Volume-targeted ventilation: one size does not fit all. Evidence-based recommendations for successful use

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ABSTRACT

Despite level 1 evidence for important benefits of volume-targeted ventilation (VTV), many vulnerable extremely preterm infants continue to be exposed to traditional pressure-controlled ventilation. Lack of suitable equipment and a lack of appreciation of the fact that 'one size does NOT fit all' appear to contribute to the slow uptake of VTV. This review attempts to improve clinicians' understanding of the way VTV works and to provide essential information about evidence-based tidal volume (V_T) targets. Focus on underlying lung pathophysiology, individualised ventilator settings and V_T targets are keys to successful use of VTV thereby improving important clinical outcomes.

BACKGROUND

Acceptance of volume-targeted ventilation (VTV) in newborn intensive care has been unexpectedly slow, despite sound a physiological rationale for its use and a growing body of evidence for its safety and efficacy.[1] The most recent Cochrane meta-analysis that included 16 parallel studies with 977 infants and 4 cross-over trials concluded that VTV, compared with pressure-limited ventilation, offered a number of important benefits with no apparent adverse effects (table 1).[2] An earlier meta-analysis by Peng *et al* had come to similar conclusions.[3] While these meta-analyses share the inevitable limitations of combining different modalities of ventilation and study designs, they nevertheless provide a stronger evidence base for VTV than that available for currently preferred ventilation approaches. Yet, while acceptance of VTV is high in Scandinavian countries, Australia and New Zealand,[4] it appears to be more spotty in much of the rest of the world[5] and especially in USA (Gupta *et al*, 2017, unpublished).

Although it may be tempting to attribute the reluctance of clinicians to embrace VTV to simple inertia, there are real frustrations and barriers to adopting the paradigm shift that this approach to respiratory support of sick newborn infants represents. The goal of this review is to improve clinicians' understanding of the way VTV works and the importance of individualising its application to specific clinical situations and individual patients. A major barrier to success appears to be a lack of appreciation of the fact that 'one size does NOT fit all'. I will review basic principles of VTV, identify some of the barriers and pitfalls in its application and provide evidence-based guidelines for optimal use of VTV in different clinical situations.

WHAT IS VTV AND HOW DOES IT WORK?

Although the rationale for the use of VTV and its operational characteristics have been described in detail in earlier publications,[1 6] it is important to briefly review the working principles of VTV and the distinction between VTV and volume-controlled ventilation before exploring the caveats and barriers to its use. Some confusion exists in describing approaches to regulating tidal volume (V_T) delivery. Many authors refer to all modalities that seek to control V_T as VTV; however, failing to distinguish between volume-controlled ventilation of the 'adult' type (VC) and volume-targeted modalities that are specifically designed for newborn ventilation may, in fact, be one of the barriers to its wider acceptance.

VTV is a term that should be reserved for pressure-controlled modalities of ventilation with automatic adjustment of peak inflation pressure (PIP) to target a user-set V_T measured at the airway opening. Thus, VTV is fundamentally different from VC modes of ventilation that are widely used in adult and paediatric applications (figure 1). In VC ventilation (also known as volume-cycled ventilation), a user-set V_T is introduced into the proximal (ventilator) end of the patient circuit. Pressure rises passively, in inverse proportion to lung compliance, reaching its peak just before exhalation. In larger patients with cuffed endotracheal tubes (ETTs), there is a good correlation between the set V_T and the V_T that reaches the patient's lungs. In extremely low birthweight (ELBW) infants, much of the set V_T is lost to compression of gas in the circuit and leak around uncuffed ETT,[7] necessitating a much higher set V_T in order to deliver a physiological V_T to the patient. Additionally, because ETT leak fluctuates and the degree of loss of volume to compression varies with PIP, the relationship between set and delivered V_T is not constant (figure 2). Use of a separate flow sensor at the airway opening to monitor exhaled V_T can overcome some of these limitations, allowing the operator to manually adjust the set V_T to deliver the desired V_T to the infant's lungs. However the ETT leak is usually variable necessitating frequent monitoring and adjustment, thus making this approach less attractive. An alternate, less desirable approach that is still used by some clinicians is to rely on clinical assessment of chest rise and breath sounds to select the set V_T, with subsequent adjustments based on blood gas measurement. However, there is evidence that clinical assessment of adequacy of V_T is poor[8] and therefore this approach cannot be recommended. Despite these limitations, VC has been shown to be feasible, at least under research conditions, even in

