



## September 2007: VOLUME 5, NUMBER 1

### *Advances and Options in Neonatal Mechanical Ventilation*

#### In this Issue...

The majority of infants that require ventilation are premature infants born with surfactant deficient lungs that lead to the development of Respiratory Distress Syndrome (RDS). Historically, these neonates have been ventilated with continuous flow, time cycled, pressure-limited ventilators. Early efforts at volume-cycled ventilation with first-generation ventilators in the 1980s did not meet with consistent success for many practical and technical issues. However, the advent of microprocessor-controlled devices in the early 1990s created a new generation of volume ventilators that allow for much improved monitoring, sensitivity, and feedback mechanisms that can respond to changes in milliseconds. These technical advances allow for more consistent tidal volume delivery and the ability to compensate for endotracheal tube leaks.

In this issue, we review current research on volume ventilation in the neonatal population.

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## GUEST AUTHOR OF THE MONTH



Commentary & Reviews:  
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### **Guest Faculty Disclosure**

**Timothy R. Myers, BS, RRT-NPS** has indicated that he has not received financial support for consultation, research or evaluation and does not have a financial interest relevant to this literature review.

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## LEARNING OBJECTIVES

**At the conclusion of this activity, participants should be able to:**

- Discuss the current research in volume-targeted ventilation in RDS
- Explain the potential advantages of volume-targeted ventilation on managing oxygenation and ventilation parameters
- Describe the differences in accuracy of different manufacturers' volume-targeted ventilators

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## COMMENTARY

For nearly 3 decades, mechanical ventilation of neonates has relied on some form of pressure-controlled ventilation, where the ventilator delivers a variable volume with a constant pressure throughout the entire inspiratory cycle. The tidal volume (Vt) delivered, while dependent on many of the ventilator's set parameters, is also dependent on the infant's lung compliance and airway resistance. In contrast, in volume-targeted ventilation (VTV), the clinician sets a tidal volume, which generates

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a variable inspiratory pressure that is dependent primarily on the patient's lung compliance and airway resistance.

The complexity in ventilating infants with lung diseases like RDS in pressure control modes is that surfactant-deficient lungs frequently develop rapid changes in compliance and resistance, resulting in altered tidal volumes and minute ventilation. These alterations can potentially result in excess tidal volumes (ie, volutrauma or stretch injury) or decreases in tidal volume (atelectrauma or collapse injury) or, at the very least, unacceptable fluctuations in carbon dioxide.

A review of the growing literature over the last decade has consistently demonstrated that these rapid changes in compliance and resistance can result in excessive tidal volumes that cause either ventilator-induced lung injury and inflammation,<sup>1,2</sup> or excessive hypocarbia that can result in cystic periventricular leukomalacia (PVL) injury of the neonatal brain.<sup>3,4</sup> In part due to these types of iatrogenic complications, clinicians have developed a renewed interest in controlling or targeting specific tidal volumes.

Fourth generation microprocessor-controlled ventilators have hypothetically addressed many of the original concerns that arose from the initial attempts of VC ventilation in the early 1980s<sup>5</sup> and provide a number of different methods of VTV. For example, today's VTV allows for the computer microprocessor to modify inspiratory pressures and/or times to achieve the target volume on either a breath-by-breath basis or within a breath.

A recent Cochrane Review meta-analysis<sup>6</sup> concluded that VTV was associated with significant reductions in pneumothoraces and ventilator lengths of stay, but was not associated with an improvement in mortality or bronchopulmonary dysplasia (BPD) rates. The difficulty with this meta-analysis is that it involved only 4 clinical trials of slightly less than 200 patients, and utilized multiple nuances of VTV. While each of the modes of VTV has its advantages and disadvantages, and the results obtained are often times contradictory, the potential advantages offered from pulmonary, cardiovascular, and cerebral standpoints are without a doubt important and worth pursuing.

