

Mechanical Ventilation of the Neonate: Should We Target Volume or Pressure?

Steven M Donn MD and Win Boon MD

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For more than 40 years conventional mechanical ventilation has been used for the treatment of neonatal respiratory failure. Until relatively recently, this was accomplished with time-cycled pressure-limited ventilation, using intermittent mandatory ventilation. Earlier attempts at volume-targeted ventilation were largely ineffective because of technological limitations. The advent of microprocessor-based devices gives the clinician an option to choose either target variable to treat neonatal patients. This paper reviews the principles of each and the accumulated evidence. Key words: newborn, respiratory failure, mechanical ventilation, pressure-targeted, volume-targeted. [Respir Care 2009;54(9):1236–1243. © 2009 Daedalus Enterprises]

Steven M Donn MD and Win Boon MD are affiliated with the Division of Neonatal-Perinatal Medicine, Department of Pediatrics, CS Mott Children's Hospital, University of Michigan Health System, Ann Arbor, Michigan.

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Introduction

The traditional method of mechanical ventilation to treat neonatal respiratory failure has been time-cycled pressure-limited ventilation. Originally this was accomplished by modification of adult ventilators. Time-cycled pressure-limited ventilation was easy to use and was felt to safeguard against barotrauma because the peak inspiratory pressure (PIP) could be limited and the ventilator would not exceed this pressure. Unfortunately, the delivered tidal volume (V_T) would fluctuate according to pulmonary compliance; a smaller volume of gas would be delivered at low

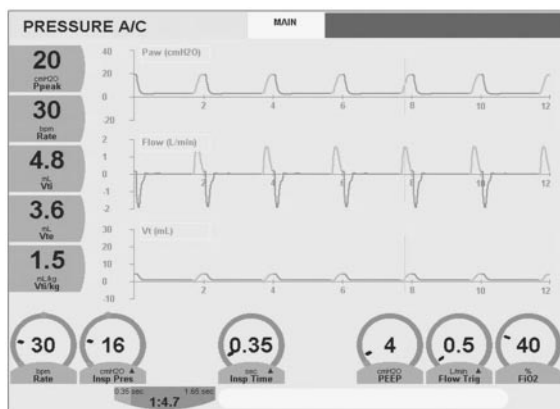


Fig. 1. Graphic representation of flow waveform (middle panel) in pressure-control ventilation. Note the rapid acceleration and deceleration of inspiratory flow, producing a peaked waveform.

compliance, whereas a higher volume would be delivered as compliance improved, unless the clinician vigilantly adjusted the PIP.

In the mid-1970s an infant ventilator was specifically designed to deliver volume-controlled breaths to newborn infants. The clinician would target a volume of gas to be delivered to the baby, and the pressure was permitted to fluctuate to deliver the desired V_T . Although the principle seemed sound, there were severe technological limitations, including the inability to measure V_T , compliant ventilator circuits that increased compressible volume loss, slow response times, incompatibility with continuous flow, and, most importantly, insufficient knowledge about neonatal lung mechanics. In the early 1980s the manufacturer stopped producing the ventilator, and for the next decade almost all neonatal ventilation was pressure-limited.

The incorporation of microprocessor-based technology into neonatal ventilators and the development of small, lightweight, and low-dead-space transducers and accurate real-time monitoring enabled the reintroduction of volume-targeted ventilation into neonatal intensive care.¹ This paper will examine the current controversy as to which target variable, pressure or volume, is better for the treatment of neonatal respiratory failure.

Gas Delivery

The major difference between pressure and volume breaths is the way in which inspiratory gas flow is delivered to the patient. In both time-cycled pressure-limited ventilation and pressure-control ventilation there is a rapid

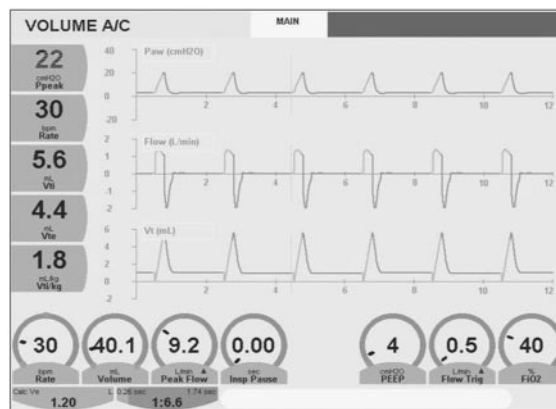


Fig. 2. Graphic representation of flow waveform (middle panel) in volume-targeted ventilation. Note the constant inspiratory flow, producing a square waveform.

