



## POINT OF VIEW

# ECMO in ARDS: Key points of indication criteria and management<sup>☆</sup>



## ECMO en SDRA: puntos clave en la indicación y en el abordaje asistencial

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«Quality is the continuing stimulus which our environment puts upon us to create the world in which we live»

Robert M. Pirsig, *Zen and the Art of Motorcycle Maintenance: An Inquiry into Values*

The use of the extracorporeal membrane oxygenation (ECMO) technique in its venovenous configuration (VV) in patients with acute respiratory distress syndrome (ARDS) has increased over the last 15 years as a consequence of a notable optimization of devices (more biocompatible, more compact), and the appearance of solid studies in relation to the benefits of its application.<sup>1,2</sup> During the COVID-19 pandemic this use has increased due to the profile of this disease regarding severity and contagiousness.<sup>3</sup> This is very much so to the extent that on demand peaks there was a significant lack of these devices. Currently, the VV ECMO indication

criteria, and the management of patients who receive this support have been perfected.

This manuscript discusses the role of this therapy for the management of ARDS schematically. Initially, an analysis of the latest news regarding the indication of the technique is performed. Then, the key takeaways in the complex clinical approach of critically ill patients with this kind of support are revisited.

### Indication for VV-ECMO in patients with ARDS

To this date, despite being a very effective tool to guarantee proper gas exchange and reduce significantly pulmonary aggression, it is the ultimate step in the healthcare algorithm of refractory hypoxemia. This is so due to the complexity associated with its proper management, and association with an elevated use of resources and a higher risk for developing serious complications. Currently, the indication for this kind of support should only be considered if the prone positioning maneuver has proven ineffective. The definition of maneuver ineffectiveness varies depending on the different studies and protocols regarding the duration of prone positioning trial (from 6 h to 12 h), and on the

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impact the maneuver has (from any increase up to a cut-off value of 20% of  $\text{PaO}_2/\text{F}_1\text{O}_2$ ).

One of the keys of success of the ECMO program is to indicate the technique in patients who will benefit from it, which puts ECMO in no one's land between 2 extremes that are that scenario where the indication is futile, and that other scenario where less aggressive maneuvers would be enough to reach respiratory stability. The indications and contraindications proposed by the Extracorporeal Life Support Organization (ELSO), and the exclusion and inclusion criteria used in the CESAR and EOLIA clinical trials are shown on Table 1. In the analysis of these variables the following points should be stressed out—considered of special interest—due to their great impact in the assessment of cases and for the lack of new information from recent studies:

