Ventilating the Lungs Safely: What's New for Infants and Children?

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Abstract The concept of lung protection ventilation is based on a multimodal approach aimed at preventing the occurrence of ventilator-induced lung injury (VILI). The strategies used include (i) alveolar recruitment maneuvers in order to open up the closed lung units, (ii) application of optimal positive end-expiratory pressure adapted to the expiratory limb of the pressure–volume curve to prevent airway closure at small tidal volume ventilation, (iii) the use of small tidal volume ventilation to avoid overdistending alveoli and/or alveolar shear stress injury by the cyclical opening and closing of lung units, and lastly, (iv) the application of new ventilation modes that take into account the physiological concept of respiratory variability and in particular, neurally-adjusted ventilatory assist, which enhances both patient-ventilator synchrony and lung protective strategy.

Keywords Lung protection ventilation · Recruitment maneuvers · End-expiratory pressure · Low tidal volume · Proportional assisted ventilation · Neurally adjusted ventilatory assist · Patient-ventilator synchrony · Neural trigger · Non-conventional ventilation

Introduction

Recently, effort has been expended to broaden the application of lung protective ventilation strategies in both the operating room and the pediatric and neonatal intensive care units. These efforts have resulted from an increasing body of evidence that demonstrated the beneficial effects of these strategies, even in children with normal lungs. Lung protective ventilation strategies include low tidal volume, moderate to high PEEP, alveolar recruitment maneuvers, and new modes of ventilation promoting noninvasive ventilation and supporting the spontaneous ventilation efforts of the patient. This “multimodal approach” aims to recruit, open, and protect the lungs, and has led to the “open lung” strategy, which has become the standard of care today in routine clinical practice. However, there is currently little evidence that these new strategies improve patient outcomes. In fact, many of these strategies remain contentious, particularly in terms of their potential to prevent VILI and to confer lung protection. In this review, we focus on the most recent evidence for the use of these ventilation strategies in children, including their advantages and limitations.

Lung Recruitment

“Open up the lung and keep it open” [1] has been advocated for two decades now. The rationale for this statement is the belief that VILI results primarily from the cumulative damage that occurs from the repeated opening and closing of collapsed alveoli. Therefore, applying this concept of open lung with low tidal volume ventilation would ensure alveolar recruitment without overdistension of non-collapsed regions of the lungs and excessive peak airway

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pressures, both of which are recognized determinants for lung injury during mechanical ventilation [2, 3]. To recruit collapsed alveoli, one should apply a sustained increase in airway pressure to reach the critical opening pressure necessary to open the collapsed alveoli. Once the alveoli are open, the application of a PEEP above the “critical level” for airway closure will maintain the open alveoli, and a reduced pressure would be required thereafter to ensure adequate gas exchange and, thus, a reduction in the shear forces [2]. Early publications suggested that the analysis of the pressure–volume (P – V) curve of the respiratory system might be an effective metric to optimize ventilation. It was believed that the lower inflection point of the P – V curve could be regarded as the critical level for alveolar recruitment, while the upper inflection point could be an indicator of alveolar overdistension [4]. However, recent studies demonstrated that alveolar recruitment is a continuum phenomenon that occurs along the entire inflation limb of the P – V curve. A superior correlation was found between alveolar de-recruitment and the deflation limb of the P – V curve [5, 6]. This finding may be explained by ventilation heterogeneity that has been observed in both healthy and injured lungs [7, 8].

While the most commonly used and investigated alveolar recruitment maneuver is the sustained inflation, new strategies such as prolonged or increasing PEEP, pressure-controlled ventilation with fixed PEEP and increased driving pressure, pressure-controlled ventilation applied with escalating PEEP and constant driving pressure, and long and slow increase in pressure have been reported in several clinical studies in adults [9]. Although all inflation maneuvers improve oxygenation by increasing the arterial oxygen tension, decreasing atelectasis [10, 11] and restoring end-expiratory lung volume, they differ in their effects to increase afterload on the right ventricle and thus, impair cardiac output [12, 13]. However, a recent systematic review on the hemodynamic effects of alveolar recruitment maneuvers performed in adult patients with acute lung injury demonstrated that hemodynamic instability was transient, and hypoxemia was self-limited without serious short-term sequelae [14]. This observation was also reported after the use of a sustained inflation in the pediatric intensive care setting [15]. However, the lack of evidence of the effects of various recruitment maneuvers on clinical outcomes and the lack of a consensus in the literature prevents us from recommending one technique over another. Nonetheless, the goal of the different methods to recruit alveoli is to inflate the lungs to near vital capacity, which corresponds to an airway pressure of 35–40 cmH₂O. The role of the time and the pressure–time product during the recruitment maneuver appears to be the most critical criterion [16]. Although a recent study suggested that only 7–8 s of sustained lung inflation are

