Editorial

Preventing ventilator-induced lung injury—what does the evidence say?

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Since the first description of ARDS by Asbaugh *et al.* in 1967 decades of research brought further insight into the pathomechanistic background of the Acute Respiratory Distress Syndrome (ARDS). However, at present there is still no specific treatment available that targets the underlying mechanisms and can control the course of the disease. Therefore, the mortality rate for severe ARDS remains as high as 30–40%. The most important supportive care has become the introduction of lung protective ventilation strategies thereby lowering barotrauma and ventilator-induced lung injury (VILI) in ARDS.

In May 2017, the official clinical practice guidelines of the ATS, ESICM and CCM on the use of mechanical ventilation in adult ARDS patients were published providing up-to-date evidence-based recommendations in ARDS (1). An interprofessional panel with a broad sample (junior and senior professionals) of clinical epidemiologists, clinical trialists, physiologists, methodologists from different disciplines and jurisdictions, one ARDS survivor and an additional methodology subcommittee including a medical librarian were part of the Committee. This reflects that ARDS is an interdisciplinary syndrome that can be seen on surgical, medical or otherwise specialized ICUs. Furthermore, ARDS is a complex and heterogeneous disease that is not associated with, or caused by, a single etiology. This heterogeneity makes therapeutic management and performing clinical studies challenging. The authors were aware that no recommendation can take into account the compelling and unique clinical features of individual patients. However, the panel was able to provide the reader with scientifically-grounded answers to six specific questions pertinent to the ventilatory management of critically ill patients with ARDS. A summary of their recommendations according to the GRADE approach is as follows (2).

The recommendations for the use of low tidal volume and lower inspiratory pressure ventilation were strong. In patients with severe ARDS prone positioning for more than 12 hours a day is recommended. Additionally, there is a strong recommendation against the routine use of high-frequency oscillation (HFOV) in patients with moderate to severe ARDS. A conditional recommendation can be given for higher positive end-expiratory pressure (PEEP) and recruitment maneuvers in patients with moderate to severe ARDS. Additional evidence (from multicenter randomized controlled trials, RCTs) is necessary to make a definitive recommendation for or against the use of extracorporeal membrane oxygenation (ECMO) in patients with severe ARDS.

Implemented almost 2 decades ago, the most important strategy preventing VILI remains ventilation with low tidal volumes (4–8 mL/kg predicted body weight) and low inspiratory pressures (plateau pressure <30 cmH_2O). Although the Committee only included seven studies with

1,481 patients in their primary analysis, the boundary of the confidence interval consistent with the largest plausible effect suggests that low tidal ventilation might reduce the relative risk of death by as much as 30%. Some professionals even suggest lung protective ventilation strategies as standard practice for every patient needing artificial ventilation. Recent meta-analyses and clinical trials have shown that preemptive application of protective ventilation in high-risk ICU patients can reduce the incidence of ARDS (3,4).

The panel makes the good point that the potential benefits and harms of spontaneous breathing in patients with ARDS need to be evaluated in further studies. It is difficult to distinguish the effects of spontaneous, partially assisted breathing modes from the effects of the requirement of higher concentration of sedatives and neuromuscular blocking agents (NMBAs) during strictly controlled ventilation. Sedation management is a key component of the care in ARDS, as sedation improves comfort for critically ill patients. But it may also prolong duration of mechanical ventilation and increase risk of delirium. One of the main benefits of minimizing sedation in ARDS patients include facilitating early mobilization, potentially improving mortality and long-term recovery (5). Spontaneously breathing patients might have an increased risk for barotrauma because the spontaneous tidal volume exceeds the low tidal volume strategy.

In severe ARDS, NMBAs can help to reduce patient/ventilator asynchrony, with a better control of tidal volume, leading to a decrease of baro-, volu- and atelectrauma. NMBAs might also have direct anti-inflammatory effects and therefore can decrease local and systemic concentrations of proinflammatory cytokines (i.e., biotrauma). Clinical trials of a research group in France showed that the use of cisatracurium during early ARDS improved oxygenation and decreased mortality rate (6). However, extended use of NMBAs might increase the risk of ICU-acquired weakness (7). So far, hard criteria when to use NMBAs and controlled ventilation versus preserving muscle activity to maintain spontaneous breathing modes are still missing and further studies are necessary.

