Advances in Ventilatory Support of Critically Ill Children

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Abstract Advances in pediatric medical practices often lag behind the progress made in adult patients, primarily because of the limited number of randomized, controlled, clinical trials. Recent advances in mechanical ventilation derived from successful application in adults include neurally adjusted ventilatory assist, noninvasive ventilation, and protective lung strategies. NAVA improves patient/ventilator synchrony and reduces the work of breathing, which allows for a decreased use of sedation. This should decrease the length of time patients are intubated and mechanically ventilated. The use of noninvasive ventilation eliminates the need for endotracheal tubes and complications associated with them including tracheal injury, pressure ulcers, issues with oral hygiene and ventilator associated pneumonia. Application of lung protective strategies to pediatric patients with acute lung injury and/or ARDS results in increased oxygenation, less lung injury, and improvements in morbidity and mortality.

Keywords Noninvasive ventilation · Pressure support ventilation · Neurally adjusted ventilatory assist · NAVA level · Electrical activity of the diaphragm · Acute lung injury · Acute respiratory distress syndrome · PEEP

Introduction

Mechanical ventilation of critically ill children can be an extremely difficult undertaking. It requires that the clinician be familiar with patients of various sizes and age groups,

ranging from infants to toddlers and adolescents to young adults. Lessons learned in the neonatal intensive care unit (NICU) do not necessarily apply to infants in the pediatric intensive care unit (PICU) nor do those from the adult intensive care units (ICU) always apply to a 17- or 18-year-old in the PICU. Additionally, in larger tertiary care centers, adult ICUs tend to specialize in specific patient populations, e.g., medical, surgical, neuroscience, etc. while the pediatric intensivists must be familiar with all types of patient ailments and injuries including those acute processes superimposed on chronic and/or congenital problems.

Many times, advances in technology, such as newer modes of mechanical ventilation, that are available for adult patients may not be options for pediatric patients. For example, proportional assist ventilation (PAV) is a closed-loop control mode of ventilation that provides an increasing level of pressure support (PSV) in response to increased patient effort. Unfortunately, this mode of ventilation is only available for patients weighing at least 25 kg and may only be used with endotracheal or tracheostomy tubes sized 6–10 mm ID.

Noninvasive ventilation (NIV) has been used for many years for adult patients, and as nasal CPAP for neonates, to decrease the work of breathing (WOB), prevent intubation for impending respiratory failure and reduce the likelihood of extubation failure. Arguably, the greatest improvement for this technology has been the constant evolution of patient/ventilator interfaces improving the fit, comfort and ultimately the success of this modality. However, pediatric application of NIV has been limited by the lack of availability of these interfaces. This has led to the need for custom fitted masks [1], nonconventional interfaces such as helmets [2, 3], or failure of this approach to ventilatory support when such masks are unavailable. These issues are compounded by the fact that because of the more diverse

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population, infrequent mortality, and shorter duration of mechanical ventilation, fewer randomized controlled trials (RCTs) are available in pediatric patients than adults [4].

The purpose of this article is to review advances in ventilatory support of critically ill children that include technological innovations such as new modes of ventilation, improved design that allows pediatric application of existing devices such as NIV, and rethinking the bedside goals of mechanical ventilation by applying lung protective strategies to patients with acute lung injury.

Neurologically Adjusted Ventilatory Assist

Neurologically adjusted ventilatory assist (NAVA) is a mode of ventilation that delivers varying levels of respiratory support in response to the electrical activity of the diaphragm (EAdi) [5].

Most ventilators respond to patients' inspiratory efforts as a result of a pressure drop at the airway or redirection of bias flow. Conditions that may interfere with the ventilator's response to patient respiratory efforts (triggering) include incomplete exhalation (auto-PEEP), leaks around the endotracheal tube (ETT), partial obstruction of the ETT from impacted secretions or kinking of the tube, and inappropriate setting of the sensitivity control on the ventilator. Any one of these may cause missed triggering and/or trigger delays resulting in patient/ventilator asynchrony.

