

Less Invasive Mechanical Ventilation Strategies in ARDS: the Future?

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ABSTRAK

Penanganan ventilasi mekanik yang sangat berhasil terakhir kalinya adalah di tahun 2000, yakni ketika pemakaian volume tidal rendah dan tekanan sedang diperkenalkan. Hal ini kemudian diikuti oleh konsep paru terbuka dan paru bayi (*open- and baby-lung concept*) untuk membuka paru-paru dan menjaga agar paru-paru tetap terbuka. Meskipun demikian, strategi-strategi tersebut diikuti oleh sejumlah efek samping. Oleh karena itu, sejumlah penelitian dilakukan untuk meningkatkan keluaran atau hasil ventilasi mekanik dengan strategi yang kurang invasif. Kajian ini bertujuan untuk meringkas konsep terkini mengenai ventilasi mekanik yang kurang invasif.

Kata kunci: NIV, NAVA, ventilasi mekanik, kajian, ECMO, ventilasi paru terbuka.

ABSTRACT

The last very-successful management of mechanical ventilation was in 2000 when application of low tidal volume and moderate pressure was introduced. It was then followed by the *open- and baby-lung concept* in order to open up the lung and keep the lung open. However, these strategies are followed with several adverse effects. Therefore, studies were performed in order to improve the outcome of mechanical ventilation with less invasive strategy. This review aims to summarize recent concept of less invasive mechanical ventilation.

Key words: NIV, NAVA, mechanical ventilation, review, ECMO, open lung ventilation.

INTRODUCTION

Already in 2000, it was shown that mechanical ventilation with low tidal volume (6 ml/kg) was superior to high tidal volume (12 ml/kg) in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).¹ This result was somewhat surprising that mechanical ventilation with smaller tidal volume could reduce mortality rate. The most common cause of death in these patients is multiple organ failure (MOF). High tidal volume ventilation in the presence of atelectasis, as seen in patients with ALI/ARDS, leads to over distention of the 'healthy' aerated

lung regions causing barotrauma and volutrauma, and this provokes biotrauma by the sign of lung inflammation with the release of cytokines and mediators. This inflammatory response is called ventilator-induced lung injury (VILI), and leads to a higher mortality rate.¹⁻⁵

This low tidal volume ventilation is nowadays called protective mechanical ventilation but the question arises if this can also be achieved by other methods, such as better patient-ventilator synchrony during support or non-invasive ventilation. In addition, low tidal volume with high positive end expiratory pressure (PEEP)

levels after a recruitment maneuver (RM), the so-called open lung strategy, high frequency oscillation, and the use of venous venous extracorporeal membrane oxygenation (vv-ECMO) have been investigated in order to prevent VILI in patients with acute respiratory failure. In this review we summarized the recent literature with respect to these new concepts of protective mechanical ventilation.

SEARCH STRATEGY

We used PubMed to search clinical trials and Meta analysis publications in adult to elderly subjects with keyword of “mechanical ventilation”. We used the following key words: patient-ventilator synchrony, non-invasive ventilation, protective ventilation strategy, recruitment maneuver, prone position ventilation, high frequency oscillation and ECMO. We used two highlights studies: the ARDS network trial and the baby-lung concept.

OPEN LUNG VENTILATION

The open lung concept which was introduced in Rotterdam is a method of ventilation intended to maintain end-expiratory lung volume by increased airway pressure to reduce shear forces caused by repeated opening and closing atelectatic lung. This is done by a recruitment maneuver and application of sufficient PEEP to counterbalance retractive forces, and with ventilation with the smallest possible pressure amplitude to prevent lung overdistention.⁶ Studies in which higher PEEP levels were used showed improved oxygenation and compliance but could not further reduce mortality rate.^{2,7,8} A multicenter study of 767 adults with ALI in 37 ICU in France was conducted to compare the effect of moderate PEEP (5-9 cm H₂O) to a level of PEEP set to reach a plateau pressure of 30 cm H₂O.⁸ They concluded that a strategy for setting PEEP aimed to increase alveolar recruitment while limiting hyperinflation improved lung function and reduced the duration of mechanical ventilation.⁸ The advantage of this method is that PEEP is titrated in each patient and is changed over time during lung function improvement. However, patients with the lowest compliance will receive lower levels of PEEP with this

