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Mechanical ventilation strategies

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A B S T R A C T

Although only a small proportion of full term and late preterm infants require invasive respiratory support, they are not immune from ventilator-associated lung injury. The process of lung damage from mechanical ventilation is multifactorial and cannot be linked to any single variable. Atelectrauma and volutrauma have been identified as the most important and potentially preventable elements of lung injury. Respiratory support strategies for full term and late preterm infants have not been as thoroughly studied as those for preterm infants; consequently, a strong evidence base on which to make recommendations is lacking. The choice of modalities of support and ventilation strategies should be guided by the specific underlying pathophysiologic considerations and the ventilatory approach must be individualized for each patient based on the predominant pathophysiology at the time.

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1. Introduction

Despite appropriate emphasis on non-invasive respiratory support when feasible, mechanical ventilation remains an important therapy in the sickest infants. Although frequently life-saving, invasive mechanical ventilation has many untoward effects on the cardiovascular system, brain and lungs. Whereas preterm infants are most vulnerable, term newborns are not immune from these adverse effects [1,2]. The endotracheal tube (ETT) acts as a foreign body, quickly becoming colonized and acting as a portal of entry for pathogens, increasing the risk of ventilator-associated pneumonia and late onset sepsis [3]. For these reasons, avoidance of mechanical ventilation in favor of non-invasive respiratory support remains the most important step in preventing neonatal morbidity. When mechanical ventilation is required, the goal is to liberate the patient from invasive ventilation as soon as feasible in order to minimize ventilator-associated lung injury (VALI) and other ventilator-related complications.

2. Ventilator-associated lung injury

Many terms have been used to describe the mechanism of injury in VALI. Barotrauma refers to damage caused by pressure. The conviction that pressure is the key determinant of lung injury has led clinicians to focus on limiting inflation pressure, sometimes to the point of precluding adequate ventilation. However, there is convincing evidence that high pressure by itself, without correspondingly high volume, does not cause lung injury. Rather, injury related to high inflation pressure is mediated through the tissue stretch, resulting from excessive tidal volume (V_T) or from regional overdistention when ventilating a lung with extensive atelectasis. Dreyfuss and colleagues demonstrated more than twenty 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 inflation pressure [4]. In contrast, animals exposed to the same high pressure but with an elastic bandage constraining chest excursion to limit V_T delivery suffered substantially less acute lung injury. In a similar study, Hernandez et al. showed that animals exposed to pressure of 45 cmH_2O did not show evidence of acute lung injury when their chest and abdomen were enclosed in a plaster cast [5]. Volutrauma is injury caused by over-distention and excessive stretch of tissues, which leads to disruption of alveolar and small airway epithelium, resulting in acute edema, outpouring of proteinaceous exudate, release of proteases, cytokines and chemokines, which in turn lead to activation of macrophages and invasion of activated neutrophils. Collectively, this latter process is referred to as biotrauma. Another important concept is that of atelectrauma, or lung damage caused by tidal ventilation in the presence of atelectasis [6]. Atelectrauma causes lung injury via several mechanisms. The atelectatic portion of the lungs experiences increased surfactant turnover and high critical opening pressure. Shear forces at the boundary between aerated and atelectatic parts of the lung cause structural tissue

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damage. Ventilation of injured lungs using inadequate end-expiratory pressure results in repeated alveolar collapse and expansion with each inflation, which rapidly injures the lungs. Finally, when a large portion of the lungs is atelectatic, gas entering the lungs will preferentially distend the aerated portion of the lung, which is more compliant than the atelectatic lung with its high critical opening pressure. This fact is evident from LaPlace's law and corroborated by experimental evidence, showing that the most injured portion of the lung was the aerated non-dependent lung [7].

2.1. How can we reduce VALI?

As is evident from the prior discussion, the process of lung damage from mechanical ventilation is multifactorial and cannot be linked to any single variable. Consequently, any approach to reducing lung injury must be comprehensive and begin with the initial stabilization of the infant in the delivery room [8].

2.2. Non-invasive respiratory support

There is little doubt that, in general, avoiding mechanical ventilation will reduce iatrogenic lung injury, but this issue has been studied much more thoroughly in preterm infants [9], with little available information regarding the use of non-invasive support in late preterm and term newborns. Only observational studies are available and thus there is wide variation in practice style. Nonetheless, based on sound physiologic principles, it is reasonable to attempt initial support with non-invasive modalities in an effort to prevent progression to more severe illness and need for mechanical ventilation.

3. Strategies of mechanical ventilation

Mechanical ventilators are devices designed to replace or augment the patient's inadequate respiratory effort. Ventilators are simply tools in our hands and we need to employ them thoughtfully in order to optimize outcomes. There are many devices and modes of ventilation to choose from, with limited high-quality data to guide the clinician's choice. The goal of mechanical ventilation is to maintain acceptable gas exchange with a minimum of adverse effects and to wean from invasive support as expeditiously as possible. Because of the wide range of clinical conditions of neonatal patients, no simple rules can define indications for intubation and initiation of mechanical ventilation. Similarly, “cookbook” settings that are often provided in texts on this subject have limited utility. Instead, choice of modalities of support and ventilation strategies should be guided by the specific underlying pathophysiologic considerations. In the following paragraphs, I review basic concepts of synchronized mechanical ventilation and general concepts of lung-protective ventilation strategies, followed by a discussion of specific strategies suitable for treatment of term and late preterm infants with respiratory failure.

