



# Protocol-driven daily optimisation of venovenous extracorporeal membrane oxygenation blood flows: an alternate paradigm?

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**Abstract:** Venovenous extracorporeal membrane oxygenation (VV ECMO) is now an established modality of support for patients with the who are failing evidence-based conventional therapies. Minimising ventilator-induced lung injury is the guiding principle behind patient management with VV ECMO. Patients with acute respiratory distress syndrome (ARDS) supported with VV ECMO are liberated from ECMO at a stage when native lungs have recovered sufficiently to support physiologic demands and the risks of iatrogenic lung injuries after discontinuation of ECMO are perceived to be small. However, native lung recovery is a dynamic process and patients rely on varying degrees of contributions from both native lungs and ECMO for gas exchange support. Patients often demonstrate near total ECMO dependence for oxygenation and decarboxylation early in the course of the illness and this may necessitate higher ECMO blood flow rates (EBFRs). Although, reliance on high EBFR for oxygenation support may remain variable over the course of ECMO, blood flow requirements typically diminish over time as native lungs start to recover. Currently, protocol-driven modulation of the EBFR based on changing physiologic needs is not common practice and consequently patients may remain on higher than physiologically necessary EBFR. This exposes the patient to potential risks because maintaining higher blood flows often requires a less restrictive fluid balance and deeper sedation. Both may be harmful in the setting of recovery from ARDS. In this article, we propose a strategy that involves daily assessments of native lung function and a protocol-driven daily optimisation of EBFR. This is followed by optimisation of sweep gas flow rate (SGFR) and the fraction of delivered oxygen in the sweep gas (F<sub>dO<sub>2</sub></sub>). This staged approach to weaning VV ECMO allows us to fully utilise the “decoupling” of oxygenation and decarboxylation that is possible only during extracorporeal support. This approach may benefit patients by allowing for greater fluid restriction, more aggressive fluid removal, expedited weaning of sedation and neuromuscular blocking agents (NMBAs), and early physical rehabilitation. Ultimately, prospective studies are needed to evaluate optimal VV ECMO weaning practices

**Keywords:** Extracorporeal membrane oxygenation (ECMO); acute respiratory distress syndrome (ARDS); awake ECMO; weaning

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The optimal technique for weaning venovenous extracorporeal membrane oxygenation (VV ECMO) in the setting of the acute respiratory distress syndrome (ARDS) has not been clearly established and remains variable indicating that there may be multiple techniques possible (1-3). Traditional approaches to weaning VV ECMO typically consider the ECMO blood flow rate (EBFR) as a “fixed” variable, and recommend a weaning strategy (4) based on down-titration of the sweep gas flow rate (SGFR) or the fraction of delivered oxygen in the sweep gas flow ( $FdO_2$ ). While this approach is physiologically sound, it preserves the EBFR rate even though the patient’s need for support may decrease as the patient approaches weaning readiness with diminishing dependency on the EBFR for adequate arterial oxygenation over time. Assuming sweep gas flow is turned on,  $FdO_2$  is set appropriately, and the gas exchange device is functioning adequately, oxygenation in the pulmonary artery during ECMO is then largely driven by the EBFR relative to the native cardiac output (CO) of the patient.

The EBFR is controlled by changing the power of the pump. It is dependent on cannula type, size and location—affecting drainage and reinfusion pressures—and on the venous return (5,6). As the patient’s CO, oxygen consumption and ability to oxygenate through the native lung are dynamic variables, EBFR may be actively titrated to optimize the ECMO blood flow/CO ratio in order to achieve a desired oxygenation target (5,7). Patients typically transition from a state of total or near total ECMO dependency (for oxygenation and decarboxylation) in the initial days of support to partial ECMO dependency, to some ECMO dependency, which in the majority of cases is largely for decarboxylation as ECMO weaning becomes imminent (*Figure 1*). In this setting, maintaining high EBFRs for the entire duration of ECMO provision may potentially lead to unnecessary and potentially harmful support levels. High EBFR relative to cannula size may cause high pressures and cellular destruction (8). In addition, the perceived need to maintain what are essentially higher than necessary EBFRs, requires the maintenance of adequate venous filling. Since negative fluid balance is one of the main treatment options in ARDS, this may impair diuresis or hemofiltration and could therefore lead to delays in weaning from VV ECMO.