When NAVA is used, a specialized nasal gastric tube with an array of electrodes that is connected to a special cable and interfaced with the ventilator, is inserted across the diaphragm. These electrodes measure the EAdi which is immediately transmitted to the ventilator effectively eliminating the delay in response associated with generating negative intrathoracic pressure that must be sensed by the ventilator. This "neuroventilatory coupling" results not only in quicker ventilator triggering but also the delivery of a variable level of support that is proportional to the patient's inspiratory demand. Basic ventilator settings used with NAVA are NAVA level, PEEP, FIO₂, and EAdi trigger. The level of support is determined by the NAVA level and is equal to $\text{NAVA level} \times (\text{EAdi peak} - \text{EAdi min}) + \text{PEEP}$. EAdi trigger is set at the minimal level that does not result in auto-triggering from background noise. This is usually less than 0.5 μV which is the default value. Secondary PSV triggering (pneumatic or flow) and cycle off sensitivity are also set in the event there is catheter malfunction or misplacement. In healthy individuals, the amount of energy required for ventilation is minimal. However in the presence of disease and/or poor muscle performance there is increased neurological output from the respiratory center, thus increased EAdi, resulting in

increased support from the ventilator coinciding with increased patient demand.

Several studies of NAVA demonstrated improved patient/ventilator synchrony, reduced ventilatory drive, increased patient comfort, less trigger delay, improved ventilator response times and decreased WOB. Breatnach et al. [6] compared NAVA to PSV in 16 patients aged 2 days to 4 years. They found patient ventilator synchrony was improved. Peak pressure was lower with NAVA than with PSV with a 28 and 32 % decrease at 30 min and 3 h respectively. There were no changes in hemodynamics or gas exchange.

Bengtsson et al. [7] studied 21 patients ranging in age from 2 days to 15 years with NAVA. Patients were ventilated with PCV, changed to NAVA and then switched back to PSV at the previous settings. Treatment time ranged from 1–8 h (median = 2.5 h) during which peak inspiratory pressure (PIP) was lower compared to pressure support. Respiratory rate increased and tidal volume decreased such that minute volume was not significantly changed. NAVA allowed earlier ventilator triggering; inspiration was triggered first 68 % of the time and cycling to expiration first 88 % of the time when compared to pneumatic triggers. There were no significant changes in blood gas values and no adverse events occurred. However one patient experienced total EAdi asynchrony, which was attributed to catheter misplacement.

In a non-randomized, short-term cross-over trial of 12 patients aged newborn to 16 years in a medical/surgical ICU, de la Oliva et al. [8•] compared NAVA to PSV. Patients were ventilated for a 10 min study period following 20 min of stabilization according to four separate conditions: baseline PSV as determined by the attending physician; optimized PSV where the rise time, inspiratory termination criteria, pressure level, sensitivity, and applied PEEP were optimized; NAVA with the NAVA level set so that maximum inspiratory pressure was equal to pressure support; and finally a repeat of the optimized PSV. Major findings were that NAVA decreases the frequency of major asynchronous events, improves inspiratory trigger synchronization, and decreases the neural drive to trigger ventilation. EAdi activity exhibited a high intra-patient breath to breath variability in NAVA and PSV, with NAVA increasing the mechanical ventilator breath to breath variability. With the ventilator adjusting to the patient, NAVA improved patient comfort, as demonstrated by a lower median COMFORT score when compared to optimized PSV.

Moerer et al. [9] studied a noninvasive application of NAVA using a helmet interface in seven healthy subjects. NIV was applied with pneumatic (conventional) triggering and cycling off, and neural triggering and cycling off. Triggering was set at the minimal level that avoided auto-triggering. Cycle-off criteria for conventional and neural

modes were set at 5 % of peak inspiratory flow and 60 % of peak EAdi respectively. They found no significant differences in neural inspiration with neural versus pneumatic triggering at PSV levels of 5 and 10 cm H₂O, however at 20 cm H₂O of PSV the height of the neural inspiration was significantly different indicating an increased pressure time product of the diaphragm. During pneumatic triggering the number of missed triggers was higher at increased respiratory rates and with increased levels of pressure support. There were no missed triggers with neural control. Expiration was similarly effected. There were delays in cycling-off at all levels of PSV. Overall patient/ventilator asynchrony increased with increasing respiratory rate and PSV with pneumatic control of triggering and cycle-off as compared to neural control.

In a prospective cross-over study, Clement et al. [10] compared the effectiveness of NAVA versus volume support ventilation (volume targeted PSV or VSV) in reducing the WOB in 23 patients with bronchiolitis. The mean age and weight of the patients was 1.6 months and 4.2 kg respectively. VSV settings were determined by the attending physician and NAVA level was set to deliver the same tidal volume as in VSV. Patients were sedated based on recommendation from the attending physician and assessed before the start of each experiment to maintain a COMFORT scale of 8–26.