acceleration of gas flow at the onset of inspiration, resulting in rapid pressurization of the circuit and the achievement of peak pressure and volume delivery early in inspiration. Flow then decelerates. This creates a peaked flow waveform and rapidly rising and falling pressure waveform (Fig. 1). Thus, breaths may be considered as being “front-end loaded.” Theoretically this might be advantageous when the primary pathophysiology is diffuse and characterized by the need for a high opening pressure. In contrast, flow delivery during volume-controlled ventilation (VCV) accelerates at the start of inspiration but is held constant throughout inspiration, creating a square waveform (Fig. 2). This results in a ramping effect, where peak pressure and peak volume delivery occur late in inspiration. These breaths are “back-end loaded,” resulting in slower inflation of the lung. VCV might be advantageous when lung disease is more heterogeneous and in situations where compliance changes quickly, such as following the administration of surfactant.²

Limitations of Volume Ventilation

The major drawback to the use of volume ventilation in newborns is related to the use of uncuffed endotracheal tubes. This results in a variable degree of leak around the endotracheal tube, which affects the volume of gas the baby actually receives. Ventilators are set to deliver a targeted V_T , but this is based on how much gas leaves the machine. A certain amount of this gas will be compressed within the ventilator, and this is referred to as compressible volume loss. This is affected by the compliance of both the lungs and the circuit, in addition to other factors, such as humidification. Because of compressible volume loss, it is imperative to measure the delivered V_T as close to the airway as possible.³

Correspondence: Steven M Donn MD, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, F5790, Mott Children's Hospital, University of Michigan Health System, 1500 E Medical Center Drive, Ann Arbor MI 48109-0254. E-mail: smdonnmd@med.umich.edu.

Volume-Targeted Modalities

Volume-targeted ventilation has been achieved in several ways. True volume-targeting involves all of the features described earlier, including constant flow delivery (square waveform) and auto-adjustment of pressure as compliance changes (Fig. 3). There are several hybrid forms of volume-targeting, where pressure adjustments are made to assure the delivery of a minimal V_T . One might also argue that volume-targeting of time-cycled pressure-limited ventilation is possible if the clinician is vigilant and constantly attends to the ventilator so that delivered V_T stays within a tight range. However, delivered breaths will still have the characteristics of pressure-targeted breaths, and it seems doubtful that even the most astute clinician could make adjustments as fast as a microprocessor.

Hybrid Modalities Providing Volume-Targeted Ventilation

Both VCV and time-cycled pressure-limited ventilation have certain advantages and disadvantages. Hybrid modalities try to combine the most desirable features of each. These include volume guarantee, pressure-regulated volume control, and volume-assured pressure support. They are essentially pressure-targeted forms of ventilation, but utilize microprocessor servo-controlled ventilation with an algorithm that adjusts the rise and fall of pressure for V_T delivery within a desired range. Volume guarantee and pressure-regulated volume control use the V_T of previous breaths as a reference, with follow-up adjustments in PIP on averages of 4–6 breaths. Volume-assured pressure support makes intra-breath adjustments of inspiratory time and/or pressure, until the desired volume has been delivered. All of these try to optimize V_T delivery, although each does so differently.

Volume-Guarantee Ventilation

Volume-guarantee ventilation, available on the Babylog 8000-plus ventilator (Dräger Medical, Telford, Pennsylvania), is a popular form of volume targeting. It is best described as a dual-loop synchronized modality that ventilates with time-cycled pressure-limited ventilation but allows pressure to be adjusted to deliver a V_T in a clinician-chosen range. The clinician selects a target V_T and limits the pressure (referred to as the working pressure). The device measures the exhaled V_T of the previous breath as a reference and adjusts the working pressure to reach the target volume over the next few breaths. The feedback loop has some limitations. For example, because adjustments to PIP are based on the exhaled V_T and are made in small increments to avoid overcompensation, the delivered V_T may not compensate for substantial breath-to-breath fluctuations in the presence of large leaks. When the leak

