Online version at https://www.minervamedica.it

Minerva Anestesiologica 2025 January-February;91(1-2):92-100
DOI: 10.23736/S0375-9393.24.18228-4

EXPERTS' OPINION

Awake veno-venous extracorporeal membrane oxygenation: practical aspects and considerations

Gianluca PATERNOSTER [1] *, Pietro BERTINI [2], Fabio SANGALLI [3], Sabino SCOLLETTA [4]

[1]Department of Health Science Anesthesia and ICU, School of Medicine, San Carlo Hospital, University of Basilicata, Potenza, Italy; [2]Department of Anesthesia and Intensive Care, Casa di Cura San Rossore, Pisa, Italy; [3]Department of Anesthesia and Intensive Care, ASST Valtellina e Alto Lario, University of Milano-Bicocca, Sondrio, Italy; [4]Department of Medical Science, Surgery and Neurosciences, Anesthesia and Intensive Care Unit, University Hospital of Siena, Siena, Italy

*Corresponding author: Gianluca Paternoster, Department of Health Science Anesthesia and ICU, School of Medicine, San Carlo Hospital, Potenza, Italy. E-mail: paternostergianluca@gmail.com

ABSTRACT

Veno-venous extracorporeal membrane oxygenation (ECMO) is a life-saving technique in the armamentarium of critical care medicine. It involves extracorporeal blood circulation outside the body, providing temporary respiratory support while allowing the lungs to heal. Traditionally, patients undergoing ECMO require sedation to minimize discomfort and facilitate mechanical ventilation. The "awake ECMO" concept emerged as a promising strategy to mitigate sedation-related complications and facilitate early mobilization in critically ill patients. In this article, we describe the potential advantages of awake ECMO and its role in preserving respiratory muscle function, enhancing rehabilitation prospects, and improving patient outcomes.

(*Cite this article as:* Paternoster G, Bertini P, Sangalli F, Scolletta S. Awake veno-venous extracorporeal membrane oxygenation: practical aspects and considerations. Minerva Anestesiol 2025;91:92-100. DOI: 10.23736/S0375-9393.24.18228-4)

Key words: Extracorporeal membrane oxygenation; Artificial respiration; Lung transplantation; Respiratory insufficiency.

ECMO is a cutting-edge life-support measure for critically ill patients, particularly those with severe acute respiratory failure, such as acute respiratory distress syndrome (ARDS). Veno-venous ECMO (VV ECMO) is the configuration of choice in respiratory failure with preserved heart function, offering a lifeline by providing temporary respiratory support while "buying time" for the lungs to heal.

Definition of veno-venous extracorporeal membrane oxygenation (VV ECMO)

VV ECMO temporarily assists the failing lungs by circulating the patient's blood through an extracorporeal circuit that is oxygenated and decarboxylated. It provides adequate oxygenation and carbon dioxide (CO_2) removal while allowing the lungs to be ventilated with an ultraprotective strategy and heal, preventing further damage and improving patient outcomes.[1]

Various cannulation sites are available for VV ECMO. Typically, the drainage cannula is placed in the femoral vein or (less frequently) in the internal jugular vein, while the return cannula can be inserted into the internal or femoral vein. Alternatively, a dual-lumen cannula can be used. In such a case, the cannula is placed via the internal jugular vein. The blood drawn is oxygenated and decarboxylated as it passes through a membrane oxygenator, and both oxygenation and CO_2 removal can be modulated by adjusting FiO_2 and blood flow, as well as sweeping gas flow, respectively. This continuous cycle of oxygenation and carbon dioxide removal effectively bypasses the patient's native lung function, providing essential respiratory support.

Use of ECMO in early ARDS treatment

The scope of ECMO application in ARDS has evolved significantly over time, driven by technological advancements, enhanced understanding of pathophysiology, and accumulating clinical evidence. Initially, ECMO was mainly used as a rescue therapy for patients with severe ARDS refractory to conventional mechanical ventilation. However, with growing evidence supporting its efficacy and safety profile, ECMO has gradually become integrated into the standard management approach for ARDS, particularly in cases of profound hypoxemia and severe hypercapnia.[2]

Following the influenza A H1N1 pandemic in 2009 and the publication of the observational results from the Australia/New Zealand experience[3] the use of VV ECMO to treat refractory respiratory failure increased significantly, despite two subsequent randomized trials failing to demonstrate a clear benefit of VV ECMO as compared to conventional therapies in terms of survival.