3.1. Basic modalities of synchronized ventilation

Despite lack of a strong evidence base, the use of synchronized mechanical ventilation has become standard in our neonatal intensive care units (NICUs), but there is no clear consensus about which modality of synchronization is optimal. Synchronization of ventilator inflations with the infant's spontaneous breaths makes it possible to minimize sedation and muscle paralysis and to maximally utilize the patient's spontaneous respiratory effort. Whereas allowing the patient to breathe spontaneously during mechanical ventilation has clear advantages, it makes managing mechanical ventilation more challenging for the clinician. In order to employ assisted ventilation optimally, the clinician must understand the complex interaction between the awake, spontaneously breathing infant and the various modalities of synchronized ventilation. A key ingredient is an appreciation of the additive nature of the patient's own inspiratory effort and the positive pressure generated by the ventilator. The V_T entering the infant's lungs is driven by the sum of the negative inspiratory effort of the infant and the positive inflation pressure from the ventilator, which together constitute the transpulmonary pressure.

3.2. Synchronized intermittent mandatory ventilation (SIMV)

This is a basic synchronized modality that provides a user-set number of inflations in synchrony with the infant's breathing. If no spontaneous effort is detected during a trigger window, a mandatory inflation is delivered. Spontaneous breaths in excess of the set ventilator rate are not supported. In small preterm infants this results in uneven V_T values and high work of breathing because of the high airway resistance of the narrow ETT, coupled with the limited muscle strength and mechanical disadvantage of the infant's excessively compliant chest wall, but this is much less of a problem with term and late preterm infants. SIMV allows the operator to set the ventilator rate as well as inflation pressure and PEEP. Weaning is accomplished by gradual lowering of both rate and inflation pressure.

3.3. Assist control (AC)

Assist control is a modality that supports every spontaneous breath (“assist”) and provides a backup minimum rate of ventilator inflations in case of apnea (“control”). AC is time-cycled and can be pressure or volume controlled. Supporting every breath leads to more uniform V_T and lower work of breathing than SIMV. The goal is to have the infant and the ventilator work together, resulting in lower ventilator pressure. A backup ventilator rate provides a minimum rate in case of apnea and should be set just below the infant's spontaneous rate, usually at 30–40 inflations per minute. A backup rate that is too low will result in excessive fluctuations in minute ventilation and oxygen saturations during periods of apnea. Because the infant controls the inflation rate, gradual withdrawal of support is accomplished by lowering the peak inflation pressure, reducing the support provided to each breath and allowing the infant to gradually take over the work of breathing.

3.4. Pressure support ventilation (PSV)

A variety of modalities are referred to as PSV, a situation that greatly complicates communication. In specialty neonatal ventilators, pressure support ventilation is a flow-cycled and pressure-controlled mode that supports every spontaneous breath just like AC but is flow-cycled. Flow cycling means that inflation is terminated when inspiratory flow declines to a preset threshold, usually 5–20% of peak flow, eliminating inspiratory hold (prolonged inflation time, T_I) and providing more complete synchrony with less fluctuation in intrathoracic and intracranial pressure that occurs when infants exhale during inspiratory hold. Conveniently, PSV automatically adjusts T_I to be appropriate for the changing lung mechanics of the patient. Changing from time-cycled AC to PSV typically results in a shorter T_I and therefore lower mean airway pressure (P_{AW}). Therefore, unless positive end-expiratory pressure (PEEP) is adjusted to maintain P_{AW}, changing to PSV may lead to atelectasis. As with triggering, a substantial leak around the ETT may affect flow cycling.

Similar to AC, a backup rate will maintain a minimum inflation

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rate. In most devices PSV can also be used to support spontaneous breathing between low-rate SIMV, in order to overcome the problems associated with inadequate spontaneous respiratory effort and high ETT resistance or in a fully spontaneous mode (continuous positive airway pressure (CPAP) + PSV). When used with SIMV or with CPAP, PSV does not come with a backup mandatory rate, so a reliable spontaneous respiratory effort is required. Weaning from PSV when used as a primary mode is accomplished in the same way as for AC. When used in conjunction with SIMV, both the SIMV inflation rate and PIP should be lowered, leaving the infant increasingly breathing spontaneously with only a modest level of PSV, at which point extubation should be possible.

