Volume-Targeted Ventilation of Newborns

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Traditionally, neonatal ventilation has been accomplished using time-cycled pressure-limited ventilation (TCPLV), wherein the peak inspiratory pressure is selected by the clinician and the ventilator provides each breath without exceeding this set pressure. Because peak pressure was believed to be the primary determinant of lung injury through barotrauma, it was assumed that TCPLV would limit lung injury by its ability to control peak pressure. This is an oversimplification. From recent observations it seems that it may actually be the volume of gas delivered to the lungs that is more likely to be the primary determinant of lung damage during mechanical ventilation [1]. This finding has given rise to the concept of volutrauma, which is fundamental to understanding the concept of lung volume-pressure hysteresis and the mechanisms of ventilator-induced lung injury (VILI) [2]. It has been shown in animal models that only six manual inflations of 35 to 40 mL/kg given to preterm lambs injures lungs and reduces the response to surfactant therapy [3]. Dreyfuss and colleagues [4] observed significant increases in lung edema and transcapillary albumin flux in rats ventilated at high tidal volumes in contrast to rats ventilated with low tidal volumes and high pressures. In another study, high-pressure ventilation with high tidal volumes caused a sevenfold increase in lung lymph flow and protein clearance in sheep, whereas high pressure ventilation with a normal tidal

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volume obtained by chest strapping produced a 35% decrease in lymph flow and protein clearance [5]. Hernandez and colleagues [6] could completely block microvascular damage in ventilated rabbit lungs using tidal volume limitation. Evidence for the importance of volutrauma also comes from the adult acute respiratory distress syndrome network trial [7]. Traditional approaches to mechanical ventilation in adults used tidal volumes of 10 to 15 mL/kg in patients who had acute lung injury and acute respiratory distress syndrome. This trial was conducted to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in these patients. The trial found that using lower tidal volumes decreased mortality and increased the number of days without ventilator use.

Conversely, ventilation at low lung volumes may also cause lung injury, especially in surfactant-deficient lungs. This injury is believed to be related to the repeated opening and closing of lung units with each mechanical breath (atelectotrauma). This phenomenon may explain the observation that recruitment of lung to increase the functional residual capacity protects against VILI [8,9].

If volutrauma is indeed important in the development of VILI then volume-controlled ventilation (VCV) may have advantages over TCPLV.

One of the first ventilators designed and built specifically for use in infants was a volume-controlled device. This version was eventually discarded because of technological limitations, including long response times, an ineffective triggering system, inability to deliver the small tidal volumes needed by preterm newborns, a highly compliant circuit (which increased compressible volume loss), and a lack of continuous flow during spontaneous breathing. Since the introduction of microprocessor-based ventilators, however, it is now possible to ventilate even the smallest of babies using VCV. This use has been facilitated by the development of sensitive and accurate flow sensors and servo-controlled mechanics allowing accurate measurement and tracking of gas flow to avoid overexpansion (volutrauma) or underexpansion (atelectotrauma) of the lungs and damage attributable to airway flow that is too high or too low (rheotrauma). This development may have advantages particularly in newborns who have respiratory distress syndrome (RDS) in whom lung compliance (and hence delivery of gas volume to the lungs) may rapidly change in response to the disease process or treatment, such as surfactant therapy.

VCV differs from volume guarantee (VG), pressure-regulated volume control (PRVC) or volume-assured pressure support (VAPS), which are hybrid forms of ventilation (see related articles in this issue). These are essentially pressure-limited modes of ventilation that use dual loop control to maintain tidal volume delivery in the target range. These newer forms of ventilation often lead to confusion and it is crucial that clinicians familiarize themselves with the new nomenclature and differences among them, which are often specific to individual devices.
Principles of time-cycled pressure-limited ventilation and volume-controlled ventilation

How does VCV differ from TCPLV? The difference was elegantly described by Carlo and colleagues [10]. Ventilators can be classified by the variables that are controlled (pressure, volume, or flow, which is the integral of volume), and the phase variables, such as those that start (trigger), sustain (or limit), and end (cycle) inspiration. At any one time, a ventilator can be only pressure controlled or volume controlled. Pressure- and volume-controlled breath types have certain specific characteristics, which are retained even if changes are made in phase variables by altering the trigger, limit, or cycling mechanism. For example, in TCPLV, a peak inspiratory pressure is set by the operator, and during inspiration gas flow is delivered to achieve that target pressure. The volume of gas delivered to the patient, however, is variable depending on the compliance of the lungs. At lower compliance (such as early in the course of RDS), a given pressure generates lower tidal volume compared with later in the course of the disease when the lungs are more compliant. This phenomenon is illustrated in Fig. 1a.

