Physiologic Effects of 3 Different Neonatal Volume-Targeted Ventilation Modes in Surfactant-Deficient Juvenile Rabbits

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BACKGROUND: Different brands of volume-targeted modes may vary the location of tidal volume (V_T) monitoring and whether peak inspiratory pressure is adjusted based on inspiratory, expiratory, or leak-compensated V_T. These variables may result in different levels of support provided to patients, especially when an endotracheal tube (ETT) leak is present. We hypothesized that there would be no differences in gas exchange, triggering, or work of breathing between volume-targeted modes of 3 different brands of equipment in a surfactant-deficient, spontaneously breathing animal model with and without an ETT leak. METHODS: Twelve rabbits (mean ± SD 1.61 ± 0.20 kg) were sedated, anesthetized, intubated, lavaged with 0.9% saline solution, and randomized in a crossover design so that each animal was supported by 3 different volume-targeted modes at identical settings with and without an ETT leak. After 30 min, arterial blood gas, V_T, and esophageal and airway pressure were recorded for each condition, and pressure-rate product and percentage of successfully triggered breaths were calculated. RESULTS: Gas exchange and the pressure-rate product were not different between the ventilators in the absence of an ETT leak. When an ETT leak was introduced, volume-guarantee modes allowed a higher percentage of triggered breaths and peak inspiratory pressure, which resulted in higher minute ventilation, pH, and lower P_{aCO_2} than the pressure-regulated volume control mode ($P < .05$). CONCLUSIONS: When a moderate ETT leak was present, volume-targeted modes that used proximal V_T monitoring and triggering with adaptive leak compensation capabilities appeared more effective in providing ventilation support than did a ventilator that used measurements obtained from the back at the ventilator and does not have leak compensation. *Key words: animal model; endotracheal tube leak; neonatal; ventilator; volume-guarantee mode; volume-targeted ventilation.* [Respir Care 2019;64(4):361–371. © 2019 Daedalus Enterprises]

Introduction

Volume-targeted ventilation is a time-cycled, pressure control mode that functions to achieve a goal set tidal volume (V_T) by adjusting peak inspiratory pressure (PIP) on an ongoing basis. PIP adjustment is dependent on changes in monitored V_T, respiratory compliance and re-

sistance, and patient effort. There are several proposed advantages of volume-targeted ventilation over pressure control ventilation in neonates, which include: controlled minute ventilation to avoid hypercarbia and hypocarbia, reduction in ventilator-induced lung injury with changes in lung compliance, a lower risk of lung de-recruitment as-

sociated with variable respiratory drive in neonates, reduced work of breathing, and automatic weaning of ventilator settings.[1] A 2017 Cochrane meta-analysis of 20 randomized controlled trials, including 16 parallel trials ($n = 977$ infants) and 4 crossover trials ($n = 88$ infants), showed benefit of volume-targeted modes compared with pressure control ventilation in pre-term neonates.[2] In this meta-analysis, infants supported with volume-targeted modes had a lower incidence in combined outcome of death or chronic lung disease, hypocarbia, pneumothorax, mean days of ventilation, and combined outcome of periventricular leukomalacia or grade III/IV intraventricular hemorrhages.[2]

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Despite the positive findings in the Cochrane review,[2] widespread acceptance and implementation of volume-targeted ventilation has been slow in the neonatal ICU setting. One survey, of 50 international tertiary center neonatal ICUs, showed that only 25% of the centers used volume-targeted ventilation.[3] The leading reasons for continued use of pressure control ventilation, at the time of this publication (2011), were cited as "good outcomes with current ventilator strategy" and "insufficient evidence for the benefit of volume-targeted ventilation in neonatal ICU patients."

In addition, differences in ventilator performance related to accuracy and the location of volume monitoring and flow triggering, ability to appropriately target V_T and pressure when endotracheal tube (ETT) leaks are present, complexity in the mode operation, and lack of standardized protocols may help explain low clinical use of volume-targeted ventilation.[1] Recently, there have been significant improvements in ventilators that may address the specific needs of neonates. Some of these features include improved accuracy in V_T measurement, flow-sensor technology, rapid signal processing, adaptive leak compensation algorithms for triggering and volume targeting, and the ability to adjust PIP to target significantly smaller V_T (~ 2 mL). These proposed improvements may have important clinical implications for low birthweight infants that require invasive ventilation.

The ability to provide consistent and accurate V_T and triggering has recently been evaluated across different volume-targeted modes and ventilator brands by using neonatal lung simulators with simulated ETT leaks.[4] However, there is a lack of data from human and animal studies to indicate whether volume-targeted mode performance of different ventilator brands has any effect on physiologic outcomes. We hypothesized that there would be no differences in ventilation parameters, gas exchange, triggering, or effort of breathing in surfactant-deficient, lung-injured,

QUICK LOOK

Current knowledge

A recent meta-analysis showed that volume-targeted modes of ventilation may improve outcomes when compared with pressure control modes in premature infants. Differences in performance among the different brands of volume-targeted ventilation modes were shown in artificial lung models adapted with simulated endotracheal tube (ETT) leaks, but it was unclear whether these differences may have any physiologic impact on gas exchange or work of breathing.

What this paper contributes to our knowledge

In surfactant-deficient, spontaneously breathing rabbits, aside from triggering and minute ventilation, 3 commonly used ventilators provided similar lung support without an ETT leak. When a moderate ETT leak was present, volume-targeted modes that use proximal triggering and volume monitoring with adaptive leak compensation capabilities seemed more effective in providing ventilation support than did a ventilator that uses measurements obtained from the expiratory limb of the ventilator and does not have leak compensation.

spontaneously breathing juvenile rabbits with and without an ETT leak among 3 different volume-targeted modes that monitor V_T at different locations and regulate PIP based on inspiratory, expiratory, or leak adapted (compensated) V_T.