- Since ECMO is not a therapy *per se* but a support system it is essential to identify that the baseline process is reversible. As the CESAR trial indicates, this interpretation involves, to a greater or lesser extent, a criterion of subjectivity for physicians. In any case, the indication for this treatment can be a bridge therapy until diagnosis is achieved or else to ease off disease progression after which the intensity of the support maneuvers can be adjusted. In patients with COVID-19-related ARDS and extended ECMO therapy, the possibility of lung transplantation has been proposed as a final therapy of the baseline process.<sup>4</sup> This clinical situation is controversial due to the criterion of irreversibility of the pulmonary process and the adjustment of this *de novo* indication in a difficult context of available resources, especially in the current pandemic situation. In any case, the cases considered eligible (young patients with multi organ failure with possibility of active rehabilitation waiting for transplantation) should be assessed at a lung transplantation center.
- Regarding the identification limits of a situation of hypoxemia and hypercapnia, rather than defining a strict cut-off value regarding  $\text{PaO}_2/\text{F}_1\text{O}_2$  and/or pH or  $\text{PaCO}_2$ , what we should be doing is to examine disease progression in every patient especially if the patient is under distant assessment by the ECMO center.
- Except for the uncommon use of the Murray score, respiratory system compliance when ECMO is indicated has not been included as a criterion under consideration. However, data shows that this variable could play a relevant role in the success of the decision-making process. A still not very well-defined role to this date since excessive pulmonary elastance can translate into an irreversible pulmonary insult or else precisely patients with poorly compliant lungs may be the ones who benefit the most from the ultraprotective ventilation provided by ECMO. In the EOLIA clinical trial, the benefit of ECMO support was especially significant in patients with an indication for respiratory acidosis compared to the control group.<sup>2</sup> On the other hand, in the multivariate analysis of in-hospital mortality of the ECMOVIBER clinical trial that included 24 centers from the Iberian Peninsula that provided extracorporeal respiratory support to 319 patients with COVID-19-related ARDS, driving pressure was identified as one of the variables most associated with a higher mortality risk (higher pressure is equivalent to higher risk).<sup>5</sup> In addition to this context of uncertainty, we should mention the difficulties involved trying to obtain accurate measurements of this parameter, and the relevance of the extrapulmonary component in the values obtained. Therefore, more solid data is required to identify the actual role of respiratory system compliance when ECMO is indicated in patients with ARDS.
- The duration of mechanical ventilation (MV) when extracorporeal support is indicated is a variable that is often poorly interpreted, which has had a tremendous impact on the indication for this therapy, especially during the COVID-19 pandemic. ELSO defines this variable as a relative and specific contraindication that this criterion involves the use of aggressive MV with elevated oxygen concentration and plateau pressure levels for a 7-day period. Also, in the same chapter, ELSO claims that many centers do not consider it a contraindication. The ECMOVIBER trial did not identify any associations between this variable and in-hospital survival, a finding that is consistent with other studies.<sup>5,6</sup> However, taking this time interval into consideration in the indication for starting ECMO support is advised, not as a direct effect but by including other factors indirectly in this variable that would play a more relevant role in the risk of failure after starting ECMO support like extended sedorelaxation or a higher risk for respiratory infectious events.
- There is a clear correlation between mortality and age. Establishing a specific limit is controversial being 65 years old the most common cut-off value as a relative contraindication in patients with ARDS.
- As a common practice and yet despite the biocompatibility of the current extracorporeal systems, a patient on ECMO support would require a certain degree of *anticoagulation*. However, the impossibility of anticoagulating the patient is not longer a contraindication (present in the CESAR trial) for starting support (not included as an exclusion criterion in the EOLIA trial).
- *Immunosuppression* is a common finding as a relative contraindication to starting ECMO support. It is included by ELSO as a criterion with a remarkably non-specific definition. This is due to the negative results reported on the use of this maneuver in patients with bone marrow transplants, especially in the pediatric population. However, what probably plays a significant role is the actual impact of this immunosuppression in the clinical status of the patient. Just to mention 2 examples of this, the prognosis of a patient with Aspergillosis is worse compared to that of a patient on chronic corticoid therapy. On the other hand, this variable should be dealt with in all its complexity.
- *Obesity* has a negative impact *per se* on disease progression due to the complex mechanisms resulting from an aberrant response to the acute process. However, it should not be considered an absolute contraindication unless cannulation is impossible.
- As it occurs with reversibility, *futility* has an unquestionable subjective component that has been approached by generating different scores that can help in the decision-making process.<sup>7</sup> As Table 1 shows, in the CESAR and EOLIA clinical trials a significant number of patients were excluded because the start of ECMO support was

**Table 1** Indications and contraindications proposed by the Extracorporeal Life Support Organization (ELSO) on the start of VV-ECMO support in adult patients. Indication and exclusion criteria in the CESAR and EOLIA clinical trials. The number of patients excluded for every criterion is specified within the exclusion criteria.