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Table 1 Documented benefits of volume-targeted ventilation. Data from Cochrane meta-analysis 2017 (Ref 2)

	Relative risk or mean difference	95% CI	NNTB (95% CI)
Death or BPD at 36 weeks PMA	0.75	0.53 to 1.07	NA
BPD at 36 weeks PMA	0.73	0.59 to 0.89	8 (5 to 20)
Grade 3–4 IVH	0.53	0.37 to 0.77	11 (7 to 25)
PVL ± severe IVH	0.47	0.27 to 0.80	11 (7 to 33)
Pneumothorax	0.52	0.31 to 0.87	20 (11 to 100)
Hypocapnia	0.49	0.33 to 0.72	3 (2 to 5)
Days of mechanical ventilation	−1.35	−1.83 to −0.86	

BPD, bronchopulmonary dysplasia; PMA, postmenstrual age; IVH, intraventricular haemorrhage; PVL, periventricular leucomalacia; NNTB, number needed to benefit.

small preterm infants, when a flow sensor at the airway opening is used and appropriate adjustments to the set V_T are made to achieve the desired exhaled V_T.[9]

Various modalities of VTV were developed specifically to address the limitations of VC ventilation when applied to ELBW infants. Volume guarantee (VG) on the Babylog 8000+and VN 500 ventilators (Draeger Medical GmbH, Lubeck, Germany) is the most thoroughly studied of the VTV modalities and therefore there is a stronger evidence base for specific recommendations for its use. However, the basic control algorithm has increasingly been adopted by other manufacturers, making for greater generalisability of the available data. In VG, the user chooses a target V_T and a pressure limit up to which the ventilator operating pressure (the working PIP) can be adjusted. The ventilator then compares the exhaled V_T of the previous inflation and adjusts the PIP up or down to try to achieve the set V_T. Exhaled V_T is used to minimise artefact resulting from air leakage around the uncuffed tube, because leak is always greater during inflation.[10] The pressure increase from one inflation to the next is limited to avoid oscillation in the system that could lead to excessive V_T. Consequently, with large changes in compliance or patient inspiratory effort, several inflations are needed to reach the target V_T. An important safety feature designed to avoid delivering an excessively large V_T opens the expiratory valve and terminates inflation if the V_T of the inflation exceeds 130% of the target (corrected for leak). The algorithm is geared towards slower adjustment for low V_T and faster response to excessive, potentially dangerous V_T. Autoregulation of inflation pressure leads

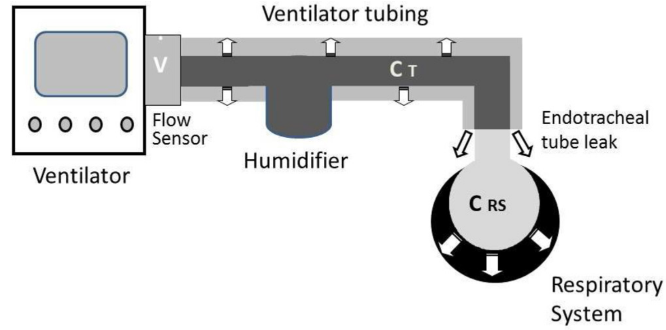

Figure 2 Limitations of volume-controlled ventilation in very small preterm infants. Tidal volume (V_T) measurement and delivery occur at the ventilator end of the patient circuit. Inflation pressure within the circuit leads to loss of volume to compression of gas (Boyle's law) and stretching of the circuit components. The amount of V_T lost is a function of the relative compliance of the circuit and the patient's respiratory system and often exceeds 50% in small infants. In addition, there is variable leak around the uncuffed endotracheal tube.