Methods

This study was funded with a grant from Dräger (Telford, Pennsylvania). The study was designed, measurements obtained, data reduced, and manuscript written by the investigators, with no input from the grantor. We evaluated 3 different commonly used ventilators that have neonatal-specific volume-targeted modes: Servo-i (Maquet, Solna, Sweden), AVEA (CareFusion, Yorba Linda, California), and Babylog VN500 (Dräger Medical, Lubeck, Germany). Ventilator brand selection was based on differences in volume-targeted mode operation, specifically, as they relate to (1) location of V_T monitoring and breath triggering, (2) ability to stabilize pressure in the expiratory phase in the presence of a leak, and (3) differences in V_T input required for PIP adjustment. The different triggering locations, V_T measurement inputs, and leak compensation variables related to the specific brand of volume-targeted modes are shown in Table 1.

Under an institutionally approved animal studies protocol, 12 juvenile female New Zealand White rabbits (Western

Table 1. Differences in Ventilator Brands' Proprietary Volume-Targeted Volume Measurement Locations and Adjustment Sequence, Triggering Locations, and Leak Compensation Algorithms

Ventilator	Mode	V_T Measurement Location (flow sensor type)	V_T Input for PIP Adjustment	Breath Triggering Location	Inspiratory-Expiratory Leak Compensation
Draeger Babylog VN500	Volume guarantee/assist control	Proximal airway (heated-wire anemometer)	Inspiratory and expiratory leak adaptive volume	Proximal airway flow sensor	Yes
CareFusion AVEA	Volume guarantee/assist control	Proximal airway (heated-wire anemometer)	Expiratory volume	Proximal airway flow sensor	Yes
Maquet Servo-i	Pressure- regulated volume control (PRVC)/assist control	Ventilator valve (ultrasonic) and proximal airway (differential pressure)	Inspiratory volume (ventilator flow valve)	Ventilator flow valve sensor	No

V_T = tidal volume
PIP = peak inspiratory pressure

Oregon Rabbit Company, Philomath, Oregon), that weighed (mean ± SD) 1.61 ± 0.20 kg, were tranquilized with 1 mg/kg acepromazine and anesthetized with 33 mg/kg ketamine and 6.6 mg/kg intramuscular xylazine. The neck and upper chest were shaved. Cetacaine spray (0.1%) was applied topically to the oral pharynx and glottis to reduce gag reflex and laryngospasm during oral intubation. Local anesthesia was provided around the trachea with lidocaine before tracheal isolation and oral intubation. The trachea was dissected, isolated, and intubated with a 2.5-mm inner diameter ETT under direct laryngoscopy. After intubation, a strand of umbilical tape was used to anchor the trachea and the ETT, to prevent displacement, gas leakage, and saline solution leakage during lavage, and to allow investigators the ability to control the magnitude of the ETT leak. Auscultation of bilateral breath sounds and the presence of end-tidal CO_2 (P_{ETCO_2}) confirmed proper ETT placement.

Each animal was initially stabilized and ventilated with pressure-continuous mandatory ventilation (BabyLog VN500): 40 breaths/min, 0.30 s inspiratory time, and 5 cm H_2O PEEP. The PIP level was adjusted for a V_T of 6.5 mL/kg. We chose 6.5 mL/kg V_T to reduce any deleterious effects that may have been created by dead space from the research pneumotachometer (~1 mL). The P_{ETCO_2} levels were monitored, and ventilator frequencies were adjusted to maintain P_{ETCO_2} between 40 and 50 mm Hg. S_{pO_2} was monitored (Rad 7, Masimo, Irvine, California) with a tail probe, and body temperature was monitored continuously with a rectal temperature probe and maintained normothermic (38–39°C) by using a warming pad. A 20-gauge angiocatheter was placed in the right jugular vein for administration of fluids and medications. Sedation and analgesia were maintained to minimize pain and promote spontaneous breathing by using continuous intravenous infusion of ketamine and xylazine (3 and 0.18 mg/kg/h, respectively) and titrated based on blood pressure, heart rate, and maintenance of the anesthetic plane. Maintenance intravenous fluids were provided with continuous infusion at 3 mL/kg/h of 0.9% saline solution that contained 5% dextrose. A 22-gauge angiocatheter was placed in the right carotid artery for heart rate and blood pressure monitoring and sampling for blood-gas analyses.

The F_{IO_2} was increased to 1.0, and the lungs were lavaged with 25 mL/kg of warmed normal (0.9%) saline solution (39°C) to induce surfactant deficiency, with 5-min recoveries between lavages until dynamic compliance was 50% of the non-lavaged value and P_{aO_2} of <70 mm Hg on an F_{IO_2} of 0.5. The animals were allowed to stabilize for 30 min. F_{IO_2} was adjusted to keep S_{pO_2} between 90 and 92%. The P_{ETCO_2} monitor was removed and a Hans Rudolph (Shawnee, Kansas) calibrated differential pressure pneumotachometer was placed in series for flow, V_T, and airway pressure measurements. Pressures were measured by
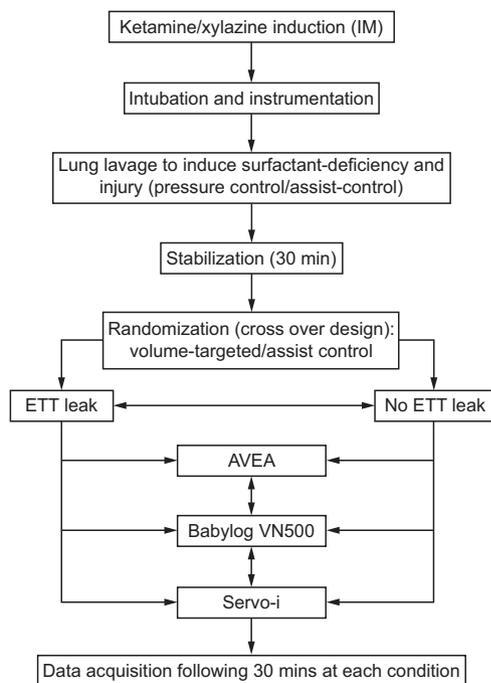
Fig. 1. Diagram of experimental procedures and testing conditions with each of the ventilator's volume-targeted modes. IM = intramuscular.

