

CURRENT TOPIC

Weaning from assisted ventilation: art or science?

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Table 1 Studies on methods of weaning from mechanical ventilation

<i>Extubation from low rate IPPV versus extubation after endotracheal CPAP</i>	
Kim <i>et al</i> (n = 27) ⁷ , Kim <i>et al</i> (n = 60) ⁸ , Tapia <i>et al</i> (n = 87) ⁹	Relative risk (RR) 0.10 (95% CI, 0.01 to 0.78), risk difference (RD) -0.201 (95% CI, -0.319 to -0.083).
Cumulative analysis ¹⁰	The use of a period of ETT CPAP before extubation confers no advantage over direct extubation. Direct extubation from low rate IPPV is associated with increased chance of successful extubation
<i>Conventional IPPV versus synchronised ventilation (PTV/SIMV)</i>	
Chan <i>et al</i> (n = 40) ¹¹ , Donn <i>et al</i> (n = 30) ¹² , Bernstein <i>et al</i> (n = 327) ¹³ , Chen <i>et al</i> (n = 77) ¹⁴	Duration of ventilation noted to be shorter with either PTV or SIMV in all studies (weighted mean difference, 45.2 hours; 95% CI -78.8 to -12.1)
Cumulative analysis ¹⁵	
<i>PTV versus SIMV</i>	
Chan <i>et al</i> (n = 40) ¹⁶ , Dimitriou <i>et al</i> (n = 40) ¹⁷	Duration of ventilation shorter with PTV than SIMV (weighted mean difference, 42.4 hours; 95% CI, -9.6 to 94.4)
Cumulative analysis ¹⁵	
<i>Volume controlled versus pressure limited ventilation</i>	
Sinha <i>et al</i> (n = 50) ¹⁸ , Piotrowski <i>et al</i> (n = 60) ¹⁹	Duration of weaning (mean time, 65.6 v 125.6 hours; p < 0.001) and duration of ventilation (mean time, 12.4 v 161.9 hours; p < 0.001) shortened in volume controlled with fewer complications
Analysis	
<i>Extubation to head box versus nasal CPAP</i>	
Engelke <i>et al</i> (n = 19) ²⁰ , Higgins <i>et al</i> (n = 58) ²¹ , Chan <i>et al</i> (n = 60) ²² , So <i>et al</i> (n = 50) ²³ , Annibale <i>et al</i> (n = 124) ²⁴ , Tapia <i>et al</i> (n = 87) ⁹ , Davis <i>et al</i> (n = 92) ²⁵ , Robertson <i>et al</i> (n = 58) ²⁶	Extubation to NCPAP leads to a lower "failure" rate but future studies required with refinement for gestational age and method of CPAP administration
Cumulative analysis ²⁷	

CI, confidence interval; CPAP, continuous positive airway pressure; ETT, endotracheal tube; IPPV, intermittent positive pressure ventilation; NCPAP, nasal CPAP; PTV, patient triggered ventilation; SIMV, synchronised intermittent mandatory ventilation.

ples of weaning, and to highlight areas still in need of investigation. This has become even more important since the advent of high frequency and patient triggered ventilation. The older practice of decreasing ventilator rate and peak pressure has limited application to newer forms of neonatal mechanical ventilation.

When and how to wean?

Weaning is the process of shifting the work of breathing from the ventilator to the patient. Although it seems intuitive to discontinue mechanical ventilation and extubate as soon as possible after the infant has demonstrated "stability", and when arterial blood gas values suggest that ventilatory needs are decreasing, the decision to extubate should be made well in advance of the procedure. Extubation from intermittent mandatory ventilation (IMV) is reasonable if the infant requires a fractional inspired oxygen value of < 0.4, is able to maintain satisfactory blood gas exchange at a low rate (for example, ≤ 20 breaths/minute) and low peak inspiratory pressure (for example, ≤ 15 cm H₂O), and is clinically and metabolically stable. The measurement of pulmonary mechanics and lung volumes, now available at the bedside, might help in gauging the capacity for weaning, but its clinical usefulness has not yet been confirmed in controlled trials.⁶

The classic approach to weaning from conventional ventilation is to extubate from low rate IMV, either directly to supplemental oxygen provided by head box or continuous positive airway pressure (CPAP). Based on the published studies,⁷⁻¹⁰ there is no rationale for trying infants on endotracheal CPAP, because this is only likely to impose a considerable breathing workload and contribute to weaning failure (table 1).

