Early Human Development 88 (2012) 925–929

Contents lists available at SciVerse ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Developing a neonatal unit ventilation protocol for the preterm baby

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ARTICLE INFO

Keywords:
Mechanical ventilation
Weaning
Lung injury
Clinical guidelines
Potentially better practice

ABSTRACT

Mechanical ventilation is a resource-intensive complex medical intervention associated with high morbidity. Considerable practice style variation exists in most hospitals and is not only confusing for parents, but the lack of consistently high standard of optimal ventilation deprives some infants of the benefits of state-of-the-art care. Developing a unit protocol for mechanical ventilation requires exhaustive research, inclusion of all stake-holders, thoughtful protocol development and careful implementation after a thorough educational process, followed by monitoring. A protocol for respiratory support should be comprehensive, addressing respiratory support in the delivery room, the use of non-invasive support, intubation criteria, surfactant administration, specific ventilation modes and settings, criteria for escalating therapy, weaning protocols, extubation criteria, and post-extubation management. Evidence favors the use of non-invasive support as first line treatment, progressing to assist/control or pressure support ventilation combined with volume guarantee, if needed, and high-frequency ventilation only for specific indications. The open lung strategy is crucial to lung-protective ventilation.

1. Introduction

Neonatal intensive care involves life-threatening illness with high morbidity, cost and resource use. Mechanical ventilation is one of the most common therapies in the newborn intensive care unit (NICU), and is associated with increased morbidity and mortality. The management of infants receiving mechanical ventilation remains largely dependent on individual preferences. Mechanical ventilation is a complex and highly specialized area of neonatology, made more complicated by the availability of many different modes, techniques and devices. Ventilator manufacturers add to the confusion by using proprietary terminology to describe the various modalities. A physician who has trained in a NICU that uses a different device may find it difficult to transition to a new device and terminology. There are at least six kinds of high-frequency and twelve conventional ventilation devices in fairly widespread use throughout the world. In most NICUs staffing is provided on a rotating basis by attending physicians with varying research and clinical foci and a large number of house-staff with diverse background and training. No wonder that mechanical ventilation has been identified as one of the major risk factors for iatrogenic errors in the NICU [1]. Excessive practice style variation may not only lead to suboptimal clinical outcomes, but appears to also increase parental stress caused by multiple changes in care and have adverse consequences for the educational experience of house staff.

2. Evidence in favor of ventilation protocols

Clinical trials evaluating various forms of mechanical ventilation have suffered from limitations related to the population studied, the specific device under study and the strategies employed. The inconsistent findings are open to interpretation and controversy continues to surround this important area. Experience has shown that there is a very long lag time between the time convincing scientific evidence becomes available and the time that a new practice becomes widely adopted. Clinical protocols, also known as "critical pathways" are formal pathways with specific inclusion and exclusion criteria that provide standardized algorithms for caring for patients with specific conditions.

Protocols are a widely used tool to help implement evidence-based therapies and reduce unnecessary variations in practice [2]. The development and implementation of mechanical ventilation protocols are well supported in the adult literature and have been recommended by the American College of Chest Physician and the American College of Critical Care Medicine [3]. In children, two RCT trials have compared the use of protocols versus physician-driven ventilation with conflicting results [4,5]. The larger trial also tested volume versus pressure targeted ventilation using a 2 by 2 design but was stopped early due to lack of differences in the primary outcome [5]. A cohort study that included some term neonates reported decreased weaning time and shorter time to initiation of spontaneous breaths [6]. In neonates, only one single center retrospective study evaluated the impact of a ventilation protocol on

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http://dx.doi.org/10.1016/j.earlhumdev.2012.09.010

the respiratory outcomes of preterm infants born with BW<1250 g [7]. In that center, the implementation of a RRT-driven protocol was associated with earlier extubation, decreased rate of extubation failure and shorter duration of mechanical ventilation, without any reported side effects.

