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EDITORIAL

Will all ARDS patients be receiving mechanical ventilation in 2035? No

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Despite serious side effects, mechanical ventilation (MV) is universally recognized as a lifesaving intervention to improve gas exchange or replace fatigued respiratory muscles of patients in respiratory failure. However, MV itself can cause ventilator-induced lung injury (VILI), as first described in the 1980s. Since then, our understanding of acute respiratory distress syndrome (ARDS) pathophysiology has dramatically improved, leading to the concept of protective MV. Scientific and clinical efforts have both led to a significant but still incomplete reduction of lung harm. Consequently, despite initial reduction, ARDS patients' deaths remain unacceptably high. Mortality rates for a recent multicenter cohort of mild, moderate, and severe ARDS patients were 35, 40, and 46 %, respectively [1]. Although lowering the tidal volume also lowered mortality—despite initially worse oxygenation—we advance that the current protective MV strategies cannot sufficiently minimize VILI and foster lung healing [2].

The strongest arguments supporting our position are that, even in 2035, MV will still be a "double-edged sword" maintaining adequate gas exchange while awaiting lung healing, and, paradoxically, sometimes inflicting lung damage, thereby substantially contributing to morbidity [3]. Excessive tidal volumes, driving pressures, respiratory rate, and inspiratory gas flows will still harm the lungs in 2035. Moreover, a growing body of evidence suggests that inappropriate MV of patients without preexisting lung injury, during the perioperative period and in the intensive care unit, might damage the lungs, thereby compromising clinical outcomes [4]. Alternative strategies are urgently needed to prevent the deleterious complications of highly invasive MV.

Early ARDS diagnosis is the first step in achieving this goal. Indeed, early improperly adjusted MV can exacerbate acute lung injury and facilitate ARDS onset [5]. Therapeutic interventions (high positive end-expiratory pressure (PEEP), lung-protective ventilation, neuromuscular blockers, prone positioning) have demonstrated benefits early during the course of severe ARDS. However, ARDS appears to be underrecognized and undertreated [1], leaving room for improvement in the near future. Early detection of initial lung damage may allow timely implementation of preventive strategies to avoid progression towards more severe ARDS.

Noninvasive MV and high-flow nasal cannula are two early strategies to avoid endotracheal intubation [6]. Although the Berlin definition of ARDS does not formally cover patients treated with high-flow nasal cannula, it must be recognized that some ARDS patients are already successfully treated without invasive or non-invasive MV [7]. However, spontaneous ventilation can also generate high tidal volumes and excessive transpulmonary pressures. Indeed, those noninvasive supports may contribute, to varying degrees, to decreasing respiratory muscle workload. However, especially in the context of lung disease, they may be inadequate to safely achieve acceptable gas exchange. Moreover, controlling the respiratory drive [8] of spontaneously breathing ARDS patients can be extremely challenging. Furthermore, the smaller the "baby lung", the larger the risk of unsafe MV and the greater the need to eliminate CO_2.

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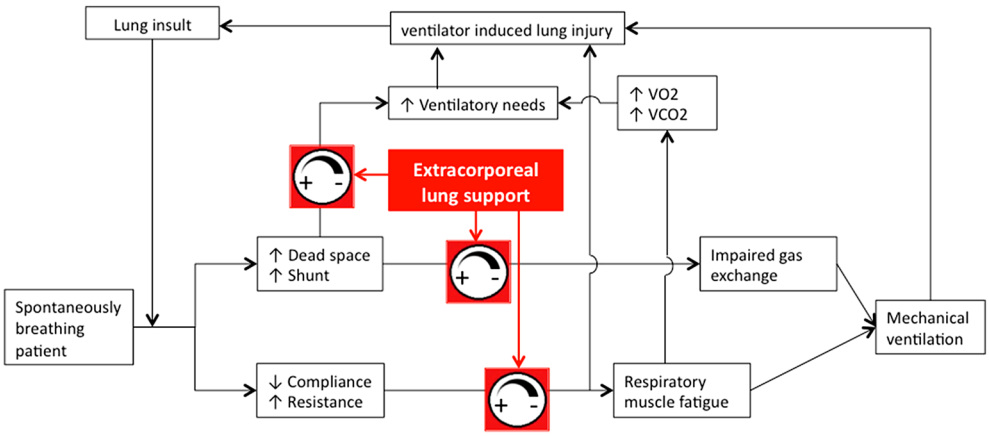