Weaning during synchronised ventilation is conceptually different than it is for conventional IMV because many of the parameters previously set by the clinician are now patient controlled, particularly during patient triggered (assist-control) ventilation (fig 1).^{28 29} During patient triggered ventilation, as long as the baby is breathing above the control (back up) rate, reduction in the rate brings about no change in ventilator cycling. Moreover, because the infant is setting his or her own inspiratory time (as in flow cycling), the inspiratory:expiratory ratio cannot be changed. Thus, reduction in peak inspiratory pressure is the primary parameter. In synchronised

intermittent mandatory ventilation (IMV), the mechanically delivered breaths are synchronised to the onset of the infant's spontaneous breaths at a predetermined rate. The flexibility of this mode in offering a range of ventilatory support from full (higher rate) to partial (lower rate) support, makes it useful as both an "acute" and "weaning" form of mechanical ventilation. However, which of the two is a better weaning mode remains unresolved.³⁰ Proponents of patient triggered ventilation argue that it involves the least effort to trigger and thus is less likely to tire the infant and cause extubation failure. Detractors, however, argue that because each breath is fully supported, the infant is not conditioned for life off the ventilator. Proponents of SIMV believe that because the infant has to "work" harder between mechanical breaths, he or she builds better tolerance. A number of methods are available by which the clinician can facilitate the weaning process in either patient triggered ventilation or SIMV. Setting a higher trigger sensitivity forces the infant to work harder to initiate mechanical breaths, thus increasing tolerance. Decreasing positive end expiratory pressure (PEEP) (while ensuring maintenance of oxygenation) might also be conducive to weaning.

An alternative approach is the use of additional modes of ventilation, which are "hybrids" of patient triggered ventilation and SIMV. One such method is pressure support ventilation (PSV),³¹ which is a patient triggered, pressure limited, and flow cycled mode of ventilation. Inspiratory flow provided during PSV is variable according to patient effort, and flow cycling assures complete inspiratory and expiratory synchrony. It is intended to give the patient an inspiratory pressure "boost" during spontaneous breathing so as to overcome the imposed work of breathing created by the endotracheal tube, ventilator circuit, and the demand valve. The major function of PSV is to assist respiratory muscle activity and thus reduce the workload. Because it is pressure limited, tidal volume delivery in PSV depends on respiratory mechanics and thus may be variable. To overcome this variability, some devices have combined pressure support with a guaranteed minimum tidal volume delivery, as described later. Pressure support can be initiated in conjunction with volume controlled SIMV. PS_{MAX} is the amount of pressure support that provides a full tidal volume breath. Lower amounts (partial pressure support) provide a smaller tidal volume and shift some of the work of breathing to the patient. Pressure support can also be used as a singular modality as long as the infant has sufficient ventilatory drive (fig 2). The variable inspiratory flow available during PSV might benefit disease states in which high pulmonary resistance occurs, such as bronchopulmonary dysplasia.³² Another promising synchronised ventilatory strategy is proportional assist ventilation, in which the ventilator generates pressure proportional to the patient's effort.³³ The more the patient "pulls", the more pressure the machine generates. To do so, the ventilator must be able to sense or