In contrast, the key differentiating feature of VCV is that the primary gas delivery target is tidal volume, which is set by the operator, and the peak inspiratory pressure may vary from breath to breath. At lower compliance higher pressures are generated to deliver the set tidal volume. As compliance improves, the pressure needed to achieve the set tidal volume is automatically reduced (auto-weaning of pressure). This relationship is illustrated in Fig. 1b.

In adult VCV inspiration is terminated and the machine is cycled into expiration when the target tidal volume is delivered. This process gave rise to the term “volume-cycled ventilation.” The use of uncuffed endotracheal tubes in newborns results in some degree of gas leak around the tube, however. True volume cycling thus is a misnomer in neonatal ventilation and the terms volume controlled, volume targeted, or volume limited better describe this modality [11]. Most modern ventilators provide the option of using a leak compensation algorithm to offset this problem. One should also realize that there is a discrepancy between the volume of gas leaving the ventilator and that reaching the proximal airway. Much of this results from compression of gas within the ventilator circuit. This phenomenon is referred to as compressible volume loss. It is greatest when pulmonary compliance is lowest. Use of semi-rigid circuits may help to minimize this. It is also affected by humidification. It is therefore critical to measure the delivered tidal volume as close to the patient as possible (ie, at the patient wye piece). Most current ventilators measure volume delivery during inspiration ($V_{T1}$) and expiration ($V_{T2}$). This measurement also enables quantification of gas leak and accurate compensation.

Another important feature of VCV differentiating it from TCPLV is the way that gas is delivered during inspiration. In traditional VCV, a square flow waveform is generated (Fig. 2) and peak volume delivery is achieved
at the end of inspiration [11]. Newer ventilators do allow the option of choosing a decelerating flow waveform. During VCV, inspiratory time is determined by the inspiratory flow rate. Because higher flow rates lead to more rapid filling of the lungs, set tidal volumes are achieved faster, which leads to an inverse relationship between flow and inspiratory time in VCV. In contrast, during TCPLV flow is sinusoidal and the opening pressure is reached quickly (see Fig. 2). After the target pressure has been reached, flow decelerates rapidly until inspiration is complete. The fixed inspiratory time allows more time for the alveoli to fill giving a theoretical advantage if high opening pressures are necessary, such as during the acute stages of RDS.

As with TCPLV, VCV can be provided in various modes, including intermittent mandatory ventilation (IMV), synchronized intermittent mandatory
ventilation (SIMV), and assist/control ventilation (A/C) (Fig. 3). It may also be combined with pressure support ventilation (PSV) during SIMV.

Hybrid ventilation

Because TCPLV and VCV have specific advantages and disadvantages (Box 1), combined or hybrid forms of ventilation have been developed in an attempt to combine the best features of each. These are primarily pressure-limited types of ventilation, but the delivered tidal volume is continuously monitored by the ventilator, and if it is less than the desired level, the peak pressure setting or inspiratory time are automatically adjusted to optimize tidal volume delivery. The available hybrid forms include VG, PRVC, and VAPS.

Volume guarantee ventilation

VG is a combined ventilator modality perhaps best described as a double or dual loop synchronized modality that ventilates using TCPL breaths with continuous flow, but it allows the pressure to be adjusted up to a clinician-set maximum using microprocessor technology to guarantee tidal volume delivery. The auto-feedback method, based on the previous breaths, aims to guarantee tidal volume delivery within a set range. The starting tidal volume target is usually 4 to 6 mL/kg. The maximum pressure limit is usually set about 20% greater than the pressure needed to deliver this tidal volume consistently. VG allows the clinician control of maximum airway pressure but also allows the ventilator to make appropriate adjustments of the
peak airway pressure up to the set maximum to achieve the set tidal volume. The peak pressure achieved by the ventilator thus varies between the baseline pressure (PEEP) and the set peak inspiratory pressure (PIP). Potential advantages of VG include (1) less risk for volutrauma, because the clinician can limit tidal volume delivery; (2) reduced peak pressure, such as when the baby makes a significant contribution from spontaneous effort; (3) more stable tidal volume delivery; and (4) auto-weaning of peak inspiratory pressure, which may reduce barotrauma. Clinicians using VG should be aware of limitations associated with the feedback loop mechanism, however, and must be willing to make necessary adjustments to minimize potential harm. For example, as adjustments to PIP are made in small increments to avoid

![Graphical waveforms](image-url)