necessary to re-expand the collapsed lung areas in adults [17], a very detailed investigation in rats suggested that 30–40 cmH₂O pressure for 30–40 s may be required to fully re-expand an atelectatic lung [18]. Nonetheless, maintaining a sustained inflation to recruit alveoli may actually be harmful to the lungs and circulation as well as to organs beyond the thorax [16]. In children with healthy lungs under anesthesia, alveolar recruitment maneuvers may be effective in restoring and maintaining adequate oxygenation and pulmonary compliance [10].

Evidence suggests that pro-inflammatory cytokines may be translocated into the systemic circulation after recruitment maneuvers [19•, 20]. Thus we should consider a recruitment maneuver each time we face derecruitment and loss in lung volume, such as after a ventilator circuit disconnect, endotracheal suctioning [21] or as a rescue maneuver to overcome severe hypoxemia in the presence of acute lung injury [9].

Applying “Optimal” PEEP Level

When considering a lung-protective ventilation strategy, it is essential to select the optimal PEEP level that maximizes alveolar recruitment, prevents lung damage from repetitive opening and closing of alveolar units and avoids alveolar overdistension. In addition, since infants have unique physiology that includes an imbalance between the inward elastic recoil of the lungs and the outward distending forces of the rib cage, airway closure occurs much more rapidly with subsequent decreases in functional residual capacity [22]. Derecruitment will be enhanced in the presence of sedation and anesthesia. Accordingly, administering PEEP even in children with healthy lungs is mandatory in order to counterbalance the heterogeneity in ventilation-induced airway closure. Many studies have highlighted the beneficial effect of PEEP in restoring end-expiratory lung volume in children after general anesthesia [11], and to counteract the atelectasis induced by oxygen resorption [23]. In children with diseased lungs, PEEP improves lung function and oxygenation and potentially reduces the duration of mechanical ventilation [24].

Evidence indicates that the PEEP that causes the maximum oxygen transport and the smallest dead-space fraction corresponds to the greatest total static compliance in children with lung disease [25]. However, setting the PEEP level based on the minimum inflection point of the static pressure/volume curve does not necessarily reflect the recruited alveolar regions because of ventilation heterogeneity both in healthy and diseased lungs. Thus, the optimal PEEP required to keep the alveoli inflated should be determined based on the deflation expiratory limb of the P – V curve [26, 27]. Some have recommended adjusting the

PEEP according to the level of oxygenation, but this could be hazardous as it may require overdistension of the alveoli in order to achieve the desired oxygen level [28]. Although computed tomography (CT) has been used to objectively assess lung aeration and regional ventilation, it is not a practical bedside technique for confirming alveolar recruitment [29–31]. Despite these physiological considerations, the choice of the optimal PEEP in clinical pediatric practice remains hotly debated.

After maximizing the dynamic lung compliance with an alveolar recruitment maneuver, a decrease in PEEP may be associated with progressive lung collapse as evidenced by the appearance of atelectasis on the CT scan and a decrease in oxygenation [32]. Continuous monitoring of the dynamic compliance may help to determine the point of optimal dynamic compliance, below which alveolar collapse begins to occur after a recruitment maneuver. This point may indicate the optimal PEEP. Another recent approach is based on the determination of the stress index, which is measured during constant flow ventilation (volume controlled) from the shape of the airway pressure (P_{aw}) versus time (t) curve. The stress index reflects the compliance of the lung and a value of 1 (P_{aw}/t curve straight) corresponds to the ventilation of a normal lung with a fixed compliance. In contrast, a stress index less than 1 (P_{aw}/t curve with downward concavity) occurs when compliance improves with time and suggests a need to increase the PEEP level [33•].

Future developments in monitoring technology will facilitate bedside measurements of end-expiratory lung volume, which in combination with estimates of compliance, will permit us optimize alveolar recruitment without overdistending alveoli [33].