3. Development of a ventilation protocol

For the development and implementation of a ventilation protocol a few general principles outlined below should be followed [8].

3.1. Involving all stake-holders

All the professionals who are involved in the care of patients receiving respiratory support or who have other legitimate reasons for having input into the process should be identified. Stake-holders include physicians at all levels, respiratory therapists, nurse practitioners and nurses. Being inclusive is important to ensure adequate discussion of the available evidence and helps in obtaining buy-in upon implementation. The multidisciplinary approach provides an opportunity for all involved to provide valuable input, which may lead to more polished protocols that can be successfully implemented.

3.2. Why is it important to get buy-in?

Studies have reported a low compliance rate (25% and 66% in studies involving adult and pediatric populations, respectively) after implementation of evidence-based ventilation protocols [5,8]. Reasons for poor compliance included lack of awareness, agreement and/or familiarity with the protocol and complaints about confusing or cumbersome protocols. Active participation in the process of protocol development improves awareness of the rationale for the specific guidelines and a sense of ownership, which was lacking in protocols that were simply handed down.

3.3. How to achieve consensus

In the face of a lack of clear scientific evidence for many aspects of mechanical ventilation in preterm infants, achieving consensus may not be easy. Careful review of the pertinent literature, emphasizing evidence from systematic reviews of randomized clinical trials and meta-analyses should be conducted by the individual(s) with the most expertise and/or motivation and be summarized in a draft of the protocol. Current unit practice (or range of practices) and protocols from other programs should be examined. Where unequivocal evidence from RCTs is lacking, recommendations may be made based on evidence of short-term benefit and even sound physiologic principles. Potentially better practices from units with better than average outcomes should be examined and potentially incorporated into unit protocols. Consultation with available local experts may be helpful.

Guidelines and protocols cannot adequately address every conceivable eventuality that may arise with a specific patient. It must be recognized that individual patients may respond differently and thus the clinician must always have the ability to individualize patient care as needed. Therefore, a balance between an excessively prescriptive protocol and one that is so vague that it fails to achieve a reasonably uniform approach to ventilation must be achieved. An initial draft of the protocol is prepared by one or more members of the core working group and this draft is revised carefully before an advanced draft is submitted to a larger stakeholder group for feedback. Finally, depending on local circumstances, this final version may need to be approved by the nursing and/or respiratory therapy practice councils, as well as physician leadership.

3.4. Implementation

The implementation process is critical to ensuring compliance and requires time and commitment. Educational sessions need to be conducted to all of the clinical staff. These sessions should include presentations at clinical rounds, a monthly newsletter and multiple in-service sessions. Education not only must include the substance of the protocol, but also must emphasize the rationale for its development, evidence that supports the use of protocols in general and the specific evidence on which the protocol is based. A quality monitoring process should be built in and involve random audits, annual education sessions, sessions for new hires and rotating house-staff, mandatory review every 1 or 2 years, and mechanisms for dealing with adverse outcomes. After protocol implementation, continuing monitoring of outcomes, as well as compliance and expertise of the people using the protocol should be put in place.

4. Proposed ventilation protocol

Ideally a unit protocol for respiratory support of newborn infants should be comprehensive and address all pertinent issues that impact on the eventual pulmonary outcome. This includes respiratory support in the delivery room (DR), the use of non-invasive support, criteria for intubation, surfactant administration, specific ventilation modes and usual range of settings, criteria for escalating therapy to high-frequency ventilation, weaning protocols, extubation criteria, and post-extubation management. In addition to guidelines for care of the preterm infant with respiratory distress syndrome (RDS), the guidelines should address the approach to patients with specific conditions, such as congenital diaphragmatic hernia, meconium aspiration syndrome, persistent pulmonary hypertension of the newborn and bronchopulmonary dysplasia. Each of these conditions has a unique pathophysiology and requires a specific approach that reflects the underlying pulmonary condition. Detailed treatment of all of these issues is beyond the scope of this paper, which will focus primarily on ventilation of the preterm infant with RDS with only a brief summary of other key aspects of respiratory support.

