9 Synchronized and Volume-Targeted Ventilation

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Mechanical ventilation has improved to the point where few infants now die of acute respiratory failure. Early mortality is now predominantly from other complications of extreme prematurity, such as infection and hemorrhage. This development has shifted the clinical focus from reducing mortality to reducing the still unacceptably high incidence of chronic lung disease. Although 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).[1] At the same time, with improved technology, 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 for neonatal ventilation. This chapter briefly reviews the basic modes of synchronized ventilation, describes the concept of volume-targeted ventilation, and discusses the clinical application of both.

Synchronized Ventilation

The standard type of mechanical ventilation used in newborn infants before the introduction of synchronized modes was known as intermittent mandatory ventilation (IMV). IMV is a time-cycled, pressure-limited mode of ventilation that provides a set number of "mandatory" mechanical breaths. The patient is able to breathe spontaneously at any time, using the fresh gas flow available in the ventilator circuit, which at the same time provides positive end-expiratory pressure (PEEP). Unfortunately, the infant's random respiratory rate frequently leads to asynchrony between the infant and the ventilator.

High airway pressures, poor oxygenation, and large fluctuations in intracranial pressure result from instances when the ventilator inspiratory cycle occurs just as the infant is breathing out. Heavy sedation and muscle paralysis were often employed to suppress the infant's spontaneous respiratory effort and prevent him 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 infant's neurologic status.

The advantages of synchronizing the infant's spontaneous effort with the ventilator cycle, instead of using muscle relaxants, seem intuitively obvious (Table 9-1). However, the introduction of synchronized ventilation into clinical practice in neonates lagged far behind its use in adults because of technological challenges imposed by the small size and rapid respiratory rates of preterm newborns.

Types of Triggering Devices

The ideal triggering device must be sensitive enough to be activated by a small preterm infant, yet relatively immune from auto-triggering. It must also have a sufficiently rapid response time to match the short inspiratory times and rapid respiratory rates seen in small premature infants. Variable leakage of gas around uncuffed endotracheal tubes (ETTs) adds another significant problem. Table 9-2 lists the types of triggering devices used in clinical care and their relative advantages and disadvantages. Clinical and laboratory experience has shown that flow triggering using a flow sensor at the

TABLE 9-1
Generally Accepted Benefits of Synchronized Mechanical Ventilation

Elimination of asynchrony
Avoidance of muscle paralysis
Decreased need for sedation
Reduction of airway pressures
Decreased risk of barotrauma and intraventricular hemorrhage
Facilitation of respiratory muscle training
Facilitation of weaning

TABLE 9-2
Comparison of Triggering Methods

Method	Advantages	Disadvantages
Pressure	No added dead space	Poor sensitivity Long trigger delay High work of breathing
Airflow	Most sensitive	Added dead space
Pneumatic capsule	Rapid response No extra dead space	Positioning is critical
Impedance	No added dead space	Poor sensitivity Artifacts

airway opening (at the ETT adapter) is ultimately the best compromise.[2,3] At this time, all infant ventilators in common use utilize this triggering mode. An attractive new concept is to use the electrical activity of the diaphragm to trigger the ventilator. This technique requires the placement of an esophageal probe to sense the diaphragmatic contraction and modulate the inspiratory pressure of the ventilator. It is unaffected by leak around endotracheal tubes and has a very rapid response time. However, currently its availability is limited to a single device, and the triggering function cannot be separated from the proportional assist component, which may not function optimally in preterm infants with immature respiratory control (see below).

Potential Pitfalls of Flow Triggering

Although flow triggering is the most widely used method, there are potential problems with this mode of triggering. The interposition of the flow sensor adds approximately 0.5–1 mL of dead space to the breathing circuit, which may become proportionally more significant with the tiniest of infants. Claure and colleagues describe introducing a small, fixed leak into the circuit, which makes it possible to effectively wash out the dead space of the flow sensor.[4] If this approach proves to be practical in the clinical setting, it would eliminate one drawback of flow triggering.

The second problem is susceptibility to auto-triggering in the presence of significant leakage around the ETT. Any substantial leakage of flow during the expiratory phase is (mis)interpreted by the device as inspiratory effort, triggering the ventilator at an excessively rapid rate. When recognized, the problem can be corrected by decreasing trigger sensitivity. Unfortunately, the magnitude of the leak often changes quite rapidly, requiring frequent adjustment. Furthermore, making the trigger less sensitive increases the effort needed to trigger the device and increases the trigger delay; both highly undesirable. One device, the Dräger Babylog 8000 plus (Dräger Medical, Inc., Lübeck, Germany), offers an elegant solution to this problem. The Babylog 8000 plus utilizes a proprietary leak compensation technology that allows the device to instantaneously derive the leak flow throughout the ventilator cycle and mathematically subtract 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.

Synchronized Ventilation Modes

Considerable confusion exists in the terminology used to describe various modalities of respiratory support. Device manufacturers often use different terms to describe essentially identical modes. In basic terms, ventilator breaths can be time or flow cycled (onset of inspiration and expiration) and pressure or volume limited. Triggering can occur at a fixed rate set by the user or at a variable rate determined by the patient. Detailed discussion of the terminology is beyond the scope of this chapter. The interested reader is referred to in-depth reviews of the subject.[5] The following sections briefly define the terminology for modes used primarily in newborns.