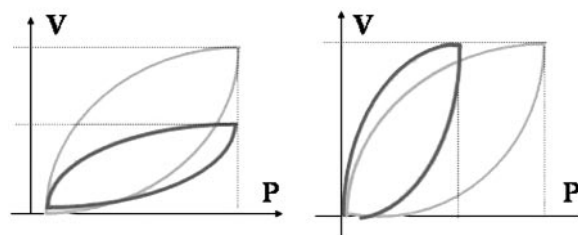


Fig. 3. Schematic comparison of pressure-volume loops in pressure-targeted (left) and volume-targeted (right) ventilation. During pressure-targeting a decrease in pulmonary compliance (moving from light loop to dark loop) results in a loss of tidal volume, despite consistency of inspiratory pressure. During volume-targeting, a decrease in compliance (moving from the dark loop to the light loop) results in an automatic increase in pressure to assure constant volume delivery.

exceeds 40%, volume guarantee is less reliable because of the inability to accurately measure the real V_T . Catch-up adjustments in pressure occur every few breaths, so if the ventilatory rate is set too low, its effectiveness may be questionable.

Potential advantages of volume guarantee include decreased volutrauma because the clinician sets a V_T that is not exceeded, and as lung compliance improves, pressure is automatically decreased.⁴ Volume guarantee can be used only with patient-triggered modes: assist-control, synchronized intermittent mandatory ventilation (SIMV), or pressure-support ventilation (PSV). The addition of volume guarantee to one of these modes enables the clinician to set a mean V_T to be delivered, as well as the standard ventilator settings of PIP, positive end-expiratory pressure, inspiratory time, and respiratory rate. No more than 130% of the target V_T is supposed to be delivered. The usual initial target is 4–5 mL/kg. The pressure limit is set approximately 15% to 20% above the peak pressure needed to consistently deliver the desired V_T . Because the adjustment of PIP is in reference to exhaled V_T and changes are made in small increments to prevent overcompensation, the PIP cannot be adjusted instantaneously to compensate for large breath-to-breath fluctuations. Consequently, although the delivered V_T is more consistent with volume guarantee than without it, there is fluctuation around the target value. Most infants can be extubated when they maintain V_T at or above the target value at a PIP < 10–12 cm H₂O with reliable respiratory effort.

Pressure-Regulated Volume Control Ventilation

Pressure-regulated volume control is another modality that attempts to combine the benefits of time-cycled pressure-limited ventilation and VCV. It is available on the Servo 300A and the Servo-i ventilators (Maquet, Bridgewater, New Jersey). It is flow-cycled and offers the “variable” flow rate of pressure-control ventilation and volume

targeting. Like volume guarantee, pressure-regulated volume control is a form of closed-loop ventilation; pressure is adjusted according to the delivered V_T . The new Servo-i ventilator measures pressure at the proximal airway, assuring better accuracy.⁵

The clinician selects a target V_T and the maximum allowable pressure. The microprocessor attempts to use the lowest pressure (with a decelerating-flow waveform) to deliver the set V_T . The first breath is delivered 10 cm H_2O above the baseline setting (positive end-expiratory pressure) and is utilized as a test breath to calculate the pressure needed to deliver the desired V_T in accordance with the patient's compliance. The next 3 breaths are delivered at a pressure that is 75% of the calculated necessary pressure. If the targeted V_T fails to be delivered, the inspiratory pressure is increased by 3 cm H_2O for each breath until the targeted volume is reached. If the targeted V_T is exceeded, the converse occurs, and pressure is decreased by 3 cm H_2O . Inspiratory pressure is regulated between the positive end-expiratory pressure and 5 cm H_2O below the clinician-limited PIP. Variations in delivered volume also occur because pressure adjustments are based on a 4-breath moving average.

Volume-Assured Pressure Support

Volume-assured pressure support is available on the VIP Bird Gold infant/pediatric ventilator (CareFusion, San Diego, California). This modality combines the advantages of pressure-targeted and volume-targeted ventilation within a single breath. It can be used with both assist-control and SIMV, or by itself in babies with reliable respiratory drive. It may be described as "variable-flow volume ventilation." This is a true hybrid modality, with decelerating, variable inspiratory flow, and guaranteed volume delivery. The breath is patient-triggered and begins as a PSV breath. The device measures delivered volume when inspiratory flow has decelerated to the set minimum. If the delivered volume exceeds the desired level, the breath is terminated by flow-cycling. However, if the preset volume has not been delivered, the breath transitions to a volume-targeted breath; the set flow will persist and the inspiratory time will be prolonged until the desired volume has been reached. In this situation the sinusoidal flow waveform transitions to a square waveform. If the delivered volume is considerably below the desired level, the pressure may also increase slightly.⁶