5. Delivery room care

There is strong evidence base in support of DR strategies aimed at facilitating lung fluid clearance and helping the preterm infant with insufficient chest wall rigidity to establish functional residual capacity (FRC). Positive pressure ventilation with high pressure and excessively large tidal volumes must be avoided. The use of a T-piece resuscitator is highly recommended, because of its ability to provide consistent, controlled inspiratory pressure and consistent positive end-expiratory pressure (PEEP). Initial FiO_2 should be between 0.30 and 0.40 for preterm infants and 0.21 for term infants. FiO_2 should be promptly titrated to maintain target saturation according to published NRP guidelines. The use of sustained inflations may be beneficial, but there is insufficient evidence at this point to recommend it as standard practice. Application of facemask CPAP via T-piece resuscitator with or without a few manual inflations is sufficient to initiate adequate respiratory effort in most infants. Non-invasive support with CPAP is the primary goal and is successful in a majority of infants >26 wk gestation. Intubation solely for the purpose of administering surfactant is no longer recommended, but if intubation is required for initial stabilization, surfactant should be administered once the endotracheal tube position has been confirmed.

6. Non-invasive support

Nasal CPAP should be provided with bi-nasal prongs and a minimal pressure of 5 cm H_2O. CPAP can be delivered with a bubble system, a constant flow ventilator, or a variable flow system. Bubble CPAP may have unique benefits, but the ease of use of ventilator CPAP and the

ease of conversion to invasive or non-invasive positive pressure ventilation (NIPPV) make it an attractive pragmatic option. NICU's should develop local protocols for CPAP administration and focus on optimal application of the patient interface to optimize effectiveness and minimize pressure necrosis.

Non-invasive PPV has gained popularity over the last few years and appears to be effective in some infants who are in danger of requiring intubation due to inadequate respiratory effort. However, only limited and inconsistent amount of pressure is transmitted to the airway and the optimal ventilator settings have not been clearly defined. Most devices cannot provide synchronization with the infant spontaneous breaths. Single center studies and a meta-analysis have reported on the advantage of this mode of non-invasive respiratory support over nasal CPAP but a recent large RCT did not confirm these benefits.

7. Intubation criteria

The need of endotracheal intubation is often based on "clinical judgment", which is highly subjective and requires considerable experience to apply well. In general, less experienced trainees are more aggressive in invading the airway, an intervention that is not without adverse effects. While latitude will always be necessary in clinical circumstances, reasonably specific criteria are needed to bring practice to a reasonable level of uniformity for all the reasons outlined previously. In the absence of direct comparison between various levels of FiO_2 or $PaCO_2$, guidelines must be established based on indirect evidence. For example, high oxygen requirement indicates significant ventilation/perfusion (V/Q) mismatch, indicating extensive atelectasis, a situation known to predispose to airleak. Arterial tension of $CO_2 > 65$ mm Hg may increase the risk of severe intracranial hemorrhage in the first days of life. In general, intubation and mechanical ventilation should be initiated when one of the following is present: 1) $FiO_2 > 0.5$ in order to maintain $SpO_2 > 88\%$ or partial pressure of oxygen (PaO_2) > 45 mm Hg, 2) partial pressure of carbon dioxide ($PaCO_2$) > 55–60 mm Hg with a pH of <7.25, 3) apnea requiring positive pressure ventilation with bag and mask or 4) more than 6 episodes of apnea over 6 h.