Volume-control ventilation is a vast departure from the historical methodologies of time-cycle, pressure limited ventilation, and while the literature is still somewhat sparse, this intervention potentially offers some unique advantages in stability and consistency of tidal volumes, especially in highly ventilated populations like RDS. However, the variations in VTV with different manufacturers' ventilators, and the parameters that they produce, demand a sense of caution until more definitive, larger randomized clinical trials are conducted.

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## VOLUME GUARANTEE AND CARBON DIOXIDE LEVELS IN NEONATES

Cheema IU, Sinha AK, Kempley ST, Ahluwalia JS. **Impact of volume guarantee ventilation on arterial carbon dioxide tension in newborn infants: A randomised controlled trial.** *Early Hum Dev.* 2007;83:183-189.

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Investigating the use of Volume Guarantee (VG) ventilation to improve the frequency of normal carbon dioxide tension in the first arterial blood gas after admission to the neonatal unit, Cheema et al prospectively randomized 40 infants from 2 participating centers to receive VG ventilation at 4 ml/kg or Synchronized Intermittent Positive Pressure Ventilation (SIPPV). The ventilator settings from the SIPPV remained unchanged from those selected by the clinical team at the time of intubation. The investigators targeted a PaCO<sub>2</sub> range of 37-52 mm Hg for their normal range. The study was completed upon analysis of the first arterial blood gas.

The authors report that the mean PaCO<sub>2</sub> value (36.8 mm Hg) for the SIPPV group was below the target range, while the mean PaCO<sub>2</sub> (42.8 mm Hg) of the VG group was well within the targeted range (p= 0.02). Further, while not statistically significant, VG demonstrated a trend for fewer out-of-range PaCO<sub>2</sub> levels and less incidence of hypocarbia. In addition, above 25 weeks gestation, the VG group had a significantly lower incidence of out-of-range PaCO<sub>2</sub> than the SIPPV group – a finding entirely related to reduced incidence of hypocarbia (p< 0.05).

The authors appropriately conclude that VG was of potential benefit in reducing hypocarbia upon initial stabilization in infants >25 weeks gestation. It is interesting to note, however, that there were only 7 patients (18%) total <25 weeks gestation entered into the study – which would leave this group underpowered.

## THE ABILITY OF VOLUME-CONTROLLED VENTILATION TO REDUCE HYPOXEMIC EPISODES IN NEONATES

Hummler HD, Engelmann A, Pohlandt F, Franz AR. **Volume-controlled intermittent mandatory ventilation in preterm infants with hypoxemic episodes.** *Intens Care Med.* 2006;32:577-584.

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This 2006 randomized, crossover design study by Hummler et al compared the use of volume-controlled (VC) ventilation versus pressure-controlled (PC) ventilation to decrease the frequency of hypoxemic desaturations in preterm infants. Fifteen preterm infants with a predefined history of frequent desaturations were ventilated in 4 hour blocks of VC or PC synchronized intermittent ventilation (SIMV). Standardized criteria and timed interventions were applied during both ventilatory conditions to adjust FiO<sub>2</sub> in relation to the SpO<sub>2</sub>, as measured by pulse oximetry.

No significant differences between ventilation modes were found for time with hypoxemia. However, compared to the PC-SIMV group, infants ventilated with VC-

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SIMV spent significantly less time ( $p=0.04$ ) experiencing hyperoxia ( $SpO_2 >92\%$ ), significantly less bradycardias with desaturation ( $p=0.03$ ), and showed a trend ( $p=0.09$ ) towards more time within the targeted  $SpO_2$  range. While the average  $FiO_2$  used during the study did not differ, the authors report a trend toward higher  $FiO_2$  (0.7–1.0), and more standardized  $FiO_2$  adjustments necessary to maintain  $SpO_2$ , within the target range than with PC-SIMV. VC-SIMV also displayed a trend for less  $SpO_2$  troughs during episodes of desaturation.