Volume-Support Ventilation

Volume-support ventilation is another hybrid modality, available on the Servo-i device (Maquet, Bridgewater, New Jersey), which is similar to PSV and pressure-regulated volume control.⁵ The volume-supported breath is patient-triggered, pressure-limited, and flow-cycled. It is used in

spontaneously breathing patients with adequate respiratory drive. Breath rate, V_T , and minute volume are chosen by the clinician; inspiratory time is determined by the patient. The algorithm adjusts the pressure limit by no more than 3 cm H_2O at a time. Adjustments are made in consecutive breaths until the targeted V_T is reached. The flow, pressure, and volume waveforms for a volume-supported breath are similar to those of pressure-supported breaths; however, the efficacy of volume support can be determined only by evaluating sequential graphic presentations. The V_T waveform will increase in a stepwise fashion until the target volume is reached.

Pressure Augmentation

Pressure augmentation, available on the Bear 1000 ventilator (CareFusion, San Diego, California), is another hybrid modality that matches the patient's flow demand while guaranteeing a minimum V_T .² Pressure augmentation is unique in the following ways: the pre-set V_T is only a minimum, and the patient can go above this; minimum V_T is guaranteed by adjustment in flow rather than pressure, which is fixed; and adjustment to flow is made within a single breath, like volume-assured pressure support. Pressure augmentation matches the patient's flow demand and lung dynamics and can be delivered in either assist-control or SIMV modes.

The Evidence

Table 1 summarizes studies on volume-targeted and pressure-limited ventilation.

Volume-Controlled Ventilation

One of the first trials evaluating VCV was conducted by Sinha and colleagues.⁷ Fifty pre-term infants with respiratory distress syndrome (RDS) and birth weights of at least 1,200 g requiring mechanical ventilation and surfactant therapy were randomized to receive either VCV or time-cycled pressure-limited ventilation. V_T was tightly maintained between 5–8 mL/kg for both treatment groups. Primary outcome measures included the time from study entry until achievement of either an alveolar-arterial oxygen difference less than 100 mm Hg, or a mean airway pressure less than 8 cm H_2O for at least 12 hours. Infants receiving VCV reached success criteria faster than the time-cycled pressure-limited ventilation group, with a mean time of 65.5 hours versus 125.6 hours ($P < .001$). The total duration of ventilation for the VCV group was lower as well (122.4 h vs 161.9 h, $P < .001$). Secondary outcomes included the incidence of intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, and bronchopulmonary dysplasia (BPD, defined as oxygen requirement beyond 36 weeks post-menstrual age,

Table 1. Summary of Key Trials Evaluating Volume-Targeted Versus Pressure-Limited Ventilation