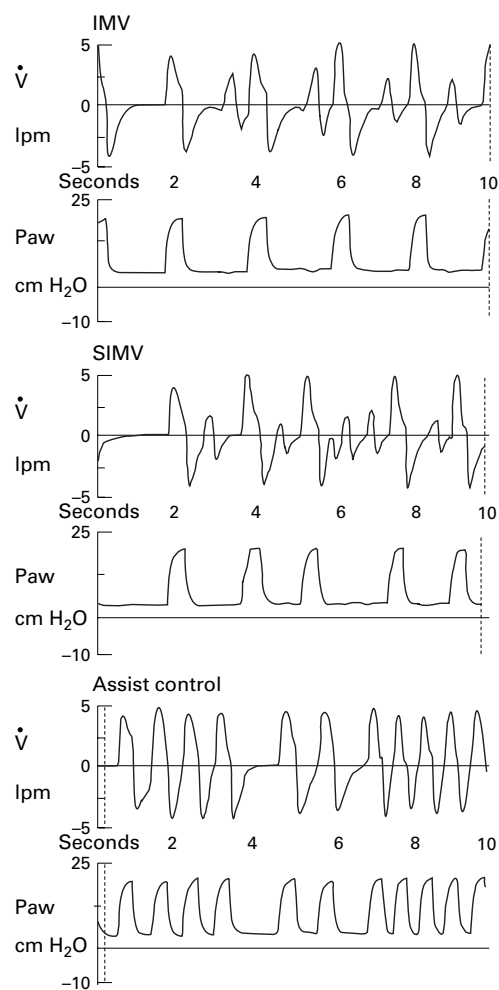


Figure 1 Flow and pressure waveforms for intermittent mandatory ventilation (IMV), synchronised intermittent mandatory ventilation (SIMV), and assist control ventilation. During IMV, note the mechanical breaths (larger flow waveforms) delivered at fixed intervals, set by the clinician. Spontaneous breaths may occur between mechanical breaths, but do not generate significant positive pressure. During SIMV, spontaneous patient effort above threshold can trigger a mechanical breath if it occurs within a "timing window". Thus, mechanical breaths occur at a slightly variable interval. Spontaneous breaths between timing windows do not result in triggering and do not generate effective pressure. During assist control, each spontaneous breath that exceeds the trigger threshold rate will vary according to the patient's own breath, and thus each breath is identical. The rate will vary according to the patient's own rate, but will not fall below the control rate chosen by the clinician.

estimate patient effort on an ongoing basis. This property makes proportional assist ventilation a useful mode for weaning infants from ventilation. Several proportional assist ventilation delivery systems are currently being evaluated for clinical use in the neonatal intensive care unit.

Two newer modes, only recently introduced to neonatal care and being evaluated in clinical practice, are mandatory minute ventilation and volume assured pressure support. Both are variants of PSV. In mandatory minute ventilation, the clinician chooses a minimal value of minute ventilation. As long as the patient meets this value during spontaneous breathing, only PSV is provided. If minute ventilation falls below this value, IMV breaths are provided so