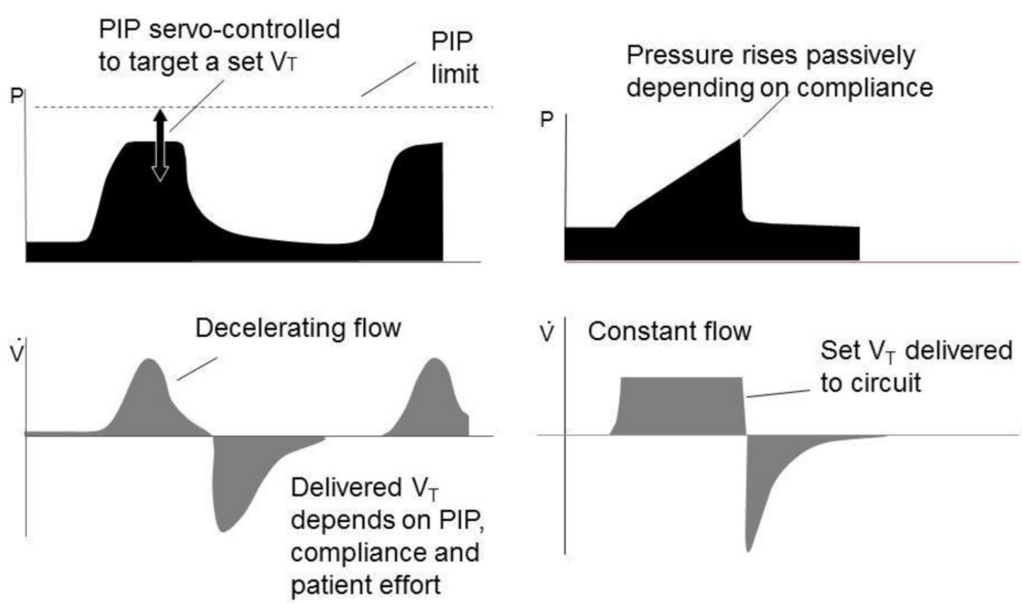

Figure 1 *With pressure-controlled ventilation* (left panel), the primary control variable is inflation pressure. When the circuit is pressurised, gas enters the lungs in proportion to inflation pressure and compliance of the respiratory system. The gas flow has a decelerating pattern. Tidal volume (V_T) is thus a dependent variable and changes with compliance. Volume-targeted ventilation modalities are modifications of pressure-controlled ventilation that automatically adjust the inflation pressure up or down to maintain a target V_T. During *volume-controlled ventilation*, the ventilator delivers a constant flow of gas into the ventilator circuit. Pressure rises passively and reaches the peak just before exhalation, which occurs as soon as the set V_T is delivered. V_T is the primary control variable and inflation pressure is a derived variable. Because the V_T is measured at the ventilator end of the circuit, the V_T reaching the patient's lungs may be different from the set V_T. PIP, peak inflation pressure .

to automatic weaning from mechanical ventilation and is one of the first examples of closed-loop ventilation technologies.[1] Because weaning occurs in real time, rather than intermittently in response to blood gases, VTV achieves faster weaning from mechanical ventilation.[2] Different manufacturers have implemented VTV modalities in different ways and it is important to be aware of some of the limitations related to specific devices. For example, pressure regulated volume control (PRVC) in the Servo-i ventilators (Maquet, Solna, Sweden) uses a control algorithm similar to VG, but the V_T measurement used for PIP adjustment is performed at the ventilator end of the circuit. V_T measurement at that site has been shown to grossly overestimate the true V_T that enters the lungs.[7] This issue has been corrected in the new Servo-n and Servo-u series, which should make PRVC behave much more like VG.

BARRIERS TO SUCCESSFUL USE OF VTV

The most obvious barrier is lack of suitable ventilators, especially in the USA, where many newborn intensive care units are equipped with ventilators primarily designed for adults (so-called universal ventilators), that have VC modes, but do not offer effective VTV modes suitable for ELBW infants. Even with the best available equipment, successful introduction of a new approach to ventilation can be challenging and should be undertaken deliberately with extensive education and planning.