3.5. Volume-targeted ventilation (VTV)

Pressure-controlled ventilation became the accepted approach to mechanical ventilation in newborn infants because early attempts at volume-controlled ventilation using equipment available at the time in infants with uncuffed endotracheal tubes (ETT) were disappointing. Pressure-controlled ventilation remains the dominant mode of ventilation in the NICU because of its simplicity, ability to ventilate despite a large ETT leak and improved intrapulmonary gas distribution due to the decelerating gas flow pattern [10,11]. The fear of pressure as the major culprit in lung injury is deeply ingrained and many clinicians continue to believe that directly controlling PIP is important, despite unequivocal evidence that volume, not pressure is the key element in VALI. The danger of using pressure control is that V_T is not directly controlled and changes when lung compliance is altered. Consequently, minute ventilation may change substantially without any alteration in ventilator settings. Rapid improvement in compliance may occur due to resorption of lung fluid, improvement in lung volume or with surfactant administration and this may result in hyperventilation and volutrauma from excessively large V_T. Insufficient V_T may be delivered with alterations in lung compliance, airway resistance or patient's spontaneous respiratory effort. Inadequate V_T leads to hypercapnia, tachypnea, increased work of breathing and oxygen consumption, agitation, fatigue, atelectasis/atelectrauma and acidosis. Additionally, low V_T leads to inefficient gas exchange due to increased dead-space:V_T ratio. Thus, relatively tight control of V_T delivery is highly desirable. It is not surprising therefore that volume-controlled ventilation remains the standard of care in adult and pediatric ventilation.

There are many ways to regulate V_T delivery during MV. Modern ventilators now make it possible to use volume-controlled ventilation in newborn infants by allowing for measurement of exhaled V_T at the airway opening, so that manual adjustment of set V_T at the ventilator end of the patient circuit can be made to achieve a desired exhaled V_T [12]. More convenient are volume-targeted modes that are modifications of pressure-controlled ventilation that automatically adjust inflation pressure and/or time to achieve a target V_T [13]. It is likely that the primary benefit of VTV rests in the ability to regulate V_T, regardless of how that goal is achieved. With V_T as the primary control variable, inflation pressure comes down as lung compliance and patient inspiratory effort improve, resulting in real-time weaning of pressure, in contrast to intermittent manual lowering of pressure in response to blood-gas measurement. Volume guarantee is the most thoroughly studied form of VTV and the basic control algorithm is increasingly being adopted by other ventilator manufacturers. Benefits documented in two recent meta-analyses that encompassed several different modalities of VTV include significant decrease in the rate of BPD, pneumothorax, severe intraventricular hemorrhage and periventricular leukomalacia, and shorter duration of mechanical ventilation (Table 1) [14,15].

3.6. High-frequency ventilation (HFV)

In contrast to conventional ventilation, the importance of optimizing lung inflation has been recognized since its early days by users of HFV, where the optimal lung volume strategy is routine and is widely understood to be critical to its success [16]. HFV dates back to the 1980s and includes high-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation (HFJV) and high-frequency percussive ventilation (HFPV), also known as high-frequency flow interruption (HFFI). The benefit of HFV is believed to be a function of reduced pressure and volume swings transmitted to the periphery of the lungs. For optimal effectiveness, the lungs need to be recruited and then stabilized with the lowest possible mean airway pressure. HFV has been studied much more extensively in preterm infants than those born full term, but there are at least some data that support its utility in the treatment of aspiration syndromes and persistent pulmonary hypertension of the newborn (PPHN) [17,18]. As with any ventilator, HFV settings must be tailored to the specific pathophysiology that is being treated and that means that HFV needs to be used differently in full term infants, generally utilizing lower frequency/rate to accommodate the longer time constants of the full-term infant.

3.7. Importance of the open lung strategy

Adequate PEEP is widely recognized as a means of mitigating lung injury and the “open lung concept” (OLC) is an integral part of HFOV. However, the importance of achieving and maintaining uniform lung aeration [19] has been largely ignored by many practitioners during conventional mechanical ventilation despite a sound physiologic basis and strong experimental evidence in its favor. While controlling V_T is important, the benefits of VTV cannot be achieved unless the V_T is evenly distributed into an “open lung”, avoiding the many components of atelectrauma. Thus, the OLC, which ensures that the V_T is distributed evenly throughout the lungs, is a fundamental component of any lung-protective ventilation strategy [16,20]. With conventional ventilation, the open lung is achieved by applying adequate PEEP [21]. Unfortunately, the fear of using adequate end-expiratory pressure, so-called “PEEP-o-phobia”, remains prevalent with many practitioners rarely increasing PEEP beyond 5–6 cmH_2O. For this reason, ventilation mode is often changed to HFOV, where lung recruitment is achieved by increasing mean airway pressure, which, for some reason, is seen as much more acceptable by many clinicians. This may be in part due to the fact that the OLC with conventional ventilation has not been extensively evaluated in the clinical setting [16].

