

# STATE-OF-THE-ART

## State of the art in conventional mechanical ventilation

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Despite a shift to noninvasive respiratory support, mechanical ventilation remains an essential tool in the care of critically ill neonates. The availability of a variety of technologically advanced devices with a host of available modes and confusing terminology presents a daunting challenge to the practicing neonatologist. Many of the available modes have not been adequately evaluated in newborn infants and there is paucity of information on the relative merits of those modes that have been studied. This review examines the special challenges of ventilating the extremely low birth weight infants that now constitute an increasing proportion of ventilated infants, attempts to provide a simple functional classification of ventilator modes and addresses the key aspects of synchronized ventilation modes. The rationale for volume-targeted ventilation is presented, the available modes are described and the importance of the open-lung strategy is emphasized. The available literature on volume-targeted modalities is reviewed in detail and general recommendations for their clinical application are provided. Volume guarantee has been studied most extensively and shown to reduce excessively large tidal volumes, decrease incidence of inadvertent hyperventilation, reduce duration of mechanical ventilation and reduce pro-inflammatory cytokines. It remains to be seen whether the demonstrated short-term benefits translate into significant reduction in chronic lung disease. Avoidance of mechanical ventilation by means of early continuous positive airway pressure with or without surfactant administration may still be the most effective way to reduce the risk of lung injury. For babies who do require mechanical ventilation, the combination of volume-targeted ventilation, combined with the open-lung strategy appears to offer the best chance of reducing the risk of bronchopulmonary dysplasia.

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### Introduction

Technological advances in the design of mechanical ventilators and improved understanding of factors responsible for ventilator-induced

lung injury (VILI) have occurred over the past two decades, resulting in improving outcomes in extremely low birth weight (ELBW) infants. Today, few infants die of acute respiratory failure; early mortality is now predominantly from other complications of extreme prematurity, such as infection, necrotizing enterocolitis or intracranial hemorrhage. Although further reduction in mortality remains an important goal, focus has shifted from reducing mortality to reducing the still unacceptably high incidence of chronic lung disease. Though high-frequency ventilation has shown promise in this regard, inconsistent results and continued concerns about the hazards of inadvertent hyperventilation have limited its acceptance as first-line therapy in infants with uncomplicated respiratory distress syndrome (RDS).<sup>1</sup>

At the present time, respiratory support in newborn intensive care continues to evolve rapidly. Utilization of noninvasive respiratory support has become widely accepted as the most effective means of reducing the risk of VILI. Although the concept is very attractive and supported by a number of uncontrolled and cohort studies, it must be pointed out that we currently lack the definitive randomized clinical trial data to validate the presumed benefits of nasal continuous positive airway pressure (N-CPAP) as the primary mode of respiratory support.<sup>2</sup> Surfactant, if used at all, is now increasingly administered without prolonged mechanical ventilation, thus potentially preserving the well-documented benefits of surfactant replacement therapy, while avoiding the dangers of prolonged mechanical ventilation. Whether and under what circumstances brief intubation for surfactant administration is indicated remains unclear. Administration of nebulized surfactant during N-CPAP is a potentially attractive approach that is currently under investigation. Nasal intermittent mandatory ventilation (IMV) may be able to augment an ELBW infant's inadequate respiratory effort without the complications associated with endotracheal intubation. This approach may be of substantial benefit in reducing the incidence of ventilator-associated pneumonia and thus avoiding the contribution of postnatal inflammatory response to the development of bronchopulmonary dysplasia (BPD). Detailed discussion of noninvasive respiratory support is beyond the scope of this paper; the reader is referred to other reviews on this important topic.<sup>3–5</sup>

Notwithstanding the lack of unequivocal data, substantial shifts in clinical practice have become evident, resulting in a reduction

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in the number of infants receiving mechanical ventilation. Most of the infants who now receive mechanical ventilation are much smaller and more immature than those ventilated only 10 years ago. They often require ventilation for extended periods for reasons not directly related to lung disease. Data from clinical trials of respiratory support conducted many years ago may thus not be directly applicable to the extremely immature infants that now constitute the majority of ventilated infants.

For the more severely ill infants who require mechanical ventilation, a new generation of microprocessor-based ventilators with technologically advanced features enabling effective synchronized (also known as patient-triggered) ventilation has become widely available. Even more promising is the advent of volume-targeted modalities of conventional ventilation that, for the first time, allow effective control of delivered tidal volume ( $V_T$ ) for neonatal ventilation. In this review, I will briefly cover the unique challenges of ventilating ELBW infants, discuss the basic modes of synchronized ventilation, describe the concept of volume-targeted ventilation, examine relevant literature and briefly discuss the clinical application of the techniques.

### Basic ventilator terminology/general classification of ventilation modes

The rapid evolution of ventilator technology with increasing availability of a variety of basic and complex modes of respiratory support has led to a great deal of confusion in terminology and general concepts of mechanical ventilation. Because different manufacturers employ different nomenclature to describe often closely related modes of ventilation, communication between users of different devices has become increasingly difficult. Most of the ventilators used in newborn infants today are designed to span the entire age range from preterm newborn to adults and may have a variety of modes that have never been evaluated in newborn infants. Detailed discussion of the terminology is beyond the scope of this paper. The interested reader is referred to in-depth reviews of the subject.<sup>6</sup> For the purpose of this review, only the basic terminology for modes that are primarily used in newborn infants will be defined briefly.

Basic modes of mechanical ventilation are best classified on the basis of three factors:

- How is each breath initiated?
- How is gas flow controlled during breath delivery?
- How is the breath ended?

Breaths can be initiated by a timing mechanism without regard to patient inspiratory effort. These modes are known as controlled ventilation. Alternately, breaths may be triggered by the patient's inspiratory effort, in which case we refer to assisted, also known as synchronized or patient-triggered ventilation.

The primary control variable for gas flow during the breath may be pressure (pressure-controlled/pressure-limited ventilation) or delivered  $V_T$  (volume-controlled ventilation, VCV).

Breath termination may occur based on elapsed time (time cycled), or based on cessation of inspiratory flow (flow or volume cycled).

In addition to these basic modes, a variety of hybrid modes have been developed that combine features of several of the basic types. A complete discussion of all available modes is beyond the scope of this paper, but the basic neonatal modes will be discussed in subsequent paragraphs.

### Unique challenges in mechanical ventilation of newborn infants

#### *Lung mechanics*

Small infants with noncompliant lungs have very short time constants and normally have rapid respiratory rates (RRs) with very short inspiratory times ( $T_I$ 's) and have limited muscle strength. This situation imposes great technological challenges on device design, especially in terms of breath triggering, breath termination and  $V_T$  measurement. These are the reasons why the introduction of synchronized ventilation into clinical practice in newborn infants lagged substantially behind its use in adults.

#### *Uncuffed endotracheal tubes*

Uncuffed endotracheal tubes (ETTs) have traditionally been used in newborn infants, because of concern about pressure necrosis of the neonatal tracheal mucosa and the small size of the tubes that makes inflatable cuffs more difficult to incorporate. As a consequence, majority of infants have some degree of leak around the ETT, especially later on in their course as the larynx and trachea progressively dilate as a result of exposure of these immature structures to cyclic stretch at a rate of as much as 3600 times per hour or more than 86 000 times per day. The leak is always greater during inspiration than in expiration, because the pressure gradient driving the leak is greater during inspiration and because the airways, including the trachea, distend with the higher inspiratory pressure. Therefore, it is important to measure both inspiratory and expiratory  $V_T$ , with the latter more closely approximating the volume of gas that had entered the patient's lungs. It is critical to appreciate that the magnitude of the leak (or indeed its presence) varies from moment to moment. This is because the ETT is inserted only short distance beyond the larynx; therefore, the leak will change with any change in the infant's head position, slight tension on the ETT and so on. Leak around ETT also imposes additional challenges in breath triggering and termination, as discussed below.