Unfortunately, often the first attempt at using a new modality occurs when a very sick baby is failing on current support prompting a trial of the new approach, sometimes before everyone is ready. When initial attempts with a new approach disappoint, it is natural to sound the retreat and go back to what has always 'worked', that is, pressure-controlled ventilation. Change does not come easily; it is human nature to hold on to the approach that is familiar and comfortable. For this reason, it is important to have a local champion or 'super-user' who becomes comfortable with the modality and will be the resource person to troubleshoot and educate when needed. Additionally, it is best to gain experience with straightforward simple patients. As experience and confidence grow, more difficult patients can then be managed effectively.

Despite previous publications on the topic,[11 12] lack of knowledge regarding the appropriate V_T targets for a given clinical scenario and a good understanding of the patient-ventilator interactions in VTV modes are the other major barriers to success (Gupta *et al*, 2017, unpublished) and will be reviewed in the following paragraphs.

PRACTICAL GUIDELINES FOR VTV

Initiation of VTV

Synchronised modes that support every patient breath (assist/control (A/C) or pressure support ventilation) are preferred when using VTV.[13] The recommended V_T targets are based on A/C; synchronised intermittent mandatory ventilation requires a slightly larger V_T for the same alveolar minute ventilation,[14] because fewer breaths are supported and volume-targeted. The choice of appropriate V_T is the key to success and depends on the infant's size, postnatal age and underlying disease process. One size truly does *not* fit all babies. Table 2 lists appropriate V_T/kg and initial PIP limit for various conditions. The larger V_T/kg requirement in the smallest infants is due to the proportionally larger impact of instrumental dead space of the flow sensor, which ranges from 0.7 mL to about 1.1 mL, depending on the device and sensor used.[15] Infants with bronchopulmonary dysplasia (BPD) or meconium aspiration need larger V_T/kg because of increased alveolar dead space due to air-trapping and heterogeneous lung inflation, which results in wasted ventilation.[16] Older former preterm infants with evolving or established BPD need larger V_T/kg as well, due to a combination of increased anatomical and alveolar dead space.[17] Many clinicians believe that infants with pulmonary hypoplasia due to congenital diaphragmatic hernia (CDH) should be ventilated with correspondingly small V_T/kg. However, observational data suggest otherwise[18] and reflect the fact that, regardless of the degree of lung hypoplasia, the CO_2 production/kg in infants with CDH is similar to babies without CDH and therefore they need similar alveolar minute ventilation. Although a faster rate can increase alveolar minute ventilation to a degree, rapid shallow ventilation is inefficient because it results in progressively higher dead space:V_T ratio. When the V_T approaches dead space volume (approximately 3 mL/kg with ETT and flow sensor) a faster rate can no longer maintain adequate alveolar minute ventilation.

When electively switching from pressure-controlled mode to VTV in a patient with satisfactory gas exchange, the simplest approach is to select a target that matches the average V_T measured prior to the change-over. When initiating VTV immediately after intubation, the target V_T should be selected based on the infant's size, age and lung pathology (see table 2). Inflation pressure limit should initially be set 3–5 cm H_2O above the level estimated to be sufficient to achieve a normal V_T. If the target V_T cannot be reached with this setting, increase the pressure limit until the desired V_T is reached. If more PIP is needed than anticipated, it is important to make sure the ETT is not

Table 2 Recommended initial tidal volume (VT) and peak inflation pressure (PIP) settings for different clinical situations and patient conditions. Individual patients may need slightly smaller or larger VT. The stated PIP is a reasonable starting point based on underlying physiology and clinical experience, not published literature