Synchronized Intermittent Mandatory Ventilation

The synchronized intermittent mandatory ventilation (SIMV) mode provides a preset number of mechanical breaths as in standard IMV, but the breaths are synchronized with the infant's spontaneous respiratory effort, if present. Spontaneous breaths in excess of the preset number are not supported, resulting in uneven tidal volumes (V_T) and potentially a high work of breathing (WOB), especially during weaning. This is an important issue, particularly in extremely small and immature infants with correspondingly narrow ETTs. The high airway resistance of a narrow ETT, the infant's limited

muscle strength, and the mechanical disadvantage conferred by the infant's excessively compliant chest wall typically result in small, ineffective V_T. Because anatomic dead space is fixed, a very small V_T that largely is dead-space gas being recirculated contributes little to effective alveolar ventilation (alveolar ventilation = minute ventilation – dead-space ventilation). To maintain adequate alveolar minute ventilation with the limited number of mechanical breaths provided by the ventilator in SIMV mode, relatively large V_T is required.

Assist/Control

Like SIMV, assist/control (A/C) is a time-cycled, pressure-limited mode, but unlike in SIMV, in A/C, every spontaneous breath that exceeds the trigger threshold is supported by the ventilator. This approach delivers more uniform V_T and lowers the WOB. The clinician still sets a ventilator rate for mandatory breaths, which provides a minimum rate in case of apnea. This rate should normally be set slightly below the infant's spontaneous rate so as not to preempt spontaneous breaths. Because the infant controls the effective ventilator rate, weaning is accomplished by lowering the peak inspiratory pressure, rather than the ventilator rate. This approach decreases the amount of support provided to each breath, allowing the infant gradually to take over the WOB. One reason for the apparent reluctance to adopt this mode appears to be this slightly less intuitive weaning strategy.

Pressure Support Ventilation

Pressure support ventilation (PSV) is a flow-, rather than time-, cycled, pressure-limited mode that supports every spontaneous breath (just as A/C does). However, PSV also terminates each breath when inspiratory flow declines to a preset threshold, usually 10–20 percent of peak flow. This feature eliminates inspiratory hold (prolonged inspiratory time, which keeps the lungs at peak inflation) and thus presumably provides more optimal synchrony. In some devices, PSV can be used to support spontaneous breathing between low-rate SIMV to overcome the problems associated with the patient's inadequate spontaneous respiratory effort and high ETT resistance. However, with some devices, PSV is used as a stand-alone technique, much like A/C.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is an interesting technique not currently available in the U.S. Based on elastic and resistive unloading of the respiratory system, PAV aims to overcome the added workload imposed by poor lung compliance and high airway and ETT/ventilator circuit resistance.[6] The ventilator develops inspiratory pressure in proportion to patient effort—in essence, it is 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 an excessively high level of assistance 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 a correspondingly high level of inspiratory pressure, potentially leading to a dangerously large V_T. Limited clinical data are available on the use of PAV in preterm infants.

Neurally Adjusted Ventilatory Assist

Neurally adjusted ventilatory assist (NAVA) utilizes the electrical activity of the diaphragm to trigger and modulate inspiratory gas flow. Similar to PAV, it assumes a mature respiratory control center. Like PAV, it is a positive feedback control mechanism, providing higher pressure when the infant breathes vigorously and less or no support when the infant hypoventilates or becomes apneic. As such, it may not be suitable for preterm infants, who are notorious for their periodic breathing. Although the available backup rate will adequately deal with apnea, the potential to accentuate periodic breathing is an issue that requires careful evaluation.