4. Treatment of specific disorders

4.1. Respiratory support of infants with respiratory distress syndrome (RDS)/pneumonia

Surfactant deficiency is not limited to very preterm infants. Late preterm and early term infants may develop RDS, especially if delivered by cesarean section without labor [22]. Most of those infants, when recognized early and treated appropriately with noninvasive support, do well and never require mechanical ventilation. If allowed to struggle without adequate support, these infants may develop progressively worsening respiratory insufficiency and climbing oxygen requirement that usually signals progressive surfactant inactivation and development of diffuse microatelectasis and they may ultimately become quite ill. The occasional infant that requires mechanical ventilation may have co-existing pathophysiologies, such as sepsis and pulmonary hypertension, which may contribute to the need for mechanical ventilation. Pneumonia is

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Table 1
Major outcomes assessed in the meta-analysis of 11 randomized clinical trials of volume-targeted vs pressure-limited ventilation [15].

Outcome	No. of studies	No. of subjects	RR (95% CI) or mean difference (95% CI)
Mortality	11	767	0.73 (0.51–1.05)
Any IVH	11	759	0.65 (0.42–0.99)[a]
Grade 3–4 IVH	11	707	0.55 (0.39–0.79)[a]
BPD at 36 weeks	9	596	0.61 (0.46–0.82)[a]
Cystic PVL	7	531	0.33 (0.15–0.72)[a]
Pneumothorax	8	595	0.46 (0.25–0.86)[a]
Failure of assigned mode	4	405	0.64 (0.43–0.94)[a]
Any hypocapnia	2	58	0.56 (0.33–0.96)[a]
Duration of supplementary O_2 (d)	2	133	−1.68 (−2.5 to −0.88)[a]

RR, relative risk; CI, confidence interval; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; PVL, periventricular leukomalacia.
[a] $p < 0.05$.

often indistinguishable clinically and radiographically from RDS and the two conditions indeed may co-exist. Both give rise to a relatively homogeneous lung disease and thus are treated in a similar fashion. Regardless of the specific diagnosis, the principles of lung protective ventilation strategies described earlier are the cornerstone of the approach to mechanical ventilation of these infants. Suggested initial ventilator settings for various modalities are shown in Table 2.

4.1.1. Non-invasive support

In mild cases, supplemental oxygen via oxyhood or nasal cannula is sufficient, but if oxygen requirement begins to increase, signaling worsening microatelectasis, provision of distending airway pressure is indicated. Some practitioners are reluctant to apply CPAP to these larger, more vigorous infants for fear of causing agitation and pneumothorax. Although these concerns are not entirely unfounded, optimal nursing care and provision of adequate support usually allow the infant to settle down and tolerate the support. The benefit of adequate distending pressure in avoiding the need for mechanical ventilation by maintaining adequate lung inflation, avoiding surfactant inactivation and improving distribution of V_T/optimizing ventilation–perfusion balance and thus reducing oxygen requirement outweigh the possible disadvantages.

4.1.2. Conventional ventilation

In general, infants with RDS have relatively homogeneous lung disease, although gravity-dependent differences in regional lung compliances exist and may be more important in the larger infants. The relative surfactant deficiency/inhibition makes the lungs prone to atelectasis; consequently, a key element in ventilatory support is recruitment and maintenance of adequate end-expiratory lung volume (EELV). The choice of synchronized ventilation modes is less critical in larger infants who cope better with the added resistance of ETTs, but in general, except for the need for somewhat longer inspiratory time and slower ventilation rate, the approach to mechanical ventilation is similar to the very low birth weight infants with RDS. The preferred approach is to use VTV to avoid volutrauma and inadvertent hypocapnia.

Table 2
Suggested initial settings for term/late preterm infants with respiratory distress syndrome or pneumonia.

	PCV	VTV	HFOV	HFJV
PIP (cmH_2O)	25	28 (limit)	–	22–24
T_I (s)	0.35–0.4	0.35–0.4	1:2 ratio	0.02
Rate (breaths/min)	40	40	–	340–360
PEEP/P_{AW} (cmH_2O)	6–7	6–7	12–14 (or 2 > CV)	8–9
Frequency (Hz)	–	–	8–10	7
Amplitude (cmH_2O)	–	–	20–24	–
Exhaled V_T (mL/kg)	–	4–4.5	2–2.5	–

PCV, pressure-controlled ventilation; VTV, volume-targeted ventilation; HFOV, high-frequency oscillatory ventilation; HFJV, high-frequency jet ventilation; PIP, peak inflation pressure; T_I, inflation time; PEEP, positive end-expiratory pressure; P_{AW}, mean airway pressure; CV, conventional ventilation; V_T, tidal volume.

When initiating mechanical ventilation, there must be a logical approach to choosing ventilator settings based on the underlying pathophysiology and an immediate assessment of their effectiveness, guided by a combination of clinical assessment and observation of waveforms and other displayed parameters on the ventilator screen. The PEEP level regulates EELV and adequacy of oxygenation, especially in the atelectasis-prone lung. An initial level of 6–7 cmH_2O is a reasonable starting point for most infants, with titration upward if FiO_2 remains >0.30. There is no universal PEEP setting that is appropriate for all patients. Even for an individual patient the PEEP requirement evolves over time and needs to be adjusted both up and down as evolving lung pathophysiology dictates. End-expiratory pressure may become excessive when lung compliance improves and lead to overdistension, incomplete exhalation with hypercapnia, increased pulmonary vascular resistance and impairment of venous return with decreased cardiac output. Very low PEEP (<4 cmH_2O) is inappropriate in the diseased lung and is likely to lead to low EELV, poor oxygenation, impaired pulmonary mechanics, greater turnover of surfactant and worsening lung injury.