A novel approach uses "driving pressure" instead of "normalized target tidal volumes to predicted body weight" as key variable for lung protective ventilation strategies (8). Driving pressure (ΔP) is the ratio of tidal volume to (static) respiratory system compliance ($\Delta P = V_T/C_{RS}$) and can be calculated in patients who are not making inspiratory efforts as the plateau pressure minus PEEP ($\Delta P = P_{plat} - PEEP$). The driving pressure seems to be an elegant concept that promises to simplify the optimization of mechanical ventilation in patients with ARDS by providing a lung-protective ventilatory strategy that is adapted to the size of the effectively aerated lung ("baby lung concept"). However, the use of driving pressure is yet to be subjected to high quality RCTs confirming its clinical utility and safety.

Prone positioning is able to improve oxygenation by increasing alveolar recruitment and enhancing ventilation-perfusion matching. Additionally, it can prevent VILI by a more homogeneous distribution of inflation throughout the lung parenchyma. The guidelines strongly recommend prone positioning for more than 12 hours per day for adults with severe ARDS. It should also be taken into account that prone positioning might be beneficial for the cardiovascular system. Prone positioning can not only reduce the transpulmonary gradient but also right ventricle pressure overload and enlargement (9). However, prone positioning requires increased sedation and bears the risk of pressure ulcers and dislocation of central lines or accidental extubation. It also increases intra-abdominal pressure leading—especially in obese patients—to reduced splanchnic perfusion causing renal failure and hypoxic hepatitis (10).

HFOV is characterized by small tidal volumes (1–4 mL/kg) delivered at high frequencies (3–15 Hz) maintaining constant lung recruitment. These characteristics make HFOV conceptually attractive as an ideal lung-protective ventilatory mode for the management of ARDS, by preventing lung injury from alveolar overdistension and loss of recruitment (atelectrauma). This unconventional form of mechanical ventilation was found to cause harm or have no benefit in two recent large, multicenter RCTs in adult ARDS patients; therefore, its routine use was discouraged by the Committee (11,12). As ARDS is a heterogenous lung disease from differing causes, there may be some patient subgroups that might benefit (e.g., patients with homogeneous, recruitable lungs) while others are harmed. Until further studies show otherwise, HFOV should only be considered as a rescue therapy in patients with refractory hypoxemia where ECMO therapy is not an option.

Preventing atelectrauma and "opening the lung and keeping it open" are the rationales for the use of higher PEEP in patients with moderate or severe ARDS. It is important to point out, that the recommendation is mainly based on an IPDMA (meta-analysis of individual-patient data) of Briel *et al.* (13). Compared to conventional meta-

analysis, an IPDMA offers the main advantage that the original research data can be re-analyzed across studies using standardized definitions and leading to more powerful investigations of subgroup effects. But how do we determine the "best PEEP" for an individual patient? Different approaches have been used, adjusting the PEEP according to oxygenation, lung mechanics or quantitative CT imaging, for example. Newer strategies include electrical impedance tomography (EIT) and measurements of transpulmonary-pressure with the use of esophageal balloon catheters. These non-invasive real-time monitoring devices need to be evaluated in larger-scale multicenter RCTs before used routinely in the clinical setting. Moerer *et al.* (14) stated that although an individualized PEEP setting is preferred, in the event of life-threatening hypoxemia, a useful instrument for verifying the clinical plausibility of the applied PEEP might be the PEEP table developed by the ARDSnet (15). Although being far from a perfect tool, it can at least help to recognize patients with a possible dangerous "PEEP-undertreatment".

The concept of recruitment maneuvers is closely related to that of PEEP, since both can open lung areas, which are not participating in tidal ventilation, and are often combined and integrated into lung protective ventilation strategies. Therefore, it is sometimes difficult to isolate the effects of recruitment maneuvers from cointerventions as often additionally to the recruitment maneuver the PEEP is increased afterwards. Different strategies to recruit the lungs are being used, but applying continuous positive airway pressure with Paw of 35–45 cmH_2O for 30–40 s has become the most commonly reported method in clinical settings (16). Recruitment maneuvers are not without risks and predicting its usefulness in increasing the alveolar-capillary units participating in gas exchange could decrease the number of patients exposed unnecessarily. It is also reasonable that in the earlier, exudative phase of ARDS recruitment maneuvers might be more effective than in the later, fibrotic phase. Additionally, patient-specific characteristics like the underlying cause of ARDS, preexisting lung diseases or the pattern of the injured lung areas might play a prominent role. Hypotension may occur due to decreased preload and increased afterload of the right ventricle due to high intrathoracic pressure, but regresses with termination of the recruitment maneuver. Fortunately, the incidence of barotrauma and pneumothoraces seem to be very low (16).