First Author	Year	Randomization	Participants	Intervention	Outcome Measures
Cheema ¹⁰	2001	Randomized double crossover trial	40 infants < 34 wk gestation requiring MV for RDS. Exclusions: Infants requiring muscle relaxants or with lethal congenital anomalies	Synchronized intermittent positive-pressure ventilation alone vs the same mode plus volume guarantee, or SIMV alone vs SIMV plus volume guarantee	Primary: Peak airway pressure Secondary: Mean airway pressure, expired V _T , minute volume, F _{IO2} and transcutaneous CO ₂ and O ₂ pressure
D'Angio ²²	2005	Randomized controlled trial	213 infants who required MV were at least 24 wk gestational age, and weighed 500–1,249 g at birth	Pressure-regulated volume control vs time-cycled pressure-limited SIMV	Primary: Proportion of infants who were alive and extubated at 14 d of age Secondary: Proportion of infants who were alive and extubated at 28 d of age or 36 wk post-conceptual age, age at final extubation, mortality, failure of ventilatory mode, incidence of BPD, air leaks, pulmonary hemorrhage, PDA, IVH, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity, home oxygen use, and numerous other variables
Herrera ¹¹	2002	Randomized crossover trial	17 infants, 600–1,200 g, with respiratory failure. Exclusions: Severe congenital anomalies, perinatal asphyxia, sepsis, symptomatic PDA, grade 3–4 IVH, sedation, and clinical instability as defined by attending neonatologist	First 9 infants: SIMV alone vs SIMV plus volume guarantee (4.5 mL/kg) Next 8 infants: SIMV alone vs SIMV plus volume guarantee (4.5 mL/kg) vs SIMV plus volume guarantee (3 mL/kg) vs Assist-control only vs assist-control plus volume guarantee	Peak inspiratory pressure, mean airway pressure, number of ventilator-generated and patient-generated breaths, V _T , F _{IO2} , S _{PO2} , and transcutaneous O ₂ pressure
Keszler ¹²	2004	Randomized controlled trial	18 infants < 34 wk gestation, with RDS, on MV Exclusions: Patients with congenital anomalies, receiving neuromuscular paralysis or narcotic agents, or with > 30% endotracheal tube leak	Assist-control only vs assist-control plus volume guarantee	Primary: Percentage of time that V _T and P _{aCO2} were outside target range (4–6 mL/kg, and 35–45 mm Hg, respectively)
Listá ¹⁶	2004	Randomized controlled trial stratified by treatment center and gestational age (25–28 wk, and 29–32 wk)	53 infants, 25–32 wk gestational age, on mechanical ventilation for severe RDS Exclusions: Lethal anomalies, use of paralytic agents, grade 3–4 IVH, sepsis, or suspected infection	Pressure-support ventilation alone vs pressure-support ventilation plus volume guarantee (5 mL/kg)	Primary: Concentrations of interleukin-6, interleukin-8, and tumor necrosis factor α in tracheal aspirates on days of life 1, 3, and 7. Secondary: Duration of ventilation, airway pressure, incidence and rate of treatment for PDA, number of surfactant doses, incidence of air leaks, IVH, periventricular leukomalacia, retinopathy of prematurity, oxygen dependency at 28 d and/or 36 wk post-conceptual age, and survival
McCallion ²³	2005	Meta-analysis of the following 4 trials: Keszler et al., 2004 Listá et al., 2004 Pirowski et al., 1997 Sinha et al., 1997	178 infants < 37 wk gestational age Exclusions: Lethal congenital anomalies, muscle relaxation, suspected sepsis, lack of arterial access, narcotic use, endotracheal tube leaks > 30%, severe IVH, asphyxia, pneumothorax, and meconium aspiration syndrome	Volume-targeted vs pressure-limited ventilation	Primary: Hospital mortality, and death or need for supplemental oxygen at either 28 d of life or 36 wk post-conceptual age. Secondary: Failure of ventilatory mode or need for new use of muscle relaxants, duration of respiratory support, adverse blood gas values, PDA, air leaks, growth, IVH, periventricular leukomalacia, neurodevelopmental outcome, need for supplemental oxygen at either 28 d of life or 36 wk post-conceptual age among survivors, and impact of mode of volume-targeted ventilation
Pirowski ²¹	1997	Randomized controlled trial	60 infants with RDS or congenital pneumonia, requiring MV, and weighing < 2,500 g Exclusions: Terminal state of infant at admission, air leaks, congenital anomalies, sepsis, and meconium aspiration	Pressure-regulated volume control vs time-cycled pressure-limited intermittent mandatory ventilation	Primary: Duration of ventilation and incidence of BPD Secondary: Incidence of air leaks, IVH, hypotension, necrotizing enterocolitis, PDA, and need for sedation
Singh ⁸	2006	Randomized controlled trial A priori stratification into 2 groups according to birth weight: 600–1,000 g, and 1,001–1,500 g	109 infants, 600–1,500 g, gestational age 24–31 wk, requiring MV and surfactant therapy Exclusions: Severe congenital malformations	Volume-controlled ventilation vs time-cycled pressure-limited ventilation. V _T maintained at 4–6 mL/kg in both groups	Primary: Time from study entry until achievement of either an alveolar-arterial oxygen difference < 100 mm Hg or a mean airway pressure < 8 cm H ₂ O for at least 12 h. Secondary: Duration of ventilation or respiratory support, survival to discharge, incidence of chronic lung disease, IVH, periventricular leukomalacia, PDA, or necrotizing enterocolitis
Singh ⁹	2009	Long-term outcomes from prior randomized controlled trial (Singh et al., 2006)	90 of the 109 infants in the 2006 study were followed. Median corrected age at follow-up was 22 months	Volume-controlled ventilation vs time-cycled pressure-limited ventilation. Patients prospectively followed with medical assessments and parental interviews via a structured questionnaire	Mortality, re-admission rate, pulmonary outcomes (including the frequency of cough or wheeze, and use of pulmonary medications), and gross neurodevelopmental outcome
Sinha ⁷	1997	Randomized controlled trial	50 pre-term infants with RDS and birth weight of at least 1,200 g, requiring MV and surfactant therapy Exclusions: Pneumonia, sepsis, congenital malformations, lack of arterial access	Volume-controlled ventilation vs time-cycled pressure-limited ventilation. V _T maintained at 5–8 mL/kg in both groups	Primary: Time from study entry until achievement of either an alveolar-arterial oxygen difference < 100 mm Hg or a mean airway pressure < 8 cm H ₂ O for at least 12 h. Secondary: Incidence of IVH, periventricular leukomalacia, PDA, or BPD at 36 wk post-conceptual age