method because the plateau pressure will reach its maximum of 30 cm H₂O earlier at lower compliance. Recently, two meta-analysis which included over 3500 patients with ALI or ARDS have shown that moderate level of PEEP is superior in patients with ALI, whereas high PEEP levels are superior in patients with ARDS.^{9,10} It is shown that PEEP levels of 15.3±3.4 cm H₂O were applied in the higher PEEP group and 9.0±3.1 cm H₂O in the lower PEEP group on the first day.¹⁰ This indicates that for ARDS one should start with a PEEP of around 15 and for patients with ALI with a PEEP of 9 cm H₂O.

Hodgson et al. performed a randomized control trial in 20 patients with ARDS. In the study group a recruitment maneuver (RM) was performed with a constant driving pressure of 15 cm H₂O, and stepwise increase of PEEP from 20 to 30 and 40 cm H₂O, each for two minutes.¹¹ After the RM, PEEP was reduced to 25, 22.5, 20, 17.5 and 15 cm H₂O every three minutes but was stopped if SaO₂ decreased by more than 1% from its maximum. Gas exchange and lung compliance were measured daily for 7 days and plasma cytokines in the first 24 hours up to 7 days. The study group had lower plasma levels of IL-8 and TNF- α compared to controls that were treated according to the ARDS network trial.¹¹ Recently, de Matos et al¹² studied a RM together with an optimal PEEP strategy based on computed tomography (CT) in 51 severe ARDS patients. A standardized recruitment maneuver (RM) was performed in which the patient was pressure controlled and ventilated with a constant driving pressure of 15 cm H₂O, and followed by stepwise increase of PEEP from 10 to 45 cm H₂O. After this RM, PEEP was decreased from 25 to 10 cm H₂O by steps of 5 cm H₂O, and after each step a lung CT was performed. Thereafter, the patients were transported to the ICU and after the same RM, they were ventilated for 48 hours with this optimal PEEP. After two days, PEEP was decreased in steps of 2 cm H₂O every 8-12 hours and when PEEP was below 20 cm H₂O, sedation was reduced and controlled ventilation was switched into support ventilation. Weaning from mechanical ventilation was started at pressure support and PEEP level of <10 cm H₂O. In these severe ARDS patients

the opening pressure was 59.6 (± 5.9 cm H₂O), and the optimal PEEP was 24.6 (± 2.9 cm H₂O). The PaO₂/FiO₂ ratio was kept above 300 mmHg throughout the first seven days, otherwise a RM was performed. They concluded that RM could efficiently reverse hypoxemia and most of the collapsed lung tissue and this could be prevented by the use of relatively high PEEP levels titrated for individual patient. This strategy should be tested in a prospective randomized clinical trial.

RECRUITMENT MANEUVER

The application of RM during mechanical ventilation remains controversial. It is an invasive technique, which is still considered to open up collapsed lung tissue, but the opening pressure is different per patient with risk for barotrauma. However, the ideal RM remains unknown. In a sepsis-induced ALI model, RM with a sustained insufflations was compared to gradual increases in airway pressure.^{13,14} The sustained inflation was performed with a pressure of 30 cm H₂O for 15 or 30 seconds. The gradual increase was performed by steps of 5 cm H₂O, 2.5 seconds per step, to a maximum airway pressure

of 30 cm H₂O for 15 or 30 seconds. (**Figure 1**) It was shown that the gradual increase in airway pressure with a sustained insufflation for 30 seconds was superior in improving lung function with less cytokines on the lung compared to the other RM settings.¹³

In a small study of 12 mechanically ventilated ALI or ARDS patients, two different recruitment strategies were applied: plateau pressure of 40 cm H₂O for 30 seconds and a sigh (twice the standard tidal volume) every 25 breaths.¹⁵ It was shown that a sigh superimposed on lung-protective mechanical ventilation was superior in improving arterial oxygenation.¹⁴ In a population of 110 ARDS patients, the 40 by 40 RM (40 cm H₂O for 40 seconds) was performed every eight hours during the first five days.¹⁶ Patients that received a RM had significantly higher oxygenation and significantly lower ICU mortality rate (32.7% vs 52.7%, $P=0.003$) compared to patients without a RM. In another study in patients with ARDS, a sustained inflation (45 cm H₂O for 40 seconds) was compared to a RM that consisted of mechanical ventilation at higher airway pressures only for 2 minutes