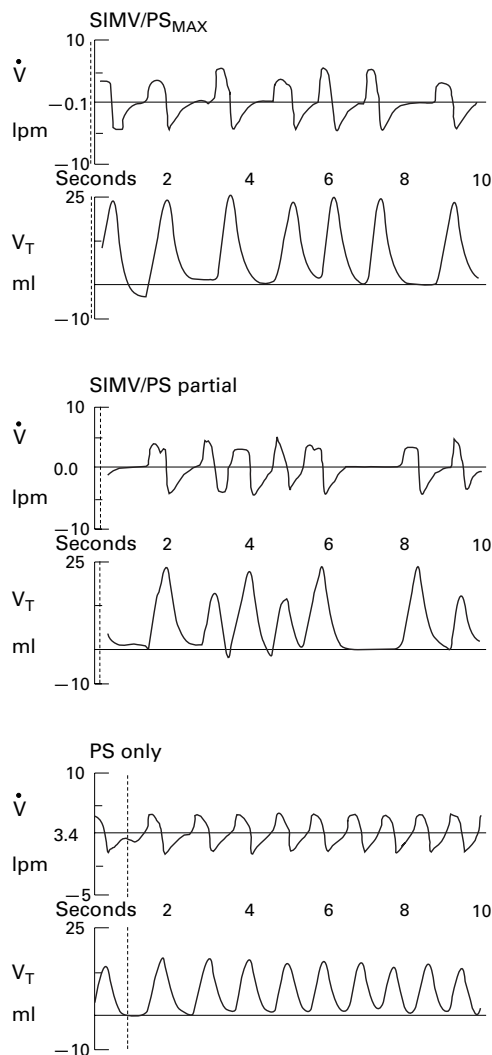


Figure 2 Various applications of pressure support ventilation (PSV) showing the relation between flow and volume waveforms. Top, synchronised intermittent mandatory ventilation (SIMV) and PS_{MAX} (the amount of pressure support that provides full tidal volume). Note that delivered tidal volumes are identical, whether the breath is a volume cycled SIMV breath or a pressure supported breath. These can be distinguished by examining the flow waveform, which is square for volume cycled SIMV and sinusoidal for PSV. Middle, SIMV with partial PSV. Note that the pressure supported breaths provide a smaller tidal volume than the volume cycled SIMV breaths. Bottom, straight pressure support ventilation. Similar to assist control ventilation (A/C), each breath that exceeds the trigger threshold results in the delivery of a pressure supported breath; however, because SIMV is not being used, cycling is totally dependent on patient effort and there is no safeguard if the baby becomes apnoeic. In clinical practice, this is generally the sequence chosen for weaning—start with SIMV and PS_{MAX} , decrease the SIMV rate and PSV value, and finally switch to straight pressure support (when the patient displays reliable respiratory effort) and continue to wean the pressure support value. Note that during PSV the peak flow rate varies because it is proportional to the patient's inspiratory effort.

that the patient can “catch up” to the expected value of minute ventilation. Thus, mandatory minute ventilation replaces the mandatory SIMV with a “prn” IMV breath. In volume assured pressure support, the clinician chooses a mandatory tidal volume that the patient is to receive during spontaneous breathing. As long as the patient is able to receive this volume, the breath is a simple pressure support breath.

However, should the delivered volume not reach the minimal value at the end of inspiration, the breath will transition to a volume cycled breath, and flow will continue, prolonging the inspiratory time until the volume guarantee is reached. Both of these modes seem ideally suited to infant weaning, where changes in either pulmonary compliance or respiratory drive occur with relative frequency and often impede the weaning process.

Clinical trials of weaning

Compared with conventional ventilation (IPPV/IMV), both patient triggered ventilation and SIMV have been shown to improve tidal volume and oxygenation, and to decrease the work of breathing.^{34–36} Based on these physiological advantages, the synchronised mode of ventilation should facilitate weaning and early extubation. Randomised trials comparing SIMV and patient triggered ventilation with continuous mandatory ventilation (CMV)^{11–14} and SIMV with patient triggered ventilation^{16 17} have been relatively few in number (table 1). Only half of published studies^{11 16 17} were primarily weaning studies. Others, designed to look into the safety and efficacy of these newer modes, only included duration of ventilation as incidental data. Although the results of these studies were analysed according to intention to treat, unfortunately, none reported whether synchronous ventilation was achieved. Cumulative data from these studies indicate that patient triggered ventilation or SIMV compared with CMV is associated with a shorter duration of ventilation.¹⁵ When patient triggered ventilation was compared with SIMV, there was a trend towards a shorter duration of weaning with the former mode. However, it is not possible to conclude from these studies whether or not these benefits were the result of achieving synchronised ventilation.

Advances in respiratory technology have reintroduced volume controlled ventilation in the newborn population. This differs from time cycled, pressure limited ventilation in that the primary gas delivery target is tidal volume, and peak inspiratory pressure might vary from breath to breath. In a recent study, 50 preterm infants with respiratory distress syndrome who weighed more than 1200 g and required mechanical ventilation were randomised to receive either volume controlled ventilation or time cycled, pressure limited ventilation. The two modes of ventilation were compared by determining the time required to achieve a predetermined “success” criterion, as a standard against which the speed of weaning could be assessed objectively. The period of mechanical ventilation was also calculated for each baby. Infants randomised to volume controlled ventilation met success criteria sooner, and had a shorter duration of mechanical ventilation.¹⁸ In another study designed to compare the effect of volume controlled ventilation versus time cycled, pressure limited ventilation, no difference was noted in the duration of ventilation between the two groups. However, when the results from a subgroup of babies weighing < 1000 g in this study were analysed, the dura-

tion of ventilation was significantly reduced in the volume controlled ventilation group.¹⁹ Both studies reported a lower incidence of complications associated with volume controlled ventilation.