8. General principles of mechanical ventilation

Optimal use of mechanical ventilation seeks to improve lung compliance, reduce oxygen requirement, prevent surfactant inactivation and ensure even tidal volume distribution by recruiting optimal lung volume and preventing atelectasis. The second key element of lung protective ventilation strategies is to minimize volutrauma and hypocapnia, the preventable elements of lung and brain injury by avoiding excessively large V_T. Mild permissive hypercapnia and minimal FiO_2 to achieve adequate oxygen saturation (88–93%) are generally appropriate [9]. There is no evidence to support the routine use of sedation or muscle relaxation and therefore infants should be allowed to breathe spontaneously. Routine suctioning should be avoided, as it leads to derecruitment, transient hypoxemia and perturbation of cerebral hemodynamics. When secretions are detected by auscultation or by perturbation of the flow waveform, gentle rapid suctioning without instillation of normal saline is indicated.

9. Choice of basic synchronized ventilation mode

Assist/Control (AC) or Pressure Support Ventilation (PSV) is preferable to SIMV in preterm infants, because the small endotracheal tubes (ETT) impose a high resistance and work of breathing during the weaning process. AC results in more even tidal volume (V_T), lower work of breathing and more rapid weaning from mechanical ventilation compared to SIMV. PSV provides more complete synchronization because it is flow-cycled, thus avoiding inspiratory hold, but may result in very short inspiratory time (T_i) and rapid respiratory rate in very small infants in the first few days of life when time constants are very short. Because the short T_i results in relatively low mean airway pressure (MAP), adequate positive end-expiratory pressure (PEEP) must be used with PSV to avoid atelectasis [10]. SIMV combined with PSV is a reasonable alternative, but a more complex support strategy.

10. Choice of pressure vs. volume as primary control variable

Pressure limited ventilation became the standard of care early in the history of neonatal respiratory support because of its ease of use and ability to cope with large leaks around uncuffed ETTs. The main disadvantage of pressure limited ventilation is the risk of volutrauma and inadvertent over ventilation when lung compliance improves, as often happens soon after birth when lung fluid is cleared, surfactant is administered and optimal lung volume is achieved. Volume controlled (VC) ventilation as implemented on available universal ventilators (neonatal to adult population) controls the V_T delivered into the proximal end of the ventilator circuit, not the V_T delivered to the patient. The loss of volume to compression of gas in the circuit and humidifier and to ETT leak may be 75% or more of the total, making standard VC ventilation difficult to use effectively in small newborn infants. Volume Guarantee (VG) is one of the several modes of volume-targeted pressure-limited ventilation. These modes control delivered V_T indirectly by adjusting either the inflation time (volume limit) or inflation pressure (VG) to target a user-selected target V_T. In VG, the microprocessor compares exhaled tidal volume of the previous breath to the desired target and adjusts the working pressure up or down to achieve the target tidal volume. Thus, inflation pressure is reduced continuously, in real time, rather than intermittently in response to blood gas measurement. VG has been studied more extensively than any of the other modes of volume targeted ventilation and shown to reduce the proportion of excessively large inflations, hypocapnia and markers of lung injury in bronchoalveolar lavage fluid, and lead to earlier extubation [10]. Detailed descriptions of VG and guidelines to the use of VG have been published [11,12].

11. Suggested settings

Ventilation should be initiated with AC + VG or PSV + VG. The choice of appropriate V_T is the key to success and depends on the infant's size, postnatal age and underlying disease process. One size does NOT fit all. Table 1 lists appropriate V_T and initial inflation pressure limit for various conditions. The larger V_T requirement in the smallest infants is due to the proportionally larger impact of instrumental dead space of the flow sensor. Infants with BPD or meconium aspiration need larger V_T because of increased physiologic dead space due to air-trapping and heterogeneous lung inflation. Inflation pressure limit should initially be set 3–5 cm H_2O above the level estimated to be sufficient to achieve a normal V_T. If the target V_T cannot be reached with this setting, the pressure limit is increased until the desired V_T is generated. It is important to make sure that the endotracheal tube is not kinked, in the main stem bronchus or obstructed on the carina. Significant volutrauma and/or air leak could result from failure to recognize single-lung intubation. Pressure limit is subsequently adjusted to be about 20% above the current working pressure and adjusted periodically as lung compliance improves and working pressure comes down. If the ventilator is unable to reach the target V_T with the set inflation pressure limit, an alarm will sound. This serves as an early warning system that should prompt an evaluation of the reason for this change.