Condition	Initial V_T	Initial PIP limit	Rationale for V_T/rationale for PIP	Reference for V_T choice
Term, late preterm, normal lungs	4–4.5 mL/kg	18 cm H_2O	Baseline/normal compliance	Dawson, *et al*[29]
Preterm RDS 1250–2500 g	4–4.5 mL/kg	26 cm H_2O	Low alveolar dead space/decreased compliance	Dawson, *et al*[29]
Preterm RDS 700–1249 g	4.5–5 mL/kg	24 cm H_2O	Dead space of the flow sensor/decreased compliance, risk of air leak	Nassabeh-Montazami, *et al*[15]
Preterm RDS <700 g	5.5–6 mL/kg	24 cm H_2O	Dead space of the flow sensor/decreased compliance, risk of air leak	Nassabeh-Monta-zami, *et al*[15]
Preterm evolving BPD, 3 weeks old	5.5–6.5 mL/kg	26 cm H_2O	Increased anatomical and alveolar dead space/worsening compliance	Keszler, *et al*[17]
Term MAS with classic CXR*	5.5–6 mL/kg	28 cm H_2O	Increased alveolar dead space/poor compliance	Sharma, *et al*[16]
Term MAS with white-out CXR	4.5–5 mL/kg	30 cm H_2O	Alveolar dead space less of a problem/very poor compliance	Keszler[30]
Term CDH	4–4.5 mL/kg	24 cm H_2O	Maintain normal alveolar minute ventilation/risk of air leak	Sharma, *et al*[18]
Established severe BPD	7–12 mL/kg	30 cm H_2O	Greatly increased alveolar and anatomical dead space; lower respiratory rate due to long time constants, needs larger V_T	Abman, *et al*[31]

* Classic CXR in MAS shows heterogeneous inflation and air trapping .
BPD, bronchopulmonary dysplasia; CDH, congenital diaphragmatic hernia; CXR, chest radiograph; MAS, meconium aspiration syndrome; RDS , respiratory distress syndrome.

kinked, malpositioned in the mainstem bronchus or obstructed on the carina. Significant volutrauma and/or air leak could result from failure to recognise endobronchial intubation. Pressure limit is subsequently adjusted to be about 25% above the current working pressure and adjusted periodically as lung compliance improves and working pressure comes down. If the ventilator is unable to reach the target V_T with the set inflation pressure limit, an alarm will sound. This serves as an early warning system that should prompt an evaluation of the reason for this change, for example, atelectasis, pneumothorax, ETT malposition or abdominal distention with upward pressure on the diaphragm.[19]

SUBSEQUENT ADJUSTMENT/WEANING

The suggested initial V_T settings are typical values, useful as a starting point. However, as is true for all physiological variables, there is considerable variation between similar patients. Patient activity, CO_2 production and presence of a base deficit for which the baby is attempting to compensate will affect the V_T requirement for an individual patient. It is therefore essential that the infant's response to the initial settings is promptly evaluated at the bedside and adjustments are made, if needed, even before a blood gas measurement is obtained. One of the important benefits of avoiding routine use of sedative and paralytic medications is the ability to observe the infant's response to initial ventilator settings unobscured by drugs. Careful observation of the patient's respiratory effort and rate, as well as assessment of the flow and pressure curves on the ventilator display will provide clues about the appropriateness of the selected V_T for this particular patient. Transcutaneous CO_2 monitoring, when available, can provide additional indication of appropriateness of alveolar minute ventilation. With actively breathing infants, the displayed values will fluctuate, therefore observations should be made over a number of ventilator cycles.

When ventilator support is adequate, the infant should be breathing comfortably without distress or tachypnoea. Persistence of significant tachypnoea and retractions indicate inadequate support and a need for a larger V_T, especially when coupled with relatively low working PIP and measured V_T that often exceeds the target V_T. To appreciate this concept it is essential to recognise that the measured V_T is the result of transpulmonary pressure, the combined positive inflation pressure from the ventilator and the negative inspiratory pressure of the infant. In the extreme case of inadequate V_T setting, the PIP may be reduced to or be near the level of positive end-expiratory pressure (PEEP). This occurs because, as long as the patient is able to spontaneously generate a V_T that exceeds the V_T target, the algorithm will continue to lower the PIP. Eventually, the infant becomes exhausted and can no longer sustain the effort. The ventilator takes over at the set backup rate and, in the absence of the infant's contribution to transpulmonary pressure, the working pressure will return to the level needed to reach the target V_T. As the partial pressure of carbon dioxide (PCO_2) rises and the pH drops, the infant will again respond to his/her respiratory drive and attempt to restore normal pH. This cycle leads to fluctuation of PCO_2 and intermittent drop in mean airway pressure that may contribute to intracranial haemorrhage and atelectasis. On the other hand, if the infant is generating V_T above the target value and is comfortable without retractions, tachypnoea or increasing oxygen requirement, despite the low working PIP, it indicates improved respiratory status and that extubation is in order.