The CESAR trial demonstrated improved survival and reduced ventilator-associated lung injury in patients with severe ARDS, emphasizing the importance of transferring patients to specialist centers for the management of severe respiratory failure. The trial supports the use of VV ECMO in appropriate cases, particularly when standard treatments, including lung-protective ventilation, prove insufficient.[4] The EOLIA trial[2] failed to demonstrate the superiority of an early VV ECMO strategy over a conventional strategy with an ECMO backup on mortality at 60 days. However, the data suggest a possible clinical benefit from ECMO over standard care, mainly when applied early. Both trials raised significant criticisms and had relevant crossover rates.

Subsequent guidelines and consensus statements, including those from the Extracorporeal Life Support Organization (ELSO) and the European Consensus Guidelines on the Management of Respiratory Distress Syndrome, have further reinforced the role of ECMO in severe ARDS management. These guidelines offer evidence-based recommendations encompassing patient selection criteria, optimal cannulation strategies, ventilatory management and ECMO circuit optimization to maximize outcomes in ARDS patients who need ECMO support.[5]

The COVID-19 pandemic further boosted the use of ECMO in severe respiratory failure, with many studies reporting favorable outcomes in COVID-19 patients supported with ECMO.[6]

In essence, the traditional utilization of ECMO in early ARDS treatment has transitioned from being a rescue therapy to an indispensable component of the therapeutic armamentarium for severe respiratory failure.

The awake ECMO strategy

The innovative concept of awake ECMO has emerged as a promising strategy to mitigate sedation-related complications and facilitate early mobilization in critically ill patients.[7] This relatively new approach represents a paradigm shift in managing severe respiratory failure.

Traditionally, patients undergoing ECMO require sedation to minimize discomfort and facilitate mechanical ventilation. However, awake ECMO, where patients remain conscious and spontaneously breathe while supported by the extracorporeal circuit, has gained momentum in recent years. This approach presents several potential advantages: by preserving respiratory muscle function, facilitating early mobilization, enhancing psychological well-being and mitigating sedation-related complications, it may enhance rehabilitation prospects and improve patient outcomes.[7]

Advantages of awake ECMO

Protection of the lungs during mechanical ventilation

The potentially injurious effects of mechanical ventilation (ventilation-induced lung injury, VILI) are well known and have led to the concept of lung-protective ventilation.[8] ECMO represents an extreme approach to lung protection in severely injured lungs.

On the one hand, having the patient under extracorporeal support may reduce superimposed lung strain to a minimum and avoid ventilation. However, this makes the patient totally dependent of the patient on extracorporeal gas exchange and, frequently, makes the right heart unable to cope with the increased workload, making it necessary to upgrade the support to VA or VAV ECMO.[9]

On the other hand, the "spontaneous" breathing that is allowed in awake ECMO is not positive *per se*.

Allowing the patient to breathe spontaneously may potentially lead to excessive breathing efforts and patient self-induced lung injury (P-SILI).[10] This is particularly true for the most severely ill patients, as well as for those supported with ECMO. Hence, it is essential to strictly monitor patients to prevent P-SILI. In this view, ECMO potentially regulates patients' respiratory efforts by cautiously adjusting the gas flow and blood flow passing through the circuit and consequently modulating the patient's respiratory drive.