In the VN 500 ventilator, the leak compensated V_T value should be selected in the ventilator default setting to minimize artifact caused by ETT leakage. The Babylog 8000 uses the uncorrected V_T measurement and this begins to progressively underestimate the true V_T with increasing ETT leak, potentially resulting in inadvertent hypocapnia. This commonly occurs if a preterm infant remains intubated for > 1–2 weeks, because of stretching of the larynx and may require re-intubation with a larger ETT.

Table 1
Suggested initial tidal volume and pressure limit settings for Volume Guarantee ventilation. These are merely starting points and are mean values based on available data. Individual patients may deviate from average values. The pressure limit should be adjusted once the working pressure needed for an appropriate tidal volume has been determined.

Clinical situation	Tidal volume	Pressure limit
Preterm infant with RDS, >2000 g	4 ml/kg	30 cm H_2O
Preterm infant with RDS, 700–1500 g	4–5 ml/kg	25–28 cm H_2O
Preterm infant with RDS, <700 g	5–6 ml/kg[a]	25 cm H_2O
Preterm infant with BPD	5–7 ml/kg[b]	30 cm H_2O
Term infant with MAS	5–7 ml/kg[b]	30 cm H_2O
Term infant with CDH	4 ml/kg[c]	25 cm H_2O
Term infant with pneumonia	4 ml/kg	25–30 m H_2O

[a] Smallest infants need larger tidal volume to compensate for the dead space of the flow sensor.
[b] Depending on the severity of the disease.
[c] Low threshold to change to high-frequency ventilation.

PEEP should be set in proportion to the current oxygen requirement because hypoxemia is usually a reflection of ventilation–perfusion mismatch due to atelectasis and low lung volume. Therefore, using a PEEP of 5 cm H_2O for all infants with RDS is not optimal for oxygenation and lung recruitment. PEEP should be optimized by stepwise increase using increments of 1 cm H_2O if oxygen requirement is >0.30. Continue to increase by 1 cm H_2O until FiO_2 drops below 0.30, a PEEP of 10 cm H_2O is reached or there is no further improvement in oxygenation with the increase. Once optimal lung volume is achieved, reduce PEEP stepwise again, until SpO_2 begins to fall, then repeat the procedure, stopping just above the point where oxygenation deteriorated. This point is considered the optimal PEEP. It is important to note that this recruitment maneuver is demanding and time-consuming and should be performed by skilled neonatologists to avoid excessive lung stretch.

Selection of *inspiratory time* (T_i) with AC should reflect the infant's time constants (a measure of how rapidly gas can get in and out of the lungs). Small preterm infants with RDS have very short time constants and should be ventilated with T_i of 0.3 s or less. Larger infants or those with increased airway resistance (e.g., those with chronic lung disease or meconium aspiration) have longer time constants and require longer T_i, up to 0.5 s. PSV is a flow cycled mode that results in automatic adjustment of effective T_i in response to the infant's changing lung mechanics. PSV is preferred in most infants, with the exception of those <1 kg during the first 2–3 days of life when their time constants are very short. During PSV, the maximum Ti should be set at about 0.4 s in preterm infants, longer in term babies and those with increased airway resistance.

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

Circuit gas flow/rise time determines how rapidly the pressure plateau is reached during inflation. Flow rate is adjusted directly by the user on the Babylog 8000, typically in the range of 4–8 l/min in preterm infants. A combination of low circuit flow and short Ti may result in inability to reach desired PIP. Circuit flow may be adjusted the same way on the VN 500, or adjusted by the device automatically when the pressure-rise time option is selected. The pressure rise time determines the time in which the PIP plateau is reached. This approach is preferable, as it avoids the pitfalls of manual flow adjustment. A pressure rise time that is 30–50% of the Ti is appropriate.