High frequency ventilation is different from tidal ventilation in that it allows the use of extremely small gas volumes, even smaller than anatomical dead space, and it does not try to mimic normal breathing.³⁷ It also provides a different distribution of gas within the lungs. Three major types of high frequency ventilation are routinely used, namely: (1) high frequency oscillatory ventilators, which provide sinusoidal push/pull, piston type ventilation from 180 to 900/min; (2) high frequency jet ventilators (not available in the UK), in which inspired gas is injected into an endotracheal tube through a jet nozzle with a typical frequency range of 240–660/min; and (3) hybrids, such as “flow interrupters”, and combined high frequency ventilation/IMV devices that may provide jet, oscillatory, or conventional ventilation over similar frequency ranges.

The clinical application of high frequency ventilation is well described in the literature. Nonetheless, this is a relatively new treatment modality in neonatal respiratory care and accordingly there is little research examining the weaning process involved in the different types of ventilators.³⁸ For example, it has not been shown that extubation directly from very low high frequency oscillatory ventilator settings to either no support or CPAP offers any advantages over switching to conventional ventilation first. Similarly, issues still to be resolved during weaning from high frequency jet ventilators include whether the conventional breaths should be of high enough pressure to “cut out” the high frequency jet ventilator breaths, and whether high frequency jet ventilator support should be gradually or abruptly stopped as the patient improves. Many of these issues might be disease specific, and strategies should be developed to minimise the most potentially damaging parameters first, while assuring adequate gas exchange at the lowest possible level of support. Monitoring of pulmonary mechanics is not yet possible during high frequency ventilation. It is hoped that the results of the ongoing UK oscillation study, which is designed to compare the benefits of high frequency oscillatory ventilators with conventional ventilation, will deal with the issue of weaning from high frequency ventilation.

Adjuncts to weaning

CONTINUOUS POSITIVE AIRWAY PRESSURE

Failure to make the transition to spontaneous breathing after extubation is a common occurrence in the neonatal population and may result from a tendency towards alveolar atelectasis and to relatively poor respiratory drive, both of which are characteristics of prematurity. CPAP appears to stabilise the upper airway, improve lung function, and reduce apnoea. A number of randomised trials have attempted to investigate the question of whether CPAP, applied “prophylactically”, reduces the need for additional ventilatory

support.^{20–26} Although results vary from trial to trial, the cumulative data²⁷ (table 1) suggest that infants extubated to nasal CPAP experience a reduction in the frequency of adverse clinical events (apnoeas and bradycardias, respiratory acidosis, and increasing oxygen requirements), a decreased need for additional ventilation, and a trend towards a decreased requirement for reintubation. However, in the absence of direct comparison of important variables such as gestational age and weight, optimal values of nasal CPAP, as well as methods (nasal versus nasopharyngeal) and duration of treatment, further trial are needed.

PHARMACOLOGICAL AGENTS

Routine administration of corticosteroids and methylxanthines is frequent adjunctive treatment for weaning and extubation. The anti-inflammatory effects of steroids and their effect on lung function^{39 40} form the basis of this approach. There is a large literature, incorporating both uncontrolled and well performed randomised controlled trials, which falls into two groups:

- (1) Peri-extubation corticosteroid treatment.^{41 42} The combined results⁴³ suggest that dexamethasone reduces the need for reintubation of newborns after a period of IMV. However, there is no evidence of its beneficial effect in low risk infants and its use can be associated with serious potential complications. It appears reasonable to restrict its use to infants at increased risk for airway oedema and obstruction, such as those who have received repeated or prolonged intubation.
- (2) Postnatal corticosteroid treatment to prevent chronic lung disease.^{44–47} Most of these studies are related to the question of prevention of chronic lung disease but suggest that steroids are effective in facilitating earlier extubation. As evidence accrues it seems that treatment at between 7 and 14 days of age might give the best outcomes.⁴⁸ However, these studies differ in dosage regimen, duration, and time of onset of treatment, and they provide information regarding immediate complications only. Clearly, more studies are needed to examine the risk to benefit ratio of this treatment, because there are potential hazards of prolonged corticosteroid treatment, including possible adverse effects on the developing central nervous system⁴⁹ and lungs.^{50 51}