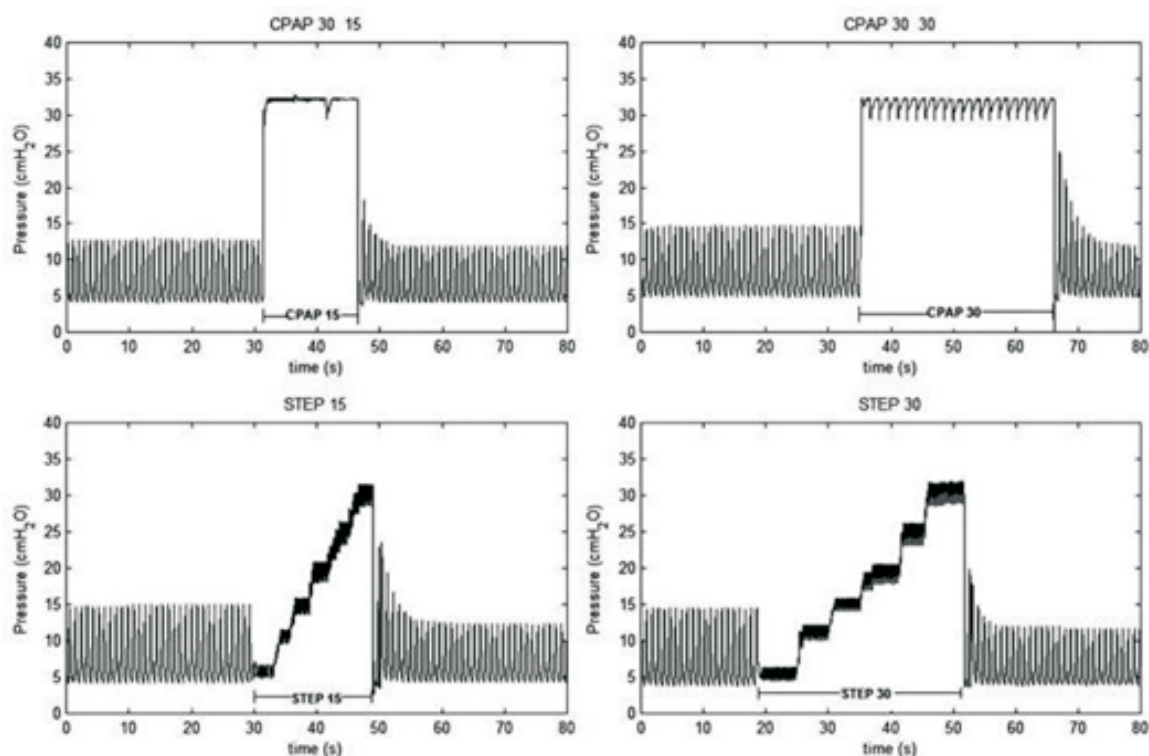


Figure 1. Representation of four recruitment maneuvers: 1) continuous positive airway pressure (CPAP) for 15 secs; 2) CPAPA for 30 secs; 3) stepwise increase in airway pressure (STEP) to reach 30 cmH₂O within 15 secs; and 4) STEP within 30 secs.¹³

(peak inspiratory pressure of 45 cm H₂O, I/E ratio of 1:2, PEEP level of 16 cm H₂O, and RR of 8 breaths/minute).¹⁷ It was shown that the RM with mechanical ventilation at higher pressures resulted in better oxygenation with less adverse hemodynamic effects than a sustained inflation.¹⁷

PATIENT-VENTILATOR SYNCHRONY

In 340 mechanically ventilated ARDS patients it was shown that the use of neuromuscular blocking agent just for the first two days during volume-controlled mechanical ventilation increased survival and ventilator free days within the first month without increasing muscle weakness compared to a control group without muscle relaxation.¹⁸ However, the mechanisms underlying this beneficial effect remain uncertain. The number of pneumothoraces and barotrauma was significantly higher in the control group (12 vs 5%), suggesting better patient-ventilator synchrony in the study group that received muscle relaxation during the first two days.¹⁸ It suggests that the use of muscle relaxant during the early application of controlled mechanical ventilation may contribute in better synchrony.

