Editorial

Awake extracorporeal membrane oxygenation in immunosuppressed patients with severe respiratory failure—a stretch too far?

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The use of rescue extracorporeal membrane oxygenation (ECMO) in immunocompromised patients with acute respiratory distress syndrome (ARDS) is increasing with 5% to 31% of patients receiving ECMO (1,2) in recent studies. In the recently published ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, 22% of the recruits were identified as immunosuppressed and the sixty-day mortality of this sub-population was 56% and 78% in the ECMO and the control groups, respectively (3). Even though a post-hoc analysis of this small subgroup may not be definitive evidence for or against ECMO use in this population, it is important to note that "salvage" VV-ECMO (4) in the immunosuppressed is a futile exercise. However, this raises two important questions beyond crude mortality of this population: (I) might this population benefit from early VV-ECMO to liberate them from invasive mechanical ventilation (IMV) as soon as feasible? and (II) can IMV be avoided altogether in this cohort?

When committing an immunosuppressed patient to ECMO, patient selection and timing of initiation of these supports are the key considerations. A recent retrospective study (5) on ECMO use in immunocompromised ARDS patients provides significant insights in this regard. Six-month overall survival was only 30% in this heterogeneous cohort. Six-month survival rates of 40%, 37%, 26%, 24% and 20% were reported in patients who were immunosuppressed as a result of solid-organ transplant, long-term or high-dose corticosteroids or other immunosuppressant, acquired immune deficiency syndrome, haematological malignancies, and solid tumors, respectively. Survival among patients who received ECMO early after an allogeneic hematopoietic stem cell transplant was dismal at 4% (6). Less than 30 days between immunodeficiency diagnosis and ECMO cannulation appears to be a major selection criterion as it was independently associated with better 6-month survival (5). Obviously, other co-morbidities also need to be considered in the decision-making process. However, once the decision has been made to offer intensive care support, including IMV, for ARDS, withholding ECMO or using it as absolute salvage may not be warranted given that well selected immunosuppressed patients appear to have similar results with ECMO as compared IMV (5). Therefore, eligible patients, based on current data, should receive timely lung protective IMV, adjuncts therapies, and early ECMO as needed if they fulfil EOLIA inclusion criteria (3,4).

It is unclear whether early VV-ECMO and liberation form IMV as soon as possible or avoidance of IMV

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altogether is a better strategy in immunosuppressed patients with severe respiratory failure. Randomised controlled ECMO trials in ARDS have always tested conventional protective IMV with adjuncts against more protective IMV and ECMO (3,7). Whether two modalities of gas exchange support are indeed required to support physiology in an ARDS patient is unclear as both carry risks and the risks may be additive. The immunosuppressed patient with ARDS may have a poor tolerance for the combined risks of IMV and ECMO. Given that IMV carries an increased rate of complications and poor outcomes in immunosuppressed (8,9), one can argue that it better to avoid risks of IMV altogether in this cohort. Extremely high mortality rates (70–80%) have been reported in immunocompromised patients who did not respond to conventional oxygen therapy or to non-invasive ventilation (9-11). So, based on an individual patient situation and logistics, application of VV-ECMO may the best approach when combined with either total avoidance of or early liberation from IMV.

Such an approach will have challenges, most significantly ECMO-related complications such as bleeding and infection (5,6). It is now possible to perform ECMO with minimal to no anticoagulation to minimize bleeding risks (12,13). Future research should investigate supportive therapies that potentially reduce time on ECMO as ECMO duration is intricately linked with risk of infection (14). Equally, meticulous percutaneous cannulation (15) and applying currently known infection prevention strategies (16) may help minimise infection risks. Other potential areas for investigation specific to the ECMO population may include use of antibiotic coated cannula and circuitry, novel cannula dressing and securement techniques (17), selective decontamination of digestive tract (18), rapid diagnostics for early detection of blood-stream infections (19), optimal antimicrobial drug dosing strategies (20,21) to minimise emergence of microbial resistance and biofilm formation (22) on cannula.

Avoiding IMV may help prevent complications such as ventilator-associated pneumonia (23), ventilator induced lung injury (24), diaphragmatic myotrauma and diaphragm atrophy (25,26). This may also help minimise sedation use, promote physical activity, speech and oral intake, and maintain cough and airway function. Patient's respiratory drive can be managed (27-29) by controlling carbon dioxide and pH through the ECMO circuit and decruitment might be avoided through the application of non-invasive positive airway pressure, as needed. Patient comfort and safety, and the staffing required to achieve a so-called 'awake ECMO' strategy are all important considerations. Except for a few case reports (30,31), the risk-benefit ratio of this strategy in the context of ARDS has not been thoroughly investigated.

Initiating and managing VV-ECMO in a non-intubated patient is an evolving art and science as complex lungs-heart-brain-ventilation-ECMO interactions in the ARDS setting are not fully understood. In addition, cannulating a non-intubated patient with severe respiratory failure is not easy and intubation prior to cannulation may be preferred for safer cannulation and improved patient comfort. As the field of extracorporeal respiratory support evolves, there will be an increased interest in embarking on techniques such as extracorporeal carbon dioxide removal ($ECCO_2R$) or ECMO with the intention of eliminating the risks of IMV. The success of these approaches depends on how well we integrate extracorporeal techniques to an awake, spontaneously breathing patient with severe respiratory failure. This will involve a more in-depth understanding of spontaneous breathing and respiratory drive in setting of diseased lungs, a marked change in ICU sedation and analgesia practices (including the use of non-sedating pharmacological adjuncts to provide anxiolysis, comfort and analgesia), improvement in delirium prevention and management, and improved adherence to other evidence-based practices in ICU.

In addition, if VV-ECMO were to be instituted in lieu of IMV, it would be important to establish that deferred intubation or delayed intubation does not exacerbate patient self-inflicted lung injury (P-SILI) (32). Although spontaneous breathing has been shown to improve ventilation in the dorsal, dependent lung segments (33), it could also lead to significant spontaneous breathing-related lung injury (34). Timely application of lung-protective IMV may be considered a prophylactic, rather than supportive, therapy, to minimize the progression of lung injury from a form of P-SILI (32). These are important considerations that require more research to better understand how an awake ECMO strategy may affect patients with ARDS.

Moving forward, if therapeutic and supportive strategies are employed to avoid intubation and IMV in ARDS, we need better definitions for acute respiratory failure and its severity. This is important both to standardise respiratory support strategies that do not rely on invasive access to patients' airways and to study these approaches in future clinical trials. Clearly, extracorporeal technologies challenge the current paradigm of both diagnosis and treatment of ARDS. Sequential use of ECMO to facilitate protective IMV will be increasingly scrutinised and there will be a

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desire to attempt extracorporeal respiratory support as first-line therapy (35), with IMV rescuing patients as needed either to support physiologic demands or to promote safety and comfort in select patients. Appropriately selected immunosuppressed patients with severe respiratory failure may stand to benefit from such an approach and may be the population most in need of further study.

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Footnote

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