Choice of the T_I should be guided by time constants of the infant's respiratory system. It should be set at around 0.35–0.4 s for term infants with RDS and adjusted as needed based on the flow curve of the pulmonary graphics display. T_I should be long enough to allow completion of inspiratory flow before the ventilator cycles off, but should avoid a substantial inspiratory hold that increases patient–ventilator asynchrony and risk of airleak. For flow-cycled modes (PSV), the T_I set value is really the upper limit that comes into play only if flow cycling fails to occur; it should be set long enough so as to not interfere with flow cycling. If using pressure-controlled ventilation, the PIP setting should be guided by adequacy of chest rise and breath sounds, as well as V_T, which should range between 4 and 5 mL/kg. When using synchronized modes that support every breath, the ventilator rate is controlled by the infant. If using SIMV, the expiratory time (T_E) and/or ventilator rate are adjusted to achieve a sufficient level of support to reduce work of breathing.

4.1.3. High-frequency ventilation

The key strategy with HFOV is to achieve initial lung volume recruitment and then to maintain optimal lung inflation with the lowest possible mean airway pressure (P_{AW}). The process for lung volume recruitment consists of three steps: (i) initial stepwise escalation of P_{AW} until oxygenation no longer improves with successive increases (the “opening pressure”); (ii) subsequent stepwise reduction in P_{AW} to a point at which oxygenation begins to

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deteriorate (the "closing pressure"); and (iii) returning the P_{AW} 1–2 cmH_2O above the closing pressure [23]. This process places the lung on the deflation limb of the pressure–volume relationship with optimal gas exchange with minimal pressures and hemodynamic consequences. Because lung compliance changes over time the appropriateness of the P_{AW} setting needs to be re-evaluated at least daily. In these larger infants, a frequency of 10 Hz is generally appropriate. Amplitude is adjusted to achieve adequate chest vibration and modified as needed in response to transcutaneous CO_2 measurement and blood gases. Whereas some practitioners increase ventilator frequency as a means of decreasing CO_2 elimination, it is simplest to reduce amplitude instead, leaving the frequency unchanged. Because lung compliance may improve quickly with optimization of lung volume, transcutaneous CO_2 measurement is recommended to minimize the risk of inadvertent overventilation. Modern HFOV devices now allow measurement of V_T and even volume guarantee combined with HFOV, which should greatly reduce the risk of hypocapnia [24].

4.2. Respiratory support of infants with meconium aspiration syndrome (MAS)

Whereas many infants are born through meconium-stained amniotic fluid and have some degree of respiratory distress, true MAS is relatively infrequent and has decreased in frequency over the past couple of decades [25–27]. Most infants born through stained amniotic fluid are well or turn out only to have transient tachypnea and do well with non-invasive support. Despite its relatively low incidence, a large proportion of infants with true MAS may require invasive or non-invasive respiratory support [25]. The pathophysiology of MAS is complex, including surfactant inactivation, inflammation and a variable obstructive component [25,28]. In many infants, the problem is compounded by their altered pulmonary vascular reactivity related to both inflammation and prenatal/postnatal hypoxia–ischemia. The phenotype of MAS is highly variable; in some infants the clinical features of MAS may be predominantly that of surfactant inactivation and inflammation, giving rise to a relatively homogeneous lung pathophysiology. Other infants have very heterogeneous lung aeration with prominent air-trapping due to aspiration of particulate meconium. Partial or complete obstruction of small airways leads to air-trapping/over-inflation and atelectasis, respectively. Air-trapping impairs ventilation and may also impair oxygenation because of local hypoxic pulmonary vasoconstriction and direct compression of the pulmonary microvasculature. This combination of airway obstruction and surfactant dysfunction results in a non-homogeneous lung disease that makes managing severe MAS such a challenge. Persistent pulmonary hypertension (PPHN) is a frequent and significant problem in infants with severe MAS [29]. Adjunctive therapy with inhaled NO and other pulmonary vasodilators, as well as inotropic support of the systemic circulation, may be required for management of the pulmonary hypertension.

