

Weaning newborn infants from mechanical ventilation

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Abstract

Invasive mechanical ventilation is a life-saving procedure which is largely used in neonatal intensive care units, particularly in very premature newborn infants.

However, this essential treatment may increase mortality and cause substantial morbidity, including lung or airway injuries, unplanned extubations, adverse hemodynamic effects, analgesedative dependency and severe infectious complications, such as ventilator-associated pneumonia.

Therefore, limiting the duration of airway intubation and mechanical ventilator support is crucial for the neonatologist, who should aim to a shorter process of discontinuing mechanical ventilation as well as an earlier appreciation of readiness for spontaneous breathing trials. Unfortunately, there is scarce information about the best ways to perform an effective weaning process in infants undergoing mechanical ventilation, thus in most cases the weaning course is still based upon the individual judgment of the attending clinician.

Nonetheless, some evidence indicate that volume targeted ventilation modes are more effective in reducing the duration of mechanical ventilation than traditional pressure limited ventilation modes, particularly in very preterm babies. Weaning and extubation directly from high frequency ventilation could be another option, even though its effectiveness, when compared to switching and subsequent weaning and extubating from conventional ventilation, is yet to be adequately investigated.

Some data suggest the use of weaning protocols could reduce the weaning time and duration of mechanical ventilation, but better designed prospective studies are still needed to confirm these preliminary observations.

Finally, the implementation of short spontaneous breathing tests in preterm infants has been shown to be beneficial in some centres, favoring an earlier

extubation at higher ventilatory settings compared with historical controls, without worsening the extubation failure rate.

Further research is still required to identify the best practices capable to shorten the duration of mechanical ventilation in term and preterm infants, at the same time keeping to a minimum the risk of extubation failure.

Keywords

Mechanical ventilation, weaning from mechanical ventilation, spontaneous breathing test, extubation, infant, newborn.

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Introduction

Invasive mechanical ventilation (MV) is a lifesaving treatment which is still routinely applied for critically ill patients of any age. Generally, MV is indicated when the patient's spontaneous ventilation is inadequate to sustain life, in the majority of cases due to acute respiratory failure, postoperative management, cardiac insufficiency, sepsis, trauma, or neurological problems. Of note, the provision of invasive respiratory support usually requires the placement of an endotracheal tube (ETT) as a conduit for mechanical ventilation, which could serve also to provide airway support for subjects with upper airway abnormalities.

Recent epidemiological investigations reported that in the United States about 800,000 paediatric and adult patients are treated with mechanical ventilation each year [1].

Indeed, MV is a critical component frequently used also in neonatal intensive care, both in term and preterm newborns, with about 27% of all infants admitted to intensive care units undergoing mechanical ventilation, predominantly for treating pulmonary insufficiency [2]. This is particularly

true in the population of the extremely low birth weight (ELBW) infants, in which modern studies indicate a very high prevalence of MV, ranging from 83 to 95% [3, 4].

However, this essential treatment may be associated with substantial risks and higher mortality. Potential critical complications include direct lung or airway injuries (trauma to the upper and lower respiratory tracts, acute ETT obstruction, oedema, tracheal stenosis, granuloma, pneumothorax, bronchopulmonary dysplasia), adverse effects on cardio-pulmonary interaction (low cardiac output) and infectious diseases (ventilator-associated pneumonia, tracheitis) [5, 6].

Moreover, in order to avoid discomfort and pain, minimize self-injury or unplanned endotracheal tube removal, patients on mechanical ventilation are often on analgosedative therapy, with possible consequent drug withdrawing problems. All the above mentioned factors may potentially contribute to higher morbidity and mortality, prolonged ICU stay and higher hospital costs. Thus, as soon as the condition that caused respiratory failure has begun to improve, the transition from full ventilatory support to spontaneous breathing should be started. The process of (gradual) reduction of ventilatory support and the transfer of respiratory control back to the patient, enabling spontaneous respiration, is commonly defined as ventilator weaning [7].

However, while indications as to when mechanical ventilation should be initiated in the presence of respiratory insufficiency and/or to protect airway at risk are quite established, the management of intubated and ventilated infants during their recovery phase remains largely subjective, being mostly based on institutional or individual practices. This can lead to infants either being left on the ventilator too long or extubated too soon, with subsequent need for a reintubation procedure and its related risks. A variety of strategies have been used to assess weaning and extubation readiness in newborns, hence to reduce the duration of mechanical ventilation, but there is a lack of consensus on criteria which can be used for this purpose (**Tab. 1**).

The aim of this article was to briefly review the current approach about neonatal weaning and extubation practice, providing some information to support neonatologists in their clinical decision-making.