Fig. 3. Graphic waveforms. Upper panel demonstrates pressure, flow, and volume waveforms during volume-controlled assist/control. Note the square flow waveform and consistent tidal volume delivery. Lower panel demonstrates pressure, flow, and volume waveforms during volume-controlled synchronized intermittent mandatory ventilation (SIMV) with pressure support (PS). SIMV breaths are recognizable by square flow waveform and “shark’s fin” pressure waveform, whereas PS breaths show a sinusoidal flow waveform.
overcompensation, the delivered tidal volume may not compensate for large breath-to-breath fluctuations. Although VG leads to more consistent tidal volume delivery, this may not always be the actual set tidal volume. Moreover, because variation in pressure is based on the exhaled tidal volume of the previous breath, it does not truly make real time adjustments. In the presence of large endotracheal tube leaks, it may underestimate tidal volume delivery and overcompensate on subsequent breaths. To date, however, three small published studies have not shown any harm in using VG [12–16].

**Pressure-regulated volume control**

PRVC is another hybrid form of ventilation. It is flow-cycled and offers the variable flow rate of pressure-control ventilation with the additional benefit of a targeted tidal volume. PRVC is also a form of closed-loop ventilation, in which pressure is adjusted according to the delivered tidal volume. The clinician sets a target tidal volume and the maximum pressure. The first breath is a VC breath and is used as a test breath to enable the microprocessor to calculate the pressure needed to deliver the set tidal volume based on the patient’s compliance. The next breaths are of variable flow. The mode therefore produces the same pressure and flow patterns as pressure control but also targets tidal volume delivered on each breath and adjusts the PIP on the subsequent breath.

**Box 1. Perceived advantages and disadvantages of volume-controlled and pressure-limited ventilation**

**Volume-controlled ventilation**

- Constant tidal volume delivery even with varying pulmonary compliance
- Linear increase in minute volume delivery as tidal volume increases
- Excessive peak pressure could increase barotraumas
- Auto-weaning of airway pressure as lung compliance improves

**Time-cycled pressure-limited ventilation**

- Limits peak airway pressure and thus limits barotrauma
- Improves gas distribution as set PIP is achieved throughout inspiratory cycle
- Reduces work of breathing by providing high initial flow
- Variable tidal volume delivery—risk for high tidal volume delivery as compliance improves or inadequate delivery if compliance worsens unless manually adjusted

*Abbreviation: PIP, peak inspiratory pressure.*
PRVC provides the benefits of pressure-limited ventilation (maximum pressure set by the clinician) with guarantee of set tidal volume delivery. The ventilator allows the delivery of PRVC with other modalities (pressure-controlled and volume-controlled ventilation) called “automode,” which allows the patient to breathe spontaneously while guaranteeing volume with pressure support and providing control ventilation in case of poor patient respiratory drive. A proximal flow transducer has also been introduced.

*Volume-assured pressure support ventilation*

VAPS is an unusual hybrid form in that it combines volume- and pressure-targeted ventilation within a single breath, rather than using a breath-averaging algorithm. VAPS can best be described as variable flow volume ventilation, which blends PSV and VCV. Each breath starts as a variable flow pressure support breath. The ventilator measures the delivered tidal volume when the inspiratory flow has decelerated to a minimum set level. If the delivered tidal volume equals or exceeds the desired tidal volume, the breath continues and then terminates as a typical flow-cycled pressure support breath. If the targeted tidal volume is not achieved, the breath transitions to a VCV breath by prolonging the inspiratory time (which can be limited) and slightly ramping up the pressure until the set tidal volume is delivered. Little clinical information on the neonatal applications of VAPS exists, but it may be advantageous in situations in which there is either rapidly changing compliance or erratic spontaneous respiratory drive.

*Clinical studies*

Compared with TCPLV, VCV is relatively new to the neonatal intensive care unit. There are not many controlled studies describing its safety and efficacy, although most published trials are favorable.

In a recent Cochrane review, McCallion and colleagues [17] identified eight randomized trials comparing the use of volume-targeted versus traditional pressure-limited ventilation in neonates. Only four met the eligibility criteria for inclusion in the meta-analysis. These four trials recruited a total of 178 preterm infants. The four trials are summarized below.