This paper describes a potential alternate approach that involves daily optimisation of the EBFR and SGFR, as appropriate, leading up to weaning of SGFR and  $FdO_2$  prior to liberation from ECMO. With this in mind, there

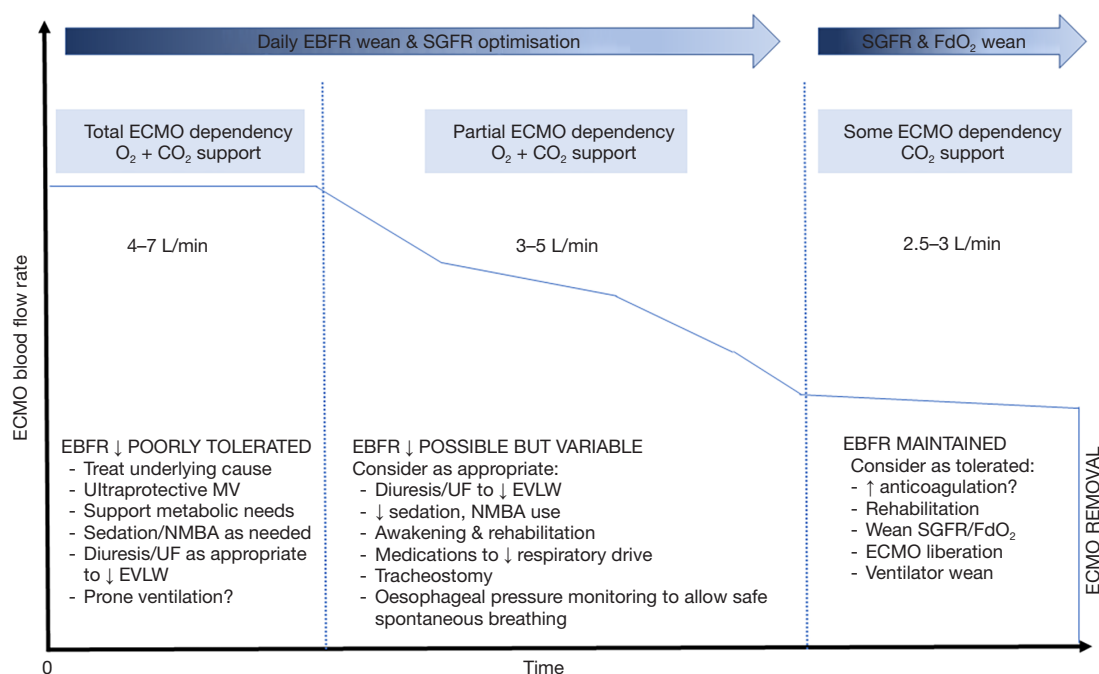
are three key steps involved (*Box 1*).

To allow for safe, gradual weaning of the EBFR, a daily EBFR down-titration test is performed in 300 mL/min decrements to establish the lowest tolerable EBFR while maintaining ultra-protective ventilation and arterial oxygen saturation  $\geq 88\%$  (some centres will choose alternate oxygenation targets that, if lower, will be easier to achieve). During this early EBFR weaning phase ventilator  $FiO_2$  is maintained at  $\leq 50\%$  if tolerated,  $FdO_2$  is set at 100%. If there is desaturation during the weaning process, the EBFR will be up titrated at 300 mL/min increments to achieve target  $SpO_2$ . If this is not possible to achieve, sources of continued hypoxemia should be identified, including high CO states, recirculation and poor gas exchange within the oxygenator. It should be noted that, similar to SGFR, EBFR can always be increased or decreased based on metabolic demands and fluctuations in CO during ongoing care between these daily tests.