Other therapeutic adjuncts for weaning and extubation, such as caffeine, steroids, non invasive positive pressure ventilation and chest

Table 1. Strategies to reduce the duration of mechanical ventilation and the risk of extubation failure.

Synchronized, volume targeted ventilatory modes are associated with a shorter duration of mechanical ventilation in comparison with pressure limited ventilatory modes	Wheeler et al. [12]
Weaning protocols may reduce the transition from assisted ventilation to spontaneous breathing and extubation	Hermeto et al. [23]
Spontaneous breathing trials (combined with measured variability in respiratory parameters) may function as reliable predictive tools to check readiness of infants for extubation	Kamlin et al. [31] Kaczmarek et al. [32]
Adjunctive therapies such as caffeine, peri-extubation corticosteroids, CPAP and non invasive ventilation, may facilitate weaning and reduce the risk of extubation failure	Sant'Anna et al. [8]

physiotherapy, are beyond the scope of this review. Further information may be found elsewhere [8].

The ventilator weaning process

Weaning is the process of discontinuation of the ventilatory support plus removing the endotracheal tube.

The first requisite for discontinuing ventilator support is the improvement or resolution of the underlying cause of respiratory failure and any related complication. At that point, once the gas exchange is adequate with low positive end-expiratory pressure and low fraction of inspired oxygen, hemodynamics is stable and the respiratory drive to initiate spontaneous breaths is maintained or re-established, the patient is usually ready for withdrawal of ventilation and extubation.

Weaning from MV must include both a systematic reduction of ventilatory support and the assessment of a patient's readiness to breathe independently. Although the process of weaning and discontinuing MV is often straightforward, for instance in patients after minor surgical interventions, in more complex clinical situations it could be very challenging. Typically, the weaning course is directed either according to individual judgment of the attending neonatologist, who may consider objective indicators of gas exchange, respiratory mechanics and the newborn's ability to protect the airway, or to predetermined protocols with settled management. However, use and evaluation of

diverse physiological or clinical indicators, as well as the vast protocols' variability among different centres, often may result in wide disparities in weaning practices, sometimes even within the same NICU. In addition, some weaning and extubation predictors potentially helpful in newborns with acute respiratory distress syndrome may result less adequate in other patients, such as chronically ventilated infants with bronchopulmonary dysplasia (BPD) or infants with upper airway malformations. Thus, an individualized approach is frequently needed, taking into account also the underlying conditions of the patient.

Which ventilatory modalities are best suitable for weaning?

A number of ventilatory modalities have been proposed to gradually get newborn infants off the mechanical ventilator, but their respective effects on the outcome of weaning from respiratory support remain unclear.

Several randomised trials have demonstrated that ventilation techniques which support every spontaneous breath are the most efficacious weaning modes. In a recent systematic review, Greenough et al. reported that synchronized ventilation was associated with a shorter duration of ventilation when compared to conventional ventilation [9].

In a randomized, controlled trial, Reyes et al. compared synchronized intermittent mandatory ventilation (SIMV) and synchronized intermittent mandatory ventilation plus pressure support (SIMV + PS) in 107 preterm infants weighing less than 1,000 g, during their first 28 days of life. Infants in the SIMV + PS support group reached minimal ventilator settings and were extubated significantly earlier than infants treated only with synchronized intermittent mandatory ventilation [10]. In addition, infants in SIMV + PS tended to have a shorter duration of supplemental oxygen and less oxygen requirement at 36 weeks' postmenstrual age, even though such differences were significant only in the subgroup of infants weighing 700- to 1,000-g at birth [10].

More recently, Shefali-Patel et al. performed a randomised weaning trial comparing assist control ventilation and pressure support ventilation in 36 neonates, with a median gestational age of 29 weeks. After adjusting the termination sensitivity of pressure support, set to maintain an inflation time of 0.25 to 0.3 seconds, there were

no significant differences between the two groups in terms of work of breathing, level of respiratory muscle strength, duration of weaning and time to successful extubation [11].

Differently, in a recent systematic Cochrane review, Wheeler and colleagues compared volume targeted ventilation modes with traditional pressure limited ventilation modes, in newborns less than 28 days of corrected age. Interestingly, infants ventilated using volume targeted modes not only had reduced death and chronic lung disease and were less likely to develop pneumothorax, but they did need ventilator assistance for a shorter duration when compared with infants supported with pressure-limited ventilation modes [12].