Also, selected patients may be extubated during awake ECMO. However, to date, clear evidence of improved outcomes has not been found in this setting. On the other hand, it is paramount to cautiously select patients, considering that any significant circuit malfunction may lead to the need for emergent tracheal intubation.[11]

Beneficial effects of spontaneous breathing

One of the primary advantages of awake ECMO is the preservation of respiratory muscle function. Sedation and mechanical ventilation during traditional ECMO can lead to muscle atrophy and weakness, prolonging the duration of mechanical ventilation and ICU stay. Awake ECMO preserves the integrity of the diaphragm and respiratory muscles by allowing patients to breathe spontaneously, reducing muscle atrophy and facilitating reduced ventilator dependency and early weaning from ECMO support.[12] Indeed, by preserving respiratory muscle strength, patients are better equipped to resume independent breathing once ECMO is discontinued, potentially reducing the duration of mechanical ventilation and ICU stay. Table I summarizes the potential advantages and disadvantages of spontaneous breathing during ECMO.[12]

Avoidance of sedatives and muscle relaxants

Awake ECMO may mitigate the risk of sedation-related complications and adverse events. Sedatives and analgesics used during traditional ECMO can contribute to delirium, prolonged mechanical ventilation, and drug-related side effects. Awake ECMO reduces the incidence of these complications by avoiding or minimizing sedation, facilitating a more favorable clinical course. Additionally, awake patients may exhibit improved hemodynamic stability and neurocog-

Table I.—*Advantages and disadvantages of awake spontaneous breathing during ECMO.*

Awake spontaneous breathing during ECMO	
Advantages	Disadvantages
Ventilation is directed towards better-perfused lung areas, optimizing ventilation-perfusion matching.	Positive transpulmonary pressure during spontaneous breathing and potential patient self-induced lung injury (P-SILI).
Active diaphragm function helps prevent ventilator-induced diaphragm dysfunction associated with controlled mechanical ventilation.	Increased oxygen consumption, carbon dioxide production and potential worsening hypoxemia due to intense respiratory muscle effort during high work of breathing.
Preserved proper chest wall and lung expansion, preventing atelectasis and maintaining functional residual capacity.	Urgent intubation and mechanical ventilation are required in the event of ECMO equipment failure.
Improved venous return, cardiac filling, and pulmonary lymphatic drainage by reducing intrathoracic pressure, in contrasting with mechanical ventilation.	
Avoided endotracheal intubation while maintaining natural defense mechanisms against bacteria, potentially lowering the risk of ventilator-associated pneumonia.	
Reduced need for deep sedation.	
Reduced occurrence of barotrauma.	

nitive function, as sedative agents do not interfere with cardiovascular or cerebral autoregulation.[13]

Physiotherapy and rehabilitation

Awake ECMO enables early mobilization and rehabilitation, which are essential critical care management components. Patients on ECMO are often immobilized due to sedation and mechanical ventilation, increasing the risk of muscle deconditioning, joint contractures, and thromboembolic events. ECMO promotes physical activity and preserves functional capacity by keeping patients awake and ambulatory in the collaborating and spontaneously breathing individual. Research has shown that early mobilization during ECMO support is associated with improved outcomes, including shorter ICU stays and enhanced long-term recovery.[7, 13]

Furthermore, awake ECMO facilitates active physical therapy and rehabilitation. Patients can participate in mobility exercises, such as sitting on the edge of the bed or ambulating with assistance while supported by the ECMO circuit. This early mobilization prevents muscle deconditioning and joint contractures and enhances cardiovascular and respiratory functions and overall functional recovery.[6]

One of the main objections to active physical therapy and mobilization in ECMO patients is a concern about safety and adverse events. Although some severe events have been reported (mainly accidental decannulation or bleeding from cannulation sites), a recent systematic review was not able to demonstrate a particular "effect of physical therapy and mobilization on adverse effects including clinically important bleeding, intracerebral hemorrhage, ischemic digits, accidental decannulation, circuit dysfunction, or new organ damage."[14]

On the other hand, the expected benefits of early rehabilitation were also recently underlined by Polastri *et al.*, who, while acknowledging the potential adverse effects of physical therapy in this setting, define mobilization while on ECMO as "a standard of care," adding that "it is crucial to acknowledge the value of patient mobility in ECMO settings, as rehabilitation has proven to be highly beneficial."[15]

Cannulation sites may influence the incidence of mechanical complications[7,] but these can be minimized by the center's experience[16] and by using a multidisciplinary approach.[17]

Active mobilization of ECMO patients is feasible and safe when undertaken by an expert multidisciplinary team and can lead to improved short- and long-term outcomes.