In 2008, Levine and his colleagues¹⁹ evaluated the diaphragms of brain-dead organ donors who underwent controlled mechanical ventilation for 18 to 72 hours before organs could be removed. It was shown that this period of controlled mechanical ventilation was associated with atrophy of myofibers of the diaphragm, which could be an important risk factor for delayed weaning.²⁰ Strøm and colleagues have demonstrated that omitting sedation in critically ill patients receiving mechanical ventilation resulted in four days reduction of ventilation and 23 days shorter stay in the hospital compared with standardized daily interruption of sedation.²¹ This result is exceptional and may suggest that optimal patient-ventilator synchrony is of particular importance.

Patient-ventilator asynchrony is commonly seen in mechanically ventilated patients. Neurally adjusted ventilatory assist (NAVA) has been developed to improve patient-ventilator synchrony. NAVA requires the introduction of a special gastric tube to measure the electrical activity of the diaphragm (EAdi). NAVA

relies on the EAdi to trigger the ventilator breath and to adjust the ventilatory assist to the neural drive.²² In 14 patients with chronic obstructive pulmonary disease (COPD), it has been demonstrated that breathing pattern and arterial blood gases were comparable between NAVA and pressure support ventilation (PSV), but NAVA reduced the delay of ventilator triggering and cycling and abolished wasted inspiratory efforts that was observed with PSV.²³ This was confirmed in 22 intubated spontaneous breathing patients with acute respiratory failure in which NAVA significantly reduced total asynchrony events without ineffective effort or late cycling compared to PSV.²⁴ Therefore, NAVA has become an alternative method of support ventilation to improve patient-ventilator synchrony and maybe its outcomes. This latter should be studied.

NON INVASIVE VENTILATION

During non-invasive ventilation (NIV), asynchrony occurred in 43% of patients, which was mostly related to leakage.²⁵ It has been suggested that this asynchrony may contribute to its high failure rate when it is used after extubation (up to 40%).²⁶ The use of NIV in the management of ALI/ARDS is controversial. A meta-analysis²⁷ showed a 50% failure rate of NIV in patients with ALI/ARDS. It was concluded that NIV should be used cautiously in these patients.²⁷ However, a randomized controlled trial was performed in 106 mechanically ventilated patients after successful spontaneous breathing trial to investigate the effectiveness of NIV after extubation in hypercapnic patients. It was shown that respiratory failure was less frequent in patients assigned with NIV than in those allocated conventional oxygen therapy (15% vs 48%), and NIV avoided re-intubation in 17 of 27 patients when it was used as rescue therapy. Furthermore, NIV was associated with lower 90-day mortality rate compared to patients assigned with conventional oxygen therapy.²⁸ A meta-analysis and systematic review on 12 trials enrolling 530 participants, mostly with COPD, found that non-invasive weaning was significantly associated with reduced mortality, ventilator associated pneumonia, length of stay in

intensive care unit and hospital, total duration of ventilation, and duration of invasive ventilation compared with invasive weaning.²⁹ Recently, NIV with the special gastric tube of NAVA has been introduced that enables diaphragmatic triggered breaths and allow leakage of the mask. We believe that this new technique will further improve the application of NIV in patients with respiratory failure but data is missing at this moment.

HIGH FREQUENCY OSCILLATION (HFO)

In the mid 80's, both high frequency oscillation (HFO) and exogenous surfactant therapy were introduced in the treatment of neonates with severe respiratory distress syndrome. HFO was performed at frequencies of 10-15 Hz (1Hz=600 breaths/min) with low mean airway pressures of around 6 cm H₂O and pressure amplitudes of around 25-30 cm H₂O, leading to tidal volumes of 1-4 ml/kg. Exogenous surfactant therapy was very successful but surprisingly HFO was not. It became clear that HFO is beneficial only when applied at higher mean airway pressure (15–20 cmH₂O), the so-called 'open lung strategy'. Thus, in neonates with RDS a RM is applied by increasing the distending pressure (mean airway pressure) to 20-24 cm H₂O and thereafter reduced to around 16-18 cm H₂O and ventilated at high frequencies (10-15 Hz). After increasing the power of the oscillators, this ventilation strategy has been used in adults with ALI or ARDS.³⁰ A meta-analysis of eight small studies in which HFO was used as an initial ventilation strategy (within 48 hours of diagnosis) for ALI or ARDS, enrolled a total of 431 patients, and found that HFO significantly reduced mortality rate (risk ratio 0.77, 95% confidence interval 0.61 to 0.98, P=0.03).³¹ Most included studies did not use protective ventilation strategy with low tidal volume and maximal plateau pressure in the controls. Therefore, two multi-center trials (Oscar trial in UK and Oscillate trial in Canada/USA) are started in which the effect of HFO on mortality rate is studied in comparison with low tidal volume protective ventilation in the treatment of adults with ARDS.