Particularly when adopting the open lung strategy, high frequency ventilation (HFV) is another well accepted ventilatory modality to support term and preterm infants with respiratory failure [13]. However, despite its increasing use, data on weaning and extubation from HFV are still limited. Traditionally, some clinicians prefer to switch from HFV to conventional modes once the acute lung disease has improved, aiming to wean and extubate from this ventilation mode [14]. Recently, in a large retrospective study, van Venzel and colleagues evaluated the feasibility of weaning and direct extubation from open lung HFV [15]. In 214 preterm infants, with a total of 242 ventilatory courses, the authors observed that weaning the continuous distending pressure below 8 cm H₂O with an FIO₂ below 0.30 was feasible. Furthermore, extubation at these settings was successful in most cases, with a remarkable 90% success rate [15]. Yet, given the retrospective design of their study, they could not demonstrate if weaning and direct extubation from HFV was superior to switching and subsequent weaning and extubating from conventional mechanical ventilation, calling for future randomized controlled trials.

Are weaning protocols useful to reduce the duration of mechanical ventilation?

Many intensive care units use protocols to guide the transition from assisted ventilation to spontaneous breathing and subsequent discontinuation of mechanical ventilation. Generally, these protocols include at least the following topics: 1) objective criteria to start the weaning process (to discern whether a patient is ready to breathe while reducing ventilatory support); 2) structured guidelines for reducing

ventilatory support (how to manipulate ventilatory parameters according to physiological or clinical response); 3) well defined criteria to establish the patient's extubation readiness.

Indeed, several studies have shown that the implementation of a standardized ventilator weaning protocol does reduce the duration of mechanical ventilation in adult patients, without adverse effects [16, 17].

Differently, results from paediatric trials implementing ventilator weaning protocols have been less convincing so far. In a large multicenter trial, performed in ten PICUs in North America by the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, there was no difference between groups randomized to either automated ventilator-adjusted volume support protocol, physician directed pressure support weaning, or no protocol [18]. In fact, protocol-driven programs were equivalent to no protocol regarding weaning time from randomization to successful extubation as well as the extubation failure rate [18].

More recently, the same study has been included in a systematic review, in which Blackwood et al. assessed the effect of weaning by protocol on invasively ventilated critically ill children [19]. Only three trials at low risk of bias were identified, for a total of 321 children [20-22]. Although there was a positive trend toward reduction of total time on ventilation and duration of weaning, available evidence was not adequate to determine whether achievement of shorter ventilation by protocolized weaning could cause benefit or harm to children [19].

Differently, Hermeto and colleagues have shown more encouraging results in a large population of severely preterm newborns. In their retrospective study, the authors evaluated the impact of the implementation of a ventilation protocol on respiratory outcomes of very premature infants [23]. By reviewing the clinical course of 301 mechanically ventilated infants, with a birth weight less than 1,250 g, they reported that the implementation of a ventilation protocol, driven by registered respiratory therapists, could significantly reduce the weaning time and duration of mechanical ventilation.

However, well designed prospective controlled studies are still needed to confirm their interesting observations, as well as to evaluate the effect of protocol-based approaches to weaning on relevant long-term outcomes, such as BPD or neurodevelopment [23].

How extubation readiness could be assessed in newborn infants?

With the aim of reducing the duration of invasive respiratory support, neonatologists should consider a shorter process of discontinuing mechanical ventilation as well as an earlier appreciation of readiness for spontaneous breathing trials. Actually, both premature and delayed extubation can cause severe harm, thus defining the precise moment for extubation could be very challenging in some patients. A delayed extubation may further increase the inherent risk of MV and ETT complications. On the other hand, premature MV discontinuation may imply a set of different problems, including difficulty in re-establishing artificial airways, compromised gas exchange and hemodynamic destabilization. Therefore, a weaning process which is both expeditious and safe is highly desirable. Most infants are easily extubated after a short period of MV. However, in some patients weaning may be much more difficult and prolonged, sometimes being complicated by one or more episodes of extubation failure. This could be due to a number of causes, including iatrogenic airway injuries, congenital airway abnormalities, respiratory muscle weakness, underlying cardiac abnormalities, recurrent apnoeic episodes, or acquired infections, among others. The prevalence of extubation failure in newborns may quite vary, ranging from 10 to 80% [8]. This large variability depends upon several factors, including marked differences in the following points: 1) definition and timing of failure; 2) gestational age (extremely preterm babies carrying the highest risk for reintubation); 3) local policies regarding the pre- and post-extubation management (e.g. use of CPAP, non invasive ventilation, steroids, methylxanthines, adrenaline). For instance, Stefanescu et al. reported an extubation failure rate of nearly 40% in 162 ELBW infants requiring mechanical ventilation. Interestingly, in these patients the main causes of extubation failure were recurrent episodes of apnea/bradycardia [24].

Patient readiness to be successfully extubated is usually based upon both clinical and objective tests. Yet, not a single index has been deemed as sufficiently sensitive and specific so far [25]. Ideally, simple measurements should be available to clinicians to best predict which newborns are ready for a spontaneous-breathing trial (SBT) and in which patients these trials are most likely to be successful.

