

# Veno-venous extracorporeal membrane oxygenation for the third millennium

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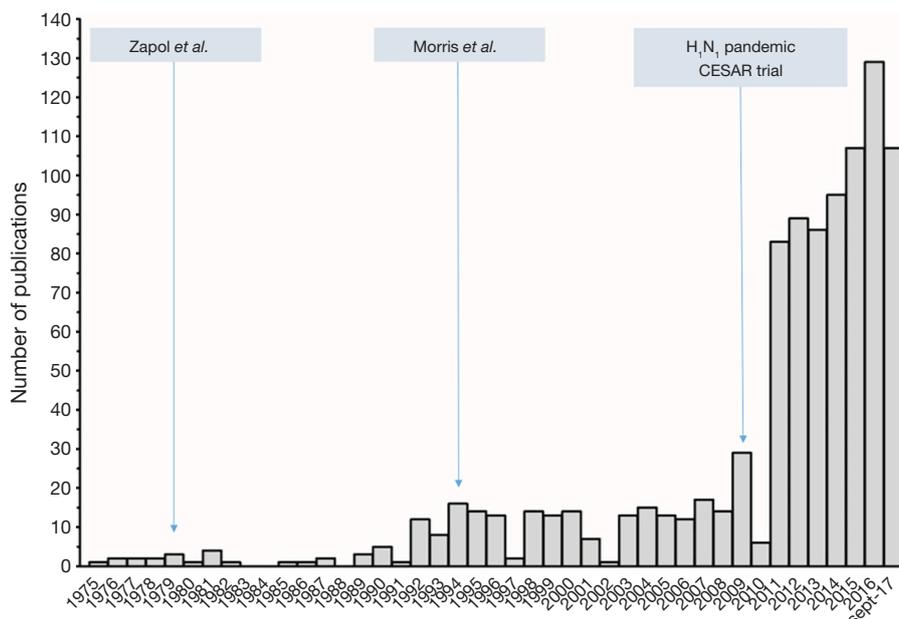
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Veno-venous extracorporeal membrane oxygenation (VV-ECMO) can now be considered as a rescue therapy for severe acute respiratory distress syndrome (ARDS) patients when mechanical ventilation is not sufficient to ensure efficient oxygenation and decarboxylation, or when high intrathoracic pressure are required to maintain adequate gas exchange (1). This support now allows for an “ultra”-protective mechanical ventilation, and the control of intrathoracic pressure, which reduces the risk of lung injury (2,3). However, these ECMO-treated ARDS patients still exhibited a high mortality, and the technique is still marred by numerous complications. Mortality has been reported from 21% to 43% (2-5), and 40% of patients developed at least one complication where bleeding is the most frequent (6). Nevertheless, it is worth considering the technical breakthrough of devices obtained for 2 decades. ECMO equipment are now more biocompatible and offer more effective gas exchange with lower flow resistance (7). In addition, it is likely that the experience gained by ECMO-referral centers, with a better identification of ECMO-indications and timing, will contribute to improve outcomes in a near future. Meanwhile, a large number of ECMO management aspects are still unclear and deserve focus of clinicians in the next years.

Although the numbers of VV-ECMO use and studies on this topic have both steadily increased since 2009, research is still limited to monocenter (8,9) or retrospective cohorts (4,5) that preclude providing strong evidence to guide clinician therapeutic strategy (*Figure 1*). In other words, international randomized controlled trials (RCTs) on modern ECMO for ARDS are urgently needed to answer several controversial management points (12) that

have not been fully clarified with the CESAR trial (3). Timing of ECMO implantation, and patient selection are the first burning points that RCTs should answer as early ECMO initiation with limitation of ventilator-induced lung injury is still balanced with inherent complications of cannulation and anticoagulation, which may limit its clinical benefits. Results of the ongoing international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA, NCT01470703), compared early ECMO initiation ( $\leq 7$  days on mechanical ventilation) with conventional ventilation management strategy in patients with severe-ARDS, is highly expected. It may contribute to clarifying the place of ECMO in the management of severe ARDS. Selection of the patients who are more likely to benefit from that technique is also a matter of concern. For instance, no change in mortality was reported in a large German cohort, between the year 2007 and 2014, where the proportion of patients older than 80 years on VV-ECMO increased over time (13). The extension of this invasive and expensive technique to older aged patients is highly questionable, as mortality is already high even when it is restricted to young patients. Moreover, their overall mortality was higher than reported in other multicenter studies (5) with mortality rates of patients on ECMO for less than 48 hours reached 70%. This aspect highlights potential procedure-related complications and patient selection issues. In order to improve patient selection for ECMO, some survival predictive models have been developed (4,5,8,9). These scores deserve external validation in international studies, where ECMO has not yet been instituted. It may provide a relevant tool for clinicians to selecting the best candidates



**Figure 1** Number of publications and randomized controlled trials (3,10,11) on extracorporeal membrane oxygenation for acute respiratory distress syndrome. Search on PubMed was performed using this formula: “(ecmo[Title/Abstract] OR extracorporeal membrane oxygenation[Title/Abstract]) AND acute respiratory distress syndrome”.

for ECMO in the light of the risk-benefit balance.