#### *Measurement of tidal volume*

The importance of very accurate  $V_T$  measurement in any sort of volume-controlled/volume-targeted ventilation of ELBW infants

should be self-evident, given that infants weighing 400 to 1000 g require  $V_T$ 's in the range of 2 to 5 ml.

Flow and volume measurement has traditionally been performed at the junction of the breathing circuit and the ventilator. This placement is convenient and avoids extra wires and the added instrumental dead space (IDS). However, in neonates this remote placement results in major inaccuracy of the  $V_T$  measurement. When the  $V_T$  is measured at the ventilator end of the circuit, the value does not account for compression of gas in the circuit and humidifier, distention of the circuit or leak around the ETT. The loss of volume to gas compression is a function of the compliance of the ventilator circuit relative to the patient's lungs and to the volume of the circuit/humidifier, relative to the patient's lungs. In large patients with cuffed ETT, the volume injected into the circuit correlates reasonably well with the actual  $V_T$  entering the lungs and the volume loss to compression of gas in the circuit can be readily corrected by available algorithms. In small infants whose lungs are tiny and stiff, compared to the volume and compliance of the circuit/humidifier, the loss of volume to the circuit is not readily corrected, especially in the presence of significant ETT leak.

### Traditional volume-controlled ventilation

Volume-controlled/volume-cycled ventilators deliver a constant, preset  $V_T$  with each ventilator breath. In theory, these volume ventilators allow the operator to select  $V_T$  and frequency and therefore directly control minute ventilation. The ventilator delivers the preset  $V_T$  into the circuit generating whatever pressure is necessary, up to a set safety pop off, generally set at a pressure  $>40$  cm  $H_2O$ . A maximum  $T_I$  is also set as an additional safety measure. Inspiration ends when the preset  $V_T$  has been delivered or when the maximum  $T_I$  has elapsed. The latter ensures that with very poor lung compliance, the ventilator does not maintain inspiration for a prolonged period trying to deliver the set  $V_T$ .

The major limitation of volume-controlled ventilators is that what they actually control is the volume injected into the ventilator circuit, not the  $V_T$  that enters the patient's lungs. This limitation is based on the fact that, as discussed previously, the  $V_T$  measurement does not account for compression of gas in the circuit and humidifier and distention of the compliant circuit. Most importantly, the variable leak around uncuffed ETTs used in newborn infants makes accurate control of delivered  $V_T$  very difficult with traditional volume-controlled modes. A recent paper by Singh *et al.*,<sup>7</sup> did demonstrate the feasibility of VCV when special measures are taken to compensate for these problems. In that study, the set  $V_T$  was manually adjusted at frequent intervals to achieve a target exhaled  $V_T$  measured by a proximal flow sensor at the airway opening.

### Pressure-controlled ventilation

Currently, the standard in neonatal mechanical ventilation is intermittent positive pressure ventilation using time-cycled, pressure-limited (TCPL), continuous flow ventilators. This practice evolved largely because of the difficulties with traditional VCV described above. The basic design of these ventilators can be thought of as a T-piece circuit with continuous flow of gas and a valve that directs gas flow into the patient or allows it to continue around the circuit. A pressure-limiting valve controls the maximum pressure in the circuit during inspiration (peak inspiratory pressure, PIP) and a second valve maintains a certain level of positive pressure during the expiratory phase (positive end-expiratory pressure, PEEP).

In their basic form these ventilators require the clinician to set inspiratory and expiratory time ( $T_I$ ,  $T_E$ , which together determine the RR), PIP, PEEP, inspiratory flow rate and  $FiO_2$ . During inspiration, the expiratory valve closes, the circuit is pressurized and gas flows into the patient. Once the pressure within the patient circuit reaches the PIP, additional gas escapes through the pressure-limiting valve. When the  $T_I$  has elapsed, the expiratory valve opens, allowing circuit pressure to fall rapidly to the level of PEEP. The valve remains open with circuit pressure at the PEEP level with fresh gas flowing in the circuit available for spontaneous breathing, until the end of  $T_E$ , at which point the valve closes again and the cycle repeats.

Pressure-limited ventilators overcome the difficulties associated with VCV and are simple to use. However, their chief disadvantage is that  $V_T$  delivery is not directly controlled, but rather is the dependent variable that fluctuates as a function of inspiratory pressure and lung compliance.

### Synchronized ventilation

#### *Rationale, types of triggering devices and potential pitfalls*

The standard mode of ventilation used in newborn infants before the introduction of synchronized ventilation was known as IMV. This TCPL mode of ventilation provides a set number of 'mandatory' mechanical breaths. The patient continues to breathe spontaneously, using the fresh gas flow available in the ventilator circuit. Unfortunately, the irregular respiratory pattern of the baby frequently leads to asynchrony between the infant and the ventilator. High airway pressure, poor oxygenation and large fluctuations in intracranial pressures result when the ventilator breath occurs just as the infant exhales. Heavy sedation and muscle paralysis were often employed to prevent the baby from 'fighting the ventilator'. These interventions resulted in greater dependence on respiratory support, lack of respiratory muscle training, generalized edema and inability to assess the neurological status. The advantages of synchronizing the infant's spontaneous effort with the ventilator cycle, rather than using muscle relaxants, are

intuitively obvious, though large clinical trials clearly documenting their superiority are lacking.

The introduction of synchronized ventilation into neonatal care lagged far behind its use in adults due to technological challenges imposed by the small size of preterm infants. The ideal triggering device must be sensitive enough to be activated by a small preemie, must be relatively immune from auto-triggering and must have a sufficiently rapid response time to match the short  $T_I$ 's and rapid RRs seen in small premature infants. Variable leak of gas around uncuffed ETTs further complicates the situation. The types of triggering devices used in clinical care and their relative advantages are listed in Table 1. Clinical and laboratory experience has shown that flow triggering using a flow sensor at the airway opening (at the ETT adaptor) is ultimately the best compromise currently available.<sup>8,9</sup> At this time, all infant ventilators in common use utilize this triggering mode. An emerging technology, which recently became available, uses the electrical activity of the diaphragm (EAdi), as assessed by trans-esophageal electromyography to trigger inspiration. This approach, though not yet adequately evaluated in newborn infants, is attractive because it has the shortest trigger delay, does not require a flow sensor and is not affected by ETT leakage.<sup>10</sup>

Although flow triggering is the best currently available method, it is important to be aware of the potential problems of this mode of triggering. The interposition of the flow sensor adds approximately 1 ml of dead space to the breathing circuit, which becomes a larger proportion of the  $V_T$  in the tiniest infants. The second problem is susceptibility to auto-triggering in the presence of a leak around the ETT. Any substantial leak flow during the expiratory phase will be (mis)interpreted by the device as inspiratory effort and would trigger the ventilator at an excessively rapid rate. When recognized, the problem can be corrected by decreasing trigger sensitivity. However, the magnitude of the leak often changes quite rapidly, requiring frequent adjustment.

**Table 1** Comparison of triggering methods

<i>Method</i>	<i>Advantages</i>	<i>Disadvantages</i>
Impedance	No added dead space, noninvasive	Poor sensitivity, many artifacts
Pneumatic capsule	Rapid response, no extra dead space, leak tolerant	Positioning is critical, no longer commercially available
Pressure	No added dead space, leak tolerant	Poor sensitivity, long trigger delay, high WOB
Airflow	Very sensitive, rapid response	Added dead space, leak sensitive
Diaphragm EMG	Sensitive, most rapid response, leak tolerant	Requires careful positioning of probe

Abbreviations: EMG, electromyography; WOB, work of breathing.

Furthermore, when the trigger is made less sensitive, increased effort is needed to trigger the device and there is a longer trigger delay; both highly undesirable. One device, the Draeger Babylog (Draeger Medical Inc., Telford, PA, USA), offers an effective solution to this problem, utilizing a proprietary leak compensation technology that derives the instantaneous leak flow throughout the ventilator cycle and mathematically subtracts this flow from the measured value. This effectively eliminates the leak-related problem of auto-triggering and allows the trigger sensitivity to remain at the most sensitive value, preserving rapid response time and minimal work to trigger the device.