using calibrated pressure transducers (XRA515GN, Honeywell, Morristown, New Jersey), and data were recorded on a desktop computer. A 6 French esophageal balloon catheter (Cardinal Healthcare, Dublin, Ohio) was positioned in the lower esophagus, and proper placement was confirmed by using the occlusion technique.[5] Changes in esophageal pressure were used to estimate changes in pleural pressures and were used in the calculations of pressure-rate product and triggered breaths (%). All the ventilators were equipped with standard neonatal ventilator circuits (Evaqua II, Fisher & Paykel, Auckland, New Zealand) and heated humidifier systems (MR 850, Fisher & Paykel). A ventilator circuit leak test and a circuit calibration were performed per manufacturer's recommendation. Proprietary proximal flow sensors were used for each of the different ventilators. Ventilators were configured to display measured V_T based on a body temperature pressure saturated condition calculation.

The spontaneously breathing, surfactant-deficient animals served as their own controls and were supported in a randomized crossover block sequence so that each animal was supported with and without an ETT leak by using each of the 3 ventilator's volume-targeted assist-control modes for 30 min. They were supported at identical V_T settings and at the same F_{IO_2}, inspiratory time, PEEP, and breathing frequency as those established with pressure control. A schematic of the animal procedures and experimental conditions is shown in Figure 1. The flow or pressure

trigger setting was carefully adjusted with the most-sensitive triggering setting that allowed the animals' ability to optimize ventilator triggering based on intrinsic efforts without creating an autocycling condition (confirmed by esophageal monitoring). The high-pressure limit on each ventilator was adjusted to 30 cm H_2O to ensure V_T delivery in the presence of an ETT leak.

The ETT leak condition was controlled between each of the 30-min testing epochs by placing rabbits back into pressure control with assist/control mode on the Dräger Babylog VN500. The umbilical tape was loosened to allow gas to exit to the atmosphere via upper airways to achieve a 50% inspiratory leak (calculated as 100% [inspiratory minute volume − expiratory minute volume]/inspiratory minute volume) at a PIP of 20 cm H_2O for 5 min. For the non-leak condition, the umbilical tape was tied so that the tracheal wall was occluded against the ETT, and 0% leak was maintained for 5 min before being supported with the different volume-targeted modes.

Blood gas measurements were obtained and blood pressure, heart rate, airway pressure, flow, and esophageal pressure were recorded for 45 s at 1040 Hz after 30 min of support with each ventilator and leak condition in all the animals. Ventilation settings and measured parameters were also obtained at this time. We processed physiologic measurements (flow, V_T, PIP, and esophageal pressure) by using Vivo Sense software (Vivonetics, San Diego, California) and obtained mean values for V_T, PIP, airway pressure, PEEP, and the pressure-rate product for each recording after removing artifacts. The pressure-rate product is the peak-to-trough change in esophageal pressure (cm H_2O) × breathing frequency (breaths/min) and is a surrogate for effort of breathing.[6-11] All measured pressure-rate products were attributable to the animal, and further subdivision of animal versus ventilator effort was not required. Triggered breaths (%) were calculated as the total number of animal-initiated respiratory efforts to the total number of corresponding breaths triggered on the ventilator.[12] The minute ventilation calculation was based on V_T, breathing frequency, and proportion of triggered efforts that resulted in ventilator-supported breaths.

Statistical Analysis

Data, as mean ± SD, were calculated for all continuous outcome variables (eg, vital signs, pressure-rate product, PIP, CO_2 levels) according to ventilator brand and leak status. We compared differences in mean variables between ventilator brands for the ETT leak and no ETT leak conditions independently. We then compared differences within the individual ventilator brand to assess differences between the leak and no leak conditions. Frequencies and percentages were calculated for ventilator and leak assignment to assess data completeness. A linear-mixed effects

model, an extension of 2-way analysis of variance that accounts for the repeated measures taken on the rabbits, was used to evaluate the association of ventilator and leak status on each continuous outcome variable.[13]

In these linear mixed-effects models, ventilator type, and leak status were treated as fixed effects. A compound symmetric covariance matrix was used in this model, which assumes that the correlation between measurements was equal for any 2 measurements taken on the same rabbit. All models were assessed for convergence, and the modeling assumptions of homogeneity of variance and normality were verified by using 2 residual diagnostics: residuals versus predicted values and normal probability plots. Differences in outcome variables for each ventilator and leak status were estimated from the model. Bonferroni correction was used to adjust for multiple comparisons. Significance testing was done at the $\alpha = 0.05$ level. SAS 9.4 (SAS Institute, Cary, North Carolina) was used for all the analyses.

Results

Animals

The rabbits weighed (mean ± SD) 1.61 ± 0.20 kg. After saline solution lavage, lung compliance decreased from 1.30 ± 0.32 to (mean ± SD) 0.62 ± 0.10 mL/cm H_2O ($P = .001$), which was well within the specified target for reducing compliance by ~50% after lavage. This result was achieved with (mean ± SD) 10.63 ± 1.21 (range, 9–13) lavages per animal. Heart and blood pressure were not different among the different ventilator modes or leak conditions.