**ELSO**

**Indications**

1. Hypoxemia
  - a) Consider when  $PaO_2/FiO_2 < 150$  mmHg with a  $FiO_2$  of 0.9, and/or a Murray score of 2-3
  - b) Indicate when  $PaO_2/FiO_2 < 100$  mmHg with a  $FiO_2$  of 0.9 and/or a Murray score of 3-4 despite bailout measures for over 6 h
2. Retention of carbon dioxide despite MV with high plateau pressure ( $> 30$  cmH<sub>2</sub>O)
3. Severe aerial leak
4. Need for intubation in patient on a lung transplant waiting list

**Contraindications**

As an absolute contraindication we would only find the futility of the technique. However, there are conditions associated with worse results after the application of support that could be considered relative contraindications:

1. Aggressive mechanical ventilation ( $FiO_2 > 0,9$ ,  $Pplat > 30$  cmH<sub>2</sub>O) for over 7 days
2. Pharmacological immunosuppression with neutrophil count  $< 400/mm^3$
3. Hemorrhage in the central nervous system
4. Age: no cut-off value established, but the risk increases proportionally to the age of the patient

Source: <https://www.elso.org/Resources/Guidelines.aspx>

CESAR clinical trial (766 patients studied, 180 randomized, 90 from the ECMO group)

**Inclusion criteria**

1. Reversible process considered as such by, at least, 1 of the 3 ECMO experts
2. Age  $> 18$  years and  $< 65$  years
3. Hypoxemia
  - a) Indicated with a Murray score of  $\geq 3.0$
  - b) Indicated with a Murray score of  $\geq 2.5$
4. Decompensated hypercapnia with  $pH < 7.2$  despite optimized conventional management

**Exclusion criteria and number of patients excluded by each criterion**

- |  |        |
|--|--------|
| 1. Futility  | 81     |
| 2. Aggressive mechanical ventilation ( $FiO_2 > 0.8$ , $Pplat > 30$ cmH <sub>2</sub> O) for $> 7$ days | 86     |
| 3. Signs of intracranial bleeding or a different contraindication to herparinization                   | 3 + 31 |
| 4. Bed not available at the ECMO Center Glenfield Hospital, Leicester, United Kingdom                  | 103    |

EOLIA clinical trial (1015 patients studied, 249 randomized, 124 from the ECMO group)

**Inclusion criteria**

1. Age  $> 18$  years
2. Hypoxemia
  - a)  $PaO_2/FiO_2 < 50$  mmHg for  $> 3$  h
  - b)  $PaO_2/FiO_2 < 60$  mmHg for  $> 6$  h
3. Hypercapnia:  $PaCO_2 > 60$  mmHg, and  $pH < 7.25$  for  $> 6$  h

Assessment conditions of these criteria:

- a)  $FiO_2 \geq 0.8$ ,  $PEEP \geq 10$  cmH<sub>2</sub>O
- b) Respiratory rate, 35 rpm
- c)  $Pplat \leq 32$  cmH<sub>2</sub>O, TV of 6 mL/kg of ideal weight
- d) Recommendation on the use of neuromuscular block, and prone positioning maneuver
- e) Use of different maneuvers (nitric, recruitment maneuvers, HFOV...) according to the treating intensivist's clinical judgement

**Exclusion criteria and number of patients excluded by each criterion**

- |   |     |
|---|-----|
| 1. Mechanical ventilation for $> 7$ days                          | 130 |
| 2. Pregnancy  | NA  |
| 3. BMI $> 45$   | 30  |
| 4. Chronic respiratory failure in need for O <sub>2</sub> or NIMV | 57  |
| 5. Hemodynamic instability with a criterion for VA-ECMO           | 66  |
| 6. Cardiac arrest   | 45  |
| 7. Neoplasm with life expectancy $< 5$ years                      | 48  |
| 8. SAPS-II $> 90$   | 86  |
| 9. Irreversible neurological region                               | NA  |
| 10. Decision on limitation of life-sustaining treatment           | 50  |
| 11. Extremely challenging femoral or jugular vascular accesses    | NA  |
| 12. ECMO device not available                                     | 4   |

considered futile. In complex cases, decision has to be collaborative including the most experienced experts from each *ECMO Center* even looking for opinions from other expert centers and using collaborative clinical networks. On this matter, it is extremely important that the *ECMO Center* stays in touch with all the centers it provides coverage to through fluid bidirectional dialogue.