Trigger delay, ventilator response time, and the area under the airway pressure curve from beginning of inspiration to the return of pressure to baseline at the onset of the breath were all significantly reduced with NAVA, indicating a decreased WOB [11].

NAVA has been shown to consistently improve patient/ventilator synchrony, decrease the WOB, and increase patient comfort. Lower peak ventilator pressures have also been demonstrated. Given these benefits, NAVA should reduce the need for sedation and thus the duration of intubation and mechanical ventilation as well as PICU length of stay, and further studies examining these end-points are needed.

In a case series of three patients aged 28 days, 2 month and 3 years with severe bronchiolitis, ventilation with NAVA resulted in improved patient/ventilator synchrony, variable respiratory rate and inspiratory pressure, and decreased oxygen requirement [12]. One patient who had severe subcutaneous emphysema was able to benefit from improved patient/ventilator synchrony and lower inspiratory pressure resulting in improved ventilation and oxygenation.

Noninvasive Ventilation

Noninvasive ventilation (NIV) has been used extensively in adult patients with acute and chronic respiratory failure [13] where it has been shown to unload respiratory muscles

and improve gas exchange [14]. It has been used with a high degree of success for preventing intubation of patients with impending respiratory failure as a result of an acute exacerbation of COPD [15, 16] as well as those with acute pulmonary edema associated with left ventricular failure [17]. Continual improvements in technology, particularly ventilator leak compensation, have contributed to the success of this treatment modality. Along with the improvements in technology have come better fitting and performing interface designs. Unfortunately, many of these improvements in equipment and supplies have not filtered down to the pediatric population. Many of the devices used to provide NIV have not been approved for use in patients under 20 kg, and the improvements in the design of interfaces for pediatric patients have not been as forthcoming, often necessitating the use of custom fitted masks, cannulae, and other types of patient ventilator interfaces. In addition, NIV is often poorly tolerated by small children [1]. However, despite the dearth of effective interfaces, some success has been realized in applying NIV to children with acute and chronic respiratory failure.

The use of NIV in asthma patients has been shown to improve gas exchange, pulmonary mechanics and subjective clinical asthma severity scores [18]. In a more recent study, Basnet et al. [19•] showed that early intervention with NIV, combined with beta agonists and steroids was safe, well tolerated and resulted in improved gas exchange and respiratory function in patients aged 3–11 years. The use of NIV unloaded inspiratory WOB and aided in improved delivery of aerosolized beta agonists, resulting in decreased respiratory rate, FIO₂, heart rate and clinical asthma score.

NIV has also been successfully applied to patients with acute bronchiolitis, where it may reduce the LOS and the rate of ventilator associated pneumonia (VAP). Javouhey et al. [20] studied the effects of NIV in infants less than 1 year old presenting with bronchiolitis. NIV, provided by bi-level positive airway pressure (BiPap) generators or as CPAP with nasal mask interface, was compared to invasive ventilation (IV) in 87 patients. NIV was associated with decreased oxygen requirement after 8 days and a decreased rate of VAP. Those infants who failed NIV had a longer duration of ventilatory support.

The precise level of NIV support required to reduce the WOB and improve clinical signs may be difficult to ascertain. Typical approaches include clinical exam, measurement of vital signs, oxygen requirement, and laboratory and X-ray data. Essouri et al. [21•] using esophageal pressure manometry, identified 7 cm H₂O as an ideal level of CPAP for spontaneously breathing infants with acute hypercapnic respiratory failure associated with age appropriate tachypnea (respiratory rate in at least the 97th percentiles for age) and transcutaneous carbon dioxide

pressure greater than or equal to 50 mmHg. Decreasing the level of CPAP to 4 cm H₂O and increasing it to 10 cm H₂O were both associated with increased WOB.

Identifying which groups of patients most likely to respond to NIV is an important challenge. As stated above, experiences in the adult patient population have shown that patients with COPD or acute hypoxemia associated with left ventricular failure and pulmonary edema are most likely to respond favorably. NIV has been used effectively in these patients to prevent intubation as well preventing post extubation respiratory failure. However, it has also been associated with an increase in morbidity and mortality when applied to patients with other forms of hypoxemic respiratory failure. Until recently, no such distinction of success versus failure has existed in pediatric patients.