Anticoagulation and drugs' pharmacokinetics on ECMO need investigation as well. Circuits are now made with more biocompatible materials and a hollow-fiber oxygenator. Thus, a decrease of platelets and plasma protein consumption with these new circuits could allow a reduction of anticoagulation on ECMO (14). Moreover, numerous published case reports of successful management on prolonged VV-ECMO with no anticoagulation have been recently reported (15). Whether a systematic reduction of anticoagulation on VV-ECMO could be safely applied without increasing venous thrombosis and oxygenator clotting is still undetermined and requires a RCT to evaluate risks and benefits of each strategy. The ECMO circuit itself, and the increase of the distribution volume, strongly impact antibiotics' pharmacokinetic and pharmacodynamics, which can lead to toxicity or therapeutic failure (16,17). The future of ECMO patient care should consider the pharmacological properties of the drug, and its kinetics on ECMO to provide a daily personalized titration (18). Similarly, mechanical ventilation on ECMO should be investigated as well. First, the benefit of “ultra”-protective ventilation, which associates very low tidal volume (19), low driving pressure (20) and a high positive end-expiratory pressure (PEEP) (21) deserve to be confirmed on a large

ECMO population. For instance, application of a high PEEP level, with reduction of the driving pressure, will depend on the distribution of the ARDS lesions and the morphology of the patient. Then, “optimal” PEEP could be very different between patients and during the course of ARDS, suggesting individualizing mechanical ventilation settings with bedside tools. For example, Franchineau *et al.* recently suggested that electrical impedance tomography could contribute to set PEEP on ECMO with a bedside monitoring of atelectasis and overdistension (22). Similarly, the use of esophageal pressure or pressure-volume curve to personalize mechanical ventilation on ECMO warrants investigation.

The ability of ECMO to fully replace lung function, even in severe ARDS and the toxicity of mechanical ventilation, may question the reasons to maintain mechanical ventilation on ECMO. A strategy of non-invasive mechanical ventilation with ECMO for severe ARDS has been reported in an uncontrolled pilot trial of six patients (23). Half of the patients died on ECMO, whereas others were successfully discharged from the hospital. In addition, this strategy allows the use of less sedative and to maintain oral feeding, muscular activity and social interaction. In a different population, an ECMO strategy without mechanical ventilation before a lung transplant was associated to a better 6-month post-transplant survival when compared to a strategy based on

mechanical ventilation only (24,25). Better understanding of the respiratory drive determinants on ECMO are urgently required to develop this strategy as inappropriate spontaneous ventilation in ARDS could also worsen lung injuries and compromise clinical outcomes (26-28). Because ECMO may run for several weeks and psychological and physical issues mar long-term quality of life of ARDS survivors, early rehabilitation and mobilization (even) on ECMO must be a priority. Abrams *et al.* recently reported that active physical therapy on VV-ECMO could be safely performed (29). Positive effects of early mobilization on physical status at hospital discharge, muscle strength and long-term outcome (30) should encourage clinicians to implement this strategy with our ECMO patients. Lastly, regional organization of ECMO activity is a major challenge. Expanding utilization of ECMO during past decades has led to increase the number of centers performing ECMO, especially Venovenous. Important disparities regarding the number of cases per center was noted with higher annual hospital ECMO volume associated with lower mortality (31). The recent report of German ECMO activity has stressed out the limits of a system without ECMO network (13). The lack of regional and/or national organization with identified ECMO referral centers led to an unexpected high mortality (58%) with an inverse relationship between annual ECMO case volume and mortality with VV-ECMO (13). This data calls for performing ECMO in expert referral centers with a 24/7 mobile ECMO team inside a regional and/or national network. In addition to improving patients' outcome, this strategy may also lead to a better cost-effectiveness balance (32).

Since 2009, we have seen a strong regain of interest for ECMO in refractory severe ARDS. The "rebirth" of this technique, after encouraging results obtained during the H1N1 pandemic and in the CESAR trial, must not hide the fact that our knowledge of its risk-benefit ratio and its daily management are actually limited. Future research and results of the EOLIA trial are highly expected to start answering to the (still) burning question of "When, to whom, and how to perform ECMO for severe ARDS?"

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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