Ventilation Parameters

The delivered PIP was not different among the 3 ventilators in the absence of an ETT leak. The PIP increased with the introduction of an ETT leak with the AVEA ($P = .004$) and Babylog VN500 ($P = .01$) ventilators (~6 and 4 cm H_2O, respectively) (Table 2). In contrast, the PIP decreased with the Servo-i ($P = .01$, ~4 cm H_2O) and was lower than the other ventilators in the presence of an ETT leak ($P < .05$). The AVEA had a higher mean airway pressure between leak and no leak conditions ($P = .02$) and was lower than the Babylog VN500 without a leak ($P = .03$). The Servo-i had higher delivered V_T than the AVEA without a leak ($P = .03$) and lower V_T than the Babylog VN500 when an ETT leak was present ($P = .03$). The AVEA had a 13% higher V_T delivery with than without a leak ($P = .002$); whereas the V_T was 19% lower with the Servo-i ($P = .001$) (Table 2). The Dräger VN500 was the only ventilator to have measured V_T accuracy (% error) (Table 2) within 5% of the pre-set value for both leak

Table 2. Physiologic Measurements of Ventilation Parameters and Vital signs

Parameter	No ETT Leak			ETT Leak		
	AVEA	VN500	Servo-i	AVEA	VN500	Servo-i
PIP, mean ± SD cm H_2O	23.67 ± 5.43*	22.67 ± 5.99*	26.17 ± 3.01*	29.58 ± 0.99†	26.75 ± 3.72	23.33 ± 4.47‡§
PEEP, mean ± SD cm H_2O	3.64 ± 0.98†‡	4.59 ± 0.83	4.51 ± 1.11	3.58 ± 0.78†‡	4.62 ± 0.95	4.45 ± 1.08
Airway pressure, mean ± SD cm H_2O	10.42 ± 2.24†	12.64 ± 2.19	11.66 ± 1.66	12.24 ± 2.92*	12.62 ± 2.77	11.78 ± 2.04
Exhaled V_T, mean ± SD mL/kg	5.59 ± 1.41	6.19 ± 1.27	6.67 ± 0.90‡	6.31 ± 1.21*	6.67 ± 1.21	5.59 ± 0.97*§
Change in V_T (after ETT leak), %	ND	ND	ND	↑13	↑7	↓19
V_T accuracy, error %	−14	−4.8	2.6	−2.9	2.6	−14
Respiratory rate, mean ± SD breaths/min	76.73 ± 17.12	76.09 ± 6.13	76.25 ± 17.95	69.52 ± 19.20	65.12 ± 16.67*	79.72 ± 13.32
Minute ventilation, mean ± SD mL/min	655.37 ± 191.56	686.07 ± 195.54	540.45 ± 199.23‡§	686.65 ± 196	630.99 ± 201.79	547.20 ± 180.87‡§

Accuracy between the pre-set V_T on the ventilators and measured exhaled V_T with a research pneumotachometer was determined by calculating accuracy: % error = (measured V_T − pre-set V_T)/preset V_T × 100.
* Between leak and no leak conditions within the ventilator brand.
† Between the AVEA and Babylog VN500 within leak and no leak conditions.
‡ Between the AVEA and Servo-i within leak and no leak conditions.
§ Between the Babylog VN500 and Servo-i within leak and no leak conditions.
ETT = endotracheal tube
PIP = peak inspiratory pressure
V_T = tidal volume
ND = no data
↑ = increase from no ETT leak condition
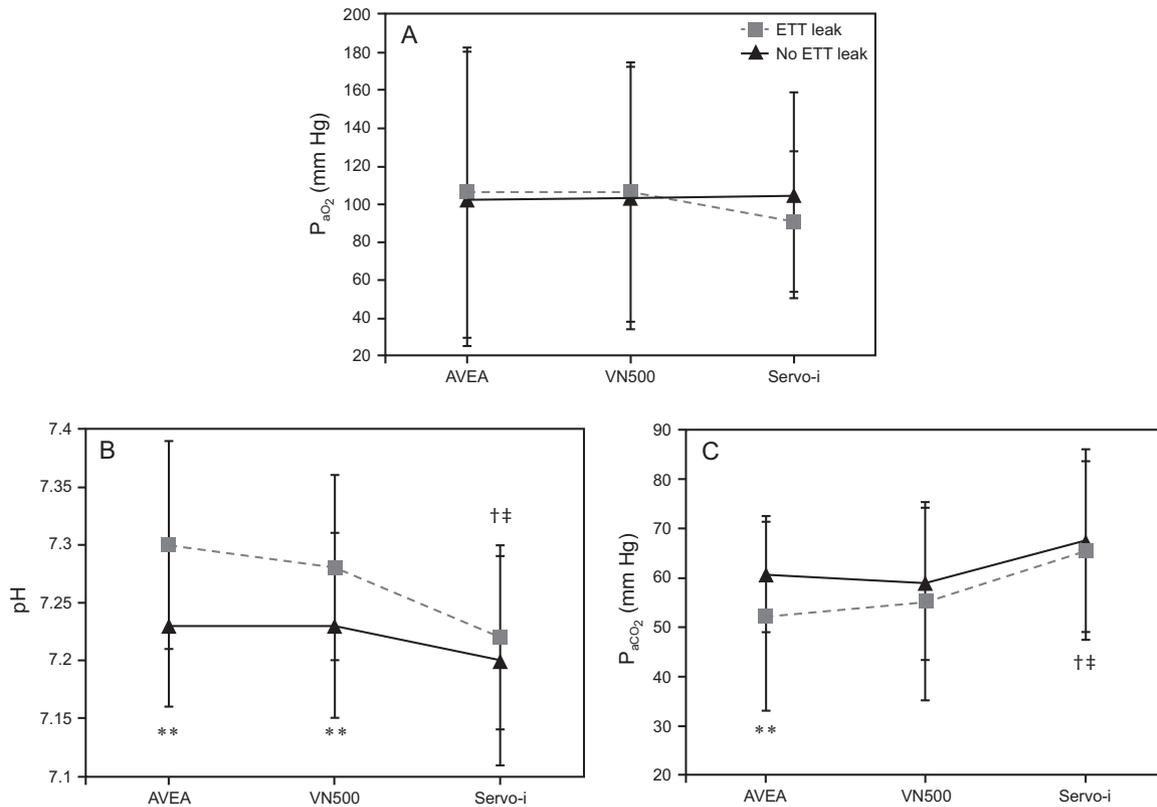↓ = decrease from no ETT leak condition