Low Tidal Volume

“Protective ventilation” including the use of a small V_T at optimal lung volume is designed to protect against VILI [34]. Optimal PEEP will increase the lung volume. Adapting inspiratory (T_i) and expiratory times (T_e), will guarantee adequate lung inflation and deflation, respectively, particularly if T_i/T_e is adjustable on the basis of the time constants [22]. This ventilation strategy may lead to mild hypercapnia 6–7 kPa (45–52.5 mmHg), which is regarded as safe in the absence of increased intracranial pressure and pulmonary hypertension. Beside the beneficial effects of mild hypercapnia on cerebral perfusion and cerebral oxygen saturation, it enhances subcutaneous tissue oxygenation [35] and reduces the affinity of hemoglobin for oxygen thereby increasing the delivery of oxygen to tissues [36]. Hypercapnia may also enhance hypoxic pulmonary vasoconstriction and improve ventilation/perfusion

matching. However, when hypercapnia is undesirable (as in the case of pulmonary hypertension, or compromised hemodynamic status), the lung-protective strategy with reduced tidal volumes can be best achieved using high-frequency oscillatory ventilation (HFOV). The latter represents the ultimate mode of ventilation in which a large lung volume is maintained in the presence of small oscillatory tidal volumes. Despite its theoretical and physiological advantages, there has been no evidence that HFOV is superior to conventional ventilation as a primary or rescue mode to ventilate the lungs of infants with acute pulmonary dysfunction [37, 38].

New Modes of Ventilation

Proportional-assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA) are two new modes of mechanical ventilation that are based on the physiological concept of respiratory variability [39]. Both modes proportionally unload the ventilatory effort of the child and prioritize patient control of the ventilatory pattern thus limiting diaphragmatic dysfunction and contributing to the lung-protective strategy. Conceptually, these non-conventional modes or proportional modes of mechanical ventilation are based on the fact that the airway pressure is proportional to either the pressures of the muscles of inspiration (PAV) or the electrical diaphragmatic activity (EA_{di}) in NAVA. In both ventilator modes, pressure, flow, volume and inspiratory time are not controlled. All variables are controlled by the child thereby improving synchrony between the child’s respiratory effort and the ventilator.

PAV

PAV is a pressure support mode that involves an algorithm that is based on the equation of motion of the respiratory system. This equation describes the relationship between the total airway pressure and the respiratory compliance and resistance as follows:

$$P_{total} = (V_T)(E_{rs}) + (V')(R_{rs}) + PEEP_{total}$$

where E_{rs} and R_{rs} are the elastance and the resistance of the respiratory system, V_T and V' are the tidal volume and flow, $PEEP_{total}$ reflects the sum of the extrinsic and intrinsic PEEP, and total pressure (P_{total}) includes the airway and the muscle pressure, respectively. In the PAV mode, the ventilator continuously measures the resistance and elastance of the total respiratory system and then delivers a pressure that is proportional to the instantaneously measured flow and tidal volume and to the pressure generated

by the respiratory muscles. The proportionality factor or “PAV gain” is set by the physician in order to balance the two components of P_{total} , namely the airway pressure generated by the ventilator and the child’s muscle pressure, which can be calculated from the equation of motion. The PAV gain will allow automatic adjustment of the flow and tidal volume based on the child’s efforts and demand. However, in the PAV mode, the child must generate a sufficient flow to trigger the ventilator, and therefore the child cannot be heavily sedated. The support is only provided during the inspiratory effort, and thus has the potential to improve the effect of respiratory muscle effort on ventilation. Moreover, PAV improves both the timing synchrony and flow synchrony by permitting adaptation of the amplitude and the slope of the ventilatory flow assist. However, some limitations for the correct functionality of PAV mode have to be considered in the presence of dynamic hyperinflation or a delay of the inspiratory trigger due to the presence of an auto-peep (intrinsic end-expiratory pressure).

While this mode has been proven to reduce the duration in ventilatory support in adults, there is a dearth of studies on the usefulness and feasibility of PAV in children. Early studies demonstrated that PAV reduces the transpulmonary pressure requirements [40], and a recent report confirmed that PAV maintains gas exchange at reduced mean airway pressures [41] in preterm infants. However, PAV is currently limited to children greater than 20 kg in weight, primarily because of difficulties in measuring the mechanical parameters in infants.