PRONE POSITION

Prone position is mostly used as rescue therapy but its use is limited by the controversial results on outcome. The timing of initiation, schedule of turning and the position of the patient in prone position is still a matter of debate. In addition, safety data from randomized trials showed infrequent local complications (e.g., facial edema, conjunctiva hemorrhage, and pressure ulcers) and those attributed to turning (e.g., dislodging of catheters and endotracheal and thoracostomy tubes).³²

The prone position could also be used as a method of recruitment maneuver by lowering the critical opening pressure with avoidance of the use of high airway pressures. This can be explained by different mechanisms: (a) the weight of the abdominal contents and heart is now at the bottom and will not compress the underlying lung tissue; (b) the dependent part of the lung is now at the top and edema fluid is floated to the underlying non-dependent parts (c) changes in regional ventilation-perfusion ratio.³² Therefore, change from supine to prone may decrease shunting and thereby improve oxygenation.

A multicenter, unblinded, randomized controlled trial conducted in 23 centers in Italy and 2 in Spain investigated the possible outcome benefits of prone positioning with moderate and severe ARDS. Patients were randomized to undergo supine (n = 174) or prone (20 hours per day; n = 168) positioning during ventilation. It was reported that prone and supine patients from the entire study population had similar 28-day (31.0% vs 32.8%) and 6-month (47.0% vs 52.3%) mortality rates, despite significantly higher complication rates in the prone group. It was concluded that prone positioning does not provide significant survival benefit in patients with ARDS or in subgroups of patients with moderate and severe hypoxemia.³³ However, two recent meta-analyses have been performed and found beneficial results if prone position was applied in the most severe patients. It improved oxygenation, decreased the incidence of ventilator-associated pneumonia and resulted in the reduction of mortality rate by 10% in severe ARDS but not less severe ARDS, the so-called

ALI patents.^{34,35} Therefore, prone position could be used as a method of recruitment maneuver to improve oxygenation in severe ARDS patients.

ECMO

Eventhough ventilation strategy with low tidal volume has been shown to be effective in improving survival, unfortunately some patients with severe ARDS cannot be managed with this strategy, especially in keeping plateau airway pressure below 32 cm H₂O. In these patients, extracorporeal devices have been applied with the goal to lower tidal volume ventilation and allowing airway pressure within the limits in order to minimize VILI. Extracorporeal devices exchange only the CO₂ when the flow through the system is limited to 25% of cardiac output, such as the pumpless extracorporeal lung assist (PECLA) and the DECAP system that uses an external pump with a maximum flow of 400 mL/min. In contrast, extracorporeal devices that use an external pump to generate flow near normal cardiac output (>3 Liter) will not only ventilate but also oxygenate a patient. These latter systems are normally used during cardiac surgery and for acute cardiac failure as a bridge

to transplant. For respiratory failure, nowadays venous-venous cannulas have been introduced as long as cardiac function is appropriate (**Figure 2**). This method has been used during the H1N1 pandemic and improved survival without serious complications.³⁶⁻³⁸

A multi centered randomized controlled trial (CESAR) was performed on extracorporeal membrane oxygenation (ECMO) vs. protective ventilation (as control) in 180 severe respiratory failure patients. The randomized ECMO patients were transferred to a center for consideration of ECMO. This study reported that the treatment of ECMO significantly increased survival without severe disability, while only half of total patients of the control group survived up to 6 months.³⁹ However, the controls received conventional management in their own hospital whereas the patients in the study group were transferred to a specialized respiratory center with ECMO facilities. It is known that ECMO is associated with major bleeding complication (in 10-30% of the patients), but this complication can be managed by reducing the heparin infusion, optimizing native coagulation status or direct surgical control.⁴⁰ Despite the inherent