Fig. 1 The vicious cycle encircling lung-injured patients on mechanical ventilation (MV). Lung damage is often associated with heightened need for MV that, in turn, worsens the preexisting lung injury. Pertinently, extracorporeal lung support can be tailored to each patient's needs to break this circle. The use of ECMO symbolized by the *dark line* of the *red knob* could alleviate each consequence of the lung insult such as high ventilatory need, impaired gas exchange, and respiratory muscle fatigue

Extracorporeal lung support (ECLS) might be a valuable option to block the vicious cycle that negatively affects the patients on MV (Fig. 1). Technical improvements of its components have extended ECLS use through two distinct modalities [9]. By using low extracorporeal blood flows (<2 L/min), extracorporeal CO_2 removal ($ECCO_2R$) systems can partially or completely remove patient-produced CO_2, while ensuring low oxygenation, whereas higher venovenous extracorporeal membrane oxygenation (VV-ECMO) blood flows (up to 6 L/min) ensure oxygenation and decarboxylation. For patients receiving invasive MV, using different ECLS devices and settings can completely or partially reduce the need for MV. Conversely, ECLS is another option for awake, nonintubated, spontaneously breathing patients, with control of the patient's respiratory drive being the key factor to making this strategy successful. Although $PaCO_2$ has been identified as a fundamental determinant of ventilator drive, other factors (agitation, lung edema, low lung compliance, dyspnea, etc.) involving bronchopulmonary C-fibers or other pulmonary receptors can also affect central respiratory drive, especially in ARDS patients.

A study comparing awake sheep on ECMO before and after ARDS induction elegantly demonstrated that ARDS sheep had significantly elevated esophageal pressure variations, which could be reduced only by extracorporeal removal of very high CO_2 levels [8]. Preventing the generation of high transpulmonary pressure produced by awake ARDS patients' strong spontaneous breathing efforts is crucial, as it can enhance lung damage [10]. To date, limited data are available on ECLS as an alternative to MV for ARDS patients.

A single-center, uncontrolled, pilot trial to assess VV-ECMO feasibility in awake, nonintubated, spontaneously breathing ARDS patients enrolled six patients (four immunocompromised) [11]. Three of the four hospital survivors were successfully managed without invasive MV after 10, 5, and 7 days on ECMO. Indeed, that strategy served as a bridge to transplantation for patients with chronic end-stage lung disease [12, 13] and achieved better survival than conventional invasive MV [13]. Notably, if ECMO-related complications (mainly associated with anticoagulation) could be prevented, ECLS for awake, nonintubated, spontaneously breathing ARDS patients could offer major advantages: prevention of prolonged invasive MV complications (ventilator-associated pneumonia, VILI, etc.), maintenance of active physical activity, social interaction, oral feeding and spontaneous coughing, and low sedation requirement.

Future development of highly efficient $ECCO_2R$ techniques [14], possibly associated with a regional anticoagulation strategy, might lower the need for MV. Such a minimally invasive approach might substantially extend the range of $ECCO_2R$ application. However, it should be emphasized that conspicuous reduction of a patient's minute ventilation, due to high extracorporeal CO_2 removal, could promote atelectasis and intrapulmonary shunt, thereby exacerbating hypoxemia. Applying intermittent optimized PEEP, through a noninvasive interface, might be necessary to prevent lung derecruitment. Lastly, because respiratory drive is not influenced only by the amount of CO_2 removed, despite similar circumstances individual patients' responses could differ, reinforcing the need to individually tailor strategies integrating ARDS patients' respiratory-drive control.

The rationale for seeking alternatives to (invasive) MV for ARDS patients is strong. MV is an effective intervention to replace respiratory muscle function but gas exchange remains fully dependent on the patient's lungs. When pulmonary function is compromised, an "artificial lung" seems the most appropriate substitute. Research in the near future should focus on preventing ECMO-related complications and improving understanding determinants of respiratory drive and dyspnea in ARDS. Indeed, ECLS is still marred by significant complications which actually jeopardize the wider use of these devices. To date, prevention of bleeding complications, clotting of the devices, and frequent neurological events [15] is required to allow one to look forward to using ECLS as a credible alternative of MV to improve patient survival. However, considering the field's major advances over the past two decades, we are confident that not all ARDS patients will be receiving invasive MV in 2035. ECLS, performed in experienced high case volume centers, could be an effective and safe alternative to invasive MV for selected patients with ARDS or at high risk of developing it. However, to achieve that objective, identification of the appropriate patient population and physiological targets, early intervention, further technological improvements, and noninvasive continuous positive airway pressure supports seem warranted.

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Compliance with ethical standards

Conflicts of interest
M.S. reports receiving lecture honoraria from Maquet. P.M.S. and A.Z. have no conflicts of interest to declare.

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