## Basic modes of synchronized ventilation

### *Synchronized intermittent mandatory ventilation*

Synchronized intermittent mandatory ventilation (SIMV) provides a preset number of mechanical breaths as in standard IMV, but these are synchronized with the infant's spontaneous respiratory effort, if present. Spontaneous breaths in excess of the set rate are not supported. This results in uneven  $V_T$ 's and high work of breathing (WOB) during weaning, an important issue particularly in extremely small and immature infants with correspondingly narrow ETT. The high airway resistance of narrow ETT, limited muscle strength and mechanical disadvantage conferred by the infant's excessively compliant chest wall typically result in small, ineffective  $V_T$ . Because instrumental dead space (IDS) is fixed, very small breaths that largely rebreathe dead space gas will contribute little to effective alveolar ventilation (alveolar ventilation = minute ventilation – dead space ventilation). To maintain adequate alveolar minute ventilation, relatively large  $V_T$  is thus required with the limited number of mechanical breaths provided by the ventilator.

### *Assist control*

Assist control (AC) is a TCPL mode that supports every spontaneous breath, providing more uniform  $V_T$  delivery and lower WOB. The clinician still sets a ventilator rate for mandatory 'backup' breaths, which provides a minimum rate in case of apnea. This rate should normally be below the infant's spontaneous rate to allow the infant to trigger the breaths. The goal here is to have the infant and the ventilator work together, resulting in lower ventilator pressure. Because the infant controls the effective ventilator rate, weaning is accomplished by lowering the PIP rather than ventilator rate. In this fashion, the amount of support provided to each breath is decreased, allowing the infant to gradually take over the WOB. This slightly less intuitive weaning strategy appears to be one reason for the apparent reluctance to adopt this mode.

### *Pressure support ventilation*

Pressure support ventilation (PSV) is a flow, rather than TCPL mode that supports every spontaneous breath just like AC but also terminates each breath when inspiratory flow declines to a preset

threshold, usually 10 to 20% of peak flow. This feature eliminates the inspiratory hold (prolonged  $T_I$  that keeps the lungs at peak inflation) and thus presumably provides more optimal synchrony. In turn, this should limit fluctuations in intrathoracic and intracranial pressure that occur when an infant exhales against the high positive pressure during inspiratory hold. In some devices, PSV can be used to support spontaneous breathing between low-rate SIMV, to overcome the problems associated with inadequate spontaneous respiratory effort and high ETT resistance. Here, the PSV support is set as 'X' cm H<sub>2</sub>O above PEEP. In other ventilators, PSV is used as a stand-alone technique, much like AC. In either case, it can be thought of as a pressure boost given for each spontaneous breath and lasting only as long as there is inspiratory flow. Unlike in adult-type ventilators, when used as a stand-alone technique, there is a backup mandatory rate, so a reliable spontaneous respiratory effort is not an absolute requirement. The pressure is set the same way as with AC, in other words PIP/PEEP. It must be recognized that changing to PSV results in shorter  $T_I$  and may lead to atelectasis, unless adequate PEEP is used to maintain  $P_{aw}$ .

### Novel techniques of assisted ventilation

#### *Proportional assist ventilation*

Proportional assist ventilation (PAV) is a technique not currently available in North America. It is based on elastic and resistive unloading of the respiratory system, aiming to overcome the added workload imposed by poor lung compliance and high airway and ETT/ventilator circuit resistance.<sup>11</sup> The ventilator develops inspiratory pressure in proportion to patient effort—in essence a positive feedback system. The concept assumes a mature respiratory control mechanism and a closed system. Unfortunately, neither of these assumptions is valid in the preterm infant with an uncuffed ETT. For example, the common problem of periodic breathing would be accentuated by the ventilator, with less support being generated with hypopnea and excessively high level of assist provided when the infant becomes agitated. Also, because the system responds to inspiratory flow and volume, a large leak around the ETT would be interpreted as a large inspiration and given correspondingly high level of inspiratory pressure, potentially leading to dangerously large  $V_T$ . Limited clinical data are available in preterm infants and the technique remains experimental.

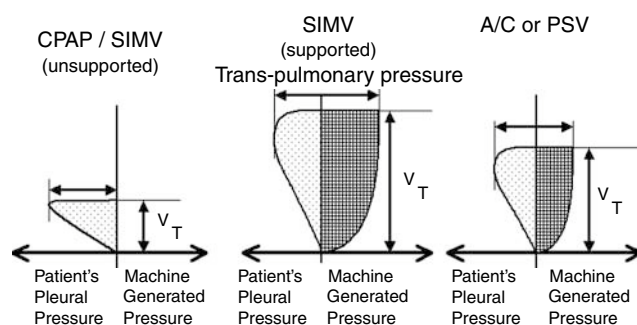
#### *Neurally adjusted ventilator assist*

Neurally adjusted ventilator assist (NAVA) is a promising approach that uses the patient's own respiratory control to drive the ventilator.<sup>12</sup> The system monitors the EAdi to trigger and modulate inspiration by means of bipolar electrodes mounted on a nasogastric feeding tube and positioned in the esophagus at the level of the diaphragm. In this way, the ventilator automatically

adjusts the level of support in proportion to the inspiratory effort. NAVA is still experimental in newborn infants, but the concept is quite attractive because the system is not affected by leak around endotracheal tubes. However, like PAV, it utilizes a positive feedback algorithm and assumes that the respiratory control center is mature, which is not a valid assumption in the preterm infant. It may be possible to overcome this limitation by incorporating minimal and maximal support levels, but this approach is yet to be fully validated.

### Choice of synchronized modes

Despite years of routine use, there is no consensus regarding the relative merits of AC and SIMV, the two most widely used modalities of synchronized ventilation. There are no large prospective trials with important clinical outcomes, such as incidence of air leak, chronic lung disease or length of ventilation to prove the superiority of one mode over the other. Short-term clinical trials have demonstrated smaller and less variable  $V_T$ , less tachypnea, more rapid weaning from mechanical ventilation and smaller fluctuations in blood pressure with AC, when compared to SIMV.<sup>13–16</sup> There are important physiological considerations suggesting that SIMV may not provide optimal support in very premature infants. However, many clinicians still prefer SIMV, especially for weaning from mechanical ventilation. This is based on the assumption, unsupported by data, that fewer mechanical breaths are *a priori* less damaging and on the belief that the ventilator rate must be lowered before extubation. It has now been unequivocally demonstrated that lung injury is most directly caused by excessive  $V_T$ , irrespective of the pressure required to generate that  $V_T$ .<sup>17–19</sup> Rate of 60 breaths per min compared to 20 to 40 was shown to result in less air leak with unsynchronized IMV,<sup>20</sup> lending further support to the putative advantage of AC with its smaller  $V_T$  and higher mechanical breath rate over SIMV. Many clinicians also believe that assisting every breath prevents respiratory muscle training. This concern is also unfounded and highlights the limited understanding of the patient–ventilator interaction during synchronized ventilation. As illustrated in Figure 1, the  $V_T$  with synchronized ventilation is the result of the combined inspiratory effort of the patient (negative intrapleural pressure on inspiration) and the positive pressure generated by the ventilator. This combined effort (the baby 'pulling' and the ventilator 'pushing') results in the transpulmonary pressure, which, together with the compliance of the respiratory system, determines the  $V_T$ . Thus, as ventilator inspiratory pressure is decreased during weaning, the infant gradually assumes a greater proportion of the WOB and in the process achieves training of the respiratory muscles. Ultimately, the ventilator pressure is decreased to the point when it only overcomes the added resistance of the ETT and circuit, at which point the infant should be extubated.