Optimal haemoglobin (Hb) targets in VV ECMO are not clearly defined. EBFR, Hb and CO play a critical role in ensuring optimal oxygen delivery during VV ECMO. Studies suggest an inverse relationship between Hb and EBFR in determining arterial and venous oxygen delivery, when CO and systemic oxygen consumption are held relatively constant (9). In this setting, although a higher Hb may appear justifiable, the risk-to-benefit ratio of maintaining a higher Hb target (e.g., 10–12 g/dL), is unknown. Available data indicate that a restrictive transfusion strategy is feasible on VV ECMO (10). Importantly, the chosen systemic oxygen target has a significant bearing on the EBFR required to achieve that target and aiming for higher targets than physiologically necessary may predispose a patient to the potential risks of these higher than necessary EBFRs.

Once a safe lower limit for EBFR for any given day is established, a 100% fraction of inspired oxygen test is performed by increasing ventilator  $FiO_2$  to 100% for 15 minutes while  $FdO_2$  is set at 100%. A  $PaO_2 \geq 250$  mmHg on a positive end expiratory pressure (PEEP) of  $\leq 10$  cmH<sub>2</sub>O is considered a successful 100% fraction of inspired oxygen test. The test can provide trends in oxygen transfer across native lungs ( $VO_{2NL}$ ), so long as the oxygen transfer through the oxygenator ( $VO_{2ML}$ ) remains stable. However, this trend is heavily influenced by changes in oxygen transfer, systemic oxygen consumption and CO. Interpretation of the test requires understanding the clinical context at the time it is performed.

Where available, volumetric capnometry can help



**Figure 1** A typical course of VV ECMO during which a patient progresses through varying degree of ECMO dependency. There is significant variability in EBFR requirements between patients and the EBFRs chosen here are for illustrative purposes only. Patients also show great variability in their lung healing process and their physiology which is dynamic and non-linear. It may be possible to down-titrate EBFRs in most patients, which may be potentially beneficial. It is easy to up-titrate EBFRs if there is increase in the metabolic needs or the CO of the patient. Similarly, SGFR may need daily optimisation based on the patient's physiology and improvements in CO<sub>2</sub> removal across the native lung over time. VV ECMO, venovenous extracorporeal membrane oxygenation; EBFR, ECMO blood flow rate; CO, cardiac output; SGFR, sweep gas flow rate; CO<sub>2</sub>, carbon dioxide; FdO<sub>2</sub>, fraction of delivered oxygen in the sweep gas flow; NMBA, neuromuscular blocking agent; UF, ultrafiltration; EVLW, extravascular lung water.

### Box 1 Daily optimisation of EBFR and SGFR

- (I) Protocol-driven daily optimisation of the EBFR
- (II) Daily assessments of native lung function and SGFR optimisation
  - (i) 100% fraction of inspired oxygen test
  - (ii) Physiological dead space (VD/VT)
  - (iii) Pulmonary system compliance and respiratory drive
- (III) FdO<sub>2</sub> and SGFR wean to liberate patient from ECMO

ECMO, extracorporeal membrane oxygenation; EBFR, ECMO blood flow rate; SGFR, sweep gas flow rate; FdO<sub>2</sub>, fraction of delivered oxygen in the sweep gas flow.

monitor the physiologic dead space (11,12). Measuring carbon dioxide (CO<sub>2</sub>) elimination across the native (VCO<sub>2NL</sub>) and membrane (VCO<sub>2ML</sub>) lungs can help estimate proportion of total CO<sub>2</sub> (CO<sub>2tot</sub>) eliminated through the

native lungs (VCO<sub>2NL</sub>/CO<sub>2tot</sub>) over time. VCO<sub>2ML</sub> can be calculated by applying volumetric capnometry to the membrane lung and measuring CO<sub>2</sub> at the sweep gas outlet using an infrared analyser (12). End tidal CO<sub>2</sub> monitoring (13) may be used as a surrogate to monitor trends in VCO<sub>2NL</sub> provided SGFR remains unchanged, when volumetric capnometry is not available. Mechanical power, plateau and driving pressures, static and dynamic compliance of the native lungs are assessed daily to ensure ongoing ultra-lung-protective ventilation. Oesophageal pressure monitoring, if available, may help measure swings in oesophageal pressure and further optimisation of transpulmonary pressures and respiratory effort.