The goal of respiratory support is to optimize lung inflation by recruitment and maintenance of under-inflated airspaces while attempting to minimize over-inflation of the more compliant regions of the lung and air-trapping. Acquired surfactant dysfunction may be treated with exogenous surfactant and lung volume is optimized through judicious application of distending airway pressure. If mechanical ventilation is needed, appreciation of the prolonged time constants present in MAS is critical to choosing rates and inspiratory times that allow for adequate exhalation. Co-existing conditions, such as infection, hypovolemia and multiple organ dysfunction must be addressed as necessary. There is no uniformity in the choice of respiratory support. Many clinicians use HFOV or HFJV, but volume-targeted conventional ventilation may be used in the initial management of MAS with similar success, provided that the V_T selected is appropriate for the underlying pathophysiology [30]. The key to management includes recognition of the predominant underlying pulmonary pathophysiology and appropriate supportive measures for other organ dysfunction. Whereas the majority of infants with MAS may be managed with supplemental oxygen alone or with CPAP, such infants are often quite ill and may already have airleak, as well as severe PPHN. The pathophysiology evolves over time and may change fairly rapidly during the course of caring for a particular infant. Consequently, the ventilatory approach must be individualized and the strategy frequently reassessed based on the predominant pathophysiology at the time. Suggested initial ventilator settings for various modalities are shown in Table 3.

4.2.1. Non-invasive support

Infants with mild aspiration pneumonia, which sometimes can only be distinguished from delayed clearance of lung fluid in retrospect, can usually be managed with supplemental oxygen via oxyhood or nasal cannula. With more severe disease, nasal CPAP may be required. There is good physiologic rationale for the use of distending pressure in dealing with the surfactant dysfunction component of MAS. Additionally, much like in infants with BPD or tracheobronchomalacia, air-trapping may be relieved by stabilizing airway diameter during the expiratory phase, allowing more adequate exhalation in the face of partial airway obstruction by splinting the airways with CPAP. Although no randomized trials are available to allow evidence-based recommendations, a substantial number of infants with MAS do appear to respond to CPAP [25,29]. One observational study concluded that CPAP, when applied early, may reduce the need for mechanical ventilation in newborns with moderate to severe MAS infants [31].

4.2.2. Conventional ventilation

The guiding principles noted above should be used in initiating and adjusting support regardless of the specific modality of conventional ventilation. Because of the longer time constants in MAS, SIMV may be preferred in order to control the ventilator rate and ensure adequate expiratory time to avoid dynamic (inadvertent) PEEP. However, because both inspiratory and expiratory time constants are prolonged, the T_I must also be adequate to achieve complete V_T delivery. For infants in whom the predominant pathology is alveolar disease with low lung volumes due to surfactant inactivation, PEEP should initially be set at higher levels (6–8 cmH_2O) and increased as needed to achieve an acceptable EELV. When air-trapping is the predominant pathological problem, PEEP should be limited (typically 5–6 cmH_2O) and the ventilator rate should be kept relatively low (typically $\leq$30 bpm), with adequate expiratory time to minimize gas-trapping. Over-expansion is most

Table 3
Suggested initial settings for term/late preterm infants with meconium aspiration syndrome.

	PCV	VTV	HFOV	HFJV
PIP (cmH_2O)	25	28 (limit)	–	24–25
T_I (s)	0.5–0.65	0.5–0.65	1:2 ratio	0.02
Rate (breaths/min)	30	30	–	240–300
PEEP/P_{AW} (cmH_2O)	5–7	5–7	10–12 (or 2 > CV)	8
Frequency (Hz)	–	–	6–8	4–5
Amplitude (cmH_2O)	–	–	25	–
Exhaled V_T (mL/kg)	–	5.5–6.0	2.5–3.5	–

PCV, pressure-controlled ventilation; VTV, volume-targeted ventilation; HFOV, high-frequency oscillatory ventilation; HFJV, high-frequency jet ventilation; PIP, peak inflation pressure; T_I, inflation time; PEEP, positive end-expiratory pressure; P_{AW}, mean airway pressure; CV, conventional ventilation; V_T, tidal volume.

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often caused by dynamic PEEP due to insufficient expiratory time. Very low PEEP is recommended by many, but this recommendation is neither evidence-based nor physiologically sound. In the absence of dynamic PEEP, air-trapping may be relieved by stabilizing airway diameter during the expiratory phase and preventing airway collapse around the particulate meconium that is causing a ball-valve effect. Pressure support may be used to assist spontaneous breaths with a goal of reaching adequate V_T of spontaneous breaths. VTV is preferable over pressure-controlled modes. Because the pathophysiology of MAS includes increased alveolar dead space, these infants require a larger V_T per kilogram than similar infants with more homogeneous lung disease [30].

4.2.3. High-frequency ventilation

The literature is sparse in this area, but both HFOV and HFJV may offer benefit in the sickest infants [17,18]. The key to safe and effective use of HFOV in this condition that is characterized by long time constants is the use of a substantially lower rate, typically 6–8 Hz with HFOV and 240–300 cycles/min with HFJV. The mean airway pressure (P_{AW}) should be set based on the overall pattern of lung inflation. For infants with significant air-trapping, the low end of the frequency range 6 Hz is recommended with a P_{AW} similar to that on conventional ventilation. Amplitude (ΔP) is adjusted to generate adequate chest vibration. If using a modern HFOV device with V_T measurement or targeting, expect to use V_T of 2.5–3.5–mL/kg. For those infants with MAS who have relatively poor lung inflation, the P_{AW} is typically started at 2–4 cmH_2O above that on conventional ventilation. Subsequent adjustments are made based on FiO_2 response and radiographic assessment of lung inflation. Lower rate is even more critical with HFJV, which depends on passive exhalation; air-trapping could be aggravated if sufficient expiratory time is not provided. It may be necessary to increase the I-time from 0.02 to 0.03 s to generate a larger V_T with these lower rates when approaching the upper limits of PIP setting. A sigh rate of 2–5/min may be helpful in improving gas exchange with HFJV [32].