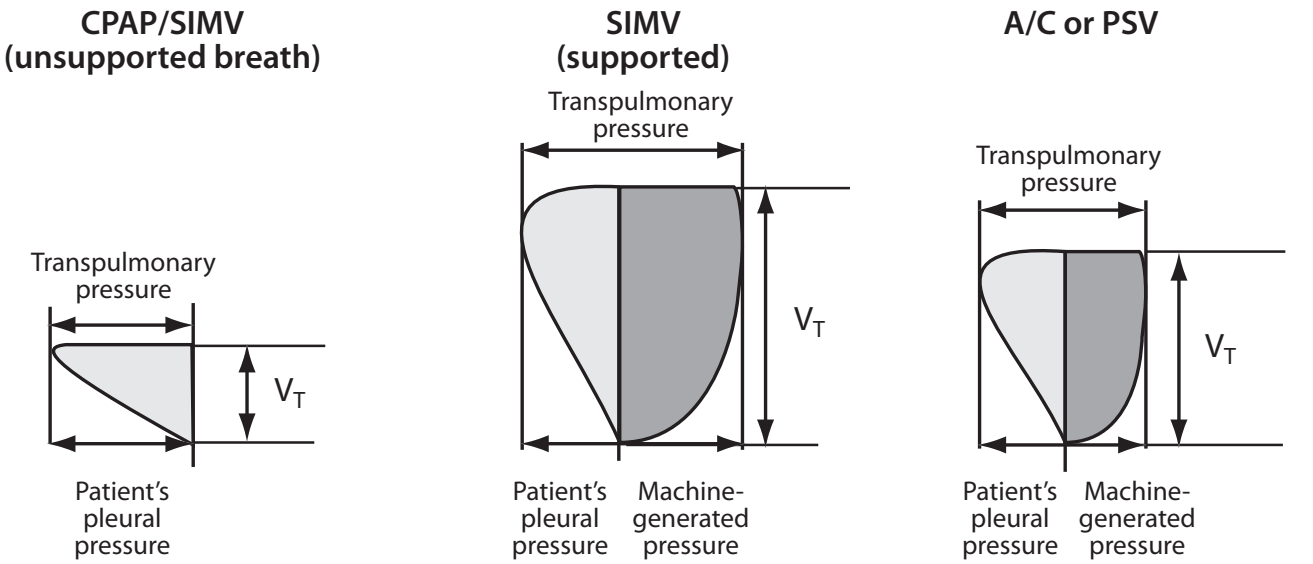
Choosing a Synchronized Mode

Despite years of routine use, there is no clear consensus regarding the relative merits of A/C and SIMV, the two most widely used modalities of synchronized ventilation. Information documenting the superiority of one mode over the other is limited. There are no large prospective trials with important clinical outcomes, such as incidence of air leak, chronic lung disease, or length of ventilation. However, 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 A/C than with SIMV.[7–10]

There are important physiologic considerations, as outlined earlier, why SIMV may not provide optimal support in very premature infants. However, many clinicians still prefer SIMV, especially for weaning from mechanical ventilation. This preference is based on the assumption, unsupported by data, that fewer mechanical

FIGURE 9-1
Interaction of patient and ventilator pressures to generate delivered 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") results in the transpulmonary pressure, which together with the compliance of the respiratory system, determines the V_T.



breaths are less damaging and on the belief that weaning of ventilatory rate is necessary before extubation. It has been unequivocally demonstrated that lung injury is most directly caused by excessive V_T, irrespective of the pressure required to generate that V_T.[11–13] A rate of 60 breaths per minute, compared with rates of 20–40 breaths per minute, was shown to result in less air leak with unsynchronized IMV.[14] This finding lends further support to the putative advantage of A/C, with its smaller V_T and higher mechanical breath rate, over SIMV.

Some clinicians also believe that supporting every breath does not provide the infant with an opportunity for respiratory muscle training. This concern is also unfounded and highlights some clinicians' limited understanding of the patient-ventilator interaction during synchronized ventilation. As Figure 9-1 illustrates, with synchronized ventilation, V_T is the result of the inspiratory effort of the patient (negative intrapleural pressure on inspiration) combined with the positive pressure generated by the ventilator. This combined effort (the baby "pulling" and the ventilator "pushing" the gas) 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 work of breathing; in the process, the respiratory muscles are trained. Ultimately, the ventilator pressure is decreased to the point where it is overcoming only the added resistance of the ETT and circuit. At that point, the infant is ready for extubation.

Finally, extensive experience with high-frequency ventilation (HFV) makes it clear that lowering pressure amplitude and leaving the rate unchanged is an effective way of reducing ventilator support to the point of extubation. Although we cannot make a direct parallel between A/C and HFV, it is reasonable to accept that a larger number of smaller breaths with A/C need not be detrimental. But a definitive large study comparing the relative merits of SIMV and A/C is lacking.

Clinical Trials of Synchronized Ventilation

Despite widespread 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, and length of hospitalization. A number of small studies have shown improvement in short-term physiologic outcomes (Table 9-3), but demonstrating "bottom line" long-term outcome improvement has been elusive.[15] Unfortunately, the only available studies suffer from important design and device

TABLE 9-3
Demonstrated Short-Term Benefits of Synchronized Ventilation

Reference	Population	Mode	Benefit
Berenstein et al., 1994[37]	30 NB	SIMV	Higher and more consistent V_T
Cleary et al., 1995[38]	10 NB <32 weeks <12 hours	SIMV	Improved ventilation and oxygenation
Jarreau et al., 1996[39]	6 NB with RDS	A/C	Decreased work of breathing
Quinn et al., 1998[40]	59 NB <32 weeks	A/C	Decreased catecholamine levels
Smith et al., 1997[41]	17 NB with RDS	SIMV	Less tachypnea

Key: A/C = assist/control ventilation; NB = newborn; RDS = respiratory distress syndrome; SIMV = synchronized intermittent mandatory ventilation.

limitations, leaving clinicians with the unsatisfactory situation of using an "unproven" therapy day after day.