MV = mechanical ventilation
RDS = respiratory distress syndrome
SIMV = synchronized intermittent mandatory ventilation
V_T = tidal volume
F_{IO2} = fraction of inspired oxygen
BPD = bronchopulmonary dysplasia
PDA = patent ductus arteriosus
IVH = intraventricular hemorrhage
S_{PO2} = oxygen saturation measured via pulse oximetry

with correlating radiographic findings). The frequency of major scan abnormality (large intraventricular hemorrhage, ventriculomegaly, and intraparenchymal echodensities) was lower in the VCV group than in the time-cycled pressure-limited ventilation group ($P = .5$). While there was less BPD in the VCV group (4% vs 25%), this did not reach statistical significance. There were no significant differences in the incidence of air leaks or patent ductus arteriosus requiring therapy. The authors concluded that VCV appeared to be both safe and effective in this group of patients. At the time of this study, technological limitations of the ventilator precluded enrolling smaller infants.

A subsequent study by the same group further bolstered the efficacy of VCV.⁸ Refinements in ventilator design eventually led to the ability to deliver even smaller V_T , therefore providing VCV as an option to smaller babies than before. The second trial enrolled 109 infants, weighing 600–1,500 g, with gestational ages of 24–31 weeks. These babies also had RDS requiring mechanical ventilation and surfactant therapy, and were randomized to receive either VCV or time-cycled pressure-limited ventilation. A priori stratification into 2 groups according to birth weight was performed (600–1,000 g, and 1,001–1,500 g). Target V_T was 4–6 mL/kg for both groups. Primary outcomes evaluating the alveolar-arterial oxygen difference or mean airway pressure were identical to their prior study. There were no statistically significant differences in primary outcomes between the 2 groups in aggregate, although there was a trend toward faster weaning from the ventilator in the VCV group. However, in the cohort of infants weighing 600–1,000 g, those assigned to VCV reached their primary end point faster than those assigned to time-cycled pressure-limited ventilation, with a mean time of 21 hours versus 58 hours ($P = .03$). No statistically significant differences were found among the secondary outcomes, which included duration of ventilation and respiratory support, survival to neonatal intensive care unit discharge, and frequency of other complications, such as intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, and necrotizing enterocolitis Bell stage II or greater. The authors concluded that VCV is safe and efficacious in very-low-birth-weight infants and may have advantages over time-cycled pressure-limited ventilation, especially in smaller infants.

Singh and colleagues later reported the long-term outcomes of this study population.⁹ Ninety of the 109 infants enrolled in the initial study were prospectively followed using medical assessments and parental interviews via a structured questionnaire, to obtain masked evaluation of health status and gross neurodevelopment. The median corrected age at follow-up was 22 months. Fewer children in the VCV group required inhaled medications at the time of follow-up (odds ratio of 0.3, with a 95% confidence interval [CI] of 0.09–0.98, $P = .04$). Mortality, readmis-

sion rate, and frequency or severity of respiratory dysfunction were not affected by the type of ventilation received. The authors noted that the trend toward less chronic lung disease at 36 weeks post-conceptual age has a clinical correlate at 22 months, with fewer children requiring inhaled medications for chronic lung disease.