Upon a successful 100% oxygen test, ventilator FiO<sub>2</sub> is reduced to ≤50% and FdO<sub>2</sub> and SGFR wean (step III) are commenced. Ultra-protective ventilator settings are maintained by adjusting SGFR. In the light of the recent ECMO to Rescue Lung Injury in Severe ARDS (EOLIA)

trial (14), it may be prudent to adjust tidal volumes for a goal plateau airway pressure of  $\leq 24$  cmH<sub>2</sub>O in conjunction with PEEP  $\geq 10$  cmH<sub>2</sub>O (corresponding to a driving pressure  $\leq 14$  cmH<sub>2</sub>O) and a respiratory rate of  $10 \leq$  breaths per minute (15). It is important to be aware that, decreasing tidal volume  $< 4$  mL/kg PBW may increase atelectasis and may result in severe ventilation/perfusion mismatch and higher EBFR requirement unless PEEP is appropriately increased. Sedation and neuromuscular blocking agents (NMBAs) are adjusted according to unit policy and patient needs. In spontaneously breathing patients, SGFR is also useful to control respiratory drive and work of breathing. While maintaining protective ventilation, the intensity of mechanical ventilation is gradually increased. It is possible to measure both driving pressures during spontaneous breathing (16) to ensure protective ventilation. Oesophageal pressure monitoring, if available may be an useful tool to monitor the intensity of spontaneous effort in patients (17).

Clearly, based on CO, degree of lung rest, transpulmonary shunting/deoxygenation (18) and metabolic demands, each patient may respond differently to EBFR down-titration. As the hyperacute phase of illness starts to resolve (typically at the end of the first week, although this may vary widely, depending on the underlying pathology in any given patient), it may be possible to significantly reduce EBFRs (*Figure 1*) over time. This may allow for greater fluid restriction, more aggressive fluid removal, expedited weaning of sedation and NMBAs and early rehabilitation without compromising the EBFR. A well-timed tracheostomy may be a useful adjunct in this setting. Emerging data indicates that a percutaneous tracheostomy can be safely performed during ECMO (19) and an early tracheostomy may be potentially beneficial (20,21). Every patient is unique, some may be endotracheally extubated, while some others are endotracheal tube intolerant or have higher airway secretion burden or perceived work of breathing and may benefit from a tracheostomy. Ultimately, tracheostomy should be individualised to each patient's needs. The EBFR wean protocol proposed here is intended for patients with severe forms of ARDS supported with VV ECMO as a bridge to recovery. However, broadly speaking, the principles behind this strategy may also be applied to patients with end-stage lung disease who receive VV ECMO as a bridge to transplant in so far as titration of EBFR may be tailored to the needs of the patient (22), keeping in mind that the goal of ECMO support in bridge to transplant is typically to support a patient who is not able to be weaned prior to transplantation.

Once EBFRs are weaned down to the lowest possible levels while maintaining ultra-lung protection, minimal sedation and a SpO<sub>2</sub>  $\geq 88\%$  (typically this may occur with an EBFR of around 2.5–3 L/min), a typical weaning strategy targeting the incremental weaning of the SGFR or FdO<sub>2</sub>, or simply turning off the sweep gas flow to see if the patient tolerates being off support, may be attempted. Depending on the ECMO circuit used, a minimal threshold for EBFR should be defined to avoid the haemolysis that may accompany low EBFRs (23), along with thromboembolic complications. Relative increases in the intensity of anticoagulation may be indicated during the EBFR wean phase, while carefully monitoring transmembrane pressures and for haemolysis. Oxygenator performance should be monitored by measuring the post-membrane PO<sub>2</sub>, VO<sub>2ML</sub>, and VCO<sub>2ML</sub> (12). It should be noted that, regardless of the EBFR, anticoagulation practices vary quite substantially around the world (24) and there is no universal agreement on the degree of anticoagulation needed for any given device or patient. There may be a higher risk of thrombotic events with the use of dual-lumen cannula (25) and a greater degree of anticoagulation may be indicated in these patients, although this remains controversial.