NAVA

NAVA is used in invasive and non-invasive settings of ventilation. It provides proportional pressure support that relies on detecting the electrical activity of the diaphragm and therefore coordinating the child’s respiratory neural drive with the ventilator. More precisely, NAVA mode delivers a pressure which is proportional to the electrical activity of the diaphragm (EA_{di}) that is recorded through electrodes integrated in a nasogastric tube. By extrapolation, NAVA may be regarded to be proportional to the neural output of the child’s respiratory center. Therefore, this mode needs an intact ventilator drive and intact respiratory breathing reflexes. The neuro-ventilatory coupling determines the entire breathing cycle [42].

The EA_{di} signal depends on the frequency and the intensity of the diaphragmatic muscular activity. An algorithm filters the electrical signals of the heart, oesophagus and other muscles from the input. The amplified and filtered signal is then used to synchronize the ventilator. The EA_{di} signal triggers the timing of the ventilator breath and

the pressure delivery (P_{aw}), which is an amplification of the EA_{di} according to the following equation:

$$P_{\text{aw}} = \text{NAVA level} \times EA_{\text{di}}$$

The amplification factor, “NAVA level”, is set by the physician and is expressed as the proportionality constant in $\text{cm H}_2\text{O}/\mu\text{V}$. When using this mode, physicians face two major challenges, correct positioning of the electrodes and titration of the NAVA level. Mechanical inflation commences according to a set deflection threshold of the EA_{di} signal (usually $0.5 \mu\text{V}$). EA_{di} signals vary among individuals as there are no existing normal values. The EA_{di} signal is variable among healthy individuals and according to the physiological reserve available for the neuro-ventilatory coupling. For instance, a large EA_{di} signal in patients with respiratory insufficiency can be regarded as a sign of their reduced respiratory reserve. The EA_{di} signal may also vary with the stages of a disease and thus, the monitoring of the EA_{di} signal may be a surrogate for diaphragmatic activity and help physicians monitor the course of a disease and ease the weaning from the ventilator.

The specificity of the ventilation with NAVA stems from the EA_{di} itself, which triggers the inspiratory effort. Thus, the delivered pressure is synchronous with the diaphragmatic activity. Termination of the inspiration is driven by a decrease in EA_{di} : with the expiratory valve opening when the EA_{di} signal has decreased to 40–70 % of the peak EA_{di} signal. Therefore, the tidal volume during the NAVA ventilation is completely controlled by the child, and more specifically by his or her respiratory center. The resulting breath-to-breath variability in the EA_{di} signal leads to variability in the tidal volume and promotes the NAVA as a protective and enabling patient-ventilator synchrony. Finally, since NAVA is independent of measuring airway pressure or flow, it detects and assists inspiratory efforts even in the presence of leaks or intrinsic PEEP.

The important issue of setting the NAVA level is still debated in the literature. The current setting proposals are either based on using the electromyographic activity of the diaphragm or by performing an empirical titration procedure. Moreover, most studies that address this issue were performed in adults, with few investigations of similar nature having been undertaken in children. Some authors have suggested that the EA_{di} target should be 60 % of the largest EA_{di} value recorded during spontaneous breathing [43]. Recently, it was suggested that the EA_{di} be titrated to the airway pressure (P_{aw}). This involves increasing the NAVA level in a stepwise manner by $1 \text{ cmH}_2\text{O}$ increments and when the P_{aw} response observed in a trend graph change from a steep to a less steep increase (i.e., blunted gain in P_{aw} and tidal volume), indicates the optimal NAVA

level [44•]. Very recently, increasing the levels of assistance during NAVA ventilation may identify a threshold above which we observe a small increase in tidal volume and an increase in child's variability of EA_{di} and consequently V_T [45].

There are several safety mechanisms integrated to the ventilator, which allows a switch to pressure support ventilation if insufficient EA_{di} signal is detected, or to pressure control ventilation if there is no spontaneous respiratory drive detected from the child. In addition, monitoring the EA_{di} signal may give important information on child's respiratory activity and on the integrity of the neuromuscular connection from the respiratory center to the diaphragm, and thus may be an important help in the weaning process.