Fig. 2. Effect of each ventilator's volume-targeted mode with and without ETT leak on gas exchange: P_{aO_2} (A), pH (B), and P_{aCO_2} (C). Data are presented as mean ± SD. Linear-mixed effects models were used to evaluate the association of ventilator and leak status on each continuous outcome variable with ventilator type and leak status treated as fixed effects; $P < .05$ was considered significant: *$P < .05$ between the AVEA and Babylog VN500 within leak and no leak conditions; †$P < .05$ between the AVEA and Servo-i within leak and no leak conditions; ‡$P < .05$ between the Babylog VN500 and Servo-i within leak and no leak conditions; **$P < .05$ between leak and no leak conditions within the ventilator brand.

and no leak conditions. There were no differences in breathing frequency between the different modes during the no leak condition, but the breathing frequency was lower during ETT leak conditions with the Babylog VN500 ($P < .05$). The minute ventilation was lower with the Servo-i than with the other 2 ventilators within both leak conditions ($P < .05$).

Oxygenation and Ventilation

There were no differences in P_{aO_2} among the different volume-targeted modes under no leak and ETT leak conditions (Fig. 2A). When no leak was present, P_{aCO_2} was not different among the 3 ventilator brands. However, when an ETT leak was introduced, the AVEA ($P = .009$) and Babylog VN500 ($P = .047$) had lower P_{aCO_2} and higher pH ($P = .001$) than the Servo-i ($P < .05$) (Fig. 2, B and C). The AVEA had lower P_{aCO_2} ($P = .02$) and the AVEA and Babylog VN500 ($P = .001$) had higher pH ($P = .003$) between the ETT leak and non-leak ETT conditions (Fig. 2B).

Effort of Breathing and Triggering

The pressure-rate product measurements were similar among all 3 ventilators when there was no ETT leak (Fig. 3A). When an ETT leak was introduced, the pressure-rate product decreased significantly when animals were ventilated with the AVEA ($P = .01$) and Babylog VN500 ($P = .006$). There was no difference in the pressure-rate product between the leak and no leak conditions when using the Servo-i ventilator. The Babylog VN500 had a lower pressure-rate product than the Servo-i when an ETT leak was present ($P = .042$). There were no differences in triggered breaths between the AVEA and Babylog VN500 ventilators, with both ventilators having >90% triggered breaths under each of the leak conditions. The Servo-i had fewer successfully triggered breaths than the other 2 ventilators, regardless of leak condition ($P < .05$) (Fig. 3B). Approximately 67% of breaths were successfully triggered by the animals while on the Servo-i ventilator when there was no leak. This increased to ~78% when a leak was introduced.
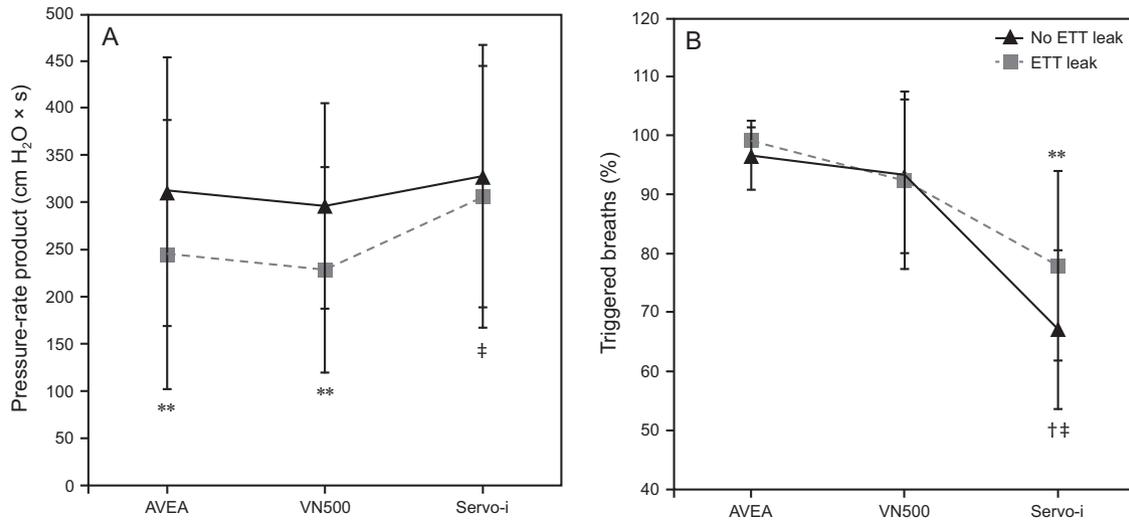
Fig. 3. Effect of each ventilator's volume-targeted mode with and without ETT leak on pressure-rate product (A) and percentage of triggered breaths (B). Data are presented as mean ± SD for 45 s of recorded data. Linear-mixed effects model was used to evaluate the association of ventilator and leak status on each continuous outcome variable, with ventilator type and leak status treated as fixed effects; $P < .05$ was considered significant: †$P < .05$ between the AVEA and Servo-i within leak and no leak conditions; ‡$P < .05$ between the Babylog VN500 and Servo-i within leak and no leak conditions; **$P < .05$ between leak and no leak conditions within the ventilator brand.