Neuropsychological aspects

In addition to physiological benefits, awake ECMO offers psychological advantages for patients. Besides the reduction in sedative medicines and the resulting decrease in the incidence of delirium and other negative effects of deep sedation, interacting with relatives, friends, and medical staff brings evident benefits. This includes the ability to cope with the "hostile" ICU environment for patients and families. Moreover, the possibility of communicating symptoms and needs to the caring team represents a fundamental tool for the patient from a physical and psychological point of view.[9]

Maintaining consciousness and communication during ECMO support fosters a sense of control and empowerment, alleviating anxiety and mitigating psychological distress. Patients can actively participate in their care decisions, communicate with healthcare providers, and engage in meaningful interactions with family and friends. This patient-centered approach enhances the overall experience of ECMO support and may positively impact psychological well-being and coping mechanisms during critical illness.[7]

Healthcare system

Awake ECMO may offer several economic advantages from a healthcare resource utilization perspective. Reduced sedation requirements and shorter duration of mechanical ventilation can lead to decreased ICU length of stay and lower healthcare costs. Furthermore, early mobilization and rehabilitation may accelerate recovery, potentially reducing the need for prolonged post-ICU care or rehabilitation services. Awake ECMO aligns with values-based care and healthcare sustainability by optimizing resource allocation and promoting efficient use of healthcare resources.

Despite its numerous advantages, awake ECMO presents unique clinical considerations and challenges. Patient selection is crucial, as not all individuals with severe respiratory conditions may be suitable candidates for awake ECMO. Careful assessment of cognitive function, hemodynamic stability, and respiratory drive is essential to ensure patient safety and optimize outcomes. Close monitoring and interdisciplinary collaboration are also imperative for the management of potential complications, such as circuit-related issues, bleeding, and hemodynamic instability.

Clinical applications and outcomes: improving outcomes for end-stage respiratory failure patients awaiting lung transplantation

In patients with advanced lung disease that does not respond to noninvasive ventilation (NIV), invasive mechanical ventilation is considered the only life-saving strategy. However, in cases where prolonged invasive support is required while awaiting for a suitable organ for transplantation, there is a heightened risk of ventilator-associated events and infection-related ventilator-associated complications.

During this waiting period, the ECMO usage has several advantages. It eases the burden on respiratory muscles and corrects imbalances in the oxygen and CO_2 levels, potentially obviating the need for invasive mechanical ventilation. A retrospective study conducted at a single medical center found that maintaining spontaneous breathing during extracorporeal support was associated with lower rates of complication before and after lung transplantation. This resulted in lower mortality rates and shorter hospital stays post-operation than mechanically ventilated patients.[18, 19]

Furthermore, patients on awake ECMO can actively participate in rehabilitation programs, which helps to minimise muscle weakness during transplantation.[20] An analysis of a retrospective cohort at a single centre indicated reduced overall hospital costs for patients who underwent rehabilitation while being supported with ECMO before lung transplantation. This suggests a potential economic advantage associated with physical therapy and ambulation during ECMO compared to conventional methods.[21]

Use of awake ECMO in chronic obstructive pulmonary disease (COPD) patients

Currently, NIV is the primary treatment for COPD exacerbations. However, if NIV fails and invasive mechanical ventilation is needed, the prognosis worsens. Extracorporeal CO_2 removal ($ECCO_2R$) has emerged as a potential strategy to avoid intubation and mechanical ventilation. $ECCO_2R$ in COPD patients helps alleviate respiratory distress and breaks the cycle of dynamic hyperinflation which is often worsened by mechanical ventilation. Despite limited scientific evidence, awake ECMO/$ECCO_2R$ is considered beneficial as it shows promise as an alternative to invasive mechanical ventilation for COPD exacerbations. It reduces ventilatory needs and alleviates dynamic hyperinflation.[22] However, the high rate of complications underscores the importance of carefully weighing the risks and benefits in each case.

Awake ECMO in ARDS patients: challenges in respiratory drive control and high intubation rate

Challenges in respiratory drive control

Implementing awake ECMO in patients with ARDS presents several challenges, especially in regard to controlling respiratory drive and managing the high intubation rate associated with severe respiratory failure.