The first reported randomized controlled trial of true VCV versus TCPLV, which controlled tidal volume delivery in both arms of the trial, was conducted by Sinha and colleagues [18]. Fifty preterm infants weighing 1200 g or more who had RDS were randomly allocated to either VCV or TCPLV. Tidal volume delivery was set at 5 to 8 mL/kg in both groups so that the only difference was the ventilatory modality. The two groups were compared for the time required to achieve success criteria using the alveolar-arterial oxygen gradient (AaDO₂) or the mean airway pressure (Paw).
Infants randomized to VCV met the success criteria faster (mean time 65 versus 125 hours; $P < .001$) and had a shorter total duration of ventilation (mean time 122 versus 161 hours; $P < .001$). These babies also had a significantly lower incidence of large intraventricular hemorrhages and abnormal periventricular echodensities on ultrasound scans. There were no differences between the study groups in other complications associated with mechanical ventilation. Because of technological limitations in the minimum tidal volume delivery, infants weighing less than 1200 g could not be included in this first trial.

In another study performed contemporaneously, Piotrowski and colleagues [19] compared PRVC to traditional TCPL IMV. Sixty newborn babies weighing less than 2500 g and needing ventilation for RDS or congenital pneumonia were randomized to receive PRVC or IMV. The primary outcome measures were duration of mechanical ventilation and the incidence of CLD. Pulmonary air leaks and IVH were considered major adverse outcome measures. Duration of mechanical ventilation and incidence of CLD were similar in the two groups; however, the PRVC group had a lower incidence of Grade 2 IVH ($P < .05$) and fewer infants receiving PRVC had air leaks (3 versus 7). In a subgroup of infants weighing less than 1000 g, the duration of mechanical ventilation and incidence of hypotension were reduced in the PRVC group ($P < .05$).

The third study in this meta-analysis came from Keszler and Abubakar [12], who tested the hypothesis that VG would maintain the tidal volume and PaCO$_2$ within a target range more consistently than TCPLV used alone in the A/C mode. Eighteen preterm infants were randomized. VG significantly reduced the incidence of large tidal volume breaths (>6 mL/kg) more consistently but also significantly reduced the incidence of hypocarbia. They hypothesized that the use of VG had the potential to reduce the pulmonary and neurologic complications of mechanical ventilation.

On a similar theme, Lista and colleagues [14] evaluated the lung inflammatory response in preterm infants who had RDS, who were mechanically ventilated with and without VG, by measuring proinflammatory cytokines (IL-6, IL-8, TNF-$\alpha$) in tracheobronchial aspirate fluid. Fifty-three preterm infants (gestational ages 25–32 weeks) were randomized to be ventilated using PSV with VG (tidal volume = 5 mL/kg) and PSV without VG. The trial found a significant difference in IL-8 and IL-6 levels on day 3 between the two groups. Infants who received PSV alone required 50% more ventilation (12.3 ± 3 versus 8.8 ± 3 days), although this difference was not statistically significant because of the small sample size.

These four trials included in the Cochrane review used different ventilators and techniques but shared the common aim of investigating the putative advantages of controlling tidal volume delivery in the optimal range among premature infants who required mechanical ventilation during the first 72 hours of life [17]. No significant difference was found for the primary outcome of death before discharge. None of the four trials reported the
combined outcome of death or CLD. Analysis of the trials, however, showed that VCV resulted in a significant reduction in the duration of ventilation (weighted mean difference $-2.93$ days $[-4.28, -1.57]$) and the rate of pneumothorax (typical relative risk [RR] $0.23 [0.07, 0.76]$, risk difference [RD] $-0.11 [-0.20, -0.03]$, number needed to treat [NNT] $9$). There was also a significant difference in the rate of severe (grade 3 or 4) intraventricular hemorrhage favoring VCV (typical RR $0.32 [0.11, 0.90]$, RD $-0.16 [-0.29, -0.03]$, NNT $6$). There was a reduction in the incidence of BPD (supplemental oxygen at 36 weeks) among surviving infants, of borderline statistical significance (typical RR $0.34 [0.11, 1.05]$, RD $-0.14 [-0.27, 0.00]$, NNT $7$). Long-term outcomes were not addressed.

Subsequently, technological refinements in one of the ventilators enabled performance of an additional randomized trial, this time enrolling even smaller preterm babies. Singh and colleagues [20] compared the safety and efficacy of VCV to TCPLV in very low birth weight infants who had respiratory failure at birth and required mechanical ventilation. The results are the most recent on this subject and should only strengthen the findings of the meta-analysis in support of VCV.