**Figure 1** Interaction of patient and ventilator pressures to generate delivered tidal volume ( $V_T$ ) with different modes of synchronized ventilation. The  $V_T$  is the result of the combined inspiratory effort of the patient (negative intrapleural pressure on inspiration) and the positive pressure generated by the ventilator. This combined effort (the baby 'pulling' and the ventilator 'pushing'  $V_T$ ) results in the transpulmonary pressure, which, together with the compliance of the respiratory system, determines the  $V_T$ .

### Clinical trials of synchronized ventilation

Despite nearly universal acceptance of synchronized mechanical ventilation in newborn intensive care, there is a surprising paucity of information on the impact of this modality on major outcomes, such as mortality, chronic lung disease or length of hospitalization. A number of small studies have shown improvement in short-term physiological outcomes (Table 2), but demonstrating the 'bottom line' long-term outcome improvement with synchronized ventilation has been elusive.<sup>21,22</sup> The only available randomized trials suffer from important design and device limitations, leaving clinicians with the unsatisfactory situation of using an 'unproven therapy' on a daily basis.<sup>23</sup>

### Principles of VILI and rationale for controlling $V_T$ during mechanical ventilation

Pressure-limited ventilation became the standard mode in newborn intensive care, because early attempts to use traditional VCV soon proved to be impractical in small preterm infants. Pressure-limited ventilation continues to be the primary mode of ventilation in newborns because of its relative simplicity, ability to ventilate effectively despite large ETT leak, improved intrapulmonary gas distribution due to the decelerating gas flow pattern and the presumed benefit of directly controlling PIP. The major disadvantage of pressure-limited ventilation is that the  $V_T$  varies with changes in lung compliance. Such changes may occur quite rapidly in the immediate postnatal period as a result of clearing of lung fluid, recruitment of lung volume and surfactant replacement therapy. The consequences of such rapid improvements in compliance are inadvertent hyperventilation and lung injury from excessively large  $V_T$ 's (volutrauma). As few as six excessively large breaths can cause sustained adverse effects on lung function,<sup>24</sup> suggesting that it may be impossible to respond rapidly enough

**Table 2** Demonstrated short-term benefits of synchronized ventilation

Author	Population/mode	Benefit
Berenstein <i>et al.</i> , <i>Am J Respir Crit Care Med</i> 1994	30 NB/SIMV	Higher and more consistent $V_T$
Cleary <i>et al.</i> , <i>J Pediatr</i> 1995	10 NB <32 weeks <12 h/SIMV	Improved ventilation and oxygenation
Jarreau <i>et al.</i> , <i>Am J Respir Crit Care Med</i> 1996	6 NB with RDS/AC	Decreased work of breathing
Smith <i>et al.</i> , <i>Int Care Med</i> 1997	17 NB with RDS/SIMV	Less tachypnea
Quinn <i>et al.</i> , <i>ADC</i> 1998	59 NB <32 week/AC	Decreased catecholamine levels

Abbreviations: AC, assist control; NB, newborns; RDS, respiratory distress syndrome; SIMV, synchronized intermittent mandatory ventilation;  $V_T$ , tidal volume.

with manual adjustment of inspiratory pressure to prevent lung injury. Inadvertent hyperventilation to  $\text{PaCO}_2 < 25$  mm Hg occurred in 30% of ventilated newborn infants during the first day of life in a recent study,<sup>25</sup> indicating that hypocapnia continues to be a common problem despite increasing awareness of its dangers.

Direct control of PIP is believed by many to be an important benefit of pressure-limited ventilation. Despite extensive evidence that excessive volume, rather than pressure, is the key determinant of VILI, the misconception that pressure is the main factor in VILI and air leak remains widespread. Dreyfuss and Saumon<sup>17</sup> demonstrated 20 years ago that severe acute lung injury occurred in small animals ventilated with large  $V_T$ , regardless of whether that volume was generated by positive or negative inspiratory pressure. In contrast, animals exposed to the same high inspiratory pressure but in whom the movement of the chest wall and diaphragm were limited by external binding experienced much less acute lung damage. This landmark paper and other similar experiments clearly show that excessive  $V_T$ , not pressure by itself, is primarily responsible for lung injury.<sup>18,19</sup> However, it has been only recently that full appreciation of the importance of volutrauma and the dangers of inadvertent hyperventilation<sup>26–28</sup> have brought about renewed interest in directly controlling  $V_T$  during neonatal ventilation.<sup>29</sup>

Insufficient  $V_T$  also causes significant problems. At any level of inspiratory pressure, insufficient  $V_T$  may develop because of decreasing lung compliance, increasing airway resistance, airway obstruction, air-trapping or decreased spontaneous respiratory effort. Inadequate  $V_T$  leads to hypercapnia, increased WOB, increased oxygen consumption, agitation, fatigue, atelectasis and possibly increased risk of intraventricular hemorrhage (IVH). Low  $V_T$  also leads to inefficient gas exchange due to increased dead space to  $V_T$  ratio. It should thus be obvious that relatively tight control of  $V_T$  delivery during mechanical ventilation is highly desirable. Indeed, this is the reason why VCV remains the standard of care in adult and pediatric respiratory support.

### Importance of the open-lung strategy

The clear evidence that excessive  $V_T$ , rather than high pressure, is the primary determinant of lung injury have caused most clinicians to either use one of the forms of volume-targeted ventilation or at least monitor the delivered  $V_T$ . The critical importance of distributing this  $V_T$  evenly into an optimally aerated lung has not been as widely appreciated and requires special emphasis. Caruso *et al.*<sup>30</sup> demonstrated that when using PEEP of 0, lung injury in rats was not reduced by the use of low, compared to high  $V_T$ . Tsuchida *et al.*<sup>31</sup> showed that in the presence of atelectasis, the nondependent (that is, aerated) lung was the most injured area. This is because, as can be seen in Figure 2, if extensive atelectasis is allowed to persist, the normal, physiological  $V_T$  entering only the open alveoli will inevitably lead to overexpansion of this relatively healthy portion of the lung with subsequent volutrauma/biotrauma. Atelectasis leads to exudation of protein-rich fluid with increased surfactant inactivation and release of inflammatory mediators, a process known as 'atelectotrauma'. Shear forces and uneven stress in areas where atelectasis and overinflation coexist add to the damage. The 'open-lung concept' (OLC)<sup>32</sup> is central to optimizing the impact of volume-targeted ventilation: its benefits cannot be realized without ensuring that this  $V_T$  is distributed evenly throughout the lungs!

In practical terms, the open lung is achieved by applying adequate PEEP. For a variety of reasons, including poorly conceived animal studies where moderate to high levels of PEEP were applied to animals with normal (that is, very compliant) lungs, resulting in significant hemodynamic impairment, many clinicians fear using adequate levels of end-expiratory pressure. This 'PEEP-o-phobia' is only slowly being overcome and remains one of the most important obstacles to optimizing the way conventional mechanical ventilation is practiced. By contrast, the importance of optimizing lung inflation has long been recognized by users of high-frequency ventilation, where the optimal lung volume strategy has become standard practice and is widely understood to be the key to its success. However, although there are a number of animal studies indicating that conventional ventilation with the OLC can achieve similar degrees of lung protection as high-frequency oscillatory ventilation (HFOV), suggesting that optimizing lung volume rather than frequency is the key factor,<sup>32–36</sup> the clinical application of the OLC with conventional ventilation has not been extensively evaluated in clinical trials.<sup>37</sup>

Finally, it is important to understand that there is no single 'safe' PEEP level. Optimal PEEP must be tailored to the degree of lung injury (that is, lung compliance). For infants with healthy lungs and thus normal lung compliance, PEEP of 3 cm H<sub>2</sub>O is adequate and PEEP of 6 cm H<sub>2</sub>O may result in overexpansion of the lungs with circulatory impairment and elevated cerebral venous pressure. On the other hand, atelectatic, poorly compliant lungs may require PEEP levels of 8 to 10 cm H<sub>2</sub>O or more to achieve

adequate alveolar recruitment and improve ventilation/perfusion ratio. Because we seldom ventilate infants with healthy lungs, PEEP of <5 cm H<sub>2</sub>O should be the exception, rather than the rule.