In assessing pulmonary mechanics, VC-SIMV maintained more consistent tidal volumes during episodes of desaturation ( $p < 0.01$ ) than PC-SIMV. When assessing lung compliance, PC-SIMV demonstrated ( $p < 0.05$ ) a significantly larger decline in lung compliance than VC-SIMV, as well as a trend ( $p= 0.07$ ) toward an overall lower lung compliance with desaturations.

The authors concluded that although VC-SIMV did not decrease hypoxemic episodes, tidal volume was better maintained with less frequent bradycardias during these episodes. However, several limitations – the number of participants, age at enrollment, range for acceptable  $SpO_2$ , and focus on premature infants with frequent hypoxemic episodes – restrict the ability to generalize these results.

## IS VOLUME OR PRESSURE A BETTER TARGETED VARIABLE IN LOW-BIRTH WEIGHT NEONATES?

Singh J, Sinha S, Clarke P, et al. **Mechanical ventilation of very low birth weight infants: Is volume or pressure a better target variable?** *J Pediatr.* 2006;149(3):308-13.

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Comparing the use of volume-controlled ventilation to time-cycled, pressure-limited ventilation for efficacy and safety in low-birth-weight premature infants, Singh et al performed a prospective, randomized trial of 109 low-birth-weight (600-1500 grams) infants managed according to a strict protocol. Infants received a targeted tidal volume of 4-6 ml/kg, either with volume-controlled ventilation (VC), or by hourly clinician adjustments in time-cycled, pressure-limited ventilation (TCPL). Standard parameters were utilized for ventilator manipulations in both groups. The investigators found no significant differences in the time to reach a predetermined extubation criterion (mean  $Paw$  or  $AaDO_2$ ), duration of oxygen therapy, mortality, or complication for either group. However, a trend toward faster weaning to extubation in VC infants was achieved versus TCPL ( $p = 0.15$ ) — primarily due to faster obtainment of  $AaDO_2 < 100$  mm Hg ( $p = 0.08$ ) compared to a mean  $Paw$  airway pressure  $< 8$  torr for 12 consecutive hours ( $p = 0.79$ ).

In infants weighing  $< 1000$  gm ( $n = 59$ ), a significant reduction in the time to achieve extubation criterion was realized in the VC infants compared to the TCPL arm ( $p = 0.03$ ). A post-study analysis of infants ( $n=41$ ) with moderate to severe respiratory failure ( $AaDO_2 > 100$  mm Hg) on study entry demonstrated a significantly shorter time to extubation criteria for the VC group as well ( $p = 0.03$ ).

The authors suggest that VC ventilation is safe and efficacious in very low birth weight infants and may have advantages when compared with TCPL, especially in smaller infants. The strategy to allow hourly clinician manipulations of the TCPL groups' peak inspiratory pressure (PIP) to achieve a targeted tidal volume may have made these 2 study groups more the same than different. It should be noted that real-life clinical trials are frequently difficult to conduct, and a high rate of protocol violations at one of the centers may have further biased the results in this intent-to-treat trial.

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## VOLUME CONTROL VENTILATION VERSUS HFOV ON LUNG INFLAMMATION IN PRETERM INFANTS

Dani C, Bertini G, Pezzati M, et al. **Effects of pressure support ventilation plus volume guarantee vs. high-frequency oscillatory ventilation on lung inflammation in preterm infants.** *Pediatr Pulmonol.* 2006; 41: 242-249.

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Lista G, Castoldi F, Bianchi S, et al. **Volume guarantee versus high frequency ventilation: lung inflammation in preterm infants.** *Arch Dis Child Fetal Neonatal Ed.* 2007; published on-line 3 Apr 2007.