A variation of the technique described here has been practiced by some experienced high-volume ECMO centres (1). A technique similar to the one proposed here has been described by Grant *et al.* (2). Upon clinical and radiological improvement in native lung function, the authors recommend weaning EBFR to 3–4 L/min and FdO<sub>2</sub> to 21% prior to commencing a SGFR wean and subsequent liberation from ECMO. In contrast, we recommend daily EBFR optimisation from the day of initiating ECMO support while maintaining FdO<sub>2</sub> at 100%. Given that it may take weeks to achieve notable improvement in pulmonary compliance and radiological findings, we recommend early protocol-driven EBFR optimisation. We argue that this approach allows for more aggressive fluid restriction, which may in fact expedite improvements in pulmonary compliance and radiological findings.

Weaning EBFR through the course of ECMO is not an uncommon occurrence, yet clinicians may find it challenging to make progress when they enter a perpetual vicious circle based on the high EBFR dependency for oxygenation. Attempts at maintaining such high flow rates leads to greater volume expansion, worsening extravascular lung water, generalised fluid overload, higher sedation requirements and an inability to safely awaken the patient without compromising EBFRs. This may unnecessarily

prolong the duration of ECMO support. The technique described here allows for a protocolized daily wean of the EBFR. Analogous to FiO<sub>2</sub> and PEEP down-titration in the lead up to mechanical ventilation weaning, weaning EBFR may have physiologic merit. This staged approach to VV ECMO weaning allows us to fully utilize the “decoupling” of oxygenation and decarboxylation that is possible only during extracorporeal support.

It is important to note that, the safety margins of EBFR are not established in clinical studies (23). In future, technological refinements may allow safe EBFR wean to much lower levels (e.g., 1.5 L/min) than suggested in this article to predominantly support decarboxylation requirements in later stages of an ECMO run. Ideally, ECMO circuit components should be able to operate safely across a wide range of EBFRs and whether this can be achieved with current circuitry remains unclear. Although contrasting data exists on the effects of different EBFRs on haemostatic parameters in preclinical studies, which adopted similar anticoagulation regimens at both higher and lower EBFRs (26-28), clinical validation of these findings is needed. For example, even if some unfavourable haemostatic alterations were observed in pre-clinical studies with lower EBFRs, those risks may be offset by an ability to deliver evidence-based intensive care unit practices such as fluid restriction, minimization of sedation, reduced NMBA use and early rehabilitation. As our understanding of potential ECMO-induced pathophysiological injuries improves, we will be able to better titrate VV ECMO support in the future.

Approaches to weaning VV ECMO using SGFR, FdO<sub>2</sub> and EBFR based approaches have risks and benefits. In an evolving field such as ECMO, all potential weaning techniques and management strategies merit robust debate. Physiology-based management approaches have not always been successful in the intensive care unit. Strategies such as the one proposed here that minimize the risks of sedation (29), prolonged NMBA use, and fluid overload (30,31) as well as potentially promoting early awakening and rehabilitation (32) have been shown to be beneficial in other contexts. The challenges of performing clinical trials to meaningfully test any of the proposed weaning approaches cannot be understated but are necessary to ultimately improve patient outcomes.

## Conclusions

EBFR requirements during VV ECMO are not fixed. Supporting patients with the minimum possible EBFR

while on VV ECMO may have several advantages. Daily protocol-driven optimisation of EBFR during VV ECMO support may allow a more fluid restrictive and hence lung-protective strategy. The approach proposed here may facilitate early weaning of sedation, awake ECMO, early rehabilitation and possibly liberation from mechanical ventilation in selected patients.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-1515>). DB reports grants from ALung Technologies, personal fees from Baxter, personal fees from BREETHE, personal fees from Xenios, other from Hemovent, outside the submitted work. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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