It is important to recognise that pH, not PCO_2 is the primary driver of respiratory control; the physiological response to metabolic acidosis is hyperventilation. Thus PCO_2 values must be interpreted in the context of pH. Moderate degree of metabolic acidosis is common in ELBW infants with immature renal tubular function and high protein intake in the first days after birth. These infants need a relatively lower PCO_2 target to maintain a reasonably normal pH, avoid excessive work of breathing and loss of lung volume recruitment when the PIP falls intermittently to, or near, the level of PEEP. Failure to appreciate these interactions and inappropriate weaning of V_T based on PCO_2 alone is a common reason why VTV 'does not work'. Available evidence indicates that perivascular pH, not PCO_2 primarily controls cerebral vascular tone,[20] suggesting that mild stable hypocapnia with a neutral or mildly acidotic pH is not likely to have adverse effects. However, PCO_2 much below 35 torr (approximately 4.5 kPa) should be avoided, especially if coupled with an alkalotic pH, as should rapid fluctuations in PCO_2, which have been shown to be the strongest predictor of severe intraventricular haemorrhage.[21]

Another challenge for users of VTV is leakage of air around uncuffed ETT, which is present to some degree in most intubated ELBW infants.[22 23] The problem tends to increase with time as the immature tissues of the trachea and larynx stretch due to positive pressure ventilation (acquired tracheomegaly)[24] and as the infant grows. Even though the exhaled V_T is less subject to leak-related underestimation of V_T, when the leak exceeds 35%–40%, V_T measurement is no longer accurate, potentially resulting in inadvertent hypocapnia because a proportion of the exhaled gas escapes around the ETT during expiration and is thus not measured by the flow sensor as exhaled V_T.[25] When the microprocessor detects a below-target V_T it increases PIP, resulting in an excessive V_T. For this reason, many VTV devices cannot be safely used when the ETT leak approaches this limit. The clinician must choose one of two options: replace the ETT electively to eliminate the leak, or abandon VTV in favour of pressure-controlled ventilation, which is not affected by ETT leak. Because of this issue, there has been some interest in reassessing the use of cuffed ETT in newborn care.[26] However, some of the newest infant ventilators now have the ability to calculate an estimated value for the true V_T even in the face of a very large leak,[23] thus avoiding this common problem and rendering cuffed tubes unnecessary. Nonetheless, unless extubation is imminent, the ETT should be changed to a larger size if the leak consistently exceeds 50% in order to provide a lower resistance airway for the infant during the weaning process. Understanding the capabilities your ventilator is therefore crucial to optimal care.

The process of weaning also causes some confusion. The effective closed-loop system of VTV is counterintuitive to some practitioners who are accustomed to manual adjustments of ventilator settings. This sometimes leads to inappropriate lowering of target V_T in an effort to wean the patient off the ventilator. However, the physiological V_T required by the patient does not decrease (over time it may actually increase); what comes down is the pressure required to achieve that V_T as compliance of the respiratory system improves and the infant breathes more effectively. In fact, it is important to remember to adjust V_T for weight gain in infants who remain ventilated for extended periods. Decreasing V_T target below the patient's physiological need will only increase the work of breathing[27] and may delay successful extubation.

CONCLUSION

Faced with level 1 evidence of important benefits of VTV, it is hard to justify continuing to expose infants to pressure-controlled ventilation. The way forward is for us is to be willing to abandon our comfort zone and embrace the paradigm shift that VTV represents. The transition should be undertaken deliberately and only after much training and appraisal of the available literature. Focus on underlying lung pathophysiology, individualised ventilator settings and V_T targets are keys to success. A formal ventilation protocol is an effective way to implement respiratory support, especially when transitioning to a new approach.[28]

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