### Volume-targeted ventilation modes

Confusion in terminology exists in the realm of volume-oriented ventilation as well. Although the focus on targeting an appropriate  $V_T$  is the key element, it is important to recognize that there are differences in how different ventilation modes exert control over  $V_T$ . Devices designed to span the full range of patients from newborns to adults all have the traditional volume-controlled modes we described earlier. Although the terminology of 'volume-targeted ventilation' has been recently used to describe this entity,<sup>7</sup> standard VCV is distinct from the neonatal modes of volume-targeted ventilation. For the purpose of this article, the term volume-targeted ventilation refers to modifications of pressure-limited ventilation that adjusts inspiratory pressure and/or time to target a set  $V_T$ . These modes are also distinct from other pressure-limited ventilators that also claim to offer volume-targeted ventilation but actually employ a simple volume-limit function that merely terminates inspiration when the maximum allowed  $V_T$  is exceeded, without actively modulating the inspiratory pressure.

#### Pressure-regulated volume control

Pressure-regulated volume control (PRVC) is a pressure-limited, time-cycled mode that when initially activated adjusts inspiratory pressure to target a set  $V_T$ , based on the pressure required to achieve the target  $V_T$  of four test breaths. Subsequent adjustments are based on the  $V_T$  of the previous breath. Breath to breath increment is limited to 3 cm H<sub>2</sub>O, up to 5 cm H<sub>2</sub>O below the set upper pressure limit. The main problem with the PRVC mode of the Maquet Servo 300 and to a lesser extent the Servo-i (Maquet Inc., Bridgewater, NJ, USA; formerly Siemens, Solna, Sweden) is the inaccuracy of  $V_T$  measurement performed at the ventilator end of the circuit, rather than at the airway opening.<sup>38–40</sup> The newer Servo-i has a circuit compliance compensation feature that effectively adjusts the displayed  $V_T$  to correct for loss of volume to the circuit, a major improvement over the previous version. Unfortunately, this compensation is ineffective in the presence of even small to moderate ETT leak. Any appreciable leak causes constant alarms, which typically lead the user to disable the feature with the result being inability to accurately determine the  $V_T$ . Recently, a second flow sensor that permits monitoring of actual  $V_T$  has been made available, though the  $V_T$  regulation is still based on the volume measured at the ventilator outlet.

#### Volume-assured pressure support

The volume-assured pressure support (VAPS) mode on the Bird VIP Gold (Viasys Medical Systems, Conshohocken, PA, USA) is a hybrid

mode designed to ensure that the targeted  $V_T$  is reached. Each breath starts as a pressure-limited breath, but if the set  $V_T$  is not reached, the device converts to flow-cycled mode by prolonging the  $T_I$  with a passive increase in peak pressure. This may result in a rather prolonged  $T_I$  leading to expiratory asynchrony. Targeting  $V_T$  based on inspiratory  $V_T$  is susceptible to error in the presence of significant endotracheal tube leak. Furthermore, there is no provision for automatically lowering inspiratory pressure as lung compliance improves. The focus is on ensuring an adequate  $V_T$ ; no provision is made to avoid inadvertent hyperventilation and allow for automatic weaning. The newer Avea ventilator by Viasys shares the basic concept of VAPS, but the algorithm has been refined to respond earlier in the respiratory cycle and avoid excessively long  $T_I$ 's. The Avea also adds a volume-limit function that will terminate inspiration if the upper limit of  $V_T$  is exceeded. This added function should reduce the risk of volutrauma and hyperventilation. The regulation of delivered volume based on inspiratory  $V_T$  has both advantages and disadvantages. It allows the device to respond within the given breath, but it is more susceptible to leak around ETT, which is larger during inspiration.

#### *Volume guarantee*

The Draeger Babylog 8000 plus (Draeger Medical Inc., Telford, PA) has a volume guarantee (VG) option that may be combined with any of the basic ventilator modes (AC, SIMV, PSV). Like PRVC, the VG mode is a volume-targeted, TCPL form of ventilation. The operator chooses a target  $V_T$  and selects a pressure limit up to which the ventilator operating pressure (the working pressure) may be adjusted. The microprocessor compares the  $V_T$  of the previous breath, using exhaled  $V_T$  to minimize possible artifact due to air leak, and adjusts the working pressure up or down to achieve the set  $V_T$ . The algorithm limits the amount of pressure increase from one breath to the next, to avoid overcorrection leading to excessive  $V_T$ . This, and the fact that the exhaled  $V_T$  of the prior breath, is used means that with very rapid changes in compliance or patient inspiratory effort, several breaths are needed to reach target  $V_T$ . Contrary to a widespread misconception, the microprocessor does not average the  $V_T$  of several breaths to determine working pressure. Additionally, to overcome the potential disadvantage of using the exhaled  $V_T$  of the previous breath and minimize the risk of excessively large  $V_T$ , the microprocessor opens the expiratory valve, terminating any additional pressure delivery if the inspiratory  $V_T$  exceeds 130% of the target—in essence a volume-limit function. By design the algorithm is geared toward slower adjustment for low  $V_T$  and more rapid adjustment for excessive, potentially dangerous  $V_T$ . There is a separate algorithm for spontaneous (assisted) and untriggered machine breaths to ensure that the target  $V_T$  is more stable when the infant's respiratory drive is inconsistent. The autoregulation of inspiratory pressure makes VG a self-weaning mode. Because weaning occurs in real time, rather than intermittently in response to blood gases,

VG has the potential to achieve faster weaning from mechanical ventilation.

#### *Volume limit*

Volume limit is a function of the Bear Cub 750 PSV and its equivalent in Europe, the Leoni Plus (Viasys Medical Systems). This is not true volume-targeted ventilation, as the only enhancement over simple pressure-limited ventilation is a volume-limit setting; when the limit  $V_T$  is exceeded, the device terminates inspiration thus avoiding excessive  $V_T$  delivery. This premature breath termination may lead to very short  $T_I$ 's. There is no automatic adjustment of inspiratory pressure and no provision to ensure that adequate  $V_T$  is delivered when compliance or patient effort decreases. The reliance on inspiratory  $V_T$  measurement means that significant leak around the ETT may lead to inadequate  $V_T$  delivery.

#### *Targeted tidal volume*

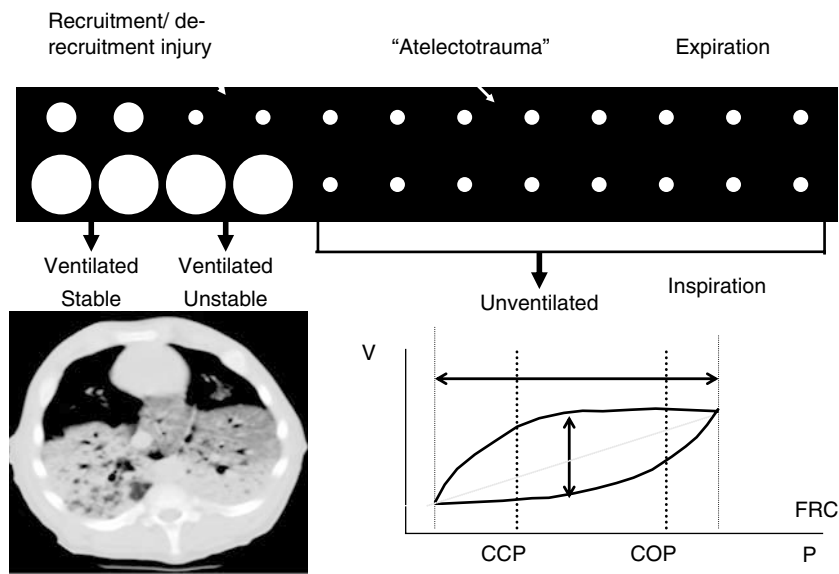
This is in essence a simple volume-limit function available on the SLE 5000 (Specialised Laboratory Equipment Ltd, South Croydon, UK). The device increases the rise time of the pressure waveform to improve the chance of effectively limiting  $V_T$  to the desired target. When the volume-limit function is turned off, the PIP automatically drops to 5 mbar above the PEEP to avoid potentially excessive  $V_T$  due to inappropriately high PIP setting; the user must then actively adjust the PIP. The same limitations of volume-limit apply: there is no automatic adjustment of inspiratory pressure and no provision to ensure that adequate  $V_T$  is delivered when compliance or patient effort decreases. Reliance on inspiratory  $V_T$  measurement may lead to inadequate  $V_T$  delivery with significant leak around the ETT.

