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Novel approaches to minimize ventilator-induced lung injury

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ABSTRACT

Purpose of the review

To discuss the mechanisms of ventilator-induced lung injury and the pro and cons of the different approaches proposed by literature to minimize its impact in patients with acute respiratory distress syndrome (ARDS).

Recent findings

Mechanical ventilation is indispensable to manage respiratory failure. The evolution of knowledge of the physiological principles and of the clinical implementation of mechanical ventilation is characterized by the shift of interest from its capability to restore "normal gas exchange" to its capability of causing further lung damage and multisystem organ failure.

Summary

If one of the essential teachings to the young intensivists in the 80s was to ensure mechanical ventilation restored being able to immediately drain a pneumothorax (barotrauma), nowadays priority we teach to young intensivists is to implement "*protective*" ventilation to protect the lungs from the pulmonary and systemic effects of ventilator-induced lung injury (biotrauma). At the same time priority of clinical research shifted from the search of optimal ventilator settings (best PEEP) and to the evaluation of "*super-protective*" ventilation that integrating partial or total extracorporeal support try to minimize the use of mechanical ventilation.

Keywords

ARDS, ventilator-induced lung injury, respiratory mechanics, low tidal volume, ultra-protective mechanical ventilation.

INTRODUCTION

Even if mechanical ventilation remains the cornerstone of treatment for respiratory failure, it is now clear that it can itself aggravate or cause lung damage inducing the so call Ventilator Induced Lung Injury (VILI) through a variety of mechanisms.

The main mechanical determinant of VILI is regional lung over-distention due to high trans-pulmonary pressure (stress) that causes the lung to deform above its resting volume (strain).[1]

In experimental models, VILI has been found to develop when a lung strain (estimated as the ratio between lung volume change and resting volume) greater than 2 is achieved, corresponding to a TV approximately greater than 20 ml/kg in healthy animals.[1, 2] Thus, the smaller the resting lung volume, the greater the strain for a given lung volume change (inflation).

But low lung volume ventilation may also be deleterious, due to regional amplification of forces and repetitive opening and closing of distal, collapsed lung units (atelectrauma).[3, 4] This condition has been advocated to provide augmented pulmonary injury when tidal ventilation starts below and ends above the lower inflection point on the P/V curve, as compared to ventilation starting above the lower inflection point.

The biotrauma concept relies on the hypothesis that lung tissue stretching might result in lung epithelium damage through the release of inflammatory mediators and leukocyte recruitment. Two mechanisms are believed to be responsible for this mechanical ventilator induced inflammatory response. The first is direct trauma to the cell with disruption of cell walls, resulting in the release of cytokines into both the alveolar space and the systemic circulation.[5] Regarding the second, *in vitro* studies have shown that most pulmonary cells can produce cytokines in response to cyclic stretch. [6]

Ranieri and coworkers were the first to suggest that the mechanical ventilator induced inflammatory response may contribute to development of multiple system organ dysfunction seen in mechanically ventilated patients with ARDS by initiating or propagating a malignant, systemic inflammatory

response.[7] Although it remains unclear how inflammatory mediators exert their detrimental effects on distal organs, experimental studies and clinical trials in ARDS have shown that the application of protective ventilator strategies are associated with decreased serum cytokine levels,[8, 9] decreased extrapulmonary organ dysfunction [7]and decreased mortality.[10]

Many factors contribute to the development of VILI: the type, duration, intensity of physical forces generated by the ventilation (volume and pressure) as well as the etiology, timing of lung injury and the general progression of the disease and a large number of trials reported the clinical efficacy of a "*protective*" ventilatory strategy based on the reduction of tidal volume to 6 ml/Kg of ideal body weight and the limitation of end-inspiratory pressure to 30 cm H_2O.