In this study, 109 newborns 24 to 31 weeks’ gestation and weighing 600 to 1500 g at birth were randomized to receive either VCV or TCPLV. In both groups, ventilator variables were set to target an $V_{Te}$ of 4 to 6 mL/kg monitored and adjusted on an hourly basis. In the VCV group, delivered tidal volume was adjusted, and in the TCPL group, the peak inspiratory pressure was adjusted. During the acute phase of illness, all infants were placed in the assist/control mode. Targeted blood gas indices, including a pH 7.25 to 7.40, $Paco_2$ 4.5 to 6.5 kPa (35–49 mm Hg), and $Pao_2$ 7 to10 kPa (50–75 mm Hg) were used during the initial stage. Subsequently, $Paco_2$ was permitted to increase to 8 kPa (60 mm Hg) if the pH remained greater than 7.20. Once the infants were recovering from acute illness (PIP $>16$ cm H$_2$O and $FiO_2 <0.3$), the ventilatory mode was changed to SIMV with PSV. The two modalities were compared by determining the time required to achieve either an $AaDO_2$ less than 100 mm Hg or a mean Paw less than 8 cm H$_2$O. Secondary outcomes included mortality, duration of mechanical ventilation, and complications associated with ventilation. The mean time to reach the success criterion was 23 hours with VCV versus 33 hours with TCPLV ($P = .15$). This difference, however, was more striking in babies weighing less than 1000 g (21 versus 58 hours; $P = .03$). Mean duration of ventilation with VCV was 255 hours versus 327 hours with TCPLV ($P = .60$). There was no significant difference in the incidence of complications between groups. All deaths in the first week of life were related to respiratory disease and occurred exclusively in infants randomized to TCPLV. This finding was unexpected, because the groups were closely matched for severity of RDS. Although the modality of ventilation did not show an independent effect on survival on multivariate analysis, there was a trend toward better survival among babies treated with VCV (odds ratio, 0.5; 95% CI,
0.2–1.2; \( P = .10 \). These findings should be interpreted with caution because of the sample size. One explanation for this difference might lie in the way in which flow (and hence volume) is delivered. During TCPLV there is rapid flow delivery, resulting in a sharp increase in airway pressure and delivery of volume early in the inspiratory phase. Theoretically, this should favor the expansion of the more compliant areas of the lung, possibly leading to nonhomogeneous gas delivery. In VCV, there is a slower but more sustained increase in inspiratory pressure, with peak volume delivery occurring at end-inspiration. This might result in more uniform filling of the lung and less atelectotrauma. A further benefit might accrue from auto-weaning. Although a similar tidal volume target was selected for both groups, changes in the TCPLV group required a clinical decision, which may not have been performed as rapidly.

Other studies have also looked at the efficacy of VCV. Weiswasser and colleagues [21] examined differences in pulmonary vascular resistance (PVR), cardiac index (CI), and dynamic compliance (Cdyn) in healthy and a surfactant-deficient neonatal piglet model. Animals were randomly assigned to VCV or TCPLV using perfluorocarbon liquid ventilation. Although there was no significant difference in healthy lungs, in the surfactant-deficient model Cdyn was significantly higher and PVR was significantly lower in the VCV group after 180 minutes of lung injury. Cardiac index declined significantly in both groups irrespective of ventilatory modality.

Hummler and colleagues [22] performed a crossover study to compare volume-controlled SIMV with pressure-limited SIMV in a population of 15 mechanically ventilated babies exhibiting frequent hypoxemic episodes. Although there was no significant difference between the two groups with respect to primary outcome measure (time with oxygen saturation < 80%), babies randomized to volume SIMV maintained tidal volume better during episodes of desaturation, and bradycardia was less frequent in the volume SIMV group.

**Summary**

VCV and other volume-targeted modalities, such as VG, PRVC, and VAPS are new to neonatal intensive care and represent a departure from traditional TCPLV. Not surprisingly, there are only a few published randomized controlled clinical trials testing these modalities in the newborn population. Nonetheless, the evidence so far is highly encouraging. It seems that the consistency of tidal volume delivery during VCV in the face of varying lung compliance and the auto-weaning of airway pressure may be clinically advantageous, especially in conditions in which lung compliance can change rapidly, such as after surfactant treatment of RDS. Volume-targeted modalities have in common an objective to control tidal volume delivery in
an attempt to provide optimal lung inflation. Stability of tidal volume delivery may be beneficial, especially in extremely low birth weight infants, who are at increased risk for sustaining complications associated with mechanical ventilation. Although the benefits of VCV in the published studies have been restricted to short-term outcomes, such as duration of ventilation, pneumothorax, and intraventricular hemorrhage, they are still important findings and should not be ignored. The preliminary trials also have laid the groundwork for larger multicenter trials of a sufficient size to be able to address the question of whether VCV improves the long-term respiratory and neurodevelopmental outcomes of preterm infants requiring mechanical ventilation [23].

References