### **Clinical studies of volume-oriented ventilation**

#### *Volume-controlled ventilation*

Two published studies evaluated the effectiveness of VCV in newborn infants in the modern era using the Bird VIP ventilator. Both used the time to achieve either alveolar/arterial oxygen difference ( $AaDO_2$ ) <100 torr or mean airway pressure <8 cm  $H_2O$  as the primary end point. The first study included 50 infants with mean birth weight (BW) close to 1800 g.<sup>41</sup> Tidal volume of 5 to 8 ml  $kg^{-1}$  was targeted in both groups. Infants randomized to VCV reached success criteria faster and had shorter duration of ventilation ( $122 \pm 65$  h for VCV vs  $162 \pm 134$  h). There was a trend toward less BPD and IVH in the VCV group. These encouraging results demonstrated feasibility of this mode of ventilation in larger preterm infants, but left the question unanswered as to whether this modality is useful in the much smaller infants who today constitute the large majority of ventilated infants.

The newer model of the Bird VIP Gold that allows lower  $V_T$  settings and accurate monitoring of exhaled  $V_T$  at the airway



**Figure 2** Nonhomogeneous aeration in respiratory distress syndrome (RDS). Atelectasis in dependent portions of the lungs is present in surfactant-deficient lungs as illustrated on the computer tomography view in lower left corner (preterm sheep, courtesy of Anastasia Pellicano). This situation is schematically represented in the middle panel. The corresponding pressure–volume loop is shown in the lower right portion of the figure. If this situation is allowed to persist, even a normal, physiological tidal volume, when it enters only the small proportion of open alveoli will inevitably lead to overexpansion and lung injury.

opening made it possible to address this question. Singh *et al.*,<sup>7</sup> randomly assigned 109 preterm infants 24 to 31 weeks and 600 to 1500 g to VCV or to TCPL ventilation using the same primary outcome. Exhaled  $V_T$  of 4 to 6 ml was targeted in both groups. There was no difference in the primary outcome in the overall group, but a *post hoc* analysis showed faster weaning from VCV in infants <1000 g. There was no difference in the duration of ventilation,  $O_2$  requirement or other secondary outcomes. Though the results did not clearly show superiority of VCV, the study demonstrated the feasibility of the mode even in ELBW infants, at least under the rigorous conditions of the study. It is important to appreciate that the set  $V_T$  was manually adjusted at least hourly to maintain the target exhaled  $V_T$  monitored at the airway opening. It remains to be seen whether this approach is feasible under routine neonatal intensive care unit (NICU) conditions. Additionally, because there is normally an inverse relationship between airway pressure and oxygenation, a more meaningful end point would have been  $AaDO_2 < 100$  torr *and* mean airway pressure  $< 8$  cm  $H_2O$ .

#### Pressure-regulated volume control

Piotrowski *et al.*,<sup>42</sup> studied 57 preterm infants <2500 g who were randomly assigned to PRVC or unsynchronized TCPL ventilation. The  $V_T$  was initially set at 5 to 6 ml  $kg^{-1}$  with additional 4 to 5 ml added to compensate for volume loss in the circuit. Subsequently, the  $V_T$  was adjusted based on clinical assessment of chest rise and on blood gas values. There was a lower incidence of severe IVH in the PRVC group and a trend to fewer pneumothoraces. Twenty-one percent of the infants died during the study, but survival and other complications were not different. Duration of mechanical

ventilation was similar for the groups overall, but significantly shorter for the PRVC group in infants <1000 g. It is unclear if the survival statistics were affected by the relatively high mortality or whether the apparent difference in pneumothorax and IVH were related to the use of unsynchronized IMV in the control group.

A more recent study using the Servo 300 ventilator evaluated 212 preterm infants randomly assigned to PRVC or to pressure-limited SIMV.<sup>43</sup> Infants were to remain on the assigned mode of ventilation until extubation or death, unless predetermined crossover criteria were met. Mean BW was similar in the SIMV ( $888 \pm 199$  g) and PRVC ( $884 \pm 203$  g) groups with mean gestational age of about 27 weeks. No differences were detected between SIMV and PRVC groups in the primary outcome, the proportion of infants alive and extubated at 14 days (41 vs 37%, respectively), length of mechanical ventilation in survivors or the proportion of infants alive without supplemental oxygen at 36 weeks postmenstrual age. More infants crossed over from PRVC than from SIMV. The authors concluded that PRVC offered no demonstrable advantage over SIMV.

#### Volume-assured pressure support

No published studies exist on the performance or clinical impact of VAPS in newborn infants.

#### Volume guarantee

Cheema and Ahluwalia<sup>44</sup> examined the feasibility of VG in 40 premature newborn infants with RDS. In a 4-h crossover trial they compared AC with and without VG in infants with acute RDS, and SIMV with and without VG during weaning. Lower PIP was seen in

both VG groups and there were fewer excessively large  $V_T$  during the VG periods. The authors concluded the VG mode was feasible and may offer the benefit of lower airway pressures.

We showed in a short-term crossover study that VG combined with AC, SIMV or PSV led to significantly lower variability of  $V_T$ , compared to AC or SIMV alone.<sup>45</sup> In contrast to the earlier study, we noted similar PIP, probably because, unlike Cheema *et al.*, we allowed the working pressure to be adjusted both up and down by raising the pressure limit from the baseline period. The use of VG does not alter the relationship between PIP, compliance and  $V_T$ , therefore, there is no reason to expect the PIP to be lower for the same  $V_T$ .

In a group of very low birth weight infants recovering from acute respiratory failure Herrera *et al.*,<sup>46</sup> showed that, compared to SIMV alone, short-term use of SIMV + VG decreased mechanical support and enhanced spontaneous respiratory effort while maintaining gas exchange relatively unchanged. The shift of the WOB to the infant is because  $4.5 \text{ ml kg}^{-1}$  is a relatively low target  $V_T$  for SIMV, where the usual  $V_T$  of machine breaths is  $6 \text{ ml kg}^{-1}$ .<sup>16,47</sup> Almost complete shifting of the WOB to the infant was seen when the target  $V_T$  was reduced to  $3 \text{ ml kg}^{-1}$ , indicating that this value is too low. There was a reduction in excessively large  $V_T$  during both VG periods.

Olsen *et al.*,<sup>48</sup> compared 4-h periods of PSV + VG with SIMV alone in a crossover trial of 14 large preterm infants with mean gestational age of 34 weeks. The AaDO<sub>2</sub>, PaCO<sub>2</sub> and dynamic compliance were similar during both periods. Minute ventilation and mean airway pressure were higher and end-expiratory volume was lower during PSV + VG compared to SIMV. The authors concluded that use of PSV + VG could not be recommended but this conclusion should be viewed with caution because of significant concerns about the study design, data acquisition and interpretation.<sup>49</sup>

In the first randomized controlled trial of VG, we demonstrated that VG combined with AC maintained PaCO<sub>2</sub> and  $V_T$  within a target range more consistently than assist/control alone during the first 72 h of life in preterm infants with uncomplicated RDS.<sup>50</sup> There was a 41% reduction in  $V_T > 6 \text{ ml kg}^{-1}$  and a 45% reduction in PaCO<sub>2</sub> < 35 mm Hg. This paper demonstrated that excessively large  $V_T$  and hypocarbia could be reduced, though not eliminated with the use of VG, suggesting the potential of VG to reduce many of the adverse effects of mechanical ventilation.