Controlling respiratory drive in ARDS patients undergoing awake ECMO is a complex clinical dilemma. While it is desirable to maintain spontaneous breathing to prevent VILI and improve patient outcomes, excessive respiratory drive can lead to patient-ventilator dyssynchrony, lung injury and hemodynamic derangement. Achieving a delicate balance between providing adequate respiratory support and avoiding lung injury poses a considerable challenge in the management of ARDS patients on awake ECMO.

Additionally, factors such as underlying lung pathology, patient comorbidities, sedation requirements and ventilatory settings can influence respiratory drive dynamics in ARDS patients. Clinicians must carefully titrate sedation and adjust ventilator parameters to optimize respiratory drive control while ensuring adequate oxygenation and ventilation. Multimodal monitoring, including respiratory rate, tidal volume, arterial blood gases and neurological assessment, is essential for assessing respiratory drive and adjusting management strategies accordingly.[23-25.]

Recent studies have highlighted the potential benefits of advanced respiratory support techniques, such as neurally adjusted ventilatory assist (NAVA) and proportional assist ventilation (PAV), in optimizing respiratory drive control and enhancing patient-ventilator synchrony in ARDS patients on awake ECMO[26-28] These modalities offer personalized respiratory support by synchronizing ventilator assistance with respiratory efforts, thereby minimizing the risk of dyssynchrony and improving patient comfort and outcomes.

High intubation rate

Despite advancements in respiratory support modalities, ARDS patients remain at high risk of requiring invasive mechanical ventilation due to disease progression or worsening respiratory failure. The decision to intubate ARDS patients receiving awake ECMO requires careful consideration, weighing the benefits of airway protection and mechanical ventilation against the potential risks of VILI and sedation-related complications.

Several factors contribute to the high intubation rate observed in ARDS patients, including disease severity, hypoxemia, hypercapnia, respiratory distress, and hemodynamic instability. Early identification of patients at risk of respiratory decompensation and prompt intervention are crucial for mitigating the need for intubation and optimizing patient outcomes.[29]

Moreover, the judicious use of adjunctive therapies, such as prone positioning, neuromuscular blockade, inhaled pulmonary vasodilators and ECCO2R can help stabilize ARDS patients and prevent or delay the need for intubation. These interventions aim to optimize oxygenation, reduce VILI and facilitate lung recovery while maintaining spontaneous breathing and avoiding the adverse effects of mechanical ventilation.[30-32]

Awake ECMO presents a promising approach to managing ARDS patients, potentially improving outcomes and reducing the need for invasive mechanical ventilation. However, challenges in controlling respiratory drive and managing the high intubation rate underscore the importance of individualized patient care and multidisciplinary collaboration in optimizing respiratory support strategies and enhancing patient outcomes.

Awake ECMO in COVID-19 patients

ECMO is a well-established method for managing patients with acute respiratory failure, including those with COVID-19-related ARDS. Although outcomes for COVID-19-related ARDS patients on ECMO tend to be worse compared to non-COVID-19 ARDS cases, evidence from simulated targeted trials suggests a potential benefit of ECMO in selected severe COVID-19-related ARDS patients.[30, 33] More significant benefits are observed in those with severe hypoxemia and those requiring high-intensity mechanical ventilation early in the illness. Success rates are higher in high-volume, specialized centers. VV ECMO has been utilized in COVID-19-related ARDS patients with right heart failure to enhance myocardial contractility by normalizing pH and reducing $PaCO_2$, thereby decreasing pulmonary vascular resistance.[29] In refractory cases, VA ECMO and hybrid configurations have shown success. In cases of prolonged respiratory failure, ECMO serves as a bridge to lung transplantation. Research is needed to identify early interventions that can enhance in-hospital outcomes and alleviate strain on healthcare systems due to later health complications.

Limited reports of awake ECMO in selected COVID-19 cases

Despite the theoretical benefits of awake-ECMO in terms of gas exchange, respiratory effort and mobility, most patients ultimately required endotracheal intubation. Acute complications such as bleeding or pneumothorax, along with bacterial superinfections, sepsis, and disease progression, led to respiratory exhaustion despite combined VV ECMO and NIV treatment.