Irrespective of the ventilatory approach used, frequent clinical, radiographic and laboratory assessments are indicated to optimize gas exchange and minimize VALI; more so following surfactant therapy and during the initial 12–24 h of support as the predominant pathophysiology often changes rapidly. Attention to cardio-respiratory interactions is an important component of management of these infants.

4.3. Respiratory support of infants with congenital diaphragmatic hernia (CDH) and other lung hypoplasia syndromes

Management of infants with CDH remains one of the most challenging problems in neonatology. The combination of pulmonary hypoplasia, abnormal pulmonary vascular bed, and altered left ventricular (LV) morphology and function render these infants uniquely susceptible to VALI, pulmonary hypertension and cardiac decompensation. The degree of pulmonary hypoplasia and associated under-development of the pulmonary vascular bed, along with the degree of LV hypoplasia, are the primary determinants of mortality. The response to inhaled NO (iNO) also appears to be impaired [33,34] and PPHN continues to be a major contributor to the continuing relatively high mortality rate among infants with CDH with limited improvement over the past two decades despite a variety of new therapeutic approaches.

In recent years, the recognition of the unique susceptibility of the hypoplastic lung to lung injury and the adverse effect of aggressive efforts to expand the hypoplastic lungs on pulmonary vascular resistance have led to the universal adoption of a “gentle” approach to ventilation of neonates with CDH [35–39]. In many centers that is accomplished by the use of HFOV, but, in light of information from VICI trial [40], the use of gentle conventional ventilation strategies is equally valid, if not more so. The primary outcome of death/BPD at 28 days was not significantly different between the two groups, but HFOV, as used in this trial, resulted in longer duration of ventilation, more need for inhaled nitric oxide/sildenafil, and greater use of extracorporeal membrane oxygenation. Therefore, the CDH EURO Consortium now recommends conventional mechanical ventilation as the initial ventilation strategy [41]. The key principles include less ambitious pre-ductal blood gas targets, acceptance of some degree of hypercapnia, avoidance of over-expansion of the hypoplastic lungs, and meticulous attention to the hemodynamics status, including management of pulmonary hypertension. Equally important is effective decompression of the gastrointestinal tract, which is crucial to the success of the delayed repair approach that has now become the standard of care. For this reason, non-invasive support with any sort of distending pressure or high-flow cannula is contraindicated.

Irrespective of the ventilatory approach used for managing CDH, we are dealing with small lungs with a functional residual capacity that is considerably less than normal. Given the effect that both atelectasis and over-expansion have on pulmonary vascular resistance, careful attention must be paid to optimizing lung inflation. However, the P_{AW} needed to achieve optimal lung inflation may be less than that required for a normal-sized lung. It is more difficult to determine optimal P_{AW} and lung inflation with lung hypoplasia than for infants with diffuse alveolar disease. For this reason, the stepwise increase in P_{AW} suggested for RDS is not recommended in CDH, because it is easy to reach excessive P_{AW} in an attempt to improvement in oxygenation, especially with the inevitable pulmonary hypertension. Suggested initial ventilator settings for various modalities are shown in Table 4.

4.3.1. Conventional ventilation

The use of synchronized conventional ventilation modes makes it possible to maximally utilize the patient's spontaneous respiratory effort and minimize ventilator support. Because the lungs are relatively small and compliance is generally poor, relatively rapid rate and short T_I are appropriate. Most CDH protocols limit PIP to ≤25 cmH_2O, preferring to switch to HFV if adequate gas exchange cannot be achieved with these settings. Although this seems reasonable, the specific value is not evidence-based. Moderate PEEP of 4–6 cmH_2O is preferred with care to avoid over-expansion of the contralateral lung. Volume-targeted ventilation is desirable and feasible. Contrary to widely held assumptions, the V_T needed to achieve adequate CO_2 elimination is not less than what would be needed for infants of a similar size without pulmonary hypoplasia [42,43]. This reflects the fact that the metabolic CO_2 production of

Table 4
Suggested initial settings for term/late preterm infants with congenital diaphragmatic hernia and other hypoplasia syndromes.

	PCV	VTV	HFOV	HFJV
PIP (cmH_2O)	20	24 (limit)	–	18–20
T_I (s)	0.3–0.35	0.3–0.35	1:2 ratio	0.02
Rate (breaths/min)	50	50	–	420
PEEP/P_{AW} (cmH_2O)	4–6	4–6	10–12	6–7
Frequency (Hz)	–	–	8–10	7
Amplitude (cmH_2O)	–	–	25	–
Exhaled V_T (mL/kg)	–	4–4.5	1.8–2.5	–

PCV, pressure-controlled ventilation; VTV, volume-targeted ventilation; HFOV, high-frequency oscillatory ventilation; HFJV, high-frequency jet ventilation; PIP, peak inflation pressure; T_I, inflation time; PEEP, positive end-expiratory pressure; P_{AW}, mean airway pressure; V_T, tidal volume.

