of breathing during nasal continuous positive airway pressure in preterm infants: a comparison of bubble vs variable-flow devices. *J Perinatol* 2005;25(7):453-458.