Volume-Guarantee Ventilation

Cheema and Ahluwalia were among the first to evaluate the efficacy of volume-guarantee ventilation in the neonatal population.¹⁰ In their crossover trial, 40 infants < 34 weeks gestation requiring mechanical ventilation for RDS received synchronized intermittent positive-pressure ventilation alone, versus synchronized intermittent positive-pressure ventilation plus volume guarantee, or SIMV alone versus SIMV plus volume guarantee. Patients who received synchronized intermittent positive-pressure ventilation were in the acute phase of RDS, while those who received SIMV were in the recovery (weaning) phase. There were slight decreases in PIP and mean airway pressure in both volume-guarantee groups, which reached statistical significance. There were no significant differences in overall gas exchange or adverse outcomes between those with and without volume guarantee. While this was a small short-term study, it did suggest that volume-targeted modalities are feasible for the neonatal population.

In another crossover trial, Herrera and colleagues noted that SIMV plus volume guarantee, compared to SIMV alone, had a statistically significant reduction in peak and mean airway pressure.¹¹

Keszler and Abubakar performed the first randomized controlled trial of volume guarantee.¹² Eighteen infants < 34 weeks gestation, who had RDS, were randomized to receive assist-control alone, or assist-control plus volume guarantee. Patients who received assist-control plus volume guarantee had fewer breaths outside the targeted V_T range, compared to assist-control alone (37% vs 61%, $P < .001$). The volume-guarantee group also had significantly fewer episodes of inadvertent hypocapnia, further supporting the potential for volume guarantee.

A more recent trial by Cheema and colleagues evaluated initial arterial blood gases in infants with RDS shortly after they were placed on synchronized intermittent positive-pressure ventilation versus synchronized intermittent positive-pressure ventilation plus volume guarantee.¹³ Stratified analysis revealed that infants > 25 weeks gestation had significantly less hypocarbia when volume guarantee was used (27% vs 61%, $P < .05$).

Further studies have addressed the efficacy of the various volume-guarantee modes. Fully supported breaths appear to be more effective, as demonstrated by Abubakar and Keszler's crossover trial of assist-control plus volume guarantee versus SIMV plus volume guarantee.¹⁴ Another

crossover trial by Scopesi and colleagues suggested that in the weaning phase, volume guarantee in modes that support every breath may be more effective than a combination of SIMV plus volume guarantee.¹⁵

The protective effects of volume guarantee are highlighted by the trial done by Lista et al, in which 53 premature infants with RDS were randomized to receive either PSV alone or PSV plus volume guarantee.¹⁶ A V_T of 5 mL/kg was targeted for all study patients. Tracheal aspirates were obtained on days of life 1, 3, and 7, and pro-inflammatory cytokines interleukin 6 (IL-6), IL-8, and tumor necrosis factor alpha were measured. Statistically significant elevations in IL-6 and IL-8 were found in patients who received only PSV, compared to PSV plus volume guarantee. The volume-guarantee group also had lower airway pressures and decreased duration of ventilation, though the latter did not reach statistical significance. Nevertheless, this study suggests that volume-targeted ventilation may reduce ventilator-induced lung injury.

A subsequent study by Lista and colleagues examined the inflammatory effects of ventilation with variable volumes.¹⁷ The targeted volume of 5 mL/kg used in their earlier study was compared to a smaller 3.5 mL/kg volume. Interestingly, the lower volume had a statistically significant increase in cytokine levels. Duration of ventilation was also prolonged for the low- V_T group (9.2 d vs 16.8 d, $P = .05$). It was hypothesized that these findings resulted from atelectrauma.

Lista et al most recently compared volume guarantee (5 mL/kg) with high-frequency oscillatory ventilation.¹⁸ This analysis revealed higher pro-inflammatory cytokine concentrations and longer oxygen dependence in patients receiving high-frequency oscillatory ventilation, compared to those receiving assist-control plus volume guarantee. These findings raise more questions regarding optimal modalities and what constitutes the ideal V_T .