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an infant with CDH is similar to that of any other infant of the same size and therefore the same alveolar minute ventilation is needed. Reducing V_T to <4 mL/kg is counterproductive because it leads to high dead space:V_T ratio, which is made worse by the fact that infants with the most severe lung hypoplasia have increased dead space:V_T ratios [44]. Nonetheless, a relatively low V_T and higher ventilation rate are appropriate, due to the decreased complement of alveoli in CDH infants. A larger V_T would likely result in volutrauma, as this volume is directed into a fraction of the normal number of terminal airspace units, and this reality provides a sound physiologic rationale for the use of HFV in infants with CDH. Mild permissive hypercapnia and pre-ductal SpO_2 in the range of 85–95% are generally accepted, though these recommendations are only based on expert opinion and observational studies. Initially, lower saturations may be acceptable in order to avoid escalation of settings as long as there is no acidosis and the saturations are trending upward.

4.3.2. High-frequency ventilation

Many retrospective observational studies describing use of HFOV in the management of neonatal CDH have been published [45,46], but only one prospective randomized trial has ever been done. As noted above, the VICI trial [40] found no benefit of HFOV over conventional ventilation, but questions have been raised about the specific approach to HFOV used in that study, including overly aggressive lung volume recruitment and use of an excessively high frequency with a 1:1 I:E ratio, which may predispose to air-trapping.

Most experienced clinicians use a relatively low P_{AW}, usually starting at 10–12 cmH_2O, and attempt to limit P_{AW} to $\leq$16 cmH_2O. Because these are larger infants a lower frequency, typically 8–10 Hz should be used with an I:E ratio of 1:2. As previously mentioned, optimizing lung inflation is difficult, but targeting contralateral lung expansion to eight or nine ribs is reasonable with frequent reassessment of lung volume. Amplitude should be just sufficient to create a gentle wiggle to mid abdomen with a goal of mild permissive hypercapnia and pre-ductal SPO_2 target of 85–95%. There is no clear evidence that HFOV offers increased benefit compared to HFJV or conventional mechanical ventilation; the mode of ventilation is likely to be less important than the skill with which it is used. This is where carefully designed and regularly updated unit protocols are invaluable [37,46].

The use of HFJV has been reported less extensively, but appears to be equally effective [37,47,48]. There is clinical evidence to suggest that HFJV may be the optimal approach for ventilation of babies with CDH because of its ability to ventilate with small V_T and lower mean airway pressures while minimizing adverse cardiovascular effects [18]. The choice of HFJV vs HFJV is a matter of personal preference and experience. The same general principles as with HFOV are used to treat infants with CDH and other lung hypoplasia syndromes. As with other devices, ventilator management is just one part of the overall support, which requires meticulous attention to hemodynamics, management of pulmonary hypertension, decompression of the gut and adequate sedation.

5. Conclusion

The evidence base for respiratory support strategies in term infants remains woefully incomplete with very few randomized trials to provide clear guidance for the clinician. Recommendations are largely based on observational studies, expert opinion and sound physiologic principles. The key concepts outlined in this review are based on the best available evidence and physiologic rationale with the hope that these strategies may provide an opportunity to minimize adverse respiratory outcomes in infants requiring respiratory support.

Practice points

- Ventilators are simply tools in our hands; to achieve the primary goal of maintaining acceptable gas exchange with a minimum of adverse effects, we need to employ them thoughtfully and utilize all available information to guide specific ventilator setting.
- The choice of modalities of support and ventilation strategies should be guided by the specific underlying pathophysiology at the time with frequent re-evaluation of the strategy.
- Optimizing lung inflation/avoidance of atelectasis is a key component of all lung-protective strategies.
- Excessive tidal volume/lung overdistention are the most important elements of ventilator-associated lung injury; volume-targeted ventilation is an evidence-based approach to reduce lung injury.

Research directions

- Prospective randomized controlled trials (RCTs) are needed to validate many of the approaches to mechanical ventilation in full term and late preterm infants. Current recommendations and guidelines are largely based on sound physiologic principles and extrapolation from studies in preterm infants.
- Specifically, we need well-designed multicenter RCTs to validate approaches to non-invasive respiratory support of RDS and MAS, as well as RCTs comparing high-frequency and conventional ventilation in MAS.
- Studies to determine means of optimizing lung inflation in infants with CDH are needed, as well as prospective comparisons of different oxygenation and ventilation (CO_2) targets for these infants.
- It is unlikely that another HFOV vs conventional ventilation RCT will be conducted, but an RCT comparing HFJV to conventional ventilation would be desirable.
- The key to the success of all of these studies would be designing the protocols in a way that allows some degree of individualization of ventilator settings, while specifying a sound overall strategy.

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