In a recent study, we identified the patients who had the Macklin effect on baseline CT; the Macklin effect is a radiological sign correlated with the onset of barotrauma, such as pneumothorax or pneumomediastinum if these patients underwent mechanical ventilation.[34] Belletti *et al.*, in a recent meta-analysis, confirmed this data.[35] Considering this alert, in our minimal case series, we have adopted a different approach; at the moment, the patient with the Macklin effect required mechanical ventilation instead of intubation, and we proceeded with the awake ECMO in spontaneous breathing.[30] We concluded that early application of awake VV ECMO without IMV in patients with COVID-19 with severe ARDS at high risk for barotrauma (defined as evidence of Macklin-like radiological sign on chest CT) resulted in no barotrauma events and low intubation and mortality rates. Future studies should confirm these findings in broader populations and different clinical settings.[30]

ECMO-related complications

ECMO complications are associated with a significantly higher rate of morbidity and mortality. These complications may arise from the underlying pathology necessitating ECMO or the ECMO procedure.

Hemorrhage is the most common ECMO complication in 10-30% of cases.[36] Hemorrhage can occur in the abdominal, retroperitoneal, or intrathoracic regions and at the site of a previous invasive procedure, the cannula site, or the surgical site. Systemic heparinization, platelet dysfunction and clotting factor hemodilution all increase bleeding. Heparin can be reduced or stopped to control bleeding, and platelets and clotting agents can be infused.[37] The infusion of activated factor VII has produced inconsistent outcomes and should be reserved for life-threatening bleeding, administered only after all other measures have been exhausted.[38]

Although systemic thromboembolism caused by thrombus formation within the extracorporeal circuit is a rare complication, it can be fatal. It has a more significant impact with VA ECMO than with VV ECMO.

Heparin-induced thrombocytopenia (HIT) can occur in patients on ECMO. Once HIT is confirmed, a non-heparin anticoagulant should replace the heparin infusion. Among these patients, 37% experienced cerebral infarction or intracranial hemorrhage (ICH), 15% had focal hemorrhage, 9% had focal infarction and 13% had general brain edema.[38, 39]

Oliguria is a common early renal complication of ECMO. Some patients exhibit acute tubular necrosis and may require hemofiltration and dialysis.[40] Septic issues may also arise due to the frequent adjustment of the ECMO circuit, increasing the risk of infection.

Metabolic problems during ECMO, such as hypo- or hyperglycaemia and electrolyte abnormalities, can also occur. Additionally, ECMO may alter the concentration and volume of certain medications due to diminished liver or kidney function and an increased volume of distribution, potentially resulting in the ineffectiveness of the administered therapies.[41]

Conclusions

Patients undergoing ECMO require sedation to minimize discomfort and facilitate mechanical ventilation. The "awake ECMO" is when patients remain conscious and spontaneously breathe while supported by the extracorporeal circuit. This approach helps preserve respiratory muscle function, facilitate mobilization, enhance psychological well-being and mitigate sedation-related complications. It presents a promising approach to the management of patients with ARDS, including those with COVID-19. It also benefits patients who underwent active physical therapy and mobility exercises while supported with ECMO before lung transplantation. This approach offers the potential to reduce the need for invasive mechanical ventilation to enhance early rehabilitation and improve patient outcomes.

Key messages

- Veno-venous extracorporeal membrane oxygenation temporarily assists failing lungs by circulating the patient's blood through an extracorporeal circuit that oxygenates and decarboxylates it.

• The innovative concept of awake ECMO has emerged as a promising strategy to mitigate sedation-related complications and facilitate early mobilization in critically ill patients.

• Advantages of awake ECMO: preservation of respiratory muscle function, reduction of muscle atrophy, reduced ventilator dependency, early weaning from ECMO support, early mobilization and rehabilitation, allowing patients to actively participate in their care decisions.

• Despite the theoretical benefits of awake ECMO in terms of gas exchange, respiratory effort, and mobility, most patients ultimately require endotracheal intubation.

References

1. Fichtner F, Moerer O, Weber-Carstens S, Nothacker M, Kaisers U, Laudi S; Guideline group. Clinical Guideline for Treating Acute Respiratory Insufficiency with Invasive Ventilation and Extracorporeal Membrane Oxygenation: Evidence-Based Recommendations for Choosing Modes and Setting Parameters of Mechanical Ventilation. Respiration 2019;98:357–72.

2. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, *et al.*; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med 2018;378:1965–75.

3. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, *et al.*; Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA 2009;302:1888–95.

4. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, *et al.*; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351–63.

5. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, *et al.*; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020;396:1071–8.

6. Alessandri F, Di Nardo M, Ramanathan K, Brodie D, MacLaren G. Extracorporeal membrane oxygenation for COVID-19-related acute respiratory distress syndrome: a narrative review. J Intensive Care 2023;11:5.

7. Cucchi M, Mariani S, De Piero ME, Ravaux JM, Kawczynski MJ, Di Mauro M, *et al.* Awake extracorporeal life support and physiotherapy in adult patients: A systematic review of the literature. Perfusion 2023;38:939–58.

8. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013;369:2126–36.

9. Langer T, Santini A, Bottino N, Crotti S, Batchinsky AI, Pesenti A, *et al.* "Awake" extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. Crit Care 2016;20:150.

10. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, *et al.* Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016;42:1567–75.

11. Belletti A, Sofia R, Cicero P, Nardelli P, Franco A, Calabrò MG, *et al.* Extracorporeal Membrane Oxygenation Without Invasive Ventilation for Respiratory Failure in Adults: A Systematic Review. Crit Care Med 2023;51:1790–801.

12. Kluge S, Braune S, Engel M. Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. Intensive Care Med 2020;46:1905–7.

13. Broman LM, Eksborg S, Nilsson K. Sedation during extracorporeal membrane oxygenation–a nationwide study. Crit Care (Fullerton) 2016;20:1–8.

14. Rivera JD, Fox ES, Fernando SM, Tran A, Brodie D, Fan E, *et al.* Physical Rehabilitation and Mobilization in Patients Receiving Extracorporeal Life Support: A Systematic Review. Crit Care Explor 2024;6:e1095.

15. Polastri M, Eden A, Swol J. Rehabilitation for adult patients undergoing extracorporeal membrane oxygenation. Perfusion 2024;39(suppl):115S–26S.

16. Tonna JE, Bailey M, Abrams D, Brodie D, Hodgson CL. Predictors of early mobilization in patients requiring VV ECMO for greater than 7 days: an international cohort study. Heart Lung 2023;62:57–63.

17. Wells CL, Forrester J, Vogel J, Rector R, Tabatabai A, Herr D. Safety and Feasibility of Early Physical Therapy for Patients on Extracorporeal Membrane Oxygenator: University of Maryland Medical Center Experience. Crit Care Med 2018;46:53–9.

18. Fuehner T, Kuehn C, Hadem J, Wiesner O, Gottlieb J, Tudorache I, *et al.* Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012;185:763–8.

19. Hakim AH, Ahmad U, McCurry KR, Johnston DR, Pettersson GB, Budev M, *et al.* Contemporary Outcomes of Extracorporeal Membrane Oxygenation Used as Bridge to Lung Transplantation. Ann Thorac Surg 2018;106:192–8.

20. Turner DA, Cheifetz IM, Rehder KJ, Williford WL, Bonadonna D, Banuelos SJ, *et al.* Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: a practical approach. Crit Care Med 2011;39:2593–8.

21. Secretariat MA. Extracorporeal lung support technologies - bridge to recovery and bridge to lung transplantation in adult patients: an evidence-based analysis. Ont Health Technol Assess Ser 2010;10:1–47.

22. Strudthoff LJ, Lüken H, Jansen SV, Petran J, Schlanstein PC, Schraven L, *et al.* In Vitro and In Vivo Feasibility Study for a Portable VV-ECMO and ECCO2R System. Membranes (Basel) 2022;12:133.

23. Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Bréchot N, *et al.* Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults. Intensive Care Med 2013;39:838–46.

24. Vaporidi K, Akoumianaki E, Telias I, Goligher EC, Brochard L, Georgopoulos D; Pathophysiology and Clinical Implications. Respiratory Drive in Critically Ill Patients. Am J Respir Crit Care Med 2020;201:20–32.

25. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81.

26. Ghizlane EA, Manal M, Sara B, Choukri B, Samia B, Abderrahim EK, *et al.* Early initiation of awake venovenous extracorporeal membrane oxygenation (ECMO) in critical COVID-19 pneumonia: A case reports. Ann Med Surg (Lond) 2021;68:102641.

27. Barbaro RP, MacLaren G, Boonstra PS, Combes A, Agerstrand C, Annich G, *et al.*; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. Lancet 2021;398:1230–8.

28. Li T, Yin PF, Li A, Shen MR, Yao YX. Acute Respiratory Distress Syndrome Treated With Awake Extracorporeal Membrane Oxygenation in a Patient With COVID-19 Pneumonia. J Cardiothorac Vasc Anesth 2021;35:2467–70.

29. Paternoster G, Bertini P, Innelli P, Trambaiolo P, Landoni G, Franchi F, *et al.* Right Ventricular Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. J Cardiothorac Vasc Anesth 2021;35:3319–24.

30. Paternoster G, Bertini P, Belletti A, Landoni G, Gallotta S, Palumbo D, *et al.* Venovenous Extracorporeal Membrane Oxygenation in Awake Non-Intubated Patients With COVID-19 ARDS at High Risk for Barotrauma. J Cardiothorac Vasc Anesth 2022;36(8 Pt B):2975–82.

31. Hoeper MM, Wiesner O, Hadem J, Wahl O, Suhling H, Duesberg C, *et al.* Extracorporeal membrane oxygenation instead of invasive mechanical ventilation in patients with acute respiratory distress syndrome. Intensive Care Med 2013;39:2056–7.

32. Galante O, Hasidim A, Almog Y, Cohen A, Makhoul M, Soroksky A, *et al.*; Awake ECMO Research Team. Extracorporeal Membrane Oxygenation in Nonintubated Patients (Awake ECMO) With COVID-19 Adult Respiratory Distress Syndrome: the Israeli Experience. ASAIO J 2023;69:e363–7.

33. Fujishima S. Guideline-based management of acute respiratory failure and acute respiratory distress syndrome. J Intensive Care 2023;11:10.

34. Paternoster G, Belmonte G, Scarano E, Rotondo P, Palumbo D, Belletti A, *et al.*; COVID-Macklin Study Group. Macklin effect on baseline chest CT scan accurately predicts barotrauma in COVID-19 patients. Respir Med 2022;197:106853.

35. Belletti A, Pallanch O, Bonizzoni MA, Guidi L, De Cobelli F, Landoni G, *et al.* Clinical use of Macklin-like radiological sign (Macklin effect): A systematic review. Respir Med 2023;210:107178.

36. Bartlett RH, Gattinoni L. Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. Minerva Anestesiol 2010;76:534–40.

37. Hemmila MR, Rowe SA, Boules TN, Miskulin J, McGillicuddy JW, Schuerer DJ, *et al.* Extracorporeal life support for severe acute respiratory distress syndrome in adults. Ann Surg 2004;240:595–605.

38. Wittenstein B, Ng C, Ravn H, Goldman A. Recombinant factor VII for severe bleeding during extracorporeal membrane oxygenation following open heart surgery. Pediatr Crit Care Med 2005;6:473–6.

39. Mateen FJ, Muralidharan R, Shinohara RT, Parisi JE, Schears GJ, Wijdicks EF. Neurological injury in adults treated with extracorporeal membrane oxygenation. Arch Neurol 2011;68:1543–9.

40. Villa G, Katz N, Ronco C. Extracorporeal Membrane Oxygenation and the Kidney. Cardiorenal Med 2015;6:50–60.

41. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care 2012;27:741.e9–18.

Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Gianluca Paternoster and Pietro Bertini made substantial contributions to the conception of the manuscript. Gianluca Paternoster, Pietro Bertini, and Fabio Sangalli wrote each paragraph after examining the most current data. Sabino Scolletta critically revised the manuscript. All authors read and approved the final version of the manuscript.

History
Article first published online: December 10, 2024. - Manuscript accepted: September 18, 2024. - Manuscript revised: September 12, 2024. - Manuscript received: April 19, 2024.