Mayordomo-Colunga, et al. [22] studied patients with both types of respiratory failure. Type 1 ARF included patients with hypoxemic respiratory failure, while Type 2 ARF included patients with hypercapnic respiratory failure. Predictors of NIV failure included lower age and weight, a minimal change in respiratory rate measured at 1 and 24 h as well as a higher pediatric risk of mortality score (PRISM), heart rate and respiratory rate at 24 h, higher EPAP and FIO₂ requirement, and higher PaCO₂.

In another study James et al. [23] divided patients into two groups. In group 1 NIV was used as a first-line treatment to prevent intubation, and in group 2 as a post-extubation intervention to prevent re-intubation. In group 1 the initial respiratory rate and degree of acidosis preceding NIV was higher in the group that failed. These patients also had a higher initial oxygen requirement which persisted even after NIV was applied. They also found that patients who required CPAP were much more likely to avoid intubation as compared to those who required BiPap. When NIV was used as a post-extubation strategy, patients with higher systolic, diastolic, and mean blood pressure 2 h after initiation of therapy were more likely to fail as compared to those with a decrease in blood pressure. Also, those patients who only required CPAP were more likely to succeed than those requiring some level of BiPap. In both the pre-intubation and post-extubation groups, patients with primary respiratory disease were more likely to succeed and avoid intubation/re-intubation. What is not clear is whether patients who fail pre-intubation NIV are more or less likely to fail post-extubation NIV.

Improvements and availability of patient ventilator interfaces have allowed for increased utilization of NIV in pediatric patients suffering from various forms of acute and chronic respiratory failure. By avoiding intubation, patients are much less likely to develop problems associated with ETTs, such as tracheal injury, often requiring surgical repair, pressure ulcers from securing the ETT, issues with oral hygiene and VAP, often referred to as ETT associated

pneumonia. NIV has been successfully applied in a number of clinical situations and the utility of NIV continues to expand.

Another form of noninvasive support is the high flow nasal cannula (HFNC). Although this is technically not a form of ventilation, HFNC is an escalation of support beyond simple oxygen therapy. It includes a heated humidifier similar to those used with IV, that allows the delivery of heated, humidified oxygen at flow rates, of up to 8 L/min for infants, 20 L/min for children, and 40 L/min for adult sized patients without damage to the nasal mucosa. Possible mechanisms of action include precise control of FIO₂, washing out the anatomical deadspace with oxygen, and delivery of CPAP [24, 25].

In a retrospective review of 115 patients less than 24 months of age, adjusted for age, weight, RSV status and gestational age, HFNC reduced the rate of intubation by 68 % [26]. In addition, Abboud et al. [27] identified predictors of failure for patients with bronchiolitis treated with HFNC. One hundred thirteen patients were placed on HFNC, of which 21 (18.6 %) required intubation. For non-responders, the PRISM III score was significantly higher than for the responders and the respiratory rate was lower and did not change after starting HFNC. Also, the pH was lower and the PaCO₂ was higher both before and after the initiation of therapy.

Lung-Protective Strategies

The use of lung-protective strategies has become the standard of care for adult patients with acute lung injury [28]. These include lower tidal volumes, typically in the range of 4–8 mL/kg of predicted body weight, recruitment maneuvers (RM), and various approaches to determining the optimal level of PEEP. Although there is some disagreement over the best way to determine the specifics, there is little if any disagreement over the concepts of achieving lung recruitment and maintaining that level through the use of optimum PEEP and preventing over-stretch of the lung during inspiration by employing a limited tidal volume. Recruitment maneuvers include sustained maximum inflation (SMI) [29–31], extended sighs [32, 33], and stepwise approaches consisting of various manipulations of pressure controlled breaths, e.g., PIP of 40 cm H₂O and PEEP of 25 cm H₂O with a prolonged inspiratory time for 1–3 min [34]. Techniques for determining the optimum PEEP level include a decremental PEEP trial [35, 36], esophageal balloon manometry [37, 38], and the stress index [39]. In any case, RMs, if performed, should be followed by some method of determining optimal PEEP so as not to lose the beneficial effects of the RM that may result from progressive de-recruitment. Methods of identifying a safe tidal volume

may include setting a volume controlled breath at a discreet value, i.e., 6 mL/kg of predicted body weight (PBW) or utilizing a pressure controlled breath to target a specific plateau pressure, such as 28 cm H₂O, and allowing breath to breath variation of the inspired volume within the 4–8 mL/kg PBW range. All of these are consistent with the notion, “Open the lung and keep the lung open” as described by Lachman et al. [40] 20 years ago. In addition, various physiologic indicators, such as ratios of PaO₂ to FIO₂ (P/F ratio) and deadspace to tidal volume (Vd/Vt), lung injury scores (LIS), and the oxygenation index (OI) may be useful in determining severity of lung injury and predicting outcome.