## Healthcare algorithm of patients with ARDS on VV ECMO support

The complexity of the clinical scenario of a critically ill patient with extracorporeal life support has to do with the presence of multiple factors that have a direct impact on the patient's survival. A well-defined anticoagulation protocol, adequate adjustment of mechanical ventilation parameters, protocolized training for the entire staff, and multidisciplinary teamwork to guarantee the patients' safety are some of these important variables that modulate the actual impact of the technique during disease progression. [Table 2](#) shows the key takeaways in the management of a patient with ARDS and VV-ECMO support. The healthcare algorithm includes:

- The *concentration of cases* in high volume centers is essential to guarantee good results.<sup>8</sup> Recommendation for centers that start a program and, therefore, have few cases at the beginning is to join forces with another more consolidated *ECMO Centers* with which to stay in touch to monitor results and receive advice from both for indication and management purposes, and even on the association between training and retraining programs.<sup>9</sup> Based on this, it is essential to structure healthcare based on the territory at stake,<sup>10</sup> and then establish collaborative networks among the different *ECMO Centers* both at clinical and research levels.<sup>3,5</sup>
- The *ECMO team* has to be multidisciplinary and involved in all the medical specialties associated with the technique like cardiac surgery, anesthesiology, and cardiology. This team needs to be led by the physician who is treating the critically ill patient. This has been associated with better outcomes and with a more comprehensive vision of this specialist in a multidimensional clinical context where a *decentralized or fragmented* model is accompanied by an inherent risk of oversimplifying the complexity associated with all the stages involved in ECMO support from indication through weaning, and even later stages.<sup>11</sup> From an organizational perspective, a director and a coordinator of the program should be defined to supervise all the clinical and organizational aspects of the team according to the recommendations detailed by the ELSO (<https://www.else.org/Resources/Guidelines.aspx>).
- The *training* of this *ECMO team* is directly associated with patient's safety and, therefore, is one of the cornerstones of the ECMO program. Training needs to be protocolized and follow the recommendations established by the ELSO (<https://www.else.org/Resources/Guidelines.aspx>). Practical training of the entire ECMO team through workshops where the teams come into direct contact with the material used in this therapy (pumps, ventilators, cannulas, circuits, monitoring systems) is especially relevant. Also, training through advanced simulations to facilitate the creation of complex clinical settings where multidimensional competences can be more easily acquired. Maintaining these competences is also important so we should take into consideration both the volume of cases managed by the center and the number of healthcare workers with specific training.
- One of the keys of success is select the right *configuration of cannulation* that should be individualized based on the clinical situations. As an example of this, patients with COVID-19-related ARDS often require an elevated blood flow that requires the insertion of a thick drainage cannula.<sup>5</sup> On the other hand, patients who require an aggressive negative fluid balance will benefit from placing drainage into the jugular vein for keeping the stability of extracorporeal flow in this context. Finally, patients with residual pulmonary function who benefit from early rehabilitation (*awake ECMO*) can benefit from placing a dual-lumen cannula into the right jugular vein although rehabilitation—even walking—in patients treated with femoral cannulation is feasible as well.
- ECMO is not a therapy *per se*, but it *facilitates the application of diagnostic-therapeutic maneuvers* that would have been unacceptably life-threatening without ECMO support. The computed tomography scan allows more refined assessments of the situation of the pulmonary parenchyma, as well as the identification of concomitant conditions due to treatment like pulmonary thromboembolism, a common finding in COVID-19. Similarly, extracorporeal respiratory support allows performing a fiber bronchoscopy that facilitates the secretion drainage and sample drawing to adjust the antibiotic therapy of these patients.
- Another 2 actions facilitated by extracorporeal support that have a relevant impact on the evolution of these patients are the adjustment of MV parameters towards *ultraprotective ventilation* facilitating the total weaning of the patient from the ventilation, and the *early start of rehabilitation* even before pulmonary recovery.<sup>12</sup> Several approaches have been described to adjust ventilation, but there is not such a thing as a *gold standard* yet. The algorithm used in the EOLIA trial, described in the supplementary material is not very specific including 2 different setting modes (ACV or APRV), wide adjustment ranges (0.3-0.5 for the  $F_{I}O_2$ , 10-30 rpm for the heart rate), and a very general recommendation to participant centers to withdraw sedatives as early as possible. In its recommendations, ELSO is a little bit more precise (<https://www.else.org/Resources/Guidelines.aspx>). It defines 2 phases, one 24-48 h early phase of moderate-deep sedation while on the APRV mode (25/15 cmH<sub>2</sub>O) followed by further phases where sedation removal is advised, and spontaneous breathing is promoted on CPAP at 20 cmH<sub>2</sub>O. Prone positioning is not proposed in either one of the 2 protocols as the maneuver that should be used in patients with ARDS on ECMO support. Its use has been associated with potential complications and the benefits derived from its use are not very clear yet.<sup>13</sup> A clinical trial would be very much welcomed to find more solid evidence on its effect as an additional lung protection maneuver and/or recruitment.