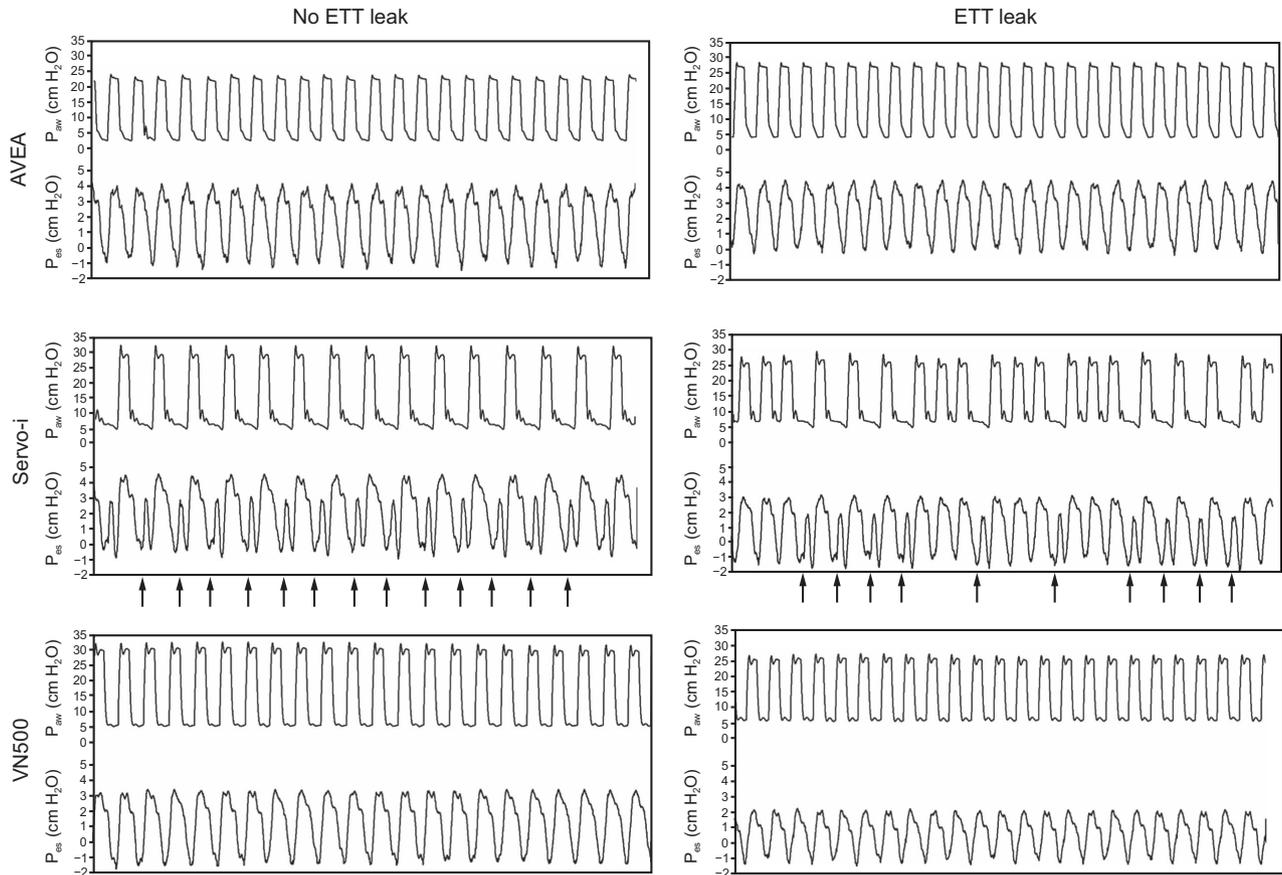Fig. 4. Airway (upper) and esophageal (lower) pressure (in cm H_2O) recorded over a 15-s period in one animal. The arrows represent the efforts being made without a corresponding ventilator-assisted breathe being delivered.

Graphic PIP and esophageal pressure waveforms in one animal, which was representative of most animals, and highlighted differences in trigger efforts among ventilator brands and leak conditions are shown in Figure 4.

Discussion

To our knowledge, these were the first physiologic data by using a spontaneously breathing animal model of surfactant-deficiency and respiratory distress syndrome to show associations between specific volume-targeted modes across ETT leak and non-leak conditions. The major finding of this study was that different volume-targeted modes may exhibit different levels of ventilator assistance and respiratory support under specific conditions. All 3 of the different volume-targeted modes supported oxygenation and ventilation similarly in a juvenile rabbit model of severe respiratory distress syndrome when there was no ETT leak. Because uncuffed ETTs are frequently used in neonatal patients, ETT leak is a common occurrence in the neonatal ICU setting, and this may result in the need for reintubation to upsize the tube, especially when ventilator volume-targeted modes are not able to provide adequate support. Based on our findings in the scenario of a moderate ETT leak, the volume-guarantee option on the AVEA and Babylog VN500 were able to provide a greater PIP and number of ventilator-supported breaths, which resulted in lower P_{aCO_2} and higher pH than did the pressure-regulated volume control (PRVC) mode on the Servo-i ventilator.

We speculated that a primary reason why the AVEA and Babylog VN500 were able to provide greater support with an ETT leak is related to the fact that V_T and flow measurements at the proximal airway are used to achieve the target V_T and provide flow triggering, respectively. Also, because these ventilators adjust PIP based on either expiratory or an adaptive leak corrected V_T, both ventilators are capable of compensating for volume loss to the atmosphere through moderately sized ETT leaks and will increase PIP to achieve the pre-set V_T. As such, we speculated that the lower observed P_{aCO_2} and higher pH, with the AVEA and Babylog VN500 volume-guarantee modes may be a direct result of CO_2 being purged from the tracheal dead space to the atmosphere through the ETT leak as PIP increases.