These strategies and techniques may also apply to children, but again there is limited data, covering the wide variation in age, size, and development of pediatric patients. As has often been stated, “Children are not just small adults.” So, one must be cautious in applying these concepts to all patients.

Boriosi et al. [41] studied the effects of a recruitment maneuver followed by a decremental PEEP trial in 21 patients, aged 1–14 years with primary and secondary ARDS. They utilized a modification of the OLT to determine critical opening pressure followed by a decremental PEEP titration to identify optimal PEEP, defined as the level of PEEP associated with the greatest dynamic compliance (C_{dyn}) plus 2 cm H₂O. They were able to show improved oxygenation immediately following the procedure that was sustained at 4 and 12 h post lung recruitment.

Wolf et al. [42] examined the effects of RMs on regional atelectasis in the dependant areas of the lung in patients with early acute lung injury. They found that in those patients who responded to the RM a stepwise lung recruitment strategy was more effective in reversing atelectasis than a SMI. There was an improvement in compliance associated with the reversal of atelectasis that preceded a physiologic indicator (P/F ratio). Overdistention occurred in the nondependent areas preceding the reversal of atelectasis, and there was a larger amount of reversible atelectasis in responders than non-responders.

The use of small tidal volumes has been associated with improved outcomes in adult patients with ALI/ARDS. The ARDS network has advocated a volume controlled tidal volume of 6 mL/kg of PBW, which may be decreased to 4 mL/kg in more severe cases. Acceptable alternatives may include a range of tidal volume, e.g., 4–8 mL/kg PBW, based on disease severity or a pressure controlled breath with a plateau pressure of <28 cm H₂O provided tidal volume was 4–8 mL/kg PBW [43, 44], but it is once again unclear whether or not these principles should be unequivocally applied to pediatric patients.

In a retrospective study of 398 patients, Khemani et al. [45] looked at the effects of tidal volume in pediatric

patients with ALI who had a P/F ratio of less than 300 within 24 h after intubation. Results revealed almost exclusive use of pressure controlled breaths with a median tidal volume of 7.4 mL/kg; however, actual body weight was used, and this most likely underestimated the tidal volume when compared to predicted body weight. On day 1, the median tidal volume ranged from 6.08 to 9.02 with higher values associated with survivors and physiologic indicators of lung injury (P/F ratio, OI, lung compliance, and LIS) suggesting that a range of target tidal volume versus a specific value such as 6 mL/kg PBW may be more appropriate. Median P/F ratio at baseline was 138 with a LIS of 2.33. Overall mortality was 20 %. Increased OI and LIS and decreased P/F ratio were all consistently associated with mortality.

Albuali et al. [46] retrospectively studied the effect of reduced tidal volumes on outcome in children with ARDS/ALI. They compared a 4-year period when tidal volume was set at 10 L/kg (past group, *n* = 79) to a later 4-year period when tidal volume was set at 8 mL/kg (recent group, *n* = 85). They used actual body weight, which may have understated the tidal volume as compared to predicted body weight. The primary outcome variable was mortality and the secondary outcome variable was ventilator free days. They found a mortality rate of 21 % in the recent group versus 35 % in the past group, and a difference in ventilator free days of 16.0 versus 12.7. There was no difference in ventilator-free days for patients who survived discharge from the unit.

It has become increasingly clear that understanding the etiology and pathology of acute lung injury has resulted in a more rational approach to ventilating ALI/ARDS patients. Improvements in outcome include decreased mortality, decreased incidence of chronic lung disease resulting from high oxygen concentrations and ventilator-induced lung injury, a decrease in the use of sedatives and neuromuscular blocking agents, and an overall improvement in the quality of life.

Summary

Advances in ventilatory support of critically ill children include technological improvements and innovation, improved product design and evidence based practice changes designed to decrease morbidity and mortality, improve quality of life, and provide more cost efficient delivery of care. NAVA, NIV and protective lung strategies are three approaches achieving these objectives.

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