Methylxanthines (theophylline and caffeine) seem to have many theoretical advantages, including increased central (respiratory) drive and increased respiratory muscle contractility and endurance.^{52 53} A review⁵⁴ of the published studies suggests that methylxanthines might increase the chances of successful extubation of some preterm infants, but individual studies do not allow a firm recommendation to be made for routine use in clinical practice. One trial suggests that the benefit of methylxanthine might be restricted to infants of extremely low birth weight (< 1 kg) who are extubated in the 1st week of life.⁵⁵ An international multicentric

Table 2 Clinical trials of predictive indices in weaning

Physiological parameters	Indices	Comments
Pulmonary mechanics ⁵⁹⁻⁶⁰	Lung compliance (ml/cm H ₂ O/kg)	Equivocal results
	Lung resistance (cm/H ₂ O/l/s)	Poor discriminatory value of individual indices
	Resistive work of breathing (gm × cm/kg)	Uncontrolled studies with fewer numbers
Pulmonary function ⁶¹	Functional residual capacity (ml/kg)	Measurement made soon after extubation
		Threshold value < 26 ml/kg for failure sensitivity 71% specificity 77%
Effect of breathing and respiratory muscle endurance ⁶²⁻⁶⁴	Spontaneous breath tidal volume (ml/kg)	Not discriminatory
	Minute ventilation (ml/min/kg) (ratio of spontaneous : mechanical breaths)	Positive predictive value 86% but requires controlled study
	Mean inspiratory flow (V _T /TI) Inspiratory pressure/maximal inspiratory pressure (PI/PI _{MAX})	Methodological inconsistency Different "threshold" values
Composite data ⁶⁵⁻⁶⁶ (integrated indices)	Respiratory frequency and tidal volume	Not assessed in homogenous neonatal population
	Ratio (fV _T breaths/minute/l)CROP index (compliance, rate, oxygenation, and pressure)	Not discriminatory as in adults

PI, inspiratory pressure; PI_{max}, maximal inspiratory pressure; TI, inspiratory time; V_T, tidal volume.

trial to examine the safety and efficacy of caffeine is under way. This trial incorporates a neurodevelopmental assessment because there are suggestions that acute methylxanthine administration might exacerbate ischaemic brain damage as a result of its antagonistic properties against adenosine receptors.⁵⁶

Predictive indices for discontinuation from mechanical ventilation

Although an astute clinician might be able to predict the time that an infant is ready to start weaning, extubation failure still occurs in about a third of cases. Attempts have been made to devise some objective predictive indices that might help to identify the optimal time for extubation. These indices or parameters assess different physiological functions of the respiratory system, including the differentiation between the elastic versus resistive component of pulmonary dysfunction; defining alteration or limitation in inspiratory/expiratory air flow; determining the magnitude of driving pressure, work and effort to maintain tidal volume; and defining sequential changes to monitor the progression and resolution of the underlying disease process.⁵⁷⁻⁵⁸ However, despite its potential clinical applicability, bedside neonatal pulmonary mechanics testing still remains a limited tool that requires clinical expertise as well as an awareness of the pitfalls. For example, neonatal respiratory data can be dis-

torted by the presence of inadvertent overdistension of the lungs and frequency dependency of the mechanical breaths.⁵⁸

Compared with adults, there have been only a few published studies⁵⁹⁻⁶⁴ on the weaning parameters used in the neonatal population (table 2). These studies are mostly investigational in nature and do not provide a "threshold" value for individual measurements that would consistently discriminate between success and failure of extubation. It is also likely that individual pulmonary mechanics or function testing criteria per se might not have the same discriminatory power as composite parameters, because the successful withdrawal of mechanical ventilation is dependent on multiple factors. For this reason, integrated indices have been proposed that are a composite of two or more measurements. Despite being inclusive of many respiratory functions and showing good predictive value in adults, these integrated indices do not seem to be reliable predictors of extubation success or failure in infants and children.⁶⁵⁻⁶⁶