Also, because these volume-guarantee modes add additional flow to maintain PEEP and triggering (expiratory leak compensation), this additional flow may reduce the amount of inspired CO_2 during exhalation, which may further improve ventilation when an ETT leak is present. Similar mechanisms of gas exchange have been described with increasing flows and pressure when using heated high-flow nasal cannula.[14-16] This study was not only the first to show differences in short-term physiologic outcomes between leak and no ETT leak conditions but also that there may be a clinical benefit to having an ETT leak (higher pH and lower pressure-rate product) but only when using modes that apply adaptive leak compensation algorithms. Additional studies are needed to determine if fewer patients may need to be reintubated with a larger-sized ETT for clinical deterioration when selecting these modes over others that are not leak compensated.

As mentioned previously, the Servo-i PRVC mode differs from the other 2 ventilators in that it uses the inspiratory V_T measurement acquired back at the ventilator in its algorithm to adjust PIP levels to achieve goal V_T during volume-targeted ventilation. The Servo-i has a proprietary disposable pneumotachometer that can be placed at the proximal airway to measure V_T and flow; however, these values are not used to guide the PRVC algorithm or assist with inspiratory-flow triggering.[17] Also, a circuit compliance compensation calculation is used to estimate V_T and account for any compressible volume loss in the circuit. Circuit compliance compensation has been shown to improve the accuracy and precision of ventilator-displayed V_T when compared with having no circuit compliance compensation.[18]

However, this calculation has also been shown to result in underestimation of delivered V_T with PRVC: ventilator displayed (estimated) values were (~1 mL/kg) lower than those actually measured when using a research pneumotachometer placed at the proximal airway in infants ≥ 2 kg.[18] The observed reduction in V_T with an ETT leak may be due, in part, to inadvertent weaning of PIP but also could be related to how V_T delivery is estimated based on the tubing compliance calculation and ability to properly measure for ETT leak, which resulted in ~1 mL/kg less V_T delivery than the other ventilators. Nonetheless, similar to our findings in animals, relatively small changes in delivered V_T (~1 mL/kg) and PIP during volume-targeted ventilation have been shown to result in clinically relevant differences in work of breathing,[19] minute ventilation and CO_2 production[20] in human premature infants.

It is unclear how effective the circuit compliance calculation with the Servo-i can be in low birthweight infants, especially with an ETT leak, but, based on our findings in animals, there was a 14% difference in accuracy between the ventilator-displayed V_T and the delivered V_T, with a 50% simulated leak. As such, the major limitation of the PRVC mode with an ETT leak is that using V_T delivery and compliance is overestimated, which may lead to undesirable reductions in PIP, which may also result in hypercapnia and lung de-recruitment.[1] In addition to poor triggering, we postulated that inadvertent PIP reduction was also a major reason why animals had lower minute ventilation and greater respiratory distress when using the Servo-i.

Conversely, a similar argument can be made that there are limitations on how the AVEA volume-guarantee mode uses exhaled V_T to guide PIP, which may underestimate the actual V_T delivery to the lungs and provide excessive V_T with an ETT leak. This excessive V_T delivery may lead to hypocarbia and air leak.[21] In fact, we did note higher V_T delivery and lower P_{aCO_2} values, along with consistent ventilation at the high pressure limit setting (30 cm H_2O with audible alarms) in many cases with the AVEA after an ETT leak. However, these values were not concerning because both the AVEA and Babylog VN500 have an integrated volume-limit feature that will terminate breath delivery when measured inspiratory V_T > 130% of the set V_T. With the Babylog VN500, these problems have been reduced because the volume-guarantee assist-control mode adjusts PIP based on a V_T that is estimated and compensated for based on the magnitude of the calculated inspiratory and expiratory leak.[21]

Our findings were an extension of a previous study that also showed variable performance among different ventilator brands' volume-targeted modes in simulated neonatal lung models (500–4,000 g) with different ETT leak conditions (0–100%).[4] The Servo-i, AVEA, and Babylog VN500 were used in assist control with proprietary proximal flow sensors and modes similar to our study. The Babylog VN500 and AVEA had acceptable V_T within 10% of the goal V_T, and the Servo-i PRVC V_T was ≥10% in most of the test conditions without an ETT leak. After implementation of the ETT leak, V_T within the lung model was not able to be measured accurately due to an inability of the lung model to effectively trigger a minimum of 5 consecutive breaths with the Servo-i PRVC mode. Unlike our findings, the AVEA volume-guarantee mode was shown to consistently deliver excessive V_T after the ETT leak (~123–137% of the set V_T, depending on patient size). It is interesting to note that, similar to our findings, the Babylog VN500 was one of the only ventilators to have minimal effects in delivered V_T (within 10% of the pre-set value) in all testing conditions, including 50 and 100% leak conditions. Another study reaffirms the importance of proximal V_T monitoring location for accurate V_T delivery with ETT leak in infants with low lung compliance.[22]

Although short-term studies evaluating patient-ventilator interaction are lacking in premature infants, there are 2 phenomena related to triggering that may contribute to poor gas exchange and asynchrony. These include: (1) an inability of the ventilator to sufficiently detect a flow or pressure signal when a patient inspiratory effort is made, and (2) auto-triggering when an ETT leak is present. In the past, an inability to provide patient-synchronized ventilation was associated with major consequences and often required muscle paralysis and heavy sedation, and was associated with prolonged respiratory support.[23] Synchronized or "patient-triggered" ventilation, according to a meta-analysis, has been shown to result in a trend toward a shorter duration of mechanical ventilation than non-patient–triggered ventilation in premature infants.[24]

We noted that triggering was more successful in our animal model when flow input for triggering was measured in the proximal airway and when using a mode that provided expiratory leak compensation. Expiratory leak compensation algorithms may help with ETT leaks by adding flow during exhalation, which stabilizes the PEEP levels and provides a sufficient bias flow from which to flow trigger breaths when respiratory efforts are being made. This was helpful in determining why AVEA and Babylog VN500 ventilators, which measure flow in the proximal airway with a flow sensor and have expiratory leak compensation capabilities, had >90% successful breaths triggered by the animals with and without an ETT leak. This was different from the Servo-i PRVC mode, which had, at best, ~60–78% of breaths successfully triggered. This may be due to a lack of expiratory leak compensation as well as the flow-triggering measurement located back at the ventilator.