The aim of spontaneous breathing trials is to assess an infant's ability to breathe while receiving minimal or no respiratory support. To achieve this, full respiratory support modes such as volume-assist control or pressure control are switched to ventilatory modes such as pressure support, continuous positive airway pressure, or ventilation with a T-piece. The latter is characterized by a complete absence of positive end expiratory pressure, thus giving the patient the lowest amount of support possible. During SBT an integrated assessment of different criteria are usually checked, including respiratory pattern and rate, gas exchange parameters, hemodynamic stability, mental status, comfort and diaphoresis. In most circumstances, SBT should be considered only if the patient is awake or not receiving excessive sedation.

In the last two decades, a variety of tests have been evaluated to improve the ability to predict a successful extubation in preterm newborns, including spontaneous minute ventilation, various spontaneous breathing tests and pulmonary function testing. In fact, none of these predictors were found to be consistently reliable [26-29].

In a small randomized clinical trial, Gillespie et al. assessed infants' readiness for extubation by using the minute ventilation test (MVT) [30]. The MVT test evaluates the effectiveness of spontaneous breathing and respiratory muscle endurance, by processing data obtained with a relatively simple pulmonary monitoring system, routinely available in any ventilator nowadays. In 42 preterm infants with respiratory distress syndrome, a significant reduction in time from randomization to extubation was observed in those evaluated by the MVT, when compared to clinical assessment only (mean time of 8 hours versus 36 hours, respectively) [30].

In a pilot study performed in Australia, Kamlin et al. evaluated a very short SBT (three minutes of spontaneous breathing during ETT continuous positive airway pressure before extubation) to predict the extubation readiness of 50 VLBW infants [27]. During such test, investigators were simply observing changes in heart rate and oxygen saturation, for three minutes, reporting very promising results in terms of positive and negative predictive values, specificity and sensitivity. SBT was then adopted as a standard of care in their Unit [27]. Subsequently, in a large prospective study, Kamlin and colleagues demonstrated that after using the 3-min SBT in their current practice, preterm infants were extubated earlier and at higher ventilatory settings compared with the period before SBT was introduced. Of note,

these results were achieved without worsening the extubation failure rate [31].

Recently, by reviewing data of their first study on 44 infants (weighing less than 1,250 g), the same group was able to improve specificity from 63 to 75%, with a positive predictive value of 95%, by combining the SBT with measured variability in respiratory parameters. More specifically, infants who eventually did need to be re-intubated had a lower variability index of mean inspiratory flow prior to extubation. Although promising, these predictive tools need to be confirmed in larger prospective trials [32].

Interestingly, the diaphragm tension time index (TTI), a measure of the load on and the capacity of the diaphragm, has been assessed in adults and children, emerging as a highly specific and sensitive predictor for extubation failure [33]. In a small prospective study, Currie et al. evaluated TTI as a predictor of extubation outcome in a population of 20 ventilated newborn infants, with a median gestational age of 31 weeks [34]. Five out of these 20 infants failed extubation and TTI performed with a specificity and sensitivity of 100%. However, given the small sample of enrolled patients, further controlled studies are required to confirm these interesting preliminary findings [34].

Conclusions

Mechanical ventilatory support is a lifesaving intervention which is frequently applied in critically ill newborns. However, MV may be associated with considerable risk of complications, increased length of NICU stay and higher hospital costs. Therefore, a timely and effective weaning is of pivotal importance for reducing duration of mechanical ventilation as well as the associated morbidity.

A variety of strategies have been used to assess weaning and extubation readiness in newborns, but there is a lack of consensus on criteria which can be used for this purpose. Actually, determining infant readiness to be weaned from ventilatory support is still frequently based on the individual judgment of caregivers.

Thus, specific assessment techniques are necessary, in order to promptly recognize newborn infants who are capable of ventilator discontinuation, at the same time keeping the rate of extubation failure at a minimum.

A synthesis of the key points of this paper is presented in **Tab. 2**.

More research is needed to tune up optimal approaches to weaning, as well as to identify clinical

Table 2. Key points.

- Mechanical ventilation is a lifesaving procedure for critically ill newborn infants but is associated with significant morbidity.
- Attempts to discontinue invasive mechanical ventilation should be tried as soon as possible.
- The use of weaning protocols, including systematic spontaneous breathing trials, has the potential to reduce the duration of mechanical ventilation.
- Future research should focus in better identifying the best predictive tools for a successful weaning, as well as the synergistic effect of adjunctive treatments in reducing the risk of extubation failure.

markers for predicting successful extubation in term and preterm newborns.

Declaration of interest

The Authors state there is no potential conflict of interest to declare. There is no professional affiliation, financial agreement or other involvement with any company whose product figures prominently in the submitted manuscript.

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