In the first large clinical trial, Bernstein and associates compared SIMV and IMV in a prospective randomized multicenter study of 327 infants ventilated with the Infant Star ventilator with Star Sync module (Grasby capsule abdominal movement sensor) (Infrasonics, Inc., San Diego, California).[16] Compared with IMV, there was a shorter duration of mechanical ventilation among infants >2,000 g on SIMV, less need for sedation for infants 1,000–1,499 g on SIMV, a lower mean airway pressure at one hour postentry in all age groups on SIMV, as well as a shorter time to regain birth weight when ventilated for >14 days on SIMV. The researchers further showed less need for oxygen at 36 weeks corrected gestational age (CGA) among infants weighing <1,000 g and less need for oxygen at 36 weeks CGA for all infants <2,000 g during SIMV. There was no difference between SIMV and IMV in the primary endpoints—survival, air leak, and overall length of mechanical ventilation—in this rather heterogeneous group. Had the investigators chosen bronchopulmonary dysplasia (BPD) at 36 weeks CGA as their primary outcome, they would have been able to report a significant improvement in their entire study population (reduction from 42 percent to 28 percent, $p < .05$) (result reanalyzed based on the published data). A much smaller single-center randomized trial by Chen and coworkers using the same device enrolled 77 neonates with RDS and meconium aspiration syndrome (MAS) requiring mechanical ventilation. Premature infants with RDS on SIMV had a significantly shorter duration of ventilation, less need for reintubation, a lower incidence of severe intraventricular hemorrhage (IVH) (grades 3 and 4), and a lower incidence of BPD than those on IMV. No differences were seen in the small number of MAS infants.[17]

Baumer and colleagues, in a large randomized trial, compared A/C with IMV in 924 preterm infants with RDS. A/C was provided using the SLE 2000 (airway pressure trigger) (SLE Ltd., South Croydon, United Kingdom) in the large majority of patients and the Draeger Babylog 8000 (airway flow trigger) in the rest. Some centers lacked prior experience with triggered ventilation. This trial showed no difference in chronic lung disease, pneumothorax, duration of ventilation, or risk of IVH between the two groups. The author and colleagues concluded that there was no observed benefit from the use of A/C, particularly in infants <28 weeks gestational age.[18] It is important to interpret the results in light of the device used in the majority of patients. The SLE 2000 uses airway pressure to sense patient effort. Pressure triggering has been shown to result in failure to trigger in a large proportion of infants <1,000 g.[3] There was a nonsignificant trend to a higher incidence of air leak in infants <1,000 g in the triggered group. Given the long trigger delay of pressure-triggered ventilators, it is tempting to speculate that the increased air leak incidence resulted from late cycling of the ventilator at a time the infant was already starting to exhale. The author and colleagues appropriately stated in their discussion that these results apply to the SLE 2000 device and to the population studied and may not be generalizable to other situations.[18]

Beresford and associates enrolled 386 preterm infants with birth weights of 1–2 kg in a randomized trial of IMV or triggered ventilation with the SLE 2000 (pressure trigger) ventilator. Infants in the trigger group were ventilated using A/C, then weaned using SIMV, whereas those in the control group had their ventilator rate adjusted manually to match each infant's own respiratory rate initially and were then weaned. Chronic lung disease, death, pneumothorax, IVH, number of ventilator days, and length of oxygen dependency were similar in the two groups. It could be concluded that careful manual synchronization of ventilator set rate with the infant's breathing is as effective as automatic synchronization by the ventilator when using pressure trigger.[19] How practical manual synchronization is outside of a study protocol remains an open question, however. Once again, the issue of the relative ineffectiveness of the pressure-triggered device adds uncertainty regarding interpretation of the data.

Clearly, the two studies using a rapidly acting surface trigger device (the Infant Star) had better results than the two trials that used the pressure-triggered

device, the SLE 2000. Ventilator studies should be interpreted with caution, and the conclusions drawn from them should be considered specific to the devices and strategies employed. These conflicting results highlight the difficulties involved in conducting ventilator studies where many different devices are used and experience with their use differs among participating centers. The characteristics of the sensing and triggering device are crucial to its performance in synchronizing infant and machine breaths, especially in the tiniest infants. Meta-analysis is an important tool to use in evaluating research to arrive at evidence-based practice, but lumping together studies using different ventilation devices and approaches to ventilation may obscure the important differences and confuse, rather than clarify, the issues.

Volume-Targeted Ventilation

The most recent—and in many ways most promising—advance in neonatal ventilation is the advent of volume-targeted ventilatory modes. The recognition that volume, rather than pressure, is the critical determinant of ventilator-induced lung injury,[12,13] along with mounting evidence that hypocarbia is associated with neonatal brain injury,[20–22] has rekindled interest in directly controlling V_T. Traditional volume-controlled ventilation is difficult in small neonates because of the unpredictable loss of V_T to gas compression in the circuit, stretching of the tubing, and variable leakage around uncuffed ETTs. Nonetheless, one publication did demonstrate feasibility of volume-controlled ventilation in infants <1,500 g, at least under carefully controlled study conditions. The study suggested that, when a proximal flow sensor is used to accurately measure exhaled tidal volume and the set V_T is manually adjusted at frequent intervals to maintain the desired exhaled V_T, it is possible to achieve effective volume control. The patients randomized to the volume control mode reached an arbitrary primary endpoint of *either* mean airway pressure of <8 cmH_2O *or* an alveolar-arterial oxygen difference ($AaDO_2$) <100, though the duration of mechanical ventilation and oxygen supplementation was not different.[23] However, monitoring of proximal tidal volume and frequent manual adjustment of set tidal volume are not routinely practiced with volume-controlled ventilation. For this reason, a number of modifications of time-cycled, pressure-limited ventilation designed to target a set tidal volume using microprocessor-directed adjustments of peak pressure or inspiratory time have recently been developed. Each of the available modes has advantages and disadvantages. The most widely available modes of volume-targeted ventilation are discussed below.