**Table 2** Key takeaways in the healthcare algorithm of patients with ARDS and VV-ECMO support.

Blood flow	<ul style="list-style-type: none"> <li>- Adjust flow with the following targets: ultraprotective MV, normal lactate levels, SpO<sub>2</sub> &gt; 80%</li> <li>- Minimize drainage pressure. Use of a thick draining cannula.</li> <li>- An excessive increase of blood flow can increase recirculation and reduce the effectiveness of ECMO support</li> </ul>
Gas flow	<ul style="list-style-type: none"> <li>- Adjustment for PaCO<sub>2</sub> 35-40 mmHg</li> <li>- Increase during rehabilitation or in the presence of an increased metabolic demand</li> <li>- Gas sweep in the presence of water condensation in the chamber</li> <li>- Monitor cerebral NIRS before making significant flow adjustments or changing ventilators</li> <li>- There is no gold standard</li> </ul>
Anticoagulation	<ul style="list-style-type: none"> <li>- The definition of an anticoagulation protocol specific to the center, and training of the entire ECMO team is advised at the follow-up of this protocol</li> <li>- Protocol should always be individualized based on the patient's underlying condition (eg, COVID-19)</li> <li>- Unfractionated heparin and ACT are the most widely used anticoagulant and monitoring system, respectively</li> <li>- Platelet dysfunction in patients on ECMO is something common. Keeping a normal blood platelet count is advised, especially in the presence of bleeding</li> <li>- The non-anticoagulation of a patient on ECMO support with high risk of bleeding is possible, although this strategy increases the risk of circuit and/or patient thrombosis. If anticoagulation is suspended, adjustment of extracorporeal blood flow &gt; 4 lpm is advised.</li> <li>- Hypofibrinogenemia, thrombocytopenia, and elevated D-dimer levels can be indicative of the presence of thrombi in the circuit, which would be suggestive of the need for replacing the circuit.</li> </ul>
Adjustment of MV	<ul style="list-style-type: none"> <li>- Overall target: Minimize aggression</li> <li>- Overall, within the first few days (24 h to 48 h), total lung rest is advised, which often involves analgosedation and relaxation</li> <li>- Afterwards, ECMO support facilitates the start of early rehabilitation while respiratory functional recovery is achieved. Performing an early percutaneous tracheostomy can make this process easier</li> <li>- There is not enough evidence supporting the routine use of the prone positioning maneuver in these patients</li> <li>- Derecruitment within the first few days is ill-advised (PEEP level &gt; 10 cmH<sub>2</sub>O)</li> <li>- Advanced multimodal monitoring with transpulmonary pressure measurement, and EIT is advised</li> </ul>
Analgosedation	<ul style="list-style-type: none"> <li>- Analgesia, deep sedation, and relaxation within the first 24 h to 72 h. Further sedorelaxation withdrawal to start rehabilitation early</li> <li>- The active rehabilitation of patients on ECMO support is feasible and beneficial for the patients. To guarantee safety during rehabilitation, the presence of a properly trained multidisciplinary team is essential</li> <li>- During the wake-up phase, a too energetic effort of breathing could worsen the evolution of breathing. Specific monitorization (eg, via esophageal pressure catheter) in this phase of respiratory stimulus recovery is advised.</li> <li>- The doses of analgesic drugs and sedatives should be adjusted while taking into consideration changes to the pharmacokinetics and pharmacodynamics of patients on ECMO support.</li> </ul>
Fluid balance and kidney support	<ul style="list-style-type: none"> <li>- Negative daily fluid balance is advised.</li> <li>- Extracorporeal blood purification systems can be integrated within the circuit. However, most circuits available are not designed for this purpose</li> <li>- Sudden worsening of renal function without a common explanation may be suggestive of circuit dysfunction, and hemolysis, and of the need for circuit replacement.</li> </ul>