However, these recommendations are challenged by results of recent studies showing that (1) patients with ARDS may be exposed to forces which can induce injurious ventilation despite values of Pplat of 30 cm H_2O or less;[11-13] (2) impairment of chest wall mechanics compromises the ability of Pplat to reflect overdistension.[1, 14, 15]

In the present paper, we will discuss the pro and cons of the different approaches proposed to minimize ventilatory induced lung injury in patients with ARDS.

"PROTECTIVE" VENTILATORY STRATEGIES

Different approaches have been proposed to minimize ventilatory induced lung injury in patients with ARDS:

Low Tidal Volume

Experimental and clinical data showed that a reduction of tidal volume reduced mortality in ARDS ventilated patients [10, 16, 17] but controversy exists regarding the extent to which TV should be reduced to protect the lungs from VILI.

The ARDS*net* study demonstrated that a 22% reduction in mortality could be obtained by using a TV of 6 ml/kg predicted body weight (PBW) instead of 12 ml/kg PBW.[10] But it's still debated

whether the tidal volume should be strictly set to 6 ml/kg PBW in all patients with ARDS, since the resulting strain will depend on the amount of ventilated tissue rather than on PBW.[11]

The development of tools for measurement of the amount of lung open to ventilation at bedside might allow for individual adjustment of TV. These include promising non-invasive imaging methods, such as electrical impedance tomography and lung ultrasound, but also functional dynamic indexes, such as the stress index, which describes the shape of the airway pressure-time curve profile and may indicate tidal recruitment or tidal over-distension.[18] Off note, patients with ARDS often "fight the ventilator," and this may aggravate VILI. [19] In a recent multicenter, placebo controlled, randomized trial involving 340 patients with ARDS and a PaO_2 : FiO_2 ratio of less than 150 mm Hg, Papazian et al. [20]found that the adjusted 90 day mortality was lower among those who received a neuromuscular blocking agent for 48 hours than among those who received placebo, without any increase in residual muscle weakness. The precise mechanism for the decreased mortality is unclear [19]but a previous study showed reduced serum cytokine levels among patients receiving a neuromuscular blocking agent.[21]

"High" Positive End-Expiratory Pressure

Early trials comparing lower with higher levels of PEEP in patients with ARDS found no difference in mortality between the two groups. However, lower rates of hypoxemia were observed when higher PEEP and recruitment maneuvers were combined with protective ventilation in an 'open lung' strategy. Furthermore, the results of a large randomized controlled trial demonstrated that an 'increased recruitment strategy', where PEEP was used to reach a plateau pressure of 28–30 cm H_2O, resulted in a greater number of ventilator-free days and days free of organ failure.[22-24] There is some evidence to suggest that higher levels of PEEP may benefit patients with a greater degree of lung injury. One recent meta-analysis demonstrated a statistically significant reduction in hospital mortality with the use of higher PEEP when compared to lower PEEP in the subset of

patients with PaO_2:FiO_2 < 200 mm Hg. No such benefit was seen in those with less severe hypoxemias.[25] This adds weight to a previous sub-group analysis of earlier trials, which concluded that higher levels of PEEP benefit the most hypoxemic patients with ARDS.[26]

Recruitment maneuvers

Although such maneuvers were used in some trials that were included in the meta-analysis described above [25]and were implemented in a protective strategy that increased the number of lungs retrieved from heart-beating donors [27]the role of recruitment maneuvers in clinical practice remains uncertain because of questions about its effect on outcomes and concerns regarding complications (e.g., hemodynamic compromise or pneumothorax).[28]

Prone position

Prone positioning may mitigate VILI in three key ways: firstly, by providing a more homogenous distribution of trans-pulmonary pressure throughout the lung, secondly, by 'resting' anterior lung units, which are subjected to the most over-distension and thirdly, by improving ventilation-perfusion matching, thereby allowing for a decrease in the inspired oxygen concentration. [29, 30]
Despite this, four randomized clinical trials [31-34] have so far failed to demonstrate a reduction in mortality with its routine use in ARDS even if four meta-analyses concluded that, although routine prone position ventilation offers no survival benefit in patients with ARDS, it does improve oxygenation.[35-38] One more, demonstrated the efficacy only in selected category of very hypoxemic patients lowering absolute mortality. Starting from these assumptions, Guérin et al. designed a prospective, multicenter, randomized controlled trial to explore whether early application of prone positioning would improve survival among patients with ARDS who, at the time of enrollment, were receiving mechanical ventilation with PEEP of at least 5 cm H_2O and in whom the PaO_2/FiO_2 ratio was less than 150 mmHg. The trial confirmed the improvement in