Improving Patient-Ventilator Synchrony

Both PAV and NAVA ventilation modes are patient-driven ventilatory assist modes with the aim of improving patient-ventilator synchrony. Both can be applied during invasive or non-invasive ventilation [46]. However, unlike PAV for which studies regarding the advantages of this technique in neonates and infants are still lacking, NAVA improves synchrony even in this small age group and has wider application in premature neonates and small infants [47, 48].

The ultimate aim of patient-ventilator synchrony is to avoid lung overdistension and integrate the physiological concept of respiratory variability in the ventilation mode, which has the potential to decrease the sedation requirements and increase the patient's comfort. Nevertheless, several conditions impede patient-ventilator synchrony during mechanical ventilation, such as the presence of intrinsic PEEP, dynamic hyperinflation, and auto-triggering due to a too-sensitive inspiratory trigger or air leaks in the ventilator circuit or the interface. In this regard, NAVA is superior to PAV in adults and children in improving patient-ventilator interaction, unloading respiratory muscles and preventing excessive lung distension [49–52]. One of the main reasons for improved synchrony during NAVA ventilation is the presence of a markedly reduced inspiratory trigger delay and an efficient expiratory cycling-off. Since ventilation of neonates and prematurely born infants is characterized by a rapid respiratory rate and fluctuation of the respiratory system compliance, better synchronization should have a greater advantage in this age group [53]. Accordingly, preliminary data in which NAVA was compared to conventional ventilation modes (pressure support ventilation and pressure support with volume guarantee) in very-low-birth-weight infants showed a good correlation between EA_{di} and ventilatory airway pressure and an

improved patient-ventilator synchrony that persisted after extubation [54].

The greater advantage of NAVA to improve patient-ventilator synchrony in children was confirmed in a crossover comparative study between three different trigger modes during their weaning phase [55]. If NAVA was applied in children with documented asynchrony (i.e., auto-triggering, double triggering or non-triggered breaths), the frequency of major asynchronous events was reduced, inspiratory trigger synchronization improved and neural drive to trigger the ventilator with NAVA decreased, which led overall to a decrease in psychological distress as assessed with the COMFORT scale [56•].

Another important feature of this synchrony is the lung protective potential of these modes in providing an assisted ventilation with a lower peak airway pressure and avoidance of lung overdistension. The advantages of NAVA in this regard have been demonstrated in several studies in children [52, 55, 57]. A prospective crossover study in which NAVA (neural trigger) was compared to pressure support ventilation (pneumatic trigger) demonstrated reduced peak airway pressures with the NAVA mode and elements for a lung protective effect [52]. This effect may be attributed to the downregulation of EA_{di} in case of high NAVA level. As EA_{di} diminishes, Paw and V_T will not increase. This phenomenon may be attributed to the Hering-Breuer reflex that reduces the output from the respiratory control center at a same V_T level. Thus, NAVA seems to decrease the risk for over-assistance since V_T remains under the control of the child's central respiratory command. The child adapts his inspiratory activity to the NAVA level in order to control V_T and to regulate $PaCO_2$ [58]. This persistence of the ventilatory adaptation under NAVA can be further demonstrated under extracorporeal membrane oxygenation where after downregulation of extracorporeal gas transfer, an immediate upregulation of ventilation was observed [59].

Despite the improved synchrony obtained in children with NAVA ventilation mode, there are still clinical situations where it wouldn't be suitable to let the child's respiratory centers to drive the ventilation. Such conditions can be observed for instance in the presence of severe metabolic acidosis where high respiratory drive would induce hyperventilation and possible lung damage.

Conclusion

Despite an increasing body of evidence that demonstrated the usefulness of lung protective ventilation strategy on a short-term basis, few studies have addressed the long-term effects on children's outcome. Most data are extrapolated from the adult literature, and randomized controlled studies

investigating the different strategies as well as the different ventilation modes are scarce. Ventilating with a low tidal volume cannot be considered without considering the open-lung strategy, which protects from the shear stress alveolar injury induced by repetitive opening and closure of closed alveolar units. However, alveolar recruitment may be harmful and should only be considered when facing a loss in lung volume. This approach is associated with the application of optimal PEEP, which should coincide with the best lung compliance. Finally, in comparison with various assisted ventilation modes, NAVA has been shown to offer a greater advantage to patient–ventilator synchrony and to reduce the risk for overventilation thus, contributing to the lung protective effect compared with conventional ventilation. An improved synchrony in children could also mean reduced doses of sedation and time of mechanical ventilation.

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