12. Target blood gas values

Mild permissive hypercapnia is appropriate in most infants. The PCO_2 should be maintained in the range of 45–50 mm Hg during the first 3 days of life with a pH above 7.25. PCO_2 >60 mm Hg during the first 3 days should be avoided due to the increased risk of intraventricular hemorrhage. Thereafter, a PCO_2 target range of 45–55 mm Hg is appropriate, as long as pH is >7.25. Minimal FiO_2 needed to achieve adequate oxygen saturation (88–93%) should be used.

13. Weaning protocol

Weaning should be initiated as soon as the patient has begun to recover from respiratory problem that required the use of mechanical ventilation. Weaning is facilitated by permissive hypercapnia. The ideal weaning mode of ventilatory support remains the subject of debate, but recent systematic review and meta-analysis concluded that the use of volume targeted ventilation compared to traditional pressure-limited ventilation resulted in lower rate of death/BPD, shorter duration of ventilation, fewer pneumothoraces, less hypocapnia and lower rates of periventricular leukomalacia/severe intraventricular hemorrhage [13]. With VG, weaning occurs automatically, in real time and requires fewer blood gas measurements. The use of evidence-based adjunctive therapies such as caffeine and cautious use of postnatal steroids should also be part of the weaning protocol. Large doses and long course of postnatal steroids should be avoided because of its deleterious effects on neurodevelopment but low doses and small course have appear to be safe and benefits outweigh the risks when the likelihood of severe BPD is high. The risk of death or moderate to severe BPD may be estimated using the Neonatal Research Network BPD risk calculator https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start.

14. Indications for high-frequency ventilation

When inflation pressures >25–28 cm H_2O are required consistently to achieve acceptable gas exchange in a preterm infant with RDS, a change to high-frequency ventilation (HFV) is recommended. For uncomplicated RDS, both jet and oscillatory ventilation may be used. When significant airleak is present high-frequency jet ventilation is preferred. HFV is also indicated in infants with congenital diaphragmatic hernia, pulmonary hypoplasia, severe abdominal distension and poor chest wall compliance [14].

15. Extubation

It is important to recognize that extubation is a critical transitional time and many patients can experience significant problems during this process. Therefore, for the extreme preterm infant, we recommend the presence of a staff with expertise in stabilization and reinstitution ventilatory support during the procedure. Mechanical ventilation protocols should incorporate extubation guidelines. In the absence of definitive trial data, these are by necessity somewhat arbitrary. In a preterm infant extubation should be attempted when FiO_2 is <0.35, PCO_2 is <50 mm Hg and MAP <7–8 cm H_2O with a consistent spontaneous respiratory effort without excessive work of breathing on current settings. If not previously administered, caffeine loading dose should be given prior to attempted extubation. A three minute spontaneous breathing test appears to improve the assessment of extubation readiness and facilitate earlier extubation. However, our ability to predict extubation readiness and avoid the risks associated with re-intubation remains incomplete [15].

16. Post-extubation support

The post-extubation respiratory support should be decided ahead of time and be available for immediate initiation after extubation. Preterm infants should always be extubated to some form of distending airway pressure. Standard CPAP is appropriate for most infants. NIPPV may be used in selected infants with questionable respiratory effort or history of extubation failure. HHFNC is less effective and should not be used as a substitute for CPAP in the immediate post-extubation period. The use of a short burst of dexamethasone for airway edema should be evaluated on a case by case basis. The chances of extubation failure should be discussed with the team members and family, given that re-intubation is not a simple procedure and is the source of significant stress to the parents.

17. Summary

Effective translation of evidence based strategies of respiratory support into practice is facilitated by the development of a unit ventilation protocol. This endeavor requires considerable commitment of time and expertise, but will reduce practice style variation, root out outmoded approaches and benefit patients, parents and trainees.

Conflict of interest statement

Dr. Sant'Anna has nothing to disclose. Dr. Keszler is a consultant to Draeger Medical and has received research grant support from the company.

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