patient survival with prone positioning reducing the rate of 28-day mortality from 32.8% (supine group) to 16.0% (prone group).[39]

High-frequency oscillatory ventilation (HFOV)

Theoretically, this technique should be ideal for minimizing ventilator-induced lung injury. [40]In a meta-analysis of eight randomized, controlled trials involving a total of 419 adults with ARDS [41]HFOV-treated patients had significantly lower mortality than did patients treated with conventional ventilation (risk ratio, 0.77; P = 0.03), which suggested that HFOV might improve survival and is unlikely to cause harm. Unfortunately, these benefits usually come at the expense of markedly increased mean airway pressures [42] and the potential deterioration in right heart function and organ perfusion.

Trans-pulmonary pressure

ARDS patients are particularly prone to VILI due to not homogeneous parenchyma damage that presents areas not aerated (with atelectasis, infiltrates or effusions), areas with low ventilation in which is prevalent the opening-closing phenomenon, areas normally aerated without signs of stress and lastly areas overinflated. In this contest, the best ventilatory strategy should be ideally adapted to the size of the aerated lung. It is hence necessary move from the selection of mode and setting of the ventilator based on a fixed set of number, to take into account the trans-pulmonary pressure,[43] i.e. the difference between alveolar pressure and pleural pressure, that is considered by some as the main determinant of VILI.[44]

The importance of trans-pulmonary pressure in adjusting mechanical ventilation setting in ARDS patients has even been studied by Talmor at al.[45] in 2008. In a randomized, single-center trial, they found an improve in oxygenation and a reduction in 28-days mortality by setting the PEEP at such a level that trans-pulmonary pressure during end-expiratory occlusion ranged between 0 and 10 cmH_2O and during end-inspiratory occlusion remained lower than 25 cmH_2O.

Different methods have been proposed in literature to estimate trans-pulmonary pressure:

1. $Pplat_L = Pplat_{RS} - Pplat_{CW}$ (where $Pplat_{CW} = Pplat_{RS} * E_{CW}/E_{RS}$) [1]
2. $Pplat_L = Pplat_{RS} - Pplat_{CW}$ [45]

Recently, Chiumello et al. [46]reported that the two methods are similar and concluded that the trans-pulmonary pressure can be satisfactorily estimated by the first one, which does not require any disconnection from the ventilator, thereby avoiding possible risks of lung de-recruitment and hypoxemia due to the loss of PEEP.

"SUPER-PROTECTIVE" VENTILATORY STRATEGY

Extracorporeal life support (ECLS) techniques, such as extracorporeal membrane oxygenation (ECMO) or extracorporeal CO_2 removal ($ECCO_2R$), are known to provide adequate gas exchange in patients with ARDS.[47] Vast improvements in ECLS technology over the last decade have made these devices less invasive, more biocompatible, and easier and safer to use. Moreover, ECLS can facilitate the use of 'ultra'-protective MV (for example, employing VT < 6 ml/kg PBW and lower airway pressures) in patients supported with ECLS, minimizing the risk of VILI. More radically, patients supported with ECLS may not require intubation or invasive MV at all: no ventilation, no VILI.

ECMO

The safety, clinical efficacy and cost-effectievess of extracoporeal membrane oxygenation (ECMO) compared with conventional ventilation support has been recently been studied in the CESAR study. [48]A significant improvement in survival without severe disability at 6 months was found in patients transferred to a specialist center for consideration for ECMO compared with continued conventional ventilation. This result has been attribute to the fact that ECMO was able to sustain life in acute lung failure long enough for diagnosis, treatment, and recovery. Moreover, ECMO was

able to rest the lungs from high pressure and FiO_2 ventilation, thereby keeping to minimum the iatrogenic contribution to lung injury.