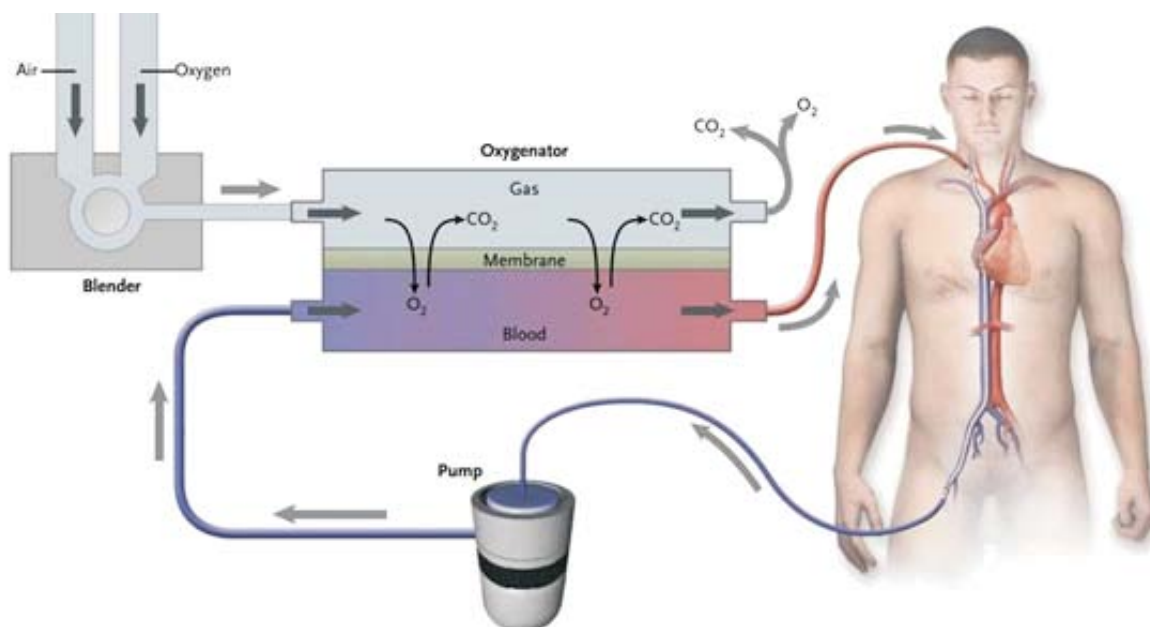


Figure 2. The oxygenator in Venovenous ECMO. The extracorporeal membrane oxygenation pump delivers venous blood to the oxygenator. This device is divided into two chambers by a semipermeable membrane. The venous blood enters the oxygenator and travels along one side of the membrane, while fresh gas, is delivered to the other side. Gas exchange takes place across the membrane. The oxygenated blood is then reinfused into the patient's venous system. The composition of gas on the gas side of the oxygenator membrane is determined by adjustment of a blender that mixes room air with oxygen delivery into the oxygenator.³⁸

limitations of the methodology of the CESAR trial, the results support the use of ECMO in appropriately selected patients with life threatening acute respiratory failure.⁴⁰ Although ECMO has shown to be beneficial in improving oxygenation at low tidal volume ventilation, its increased risk for complications from the invasive technique but also the high costs must be taken in the considerations.

CONCLUSION

Since 2000, the ventilation strategy in treating ALI or ARDS patients has been low tidal volume in order to avoid VILI, due to the change from deep to light sedation of our patients nowadays, the invasive controlled mechanical ventilation strategy has now changed into support ventilation strategies with better patient-ventilator synchrony. However, it is unknown if we should maintain the strict limits of tidal volume of 6 ml/kg and plateau pressure below 30 cm H₂O also during support ventilation. In addition, the level of PEEP is still a matter of debate but the use of high levels of PEEP in the more severe ARDS patients is now more or less accepted. Within the next coming years, the application of NIV and NAVA in awake ARDS patients should be considered but also the use of ECMO treatment as rescue therapy will be performed more frequently.

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