Lista *et al.*<sup>51</sup> provided the most convincing evidence to date about the potential benefits of volume-targeted ventilation. They randomly assigned 53 preterm infants with RDS to PSV alone or PSV + VG, using set  $V_T$  of  $5 \text{ ml kg}^{-1}$ . Pro-inflammatory cytokine levels were lower in the tracheal aspirate of infants in the VG group. Duration of mechanical ventilation was  $8.8 \pm 3$  days in the VG group compared to  $12.3 \pm 3$  days with PSV alone (mean weighted difference  $-3.5$ , CI:  $-5.13$  to  $-1.87$ ). These data strongly support the hypothesis that VG may reduce VILI.

Nafday *et al.*<sup>52</sup> compared SIMV to PSV + VG in a randomized study involving 34 preterm infants with RDS. They did not find a difference in the primary outcome, the time to extubation or other important clinical outcomes, but this 'pilot' study lacked adequate statistical power. More importantly, the original group assignment was only maintained for the first 24 h, likely negating any possible differences. Significantly fewer blood gases were needed in the VG group.

Abd El-Moneim *et al.*<sup>53</sup> studied 25 premature infants in a double crossover study with SIMV alternating with PSV + VG. The latter achieved a similar oxygenation level as SIMV but with significantly lower PIP. PCO<sub>2</sub> values were similar, but infants with strong respiratory drive had episodes of hyperventilation during PSV + VG. Infants had a more rhythmic respiratory pattern during PSV-VG, suggesting better infant-ventilator synchrony. The lower PCO<sub>2</sub> values with PSV + VG were predictable, because the  $V_T$  used during baseline low rate SIMV was by design matched during the PSV period. The mean  $V_T$  of  $5.9 \text{ ml kg}^{-1}$  is consistent with the usual  $V_T$  observed during SIMV, but 30 to 45% larger than what is normally used in PSV when each breath is supported. The authors concluded that PSV + VG is safe and feasible and felt that their results should encourage wider use of PSV-VG in premature infants.

To determine whether VG is more effective when combined with AC or SIMV, we studied 12 ELBW infants (BW  $679 \pm 138 \text{ g}$ ) in a short-term crossover trial.<sup>54</sup> As anticipated,  $V_T$  was more stable with AC + VG, because the interval between supported breaths is longer during SIMV, leading to slower adjustment of working pressure. An unexpected finding was that during SIMV, the infants had significantly lower and more variable SpO<sub>2</sub>, more tachycardia and tachypnea. By design, the  $5 \text{ ml kg}^{-1}$   $V_T$  was identical, but significantly higher PIP was required during SIMV to achieve the same  $V_T$ . The tachypnea, tachycardia and lower, more variable oxygen saturation suggest that the reason for the higher PIP was that these ELBW infants were tiring during the SIMV period and contributing less effort by the end of the 2-h period when the measurements were obtained. This conclusion is based on the realization that during synchronized ventilation, the delivered  $V_T$  is the result of the combined inspiratory effort of the baby and the positive ventilator pressure; as the baby tires and contributes less, the ventilator needs to generate higher PIP to deliver the same  $V_T$ .

Dawson and Davies<sup>55</sup> examined the relationship between  $V_T$ , minute ventilation and PaCO<sub>2</sub> in patients ventilated with SIMV + VG. They reported that 96.5% of the blood gases during the first 48 h were within their acceptable range of 25 to 65 torr when the  $V_T$  was set at a mean value of  $4 \text{ ml kg}^{-1}$ . More importantly, only 1/288 (0.3%) PaCO<sub>2</sub> values were less than 25 torr.

To determine if a lower  $V_T$  may be advantageous, Lista *et al.*<sup>56</sup> randomly assigned 30 preterm infants < 32 weeks gestation to receive AC + VG ventilation with either 3 or  $5 \text{ ml kg}^{-1}$  target  $V_T$ . Bronchoalveolar lavage on days 1, 3 and 7 revealed an increase in

pro-inflammatory cytokines in the low  $V_T$  group, most likely because of atelectasis resulting from the combination of low  $V_T$  and low end-expiratory pressure of 3 to 4 cm H<sub>2</sub>O that was used. An accompanying editorial points out the critical importance of using the open-lung approach to ensure that the  $V_T$  is evenly distributed throughout the entire lung, not just a small proportion of open alveoli.<sup>57</sup>

A similar effect may explain the findings of a small randomized study by Dani *et al.*,<sup>58</sup> which compared pro-inflammatory cytokines in a group of 25 preterm infants approximately 1100 g and 28 weeks gestation randomly assigned to receive PSV + VG or HFOV delivered by the SensorMedics 3100 oscillator using a high lung volume strategy. There was no difference in survival, length of ventilation or oxygen requirement. IL-8 and IL-10 levels were lower in infants receiving HFOV at the end of 4 days. The combination of PSV (short  $T_I$ ) and PEEP of 3 cm H<sub>2</sub>O used by the authors would result in a low lung volume strategy on PSV + VG, compared with high lung volume strategy with HFOV. Mounting evidence shows that optimization of lung volume is key to lung protection, regardless of what ventilation mode is used. VG applied to a poorly inflated lung is unlikely to be optimally lung protective.

Polimeni *et al.*<sup>59</sup> compared SIMV and SIMV + VG in ELBW infants with frequent episodes of hypoxemia (forced exhalation episodes) during alternating 2-h periods of ventilation. When using target  $V_T$  of 4.5 ml kg<sup>-1</sup>, no benefit was seen. In a second phase, 20 infants were studied with and without VG using a target  $V_T$  of 6.0 ml kg<sup>-1</sup>. The frequency of hypoxemic episodes did not change, but the mean episode duration was shorter and the proportion of mechanical breaths with  $V_T \leq 3$  ml kg<sup>-1</sup> was reduced during SIMV + VG vs SIMV alone. Because with SIMV the  $V_T$  of mechanical breaths is normally about 6 ml kg<sup>-1</sup>, SIMV + VG with a target of only 4.5 ml kg<sup>-1</sup> is therefore unlikely to overcome the effects of forced exhalation, given the low SIMV rate of 16 per min. In work only presented as abstract, we have documented more rapid recovery from episodes of forced exhalation with AC + VG and a target of 4.5 ml kg<sup>-1</sup>, compared to AC alone.

Scopesi *et al.*<sup>60</sup> compared SIMV alone to SIMV + VG, AC + VG and PSV + VG in a small crossover trial of 10 preterm infants in the recovery phase of RDS. All VG modes delivered  $V_T$  very close to the target volume. The mean variability of  $V_T$  from preset  $V_T$  was significantly lower in AC and PSV modes than in SIMV. The PIP was much lower with all VG periods than with baseline SIMV, because a  $V_T$  of only 3.5 ml kg<sup>-1</sup> was selected. These larger infants were able to generate adequate  $V_T$  on their own, but the low target  $V_T$  led to greater than usual variability in all the VG modes studied.

Cheema *et al.*<sup>61</sup> examined the effect of VG with  $V_T$  of 4 ml kg<sup>-1</sup> on the incidence of hypocapnia on the first arterial blood gas after initiation of mechanical ventilation. The incidence of hypocapnia was 32% with AC + VG, compared to 57% with AC alone, but this difference fell short of statistical significance in this small

prospective trial, possibly due to a type II error. They noted a significant negative correlation between gestational age and PaCO<sub>2</sub>. The fact that the smallest infants had higher PaCO<sub>2</sub> values reflects the impact of fixed IDS that we recently documented. When infants <25 weeks gestation were excluded, the decrease in hypocapnia became significant. The authors' conclusion that VG was not found to be effective is not warranted, as the study lacked statistical power and failed to select appropriate  $V_T$  targets.