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To evaluate the abilities of High Frequency Oscillatory Ventilation (HFOV) and VG to reduce lung inflammation, Dani et al performed a prospective randomized study of 25 infants, <30 weeks gestation, ventilated with HFOV or Pressure Support with Volume Guarantee Ventilation (PSV-VG). The PSV-VG initial targeted tidal volume was 5 ml/kg. Ventilator settings manipulation in each group was based on specific blood gas criteria. Infants were extubated within 2 hours of achieving standardized criteria, with post-extubation support at the physician's discretion. Cytokine assays were measured at 4 specific intervals for inflammation evaluation.

The study found no differences in secondary outcomes for mechanical ventilation duration, need for oxygen therapy, nasal continuous positive airway pressure (NCPAP) or second dose of surfactant, length of ICU or hospital stay, or the development of patent ductus arteriosus (PDA), pneumothorax, BPD, intra-ventricular hemorrhage (IVH), PVL, retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC). The mean values of IL-1b ( $p=0.042$ ), IL-8 ( $p=0.021$ ), and IL-10 ( $p<0.0001$ ) at extubation were significantly lower in HFOV infants. While IL-1b was significantly less with HFOV, there was no change in PSV-VG levels across the study duration. Interleukin (IL)-8 significantly increased ( $p=0.026$ ) prior to extubation in pressure sensitive ventilation (PSV)-VG ventilated infants, while remaining unchanged in HFOV infants. IL-10 levels significantly increased in the PSV-VG group at both 1 to 2 days of ventilation ( $p=0.028$ ) and prior to extubation ( $p=0.021$ ), while significantly decreasing in the HFOV group prior to extubation ( $p=0.026$ ).

Lista's group conducted a prospective, randomized study of 45 premature infants (gestation 25-32 weeks) to evaluate lung inflammation between Assist/Control Volume Guarantee (AC-VG) ventilation and HFOV during the acute phase of RDS. The AC-VG initial targeted tidal volume was 5 ml/kg. Surfactant was initially administered to all infants and re-dosed based on standard criteria. Ventilator manipulations were based on arterial blood gas values, and infants were extubated within 2-3 hours of achieving standardized criteria. Cytokine assays were obtained prior to randomization and again at 3 days and 7 days post randomization.

Ventilation randomization was maintained until the 96th hour, when HFOV neonates met unit criteria for switching to AC ventilation. By day 7, no infants randomized to HFOV were still receiving HFOV. Approximately two thirds of each group were receiving AC-VG at the final aspirate sample, while one third of each group were extubated and spontaneously breathing. The authors report no differences in mechanical ventilation duration, need for second dose of surfactant or postnatal steroids, mortality, development of pulmonary hemorrhage, pneumothorax, BPD, IVH, PVL, ROP, and NEC.

HFOV infants had significantly longer oxygen dependency ( $p<0.05$ ). Cytokines levels in AC-VG group were stable during the study. IL-6 levels were significantly



higher on day 3 ( $p < 0.05$ ) and day 7 ( $p = 0.03$ ) in HFOV infants. HFOV also demonstrated a trend for higher levels of IL-6, IL-8 and TNF- $\alpha$  levels on day 7 ( $p = 0.09$ ). Infants that developed BPD had high IL-8 ( $> 20 \text{ ng/ml}$ ) and TNF- $\alpha$  ( $> 0.35 \text{ ng/ml}$ ) levels on day 7.

Dani et al concluded that early HFOV treatment is associated with reduced lung inflammation compared with PSV-VG in preterm infants with RDS, while Lista et al concluded VG ventilation is an effective lung-protective strategy to be used in acute RDS, inducing a lower expression of early inflammation markers when compared to HFOV. Each study had some limitations that may explain the differences in conclusion (and highlight the need for additional studies). Dani's group used a spontaneous breathing mode pressure-sensitive ventilation (PSV) as a comparator to HFOV, a low positive and expiratory pressure (PEEP) (3-4 cm H<sub>2</sub>O) strategy, and possibly introduced study bias by allowing physicians to change tidal volumes in (PSV)+VG. Limitations to Lista et al include a relatively small number of patients, use of a different high-frequency ventilator (Dräger Babylog versus SensorMedics 3100), and the allowance of HFOV crossover to AC+VG ventilation prior to study conclusion.