Volume-Targeted Ventilation Modes

Pressure-Regulated Volume Control

Pressure-regulated volume control (PRVC) is a pressure-limited, time-cycled ventilation mode that adjusts inspiratory pressure to target a set tidal volume, based on the V_T of the previous breath. The main problem with the PRVC mode of the Maquet Servo 300 and to a lesser extent the Servo-i (Maquet, Inc., Bridgewater, New Jersey, 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.[24,25] This limitation can be overcome to some degree by the use of the circuit compliance feature and the use of a proximal flow sensor. More information on these ventilators can be found at www.maquet.com/criticalcare.

Volume-Assured Pressure Support

The volume-assured pressure support (VAPS) mode on the Bird VIP Gold (CareFusion, San Diego, California) is a hybrid mode, which works to ensure that the targeted V_T is reached. Each breath starts as a pressure-limited breath, but if the set tidal volume is not reached, the device converts to a flow (volume)-cycled mode. The resulting volume-controlled breath thus leads to prolongation of the inspiratory time and a passive increase in peak pressure. This rather prolonged inspiratory time may lead to expiratory asynchrony. Targeting tidal volume based on inspiratory V_T is susceptible to error in the presence of significant ETT leak. The focus is on ensuring a large enough V_T. There is no provision for automatically lowering inspiratory pressure as lung compliance improves, nor is provision made to avoid inadvertent hyperventilation and allow for automatic weaning.

The newer AVEA ventilator by CareFusion (San Diego, California) shares the basic features of VAPS, albeit with a more sophisticated microprocessor algorithm that avoids the excessively long inspiratory time, and adds a volume limit function that terminates inspiration if the upper V_T limit is exceeded. This added function should reduce the risk of volutrauma and hyperventilation, but it still does not lead to automatic weaning of inspiratory pressure and may lead to very short inspiratory times. More information on these ventilators can be found at www.carefusion.com. A new software modification that mimics the volume guarantee (VG) mode described below has recently been implemented in this device.

Volume Guarantee

The Dräger Babylog 8000 plus and the new Babylog VN500 offer a VG option that can be combined with any of the standard ventilator modes (A/C, SIMV, PSV). The VG mode is a volume-targeted, time-cycled, pressure-limited form of vetilation. The operator chooses a target V_T and selects a pressure limit up to which the ventilator operating pressure (the working pressure) can be adjusted. The microprocessor compares the V_T of the previous breath, using exhaled V_T to minimize possible artifact resulting from air leak, and adjusts the working pressure up or down to try to achieve the set V_T. The algorithm limits the amount of pressure increase from one breath to the next to avoid overcorrection that could lead 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 the target V_T. To minimize the risk of excessively large V_T, the microprocessor opens the expiratory valve, terminating any additional pressure delivery if the delivered V_T exceeds 130 percent of the previous breath. By design, the algorithm is geared toward slower adjustment for low V_T and more rapid adjustment for excessive, potentially dangerous volume delivery. 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.

Clinical Studies of Volume-Targeted Ventilation

Several early studies demonstrated the feasibility and efficacy of VG and showed that equivalent or lower peak pressures were needed to achieve similar gas exchange with a shift of the work of breathing from the ventilator to the infant.[26,27]

A short-term crossover study showed that VG combined with A/C, SIMV, or PSV led to significantly lower variability of V_T compared with A/C, PSV, or SIMV alone and that peak inspiratory pressures were similar.[28] The first randomized clinical trial of VG later demonstrated that, when combined with the A/C mode, VG maintained $PaCO_2$ and V_T within a target range more consistently than did A/C alone during the first 72 hours of life in preterm infants with uncomplicated RDS. The incidence of hypocapnia, defined as $PaCO_2$ <35 mmHg, was reduced by about 45 percent.[29] The crossover study documented that the VG device functions as intended in the clinical setting, with the anticipated reduction of V_T variability.[28] The randomized trial demonstrated that excessively large V_T and hypocarbia could be reduced, although not eliminated, with the use of VG.[29] This suggested VG's potential to reduce many of the important adverse effects of mechanical ventilation.

A 2005 short-term crossover trial studied 12 extremely low birth weight (679 ± 138 g) infants to determine whether VG is more effective when combined with A/C or SIMV. As expected, V_T was more stable when VG was combined with A/C because the interval between supported breaths is longer during SIMV, leading to slower adjustment in working pressure. An unexpected finding was that, during SIMV, the infants had significantly lower and more variable SpO_2, and significantly more tachycardia and tachypnea. By design, the V_T was identical, but significantly higher peak inspiratory pressure (PIP) was required during SIMV to achieve the same V_T. The tachypnea, tachycardia, and lower, more variable oxygen saturation suggest that the infants were tiring during the SIMV period and contributing less spontaneous effort by the end of the two-hour period when the measurements were obtained.[30] This is because, 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.