Despite the rapid evolution of ECMO technology and its growing use, there is limited evidence that ECMO therapy can help improve outcome in patients with severe ARDS (17). Further research is needed regarding the timing of the initiation of ECMO and selection of patients who will benefit most from venovenous ECMO. Hopefully, the results from an ongoing RCT (ECMO to rescue lung injury in severe ARDS, EOLIA) will contribute valuable data to guide future clinical decisions for the rational use of VV ECMO. ECMO might also enable the use of minimal tidal volume, as proper gas exchange is achieved extracorporeally, avoiding further baro- and biotrauma by VILI. However, it is unclear whether such "ultra"-protective ventilation strategies with minimal (or no) tidal volume resulting in near complete atelectasis, are more lung protective than a ventilation pattern with a lung recruitment strategy (18).

As concluded by the panel complementary pharmacologic interventions need to be addressed in future iterations of the guideline. In this context, the usefulness of inhaled pulmonary vasodilators should be discussed. The underlying rationale of using inhaled pulmonary vasodilators is based on the pathology of ARDS involving mismatching of ventilation and perfusion and pulmonary hypertension. However, in 2007 Adhikari *et al.* conducted a meta-analysis of 12 trials with a total of 1,237 patients showing that inhaled NO (iNO) is associated with limited improvement in oxygenation in patients with severe ARDS and has no beneficial effect on mortality (19). It may even cause harm by promoting renal dysfunction. Adhikari *et al.* concluded that the use of iNO should only be considered as a rescue therapy.

Synthetic prostaglandin analogs can bind to four pulmonary prostanoid receptors that have been identified to be involved in regulating vascular tone, platelet activation, and immunological cell responses. Compared to iNO, inhaled prostanoids require no special application and monitoring equipment and are therefore easier and less expensive to administer. In a meta-analysis in 2015 Fuller *et al.* demonstrated that inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures, but on the other hand can lead to significant hypotension, thrombocytopenia, anemia, or transfusion requirement (20). Due to so far only limited data on clinical benefit but possible harm, the use of inhaled prostaglandins in ARDS needs further investigation.

Also connected to the use of mechanical ventilation in ARDS patients is the question of $paCO_2$ and paO_2 management. Since the 1990s the concept of "permissive hypercapnia" was proposed for patients with acute lung injury, even suggesting that "therapeutic hypercapnia"

might be beneficial (21). However, more recent studies have reported that hypercapnia might be harmful, impairing alveolar epithelial function, cell proliferation, and muscle function as well as neutrophil function and innate immunity (22). A recent study by Nin *et al.* suggests that severe hypercapnia within the first 48 h of mechanical ventilation of ARDS patients is independently associated with higher ICU mortality. The reported data of this study may lead to a reassessment of the previous assumption that severe hypercapnia is safe during ARDS.

The rational of "permissive hypoxemia" (SaO_2 82–88 %) in patients with severe ARDS is to minimize the detrimental effects of high inspiratory oxygen concentrations by accepting a lower SaO_2 and simultaneously optimize cardiac output to maintain adequate oxygen delivery to the tissues. Unfortunately, a recent Cochrane search failed to identify any relevant studies evaluating permissive hypoxemia versus normoxemia in mechanically ventilated critically ill participants (23). Furthermore, in a retrospective analysis of ARDS patients, lower PaO_2 during mechanical ventilation was associated with a higher incidence of long-term cognitive impairment (24). Moreover, global parameters of tissue oxygenation as PaO_2, SaO_2, SvO_2 and serum lactate might be imprecise surrogates for localized, tissue specific hypoxia in ARDS patients. Therefore, in the absence of evidence-based studies we would recommend a more conservative arterial oxygenation strategy (PaO_2 =65–75 mmHg, SaO_2 =88–93%) to prevent hypoxic organ failure.

Overall, the interdisciplinary panel elaborated valuable and rational guidelines for mechanical ventilation in adult patients with ARDS. Based on these general recommendations clinicians should individualize the therapy for their patients, especially regarding the presented conditional recommendations. Personalizing mechanical ventilation to patient-specific physiology to further enhance lung protection will be a top research priority for the years ahead, as stated by the ARDSne(x)t investigators (25). Profound understanding of the heterogeneous pathophysiological processes leading to the development of ARDS is needed to tailor ventilatory and other therapeutic strategies to the individual patient. The next 20 years of ARDS research require that we ask not just whether novel preventive or therapeutic interventions work but also in whom (25).

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Footnote

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