## PRESSURE-REGULATED VOLUME CONTROL VENTILATION VERSUS SIMV

D'Angio CT, Chess PR, Kovacs SJ, et al. **Pressure-regulated volume control ventilation vs synchronized intermittent mandatory ventilation for very low-birth-weight infants.** *Arch Pediatr Adolesc Med.* 2005;159:868-875.

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D'Angio and colleagues conducted a prospective, randomized study of 213 premature infants ( $< 32$  weeks gestation) evaluating 14-day morbidity and mortality rates between pressure-regulated volume control (PRVC) and pressure-controlled, synchronized intermittent mandatory ventilation (PC-SIMV). Patients were randomized after 6 hours of ventilation. Targeted arterial blood gas values provided a standard management protocol. If the infant met any of the failure criteria, the mode of ventilation could be changed. Extubation parameters were standardized for all patients.

Upon randomization and at 6 hours post-randomization, PC-SIMV patients had a significantly lower respiratory rate, while PRVC patients had significantly lower peak pressures and tidal volumes. These significant differences continued at Days 1, 2 and 3. The investigators report a lack of adherence to PaCO<sub>2</sub> to the target range (maintained lower) at 6 hours post-randomization. Approximately a third of the patients in each group were extubated by 72 hours, with a significant difference for extubation at 14 days for PC-SIMV. The number of infants alive and extubated at 14 days, 28 days, or 36 weeks post-menstrual age (PMA) did not differ between the groups. There was no difference in BPD at 36 weeks' PMA. While not significantly different, there was a trend for PC-SIMV infants to fail their assigned mode of ventilation more than those in the PRVC group.

The authors concluded that implementation of PRVC ventilation from birth did not alter time to extubation in premature infants when compared to PC-SIMV. Some inherent problems in this trial were that the *a priori* analysis was set for a large difference in the primary outcome; there were also problems with adherence to the study protocol with blood gas parameters, as protocol deviations were identified in 29% ( $n = 61$ ) of the participants. In one third ( $n = 27$ ) of these deviations there was a brief alteration in ventilatory mode.

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## DIFFERENCES AND ACCURACY OF VOLUME-TARGETED VENTILATORS

Sharma A, Milner AD, Greenough A. **Performance of neonatal ventilators in volume targeted ventilation mode.** *Acta Paediatrica.* 2007; 96: 176-180.

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Jaecklin T, Morel DR, Rimensberger PC. **Volume-targeted modes of modern neonatal ventilators: how stable is the delivered tidal volume?** *Intens Care Med.* 2007, 33: 326-335.

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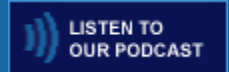
Sharma's recent bench study evaluated 4 types of volume-targeted ventilators: SLE 5000 (SLE systems, UK), Dräger Babylog 8000 (Dräger Medical, Germany), Stephanie pediatric (F Stephan Biomedical, Germany) and V.I.P. Bird® Gold (Viasys Healthcare, USA). The researchers developed a 500 ml glass bottle lung model with two inlets: one for a 3.0 mm endotracheal tube, the other with a syringe attached to simulate respiratory effort. Compliance was 0.4 ml/cm H<sub>2</sub>O and resistance was 70 cm H<sub>2</sub>O/L/sec, similar to babies with RDS. Ventilators were tested at 2 inspiratory times (IT) (0.35 and 0.5 seconds), and 2 tidal volumes (5 ml and 10 ml).