Finally, in a randomized trial of 53 infants with RDS, Lista and colleagues demonstrated decreased levels of pro-inflammatory cytokines and shorter durations of mechanical ventilation using VG combined with PSV rather than PSV alone. The duration of mechanical ventilation was 12.3 ± 3 days in the VG group compared to 8.8 ± 3 days in those on PSV alone.[31] By contrast, a subsequent similar study by the same authors, this time using a target tidal volume of 3 mL/kg, showed an *increase* in proinflammatory cytokines.[32] This was most likely a consequence of atelectasis that resulted from the combination of low V_T and low end-expiratory pressure of 3–4 cmH_2O that was used.[33]

A recent meta-analysis that included both VG studies, PRVC, and VCV studies reported that volume-targeted ventilation, compared to pressure-limited ventilation, reduced the combined outcome of death or BPD, reduced the risk of pneumothorax, and shortened the duration of mechanical ventilation. However, the included studies were quite small and, more important, many of the key outcomes reported in the meta-analysis were not prospectively collected or defined. In some of the studies,

other variables beyond volume versus pressure targeting also differed. All the included studies focused on short-term physiologic outcomes, and none included BPD as a primary outcome.[34]

Importance of Open Lung Strategy

The findings of the second Lista study bring out the critical importance of distributing delivered tidal volume evenly into an optimally aerated lung. This key concept has not been widely appreciated and requires special emphasis. Lungs of preterm infants are very prone to atelectasis as a result of surfactant deficiency and an excessively compliant chest wall. Atelectasis is not uniform, but tends to occur in the dependent portion of the lung. Even a normal, physiologic V_T entering only the population of open alveoli will inevitably lead to overexpansion with subsequent lung injury. Thus, it is important to strive to optimize lung volume by using adequate distending airway pressure. In practical terms, this "open lung concept" is achieved by applying sufficient PEEP to improve oxygenation and wean FiO_2 to $\leq$0.35. *The benefits of volume-targeted ventilation cannot be realized without ensuring that this tidal volume is distributed evenly throughout the lungs.*

It remains to be seen whether the demonstrated short-term benefits of VG translate into significant reductions in the frequency of air leak, chronic lung disease, neuroimaging abnormalities, and length of hospitalization.

Clinical Application of Ventilation

Despite the lack of definitive evidence of synchronized ventilation's superiority to standard IMV, the benefits of synchronized ventilation are generally accepted. Very few if any NICUs have not adopted these techniques. The choice of SIMV or A/C is, to some extent, a matter of clinician preference and practice style. In reality, there is little difference between the two modalities in the acute phase of respiratory failure, especially in extremely premature or gravely ill infants who have little or no respiratory effort of their own or in infants who are 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 ETTs. Prolonged ventilation with low SIMV rates should be avoided in these infants because it imposes an undesirably high work of breathing. Reyes and associates demonstrated that addition of PSV to support the spontaneous breathing during SIMV effectively compensates for the ineffective V_T during SIMV.[35]

Standard Synchronized Ventilation Modes

As with all pressure-limited, time-cycled ventilators, the operator must choose PIP, PEEP, T_I, ventilator rate (either directly or by separately adjusting inspiratory and expiratory time), and FiO_2. The initial steps are common to all forms of synchronized ventilation.

Initial Settings

PIP. Selection of the starting PIP is based on an estimation of the severity of disease and adequacy of chest rise. This setting is then adjusted to achieve an appropriate V_T, typically 4–7 mL/kg, measured at the airway opening. Contrary to popular opinion, the PIP requirement is not related to the baby's size, but to severity of illness. The misconception about PIP arose from the fact that larger babies cope with poorly compliant lungs more effectively than smaller ones because of their greater strength and endurance. Consequently, respiratory failure occurs at lesser degrees of illness severity in the smaller infant. However, even a small preterm infant may have very stiff lungs and may, at times, require fairly high pressures. On the other hand, the term infant with normal lungs who is ventilated for nonrespiratory reasons needs PIP only in the low teens to achieve a normal V_T. *Rapid improvement in compliance can take place following surfactant administration.*

PEEP. PEEP should be set in proportion to the current oxygen requirement because in virtually all neonatal lung diseases, hypoxemia is a reflection of ventilation-perfusion mismatch and intrapulmonary right-to-left shunting. This, in turn, reflects atelectasis and low lung volume. Thus, a high oxygen requirement can usually be attributed to low lung volume. It can be corrected by adequate PIP to open atelectatic alveoli and application of sufficient PEEP to maintain that recruitment. The exception to this rule is the infant with pulmonary hypertension with hypoxemia related to extrapulmonary shunting. A PEEP of 5 cmH_2O is usually adequate if the FiO_2 is 0.25–0.35, PEEP should be about 6 cmH_2O with an oxygen requirement between 0.35 and 0.5, and it should be 7–10 cmH_2O if the FiO_2 remains >0.6. Lung expansion on chest x-ray can also guide selection of the PEEP level.

Inspiratory Time. Selection of (T_I) should reflect the infant's time constants (a measure of how rapidly gas can get in and out of the lungs). Small preterm infants with RDS have very short time constants and should be

ventilated with T_I of 0.3 second or less. Large infants or those with increased airway resistance (e.g., those with chronic lung disease or meconium aspiration) have longer time constants and require longer T_I, up to 0.5 second.