Difficult weaning

Commonly, more than one factor is responsible for weaning failure and these factors might be difficult to separate. In physiological terms, effective spontaneous breathing is dependent on a delicate balance between the loads imposed on the respiratory system and its capacity.⁴ The inability to tolerate extubation is the result of poor effort, increased load on the respiratory muscles, and decreased inspiratory drive.⁶⁷ Weaning attempts that are repeatedly unsuccessful usually indicate either incomplete resolution of the underlying illness or the development of new problems. The management of such infants requires the identification and correction of all such factors that have the potential to impede tolerance of spontaneous breathing (table 3). Factors increasing the infant's respiratory workload must be examined and optimised. Where available, monitoring of pulmonary function and mechanics might be used to gain some insight into the reasons for ventilator dependency in an individual baby.⁶⁸ Careful adjustment of the ventilator triggering system to its maximal sen-

Table 3 Causes of weaning and extubation failure

Increased respiratory load	Decreased respiratory capacity
Increased elastic load	Decreased respiratory drive
Unresolved lung disease	Sedation
Secondary pneumonia	CNS infection
Left to right shunt (PDA)	PVH/PVL
Abdominal distension	Hypocapnoea/alkalosis
Hyperinflated lungs	
Increased resistive load	Muscular dysfunction
Thick/copious airway secretions	Muscular catabolism and weakness (malnutrition)
Narrow/occluded endotracheal tube	Severe electrolyte disturbances
Upper airway obstruction	Chronic pulmonary hyperinflation (BPD)
Increased minute ventilation	Neuromuscular disorders
Pain and irritability	Diaphragmatic dysfunction
Sepsis/hyperthermia	Prolonged neuromuscular blockage (in renal failure, concomitant use of aminoglycoside and phenobarbitone)
Metabolic acidosis	Myotonic dystrophy
	Cervical spinal injury

BPD, bronchopulmonary dysplasia; CNS, central nervous system; PDA, patent ductus arteriosus; PVH, periventricular haemorrhage; PVL periventricular leukomalacia.

sitivity, and appropriate setting of the ventilator inspiratory flow, might help in reducing the patient's work of breathing during mechanical ventilation.⁶⁹ Patients with dynamic hyperinflation, either related to expiratory flow limitation such as in bronchopulmonary dysplasia (BPD) or because of insufficient expiratory time, require close attention. Excessive PEEP can also be counterproductive as a result of its adverse effect on pulmonary mechanics and its fatiguing effect on respiratory muscles, particularly in newborns, because of its unique style of attachment.⁷⁰ Such patients might benefit from the use of pressure support ventilation because of its variable inspiratory flow. The maintenance of minute ventilation in a range sufficient to assure adequate removal of carbon dioxide is essential.⁵ For the healthy newborn, a tidal volume of 4–8 ml/kg and a respiratory rate of 40–60 bpm suggest that the minute ventilation should be approximately 240–360 ml/kg/min in infants with normal lungs.⁵⁸ It may be inferred that alveolar hypoventilation will occur if either tidal volume or respiratory rate is too low. In addition, the nutritional aspect of weaning, particularly in extremely low birth weight babies, cannot be overlooked. Efforts to provide an adequate energy intake to prevent catabolism might help to prevent weaning failure. On the other hand, an excessive non-nitrogen energy intake will lead to increased carbon dioxide production and might further impede the weaning process.

Conclusions

Weaning infants from mechanical ventilation involves as much “art” as “science”, and should be planned according to clearly defined clinical and physiological goals. A method that rapidly and reliably assesses the infant's readiness for extubation would provide clinicians with a useful adjunct to their clinical decision making for withdrawal of ventilatory support. In this respect, any attempt to identify objective measures that could predict successful extubation, especially in preterm infants, deserves applause but so far no single parameter can discriminate between a high and a low risk of failure. Additional clinical investigations in this area are very much needed. Until then, predicting which infant will successfully tolerate extubation depends on physical diagnostic skills and experience. Given the availability of a variety of newer ventilatory modes that were not available previously, clinicians have a choice of weaning techniques, each of which might be useful in disease specific situations. Whatever technique one uses, it is helpful to begin with an organised plan, which should be adjusted as the infant's disease process and physiological status changes. As with many challenging medical problems, the best approach often requires innovation rooted in a firm grasp of the underlying physiology.

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