For mean airway pressure, the Stephanie delivered significantly higher Paw than the Dräger (p = 0.001), SLE (p = 0.007), and V.I.P. Bird (p < 0.0001). The Dräger delivered significantly higher peak pressures at both IT (p = 0.012 and p = 0.029) than the Stephanie and SLE, while the SLE was significantly higher than the Stephanie (p = 0.001) and V.I.P. Bird (p < 0.0001). IT were significantly lower for the SLE than the Dräger (p < 0.0001) and Stephanie (p < 0.0001), while IT for the V.I.P. Bird were significantly lower than the Stephanie (p < 0.0001) and the Dräger (p < 0.0001).

There were no significant differences at 5 ml for the ventilators, while the V.I.P. Bird delivered significantly higher volumes at 10 ml for both IT than the Stephanie (p = 0.012 and p = 0.016). Overall, the mean coefficient of variation for volume delivery was 3.7%, with the V.I.P. Bird being significantly lower than the Dräger (p = 0.003), Stephanie (p = 0.017), and SLE (p < 0.0001).

Similarly, Jaecklin's group performed a bench study of 6 volume-targeted ventilators defined by their volume-targeted mode: volume guarantee (Babylog 8000, Dräger Medical, Lübeck, Germany), autoflow (Evita XL, Dräger Medical), adaptive pressure ventilation (Galileo Gold, Hamilton Medical, Rhäzüns, Switzerland), pressure-regulated volume control (Servo-i, Maquet, Solna, Sweden), targeted Vt (SLE 5000, SLE, South Croydon, UK), and volume-assured pressure support (V.I.P. Gold, Bird, Palm Springs, USA). Ventilators were compared for their ability to maintain set Vt when rapid changes in compliance, airway leak, and resistance were introduced. Tidal volumes were set at 2 levels: pre-term levels (8-10 ml) or term levels (25-28 ml).

Both increases and decreases in leak were handled well by all ventilators, with little change in Vt. With decreases in compliance in term settings, the Dräger 8000, Evita XL, and Galileo Gold all maintained volume, while only the Evita XL maintained Vt in preterm settings. With compliance increases, the only ventilator with acceptable Vt in term settings was the Evita XL, with no ventilators responding with acceptable Vt



to increases in compliance in preterm settings.

With increases in resistance, the Babylog 8000 and Galileo Gold both maintained acceptable Vt in term settings, while the Babylog 8000, Evita XL and Servo I did so in preterm settings. When resistance suddenly decreased, only the Babylog 8000 responded with appropriate Vt in term settings, while the Babylog 8000, Evita XL and Galileo Gold all responded appropriately in preterm settings.

The Sharma study indicates that different ventilators all respond differently with pressure, volume, and flow despite similar set parameters, and even under ideal conditions (ie, stable resistance and compliance) deliver variable tidal volumes. The Jaecklin study identifies how different ventilators respond to typical neonatal clinical conditions (fluctuation compliance and resistance) with tidal volume overshoot or undershoot. These bench studies are a start, but further studies and refinement of volume-target ventilation parameters are needed.

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This activity has been developed for neonatologists, NICU nurses and respiratory therapists working with neonatal patients. There are no fees or prerequisites for this activity.

## Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Discuss the current research in volume-targeted ventilation in RDS
- Explain the potential advantages of volume-targeted ventilation on managing oxygenation and ventilation parameters
- Describe the differences in accuracy of different manufacturers' volume-targeted ventilators

## Internet CME/CNE Policy — [back to top](#)

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- **Edward E. Lawson, MD** has indicated a financial relationship of grant/research support from the National Institute of Health (NIH). He also receives financial/material support from Nature Publishing Group as the Editor of the *Journal of Perinatology*.
- **Christoph U. Lehmann, MD** has indicated no financial relationship with commercial supporters.
- **Lawrence M. Nogee, MD** has received grant support from the NIH.
- **Mary Terhaar, DNSc, RN** has indicated no financial relationship with commercial supporters.
- **Robert J. Kopotic, MSN, RRT, FAARC** has indicated a financial relationship with the ConMed Corporation.

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