Ventilator Rate. The ventilator rate should reflect the severity of illness and whether the infant has much respiratory effort of his own. Infants with severe lung disease and little or no respiratory effort should generally be supported with a fairly rapid rate of 50–60 breaths per minute. Spontaneously breathing infants with less severe disease can be supported with a rate of around 40 breaths per minute, allowing them to trigger the ventilator. Because respiratory rate determines expiratory time (and vice versa), it is important to allow sufficient expiratory time to avoid air trapping resulting from incomplete exhalation. For this reason, it is important to avoid rates >60/minute in larger infants or those with increased airway resistance and >80/minute in small preterm infants. Adequacy of inspiratory and expiratory time can be verified by observing the ventilator flow waveform and making sure that flow returns to zero (baseline) before each expiration and inspiration begins.

Subsequent Adjustments

As the infant begins to improve and generate spontaneous respiratory effort, the ventilator rate should be lowered gradually to allow him to take over some of the work of breathing. This is important because a too rapid rate will override the infant's own effort and defeat the purpose of synchronized ventilation—namely, for the infant and the ventilator to work together. A low $PaCO_2$ is equally undesirable because it will suppress the infant's respiratory drive.

It is important to understand clearly how different ventilator variables affect gas exchange and how they interact with the underlying pathophysiology. A detailed discussion of these concepts is beyond the scope of this chapter, but the essentials are reviewed briefly.

Oxygenation is controlled by adjustments in FiO_2 and mean airway pressure, as discussed above. The goal should be to optimize lung volume and ventilation-perfusion matching and to lower FiO_2 to <0.35. PEEP is the most important determinant of mean airway pressure (Paw). PIP, inspiratory time, and rise time (how quickly plateau pressure is reached) are the other factors.

Ventilation (CO_2 elimination) is controlled by adjustments of ventilatory rate and V_T. In standard pressure-limited ventilation, V_T is determined by lung compliance and pressure amplitude (difference between PIP and PEEP). Thus, increasing PIP improves ventilation as well as oxygenation through its effect on V_T and Paw.

Increasing PEEP and/or lowering PIP decreases V_T if all other factors remain equal. However, if the increased PEEP results in recruitment (normalization) of lung volume, lung compliance will improve, which may improve ventilation, sometimes quite dramatically. This improvement in ventilation can lead to inadvertent hyperventilation—which the use of volume-targeted ventilation can avoid. Excessively high PEEP will cause overexpansion of the lungs, with resultant hemodynamic compromise and incomplete exhalation (lower V_T), resulting in hypercarbia. As the patient's lung disease evolves, significant changes in compliance and resistance will occur. Therefore, the appropriateness of all settings needs to be reevaluated regularly. For example, a PEEP of 6 or 7 cmH_2O, which would be quite appropriate early in the course of RDS when the lungs are stiff, becomes excessive as compliance and lung volume increase. Oxygen requirement is the best bedside tool to assess adequacy of lung volume.

Weaning

With SIMV, weaning is accomplished by reducing PIP as well as the ventilator rate. In general, the rate should not be reduced much until PIP has been reduced to relatively low values (<16–18 cmH_2O) that signify considerable improvement in lung compliance. Weaning the rate while the lungs are still quite stiff is likely to impose a high WOB. It may require excessively large V_T for the machine breaths to compensate for ineffective spontaneous breaths that may do little more than rebreathe the anatomic dead space. The rate should not be reduced to <10 breaths per minute, especially in small infants, because of the high work of breathing associated with small ETTs. Again, the addition of PSV to SIMV may compensate for these problems and is recommended if the ventilator has the capability. As a rule, infants who are able to generate adequate V_T and gas exchange with PIP of 15–18 cmH_2O and a rate of ten breaths per minute are ready for extubation.

With A/C and PSV, the infant controls the ventilator rate; therefore, lowering the set rate, which only acts as a backup in case of apnea, has little impact. Weaning is accomplished by lowering the PIP, which decreases the amount of support for each breath. This gradually transfers the WOB to the infant. When PIP has been reduced to 10–14 cmH_2O in small preterm infants and to 15–20 cmH_2O in larger infants, these infants are typically ready for extubation. In the small infants, these low

pressures serve merely to overcome the added resistance of the ETT. In very premature infants, it is appropriate to lower the backup rate to 15–20 breaths per minute for a few hours prior to extubation to uncover inconsistent respiratory effort/periodic breathing that a higher backup rate might effectively mask.

Volume-Targeted Ventilation

Because VG is the most widely used and best studied modality of volume-targeted ventilation and because it is the technique with which I have extensive clinical experience, the clinical guidelines provided are specific for this modality. Though volume-targeted ventilation modes share certain characteristics, each device functions differently and may respond to perturbations in a different way. Consult the product literature of each manufacturer for specific clinical guidelines for their respective ventilators.