In his most recent publication, Lista *et al.*<sup>62</sup> studied 40 infants with RDS randomly assigned to AC + VG ( $V_T = 5$  ml kg<sup>-1</sup>) or HFOV (both with a Draeger Babylog 8000 plus). Levels of IL-6, IL-8 and tumor necrosis factor were measured in tracheal aspirate on days 1, 3 and 7. The duration of oxygen dependency was significantly shorter and the IL-6 levels were lower on day 3 and 7 with AC + VG. The possible reasons for the different outcome of this study compared to that of Dani *et al.*<sup>58</sup> are many. Lista used a more appropriate PEEP of 5 cm H<sub>2</sub>O and the  $T_I$  was likely longer with the AC than PSV used by Dani. Though the authors state that the high volume strategy was used with HFOV, no data are provided to substantiate how effectively this was done. It is likely that there was not the same dramatic difference in lung volumes favoring HFOV as in the study by Dani, allowing for a fairer evaluation of the effect of VG.

To address the concern regarding possible untoward effects of the additional IDS of the flow sensor and to establish normative data for target  $V_T$  in ELBW infants, we reviewed 344 paired observations of  $V_T$  and arterial blood gas measurements in 38 infants <800 g at birth (mean 627 g, range 400 to 790 g) during the first 24 h of life.<sup>63</sup> The  $V_T$  per kg required for normocapnia was inversely related to BW ( $r = -0.70$ ,  $P < 0.01$ ), indicating some effect of the fixed IDS. Mean  $V_T$  of infants  $\leq 500$  g was  $5.9 \pm 0.4$  vs  $4.7 \pm 0.4$  ml kg<sup>-1</sup> for those  $\geq 700$  g ( $P < 0.001$ ). The absolute mean set and measured  $V_T$  was  $3.11 \pm 0.64$  and  $3.17 \pm 0.64$  ml, respectively, barely above the estimated instrumental plus anatomical dead space of 3.01 ml. While maintaining normocapnia, 47% of all  $V_T$ 's were less than or equal to the estimated dead space. We concluded that there is an impact of IDS in the tiniest infants but there is no need to forgo synchronized and volume-targeted ventilation due to concerns about the IDS. Effective alveolar ventilation occurs with  $V_T$  at or below dead space, suggesting that a spike of fresh gas penetrates through the dead space gas, similar to what occurs with high-frequency ventilation. In a companion study, we showed that with advancing postnatal age, the  $V_T$  needed to maintain adequate ventilation rose from a mean of just over 5 ml kg<sup>-1</sup> on day 1 to over 6 ml kg<sup>-1</sup> by the end of the third week despite mild permissive hypercapnia (PaCO<sub>2</sub> of 53) in infants <800 g.<sup>64</sup>

#### Volume limit

There are no published studies on the performance or clinical impact of volume-limit function.

## Summary of clinical trials

The body of literature on volume-targeted ventilation continues to expand rapidly, but none of the studies are sufficiently large to unequivocally demonstrate ultimate benefit of this approach. VG has been studied most extensively, but it remains to be seen whether the demonstrated short-term benefits translate into significant reduction in air leak, chronic lung disease, neuroimaging abnormalities or length of hospitalization. The Cochrane review last updated in 2005 included four randomized trials in the meta-analysis, totaling 178 preterm infants entered during the first 72 h of life.<sup>65</sup> Two studies used VCV (Piotrowski *et al.*<sup>42</sup> and Sinha *et al.*<sup>41</sup>) and two used VG (Lista *et al.*<sup>51</sup> and Keszler and Abubakar<sup>51</sup>). No significant difference was found for death at hospital discharge. Volume-controlled/targeted ventilation resulted in significant reductions in duration of ventilation (weighted mean difference (WMD)  $-2.93$  days ( $-4.28, -1.57$ )) and rates of pneumothorax (typical RR 0.23 (0.07, 0.76), risk difference (RD)  $-0.11$  ( $-0.20, -0.03$ ), number needed to treat (NNT) 9). There was a significant reduction in severe (Grade 3 or 4) IVH in the volume-controlled/targeted group (typical RR 0.32 (0.11, 0.90), RD  $-0.16$  ( $-0.29, -0.03$ ), NNT 6) and 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). Although it is debatable whether VC and VG studies should be combined and it is unknown whether when updated with the more recent studies these conclusions will be strengthened, it is clear that evidence is mounting in support of strategies that attempt to control delivered  $V_T$ .

### Clinical application

Despite the lack of definitive evidence of superiority to standard IMV, the benefits of synchronized ventilation are generally accepted with very few, if any, NICUs that have not adopted these techniques. As discussed above, the choice of SIMV or AC is, to some extent, a matter of personal preference and practice style. In reality, there is little difference between the two in the acute phase of respiratory failure, especially in the extremely premature or gravely ill infant who has little or no respiratory effort of their own, or the patient who is heavily sedated or even paralyzed. Under these circumstances, we are really providing simple IMV, regardless of the ventilator mode selection. However, the differences between SIMV and AC/PSV become more pronounced during weaning and are especially important in the smallest infants with narrow endotracheal tubes. Prolonged ventilation with low SIMV rates should be avoided in these infants, as it imposes an undesirably high WOB. To a significant degree, this problem may be overcome by adding PSV to the spontaneous breaths during SIMV.<sup>47</sup> Although this approach is effective, it adds complexity and does not appear to have any advantage over PSV used alone, as long as atelectasis is avoided by using adequate level of PEEP.

The use of volume-targeted ventilation is best implemented soon after birth, because it is the time of most rapid changes in lung compliance. The choice of optimal  $V_T$  is critical to success of any volume-targeted mode. Exhaled  $V_T$  of 4 to 5 ml  $\text{kg}^{-1}$  is appropriate in the typical preterm infant with RDS. Extremely small infants require  $V_T$  close to 6 ml  $\text{kg}^{-1}$  to compensate for the IDS of the flow sensor.<sup>63</sup> With advancing postnatal age, some increase in anatomical and physiological dead space occurs, necessitating slightly higher  $V_T$ .<sup>64</sup> If low-rate SIMV is used, the target  $V_T$  needs to be higher than with AC or PSV. Even distribution of the  $V_T$  into an adequately recruited lung is key to lung injury prevention.<sup>29</sup> With devices that measure and regulate  $V_T$  at the ventilator end of the circuit, the set  $V_T$  must be substantially higher than exhaled target  $V_T$  to compensate for the compression of gas in the ventilator circuit. The compliance compensation feature of the Servo-i is helpful in overcoming this problem, but does not function effectively in the presence of ETT leakage.

Each ventilator functions differently and it is critical that the user becomes familiar with the specific features of their device. The reader is referred to user manuals of their respective devices for further guidance. Detailed clinical guidelines for the Draeger Babylog are available in a recent publication.<sup>66</sup> A ventilator is only a tool in the hands of the clinician; a tool that can be used well, or not. Yet, we talk of 'VILI', as though the machines were to blame for the undesirable outcome. Perhaps the term 'physician-induced lung injury' is more appropriate, for we are the ones that select the ventilator settings!

## Conclusion

A host of new modalities and techniques has been made available for the treatment of respiratory failure. Our understanding of how to optimally use these devices, while improving constantly, remains somewhat behind the pace of technological innovation. Improvements in outcomes such as BPD are increasingly difficult to demonstrate, as each incremental improvement leaves 'the bar' that much higher. Avoidance of mechanical ventilation by means of early CPAP with or without surfactant administration may still be the most effective way to reduce the risk of chronic lung disease. For babies who do require mechanical ventilation, the combination of volume-targeted ventilation, combined with the open-lung strategy appears to offer the best chance of reducing the risk of chronic lung disease.

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