Table 2 (Continued)

Antibiotic therapy	<ul style="list-style-type: none"> <li>- There is no clear evidence on the benefits associated with the routine use of antibiotic prophylaxis</li> <li>- The impact infectious complications have on survival is high. Sepsis is one of the leading causes of death among these patients</li> <li>- The common signs associated with infectious processes (fever, leukocytosis, elevated CRP levels. . .) are often absent in patients on ECMO support. However, in this clinical scenario, coagulation alterations from bleeding to the excessive production of thrombi in the circuit are a common finding.</li> <li>- Drawing samples from the suspected infectious focus and blood is advised both from the patient and through the circuit if the existence of an active infectious process is suspected. Routine sample drawing is ill-advised.</li> <li>- The early administration of evidence-based antibiotic therapy is advised on suspicion of an active infectious process with broad-spectrum antibacterial and antifungal therapy</li> <li>- The dose of antibiotics should be adjusted taking into consideration changes to the pharmacokinetics and pharmacodynamics of patients on ECMO support</li> </ul>
Hemodynamics	<ul style="list-style-type: none"> <li>- Routine monitorization with echocardiography paying special attention to right ventricular function, particularly in patients with extended support or collapsed lung</li> <li>- Adjustment of vasoactive and inotropic agents according to the routine protocol</li> <li>- The routine use of advance monitoring systems is ill-advised</li> </ul>
Weaning	<ul style="list-style-type: none"> <li>- Weaning from the ECMO system can be done before, after or while weaning from MV</li> <li>- After evidence of respiratory improvement (gas exchange, pulmonary mechanics, radiological), gas flow through the ventilator is suspended and the clinical status of the patient is assessed</li> <li>- No need to reduce blood flow</li> <li>- The continuous monitorization of SvO<sub>2</sub> performed by the device often provides extremely valuable information on the weaning process from ECMO support</li> </ul>

ACT, activated coagulation time; ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; EIT, electric impedance tomography; lpm, liters per minute; MV, mechanical ventilation; NIRS, Near Infrared Spectroscopy; RDS, acuter respiratory distress syndrome; VV-ECMO, venovenous extracorporeal membrane oxygenation.

- *Weaning* from MV can be performed before ECMO. These are 2 different respiratory support systems with different peculiarities each one of them. The decision to put the weaning of one before the weaning of the other is based on a risk/benefit ratio regarding the patient who is being treated with either one of these 2 support systems (eg, in patients with barotrauma, minimizing IPPV should be the priority; in patients with bleeding issues, removing extracorporeal support should be the priority) based on the characteristics of each *ECMO Center* and the healthcare context.

In conclusion, the use of extracorporeal support in the adult patient with ARDS should be performed in the ECMO program setting of the centers managing the cases (*ECMO Center*) with multidisciplinary teams (*ECMO team*) and led by specially trained experts in the management of critically ill patients specifically trained with this technique. The success of these programs is based on the accurate identification of indication criteria, and on the capacity to balance futility and rush based on solid analysis of the scientific evidence available. Also, thanks to multidimensional healthcare protocols the include the entire complexity inevitably associated with this healthcare maneuver.

### Conflicts of interest

None whatsoever.

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