Clinical studies of conventional ventilation have thus far used target V_T of 3–6 mL/kg.¹⁹ However, it is unlikely that “one size fits all,” and more research is warranted in this area.²⁰

Pressure-Regulated Volume Control

The evidence for pressure-regulated volume control ventilation is quite sparse. Piotrowski and colleagues compared pressure-regulated volume control to time-cycled pressure-limited intermittent mandatory ventilation in a randomized controlled trial.²¹ Sixty patients with RDS or congenital pneumonia requiring ventilatory support, weighing < 2,500 g, were enrolled in this study. Primary outcomes included the duration of ventilation and the incidence of BPD. No statistically significant differences were found between the 2 groups; however, subgroup analysis of infants < 1,000 g revealed a significant decrease in both

the duration of ventilation and hypotension in the pressure-regulated volume-control group compared to the time-cycled pressure-limited ventilation group ($P < .05$). Additional outcomes included a statistically significant decrease in the incidence of severe (grade 3–4) intraventricular hemorrhage in the pressure-regulated volume-control group (11% vs 35%, $P < .05$). Air leaks were also less frequent in the pressure-regulated volume-control group, although this did not reach statistical significance.

D’Angio and colleagues compared pressure-regulated volume control to time-cycled pressure-limited SIMV.²² They studied 213 infants who required mechanical ventilation and were at least 24 weeks gestational age and weighed 500–1,249 g at birth. Primary outcome analysis revealed no statistically significant differences between the 2 groups for the number of infants who were alive and extubated at 14 and 28 days of life, and at 36 weeks post-menstrual age. There was no difference in the incidence of BPD at 36 weeks post-menstrual age. The authors noted that infants in the pressure-regulated volume-control group were less likely to fail their assigned modality than those in the SIMV group (relative risk 0.61, 95% CI 0.38–0.97). The authors concluded that pressure-regulated volume control did not provide any clear benefits over time-cycled pressure-limited SIMV.

Meta-analysis

There has been one meta-analysis comparing volume-targeted to pressure-limited ventilation in the neonate thus far.²³ Four of the trials discussed above, consisting of 178 patients, met the inclusion criteria for this meta-analysis.^{7,12,16,22} The 2 primary outcome measures were hospital mortality, and death or need for supplemental oxygen at either 28 days of life or 36 weeks post-conceptual age. There were no statistically significant differences noted in the first outcome measure. As for secondary outcomes, there was a significant reduction in the mean number of days of intermittent positive-pressure ventilation in the volume-targeted group (weighted mean difference -2.93 , with a 95% CI of -4.28 to -1.57). This volume group also had a lower incidence of pneumothorax (relative risk of 0.23, with a 95% CI of 0.07 to 0.76). Grade 3–4 intraventricular hemorrhage was less common in the volume-targeted group (relative risk of 0.32, 95% CI of 0.11 to 0.9). Furthermore, there was a trend toward decreased BPD in the volume-targeted group that approached—but did not reach—statistical significance (relative risk 0.34, 95% CI of 0.11 to 1.05). The authors concluded that statistically significant effects favoring volume-targeting were shown, but further trials are still needed. When the study by Singh et al⁸ is added to these trials, there is a statistically significant reduction in the duration of ventilation and the incidence of pneumothorax, and the relative risk of

BPD is 0.7 (95% CI 0.5 to 1.05) (personal communication, Peter G Davis, Department of Paediatrics, Royal Women's Hospital, Parkville, Australia).

Why Does It Work?

The revival of volume-targeted ventilation in the treatment of neonatal respiratory failure and its early success raises questions about mechanisms of efficacy. While it is reasonable to believe that faster reduction in pressure might obviate both barotrauma and volutrauma, other factors are no doubt involved.

A recent study by Swamy and colleagues²⁴ examined the patients in the Singh et al trial.⁸ They looked at differences in V_T delivery in babies assigned to either VCV or time-cycled pressure-limited ventilation. Although the median V_T was quite similar, there was a statistically significant reduction in the variability of V_T delivery for babies receiving VCV. This could explain why they were able to be weaned faster and perhaps why there was less lung injury.

In a study of adult patients, Kallet and colleagues²⁵ showed differences in the work of breathing among patients randomized to VCV (1.09 ± 0.59 J/L), pressure-control ventilation (1.27 ± 0.58 J/L), and pressure-regulated volume control (1.35 ± 0.60 J/L). While comparable data do not exist yet for neonatal patients, it does suggest another mechanism of benefit.

Summary

In summary, volume-targeted ventilation of newborns with respiratory failure leads to small but clinically important improvements in short-term pulmonary outcomes, including BPD. Further investigation is warranted to better comprehend and refine the technique and to determine the optimal clinical applications. These should also include an assessment of clinically relevant long-term outcomes.

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