$ECCO_2R$

In a recent study, Terragni and colleagues[12] evaluated whether VT < 6 ml/kg PBW may enhance lung protection. In 32 patients with ARDS ventilated with a VT of 6 ml/kg PBW, those with plateau pressures between 28 and 30 cm H_2O had their VT reduced to achieve plateau pressures between 25 and 28 cm H_2O. Respiratory acidosis (pH $\leq$ 7.25) was managed with $ECCO_2R$ for at least 72 h. Patients who already had plateau pressures between 25 and 28 cm H_2O continued to receive MV with VT of 6 ml/kg PBW. In the $ECCO_2R$ group (ten patients), $PaCO_2$ (mean 50 mmHg) and pH (mean 7.32) were normalized, and VT was reduced from 6 to 4 ml/kg PBW and plateau pressure decreased from 29 to 25 cm H_2O ($P < 0.001$). Moreover, there was a significant reduction in the morphological markers of lung injury and pulmonary cytokines ($P < 0.01$) in the $ECCO_2R$ group after 72 h of MV with VT lower than 6 ml/kg PBW. Of note, no patient-related complications occurred in patients receiving $ECCO_2R$.

While promising, the putative benefits of 'ultra'-protective MV with $ECCO_2R$, or more complete gas exchange support with ECMO, in patients with ARDS requires confirmation in large, randomized controlled trials.[49]

CONCLUSIONS

From a theoretical prospective, all patients receiving ventilator support should benefit for non-injurious strategies. It is advisable for clinicians to integrate physiological principles with clinical data through a "running assessment" of respiratory mechanics at the bedside useful to contain VILI by the early identification of specific lung alterations and the resulting most protective ("tailor made") ventilatory strategy.

Future study, already planned, are expected to improve further the clinical outcomes compared with

standard-of-care lung-protective ventilation in patients with ARDS. The EOLIA trial (ECMO to rescue Lung Injury in severe ARDS; ClinicalTrials.gov NCT01470703) is going to evaluate the impact of ECMO, instituted early after the diagnosis of ARDS not evolving favorably after 3–6h under optimal ventilatory management and maximum medical treatment, on the morbidity and mortality associated with this disease while the SUPERNOVA trial (A Strategy of UltraProtective lung ventilation with Extracorporeal CO_2 Removal for New-Onset moderate to seVere ARDS; ESICM trial group-registration on going) will evaluate whether a strategy of enhanced lung-protective (lower tidal volume and lower pressure) ventilation, along with control of the ensuing hypercapnia using the latest generation $ECCO_2R$ devices, will improve clinical outcomes.

Key points

- Mechanical ventilation, although necessary to preserve life, can itself aggravate or cause the so called Ventilator Induced Lung Injury (VILI) through a variety of mechanisms resulting in injury to the blood-gas barrier (endothelial, epithelial, and basement–membrane) with consequent increase in micro-vascular permeability and lung rupture.
- A large number of trials tried to identify strategies to improve the outcome of mechanically ventilated patients but only studies based on the physiological approaches for minimizing VILI really improved the outcome.
- In the last years the most important innovation is represented by the progressive change of approach, from basic mechanical respiratory support, to protective or ultra-protective non-injurious ventilation.
- It is advisable for clinicians to integrate physiological principles with clinical data through a “running assessment” of respiratory mechanics at the bedside as to set up the most protective (“tailor made”) ventilatory strategy.

Conflicts of interest

Dr. Pierpaolo Terragni and Prof. Luca Brazzi do not have conflicts of interest. Prof. Ranieri reports receiving payment for serving on advisory boards at Hemodec and receiving consulting fees from Hemodec, and Faron Pharmaceuticals.

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