Initiation

- VG should be implemented as soon as possible after initiation of mechanical ventilation because this is the time when the most rapid changes in lung mechanics are likely to occur.
- The usual starting target V_T for most infants is 4–5 mL/kg during the acute phase of the illness. Infants with MAS may require slightly larger V_T (5–6 mL/kg) due to the larger alveolar dead space related to some degree of overinflation.
- The added dead space of the flow sensor becomes proportionally more significant in the smallest infants. For this reason, extremely low birth weight infants <700 g need V_T of 5.5–6 mL/kg. The effect is not large enough, however, to preclude the use of synchronized or volume-targeted ventilation.[36]
- Larger tidal volumes (as much as 6–8 mL/kg) are needed in older infants with chronic lung disease because of increased anatomic and physiologic dead space (dilated large airways and wasted ventilation resulting from poor ventilation-perfusion matching).
- The PIP should be set about 20 percent higher than the working pressure (the PIP currently needed to deliver the target V_T) to give the device adequate room to adjust PIP.
- Record not only the PIP limit, but also the working pressure, which is the true reflection of the level of support the infant is receiving.

Subsequent Adjustments

- Subsequent adjustment to the target V_T can be made based on $PaCO_2$, although adjustment is seldom necessary. The usual increment is 0.5 mL/kg.
- The PIP limit needs to be adjusted from time to time (the usual increment is 2–4 cmH_2O) to keep the PIP limit sufficiently close to the working pressure to avoid dangerously high V_T and at the same time high enough to avoid frequent alarms. In most infants, keeping the pressure limit 4–6 cmH_2O above average working pressure is appropriate.

  Note: The working pressure will default to the PIP limit if the flow sensor is temporarily removed (such as around the time of surfactant administration or delivery of nebulized medication), if its function is affected by reflux of secretions or surfactant, or if it malfunctions for any reason. The manual inspiration (activated by depressing a key on the front panel) also uses the set PIP limit. Ideally, when removing the flow sensor for significant periods, such as when nebulizing medications, adjust the PIP limit to roughly match the average or recent working pressures. To avoid volutrauma, keep the PIP limit sufficiently close to the actual PIP (~5–10 cmH_2O).
- If the infant appears agitated, with episodes of spontaneous hyperventilation, consider light sedation. (However, avoid oversedation, with complete suppression of respiratory effort.)
- If the infant is persistently tachypneic or is consistently breathing above the set V_T, his WOB is excessive. Consider increasing the V_T target even if the $PaCO_2$ and pH are normal. (However, if the $PaCO_2$ is low and the respiratory rate is high, sedation may be indicated.)
- If the low-V_T alarm sounds repeatedly, increase the pressure limit to allow the device to reach the desired V_T. Repeated alarms suggest that there has been a change in lung mechanics or patient respiratory effort (e.g., atelectasis, pneumothorax, pulmonary edema, entry of the ETT into the right mainstem bronchus). This early warning system is an important benefit of the VG mode and should not be ignored.
- If the pressure limit has to be increased substantially and/or repeatedly, verify that the V_T measurement is accurate (assess chest rise, obtain a blood gas). If it is, seek the cause of the change in lung mechanics (examine the patient, verify ETT position, obtain a chest x-ray).

Weaning

- When the target V_T is set at the low end of the normal range (usually 4 mL/kg in the acute phase, 1–2 mL/kg higher in BPD infants) and the $PaCO_2$ is allowed to rise to the low to mid-40s, weaning occurs automatically ("self-weaning").
- If the V_T is set too high and/or the $PaCO_2$ is too low, the baby will not have a respiratory drive and will not self-wean. Instead, lack of respiratory muscle training will cause him to become dependent on the ventilator.
- Avoid oversedation during the weaning phase.
- If an infant does not appear to be weaning as expected, despite apparently improving lung disease, try lowering V_T to 3.5 mL/kg, as long as the infant's blood gases are adequate and WOB does not appear excessive. However, remember that infants with chronic lung disease need relatively larger V_T. Lowering the V_T below the infant's physiologic need will result in excessive work of breathing because the infant will have to breathe through the ETT with little or no support from the ventilator.
- If a significant oxygen requirement persists, it may be necessary to increase the PEEP to maintain mean airway pressure as the PIP is automatically lowered.
- Most infants can be extubated when they consistently maintain V_T at or above the target value with delivered PIP <10–12 cmH_2O (<12–15 cmH_2O in infants >1 kg) with FiO_2 <0.35 and good sustained respiratory effort.
- Observing the graphic display of the working pressure is helpful in assessing for periodic breathing (variable respiratory effort) that may require methylxanthine administration to facilitate extubation.

Summary

Many new modalities and techniques are available for the treatment of respiratory failure. Our understanding of how to use these devices to best effect, while improving constantly, remains somewhat behind the pace of technologic innovation. Improvements in outcomes, such as BPD, are becoming increasingly difficult to demonstrate because each incremental improvement leaves "the bar" that much higher. When combined with other lung protective strategies aimed at optimizing lung volume and ensuring even distribution of the delivered tidal volume, volume-targeted ventilation appears to offer the best hope of making a significant impact on ventilator-induced lung injury. However, avoiding mechanical ventilation through early use of continuous positive airway pressure with or without surfactant administration may still be the most effective way to reduce the risk of chronic lung disease.

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Notes