We believed that minute ventilation was negatively impacted due to an inability of the animals to effectively trigger PRVC breaths from the Servo-i. This could be a major contributing reason why ventilation was compromised when the animals were supported with the Servo-i with and without a leak. In a previous study that used a spontaneously breathing lung model of a premature infant (1–2 kg) with respiratory distress syndrome, the Servo-i PRVC assist-control mode was shown to have greater asynchrony index than Babylog VN500 and AVEA volume-guarantee modes.[4] Similar to our study, a major cause for asynchrony was related to ineffective efforts: respiratory efforts were not able to trigger a ventilator breath.

We observed that animals frequently made 2 inspiratory efforts before a breath could be triggered in PRVC with the Servo-i (Fig. 4). An increased caloric expenditure might explain why CO_2 levels were generally higher and pH lower than with the AVEA and Babylog VN500. However, it is interesting to note that triggering did improve with the Servo-i after the ETT leak. We speculated that the presence of a leak actually benefited the signal-to-noise ratio of the patient flow because the flow sensor at the ventilator was no longer required to measure near-zero flow, thus, all flows measured by the Servo-i may be biased by the ETT leak. Future ventilator improvements are needed to reduce ventilator response times and improve triggering because these may contribute to ventilator asynchrony,[25] which leads to negative outcomes, including prolonged intubation,[26,27] increased sedative use,[28-30] and higher mortality.[31]

Limitations

The major limitations of the present study derived from the use of an animal model with different pulmonary anatomies than are found in prematurely born human infants, along with mature lung structure undergoing active surfactant metabolism. This limited the ability of the lavage procedure to provide a stable surfactant-deficient model, which, in turn, limited our ability to study the long-term effects of the different modes of respiratory support studied. This was why we randomized the mode and leak order, and were only able to study short-term physiologic outcomes. Because the study was short term and the animals served as their own controls, we could not study any major complications (ie, lung injury and/or inflammation) related to mode operation and prematurity. Also, because these animals were relatively small ($\sim$1.6 kg), sedated, and had severe lung disease (similar to infant respiratory distress syndrome), it was difficult to extrapolate from these animal findings and expect similar results in human newborns, especially if they are larger, have a milder form of lung disease, or are not sedated.

We used a research pneumotachometer in series with each of the testing conditions. This may have added some dead space and resistance, and inversely impacted some physiologic measurements. However, we attempted to overcome these deleterious effects by using a flow sensor with extremely low dead space and resistance as well as increased the pre-set V_T to overcome any issues related to compressible volume loss that resulted in hypoventilation.

It should be noted that we chose to evaluate performance beyond some manufacturers' recommendations, similar to previous bench studies.[4] We evaluated the Servo-i PRVC ventilator mode with a moderately sized ETT leak (50%). The Servo-i ventilator operator's pocket guide[32] notes the following: "PRVC mode of ventilation is not recommended when a patient has leakage; which usually occurs around the endotracheal tube." However, because an ETT leak is extremely prevalent in the neonatal ICU setting, it is unclear whether small-to-moderately sized ETTs leaks would affect pressure delivery and ventilation with this ventilator.

It is also important to note that, after the completion of this experiment, a newer generation of the Servo ventilator (Servo-U) ventilator received 510(K) clearance from the FDA with PRVC. This ventilator has had several technologic enhancements, including the following: (1) proximal hotwire flow sensor for measuring and targeting V_T and for triggering, and (2) the ability to provide leak compensation during inhalation–exhalation with ETT leaks up to 60%. As such, it is important to not extrapolate findings from the current study with the Servo-i PRVC mode and assume a similar performance with the Servo U ventilator. Future studies are needed to determine if there are phys-iologic differences related to ventilator performance between PRVC modes offered with these 2 ventilators.

Clinical Implications

Increased work of breathing and poor gas exchange are 2 important clinical factors that may contribute to respiratory failure and the ongoing need for mechanical ventilation in premature infants. Differences in ventilator brands' performance and the ability to appropriately deliver V_T and PIP, and allow effective triggering with volume-targeted ventilation may have several important clinical implications in the pre-term neonatal patient population. The Servo-i uses inspiratory V_T and provides triggering and V_T measurements based on values acquired back at the ventilator and not proximal to the patient, as with the other ventilators, during volume-targeted ventilation. Also, unlike the other ventilators, the Servo-i targets a calculated inspired V_T (based on tubing compliance) and not expiratory or adaptive leak-compensated V_T, thus, it is likely that combined inadequate triggering and reduced PIP with an ETT leak condition were major contributing factors that explained some of the observed differences in minute ventilation, the effort of breathing (pressure-rate product), and gas exchange between the Servo-i and the other ventilators tested.

Conclusions

Based on our observations, we believed that clinical success and future research of volume-targeted modes in neonates should use ventilators with algorithms that incorporate expiratory V_T or leak-corrected V_T measured at the proximal airway because these ventilators may deliver better ventilation support by compensating for the leak of air around an ETT.

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