Special Issue: EuroELSO 2024

Perfusion

Perfusion
2024, Vol. 39(1S) 49S–65S

DOI: 10.1177/02676591241238156
journals.sagepub.com/home/prf

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The intricate physiology of veno-venous extracorporeal membrane oxygenation: an overview for clinicians

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Abstract

During veno-venous extracorporeal membrane oxygenation (V-V ECMO), blood is drained from the central venous circulation to be oxygenated and decarbonated by an artificial lung. It is then reinfused into the right heart and pulmonary circulation where further gas-exchange occurs. Each of these steps is characterized by a peculiar physiology that this manuscript analyses, with the aim of providing bedside tools for clinical care: we begin by describing the factors that affect the efficiency of blood drainage, such as patient and cannulae position, fluid status, cardiac output and ventilatory strategies. We then dig into the complexity of extracorporeal gas-exchange, with particular reference to the effects of extracorporeal blood-flow (ECBF), fraction of delivered oxygen (FdO2) and sweep gas-flow (SGF) on oxygenation and decarbonation. Subsequently, we focus on the reinfusion of arterialized blood into the right heart, highlighting the effects on recirculation and, more importantly, on right ventricular function. The importance and challenges of haemodynamic monitoring during V-V ECMO are also analysed. Finally, we detail the interdependence between extracorporeal circulation, native lung function and mechanical ventilation in providing adequate arterial blood gases while allowing lung rest. In the absence of evidence-based strategies to care for this particular group of patients, clinical practice is underpinned by a sound knowledge of the intricate physiology of V-V ECMO.

Keywords

acute respiratory distress syndrome, critical care medicine, extracorporeal membrane oxygenation, extracorporeal membrane oxygenation circuit, heart-lung-extracorporeal membrane oxygenation interplay, hemodynamic monitoring, pulmunary physiology, veno-venous extracorporeal membrane oxygenation, ventilator associated lung injury

Introduction

The physiology of veno-venous extracorporeal membrane oxygenation (V-V ECMO) spans from the hydrodynamics of blood drainage to the peculiarities of gas-exchange across the membrane oxygenator and the interactions between the arterialised venous blood entering the right heart and the native cardiac and lung function.

The purpose of this review is to provide a physiologically based approach to the clinical management of patients receiving V-V ECMO. We have structured this review to follow the circulation of blood during V-V ECMO: starting from the access site, following the circulation of the reinfused oxygenated blood, and the effect of the membrane and native lung function on the systemic arterial gases.

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Drainage of de-oxygenated blood from the venous system

V-V ECMO configurations

V-V ECMO configuration, i.e., the site of the access and return cannulae, is important as it can affect ECMO gas exchange efficiency, maximum blood flow, and right ventricular unloading due to:

1. Differences in oxygen saturation and in the relative proportion of venous return between the superior and the inferior vena cava (SVC and IVC);
2. Differences in the venous transmural pressure gradient across the SVC and IVC under different conditions of thoracic and intraabdominal pressure;
3. Differences in recirculation fractions with single or multistage access cannulae,[1] and with placement of the return in the same or in a separate vein;
4. Differences in right ventricular unloading with return cannula placement in the IVC, SVC, right atrium or directly in the pulmonary artery.

According to the Maastricht ELSO system[2] for nomenclature, V-V ECMO configurations can be summarized as follows:

Dual cannula approaches. Femoro-jugular (Vf-Vj): the preferred approach in the EOLIA trial.[3] A femorally inserted multistage access cannula is advanced to the distal IVC with a return cannula inserted from the right internal jugular vein and advanced to the right atrium (Figure 1).

Jugular-femoral (Vj-Vf): In this configuration the access cannula is sited in the jugular vein. This configuration is often considered optimal to drain venous blood with the lowest oxygen saturation ($ScvO_2$).[4] Indeed, the SVC has been reported to carry more deoxygenated blood than the IVC in healthy, awake subjects (venous Hb saturation 77% vs 83%) [5] due to (1) the higher oxygen consumption of the brain compared to the skin and muscles[6]; and (2) the higher proportion of cardiac output in the lower body (around 2/3 of total venous return flows through the IVC[7,8]) perfusing organs with lower oxygen extraction ratio (e.g., the kidneys).[9] However, this may be different in critical illness: saturation in the SVC is often not lower,[10] and may be higher than in the IVC[11–13] For instance, during sepsis blood flow is reduced to skin and muscles, and the metabolic rate of the liver increases more than liver perfusion,[14–17] contributing to a lower saturation of blood in the IVC. Similarly, during haemorrhage, cardiac output redistributes from kidneys and guts to the brain, heart, and liver,[18] therefore reducing the oxygen saturation in the IVC. Overall, it is not clear that the choice of Vj-Vf configuration is supported by a supposed lower oxygen saturation in the SVC during critical illness.

Femoro-femoral (Vf-Vf): this configuration gives the flexibility to advance the access cannula into a bicaval position with the tip in the superior vena cava or for the access cannula to remain in the IVC. A challenge with bifemoral insertion is that the left common iliac veins often take a more angled course into the IVC. It is also more likely to cannulate a lumbar vein with a left femoral approach[19] or encounter anatomical variants including duplicated IVC[20,21] or other variants which lead to a more tortuous left sided course.[22] A theoretical downside of this approach may be greater recirculation compared to the Vf-Vj approach (see chapter 4).

Dual lumen single cannula approaches (dl)V-V. Jugular-right atrial ((dl)Vj-Vra): use of a dual lumen cannula inserted via the right internal jugular approach is commonly used across ECMO centres[23,24] and is a common approach in the paediatric setting.[25] This approach in theory limits recirculation when correctly positioning so that the returned jet of blood is directed towards the tricuspid valve.[26] Use of a dual lumen cannula means that this advantage is offset by greater flow limitation as the maximum size of commercially available devices is 31-32Fr[27–29] with larger sizes possibly associated with a greater rate of complications, including venous thrombosis.[30]

Subclavian-right atrial ((dl)Vsc-Vra): Several centres have reported success using a subclavian approach[31,32] although this is less established. This may be useful in individuals of shorter stature in which there is inadequate space in the neck to site a jugular cannula. Although the subclavian site is generally recognised to have the lowest rate of infection, the haemodialysis literature suggests a greater propensity to deep vein thrombosis and stenosis with this site.[33] However, a dual lumen approach should mean active drainage of the left upper limb during therapy which may offset the risk of stasis. Use of a subclavian site has also been reported in dual cannula configurations.[34]

Veno-pulmonary arterial ECMO. V-Pa involves inserting a dual lumen cannula via the IJV, with access in the right atrio-caval junction (V) and return in the pulmonary artery (PA) trunk. Its use (e.g., through a ProtekDuo cannula)[35] is increasingly described in the literature, with some centers reporting it as a primary approach for patients during the COVID-19 pandemic.[36]

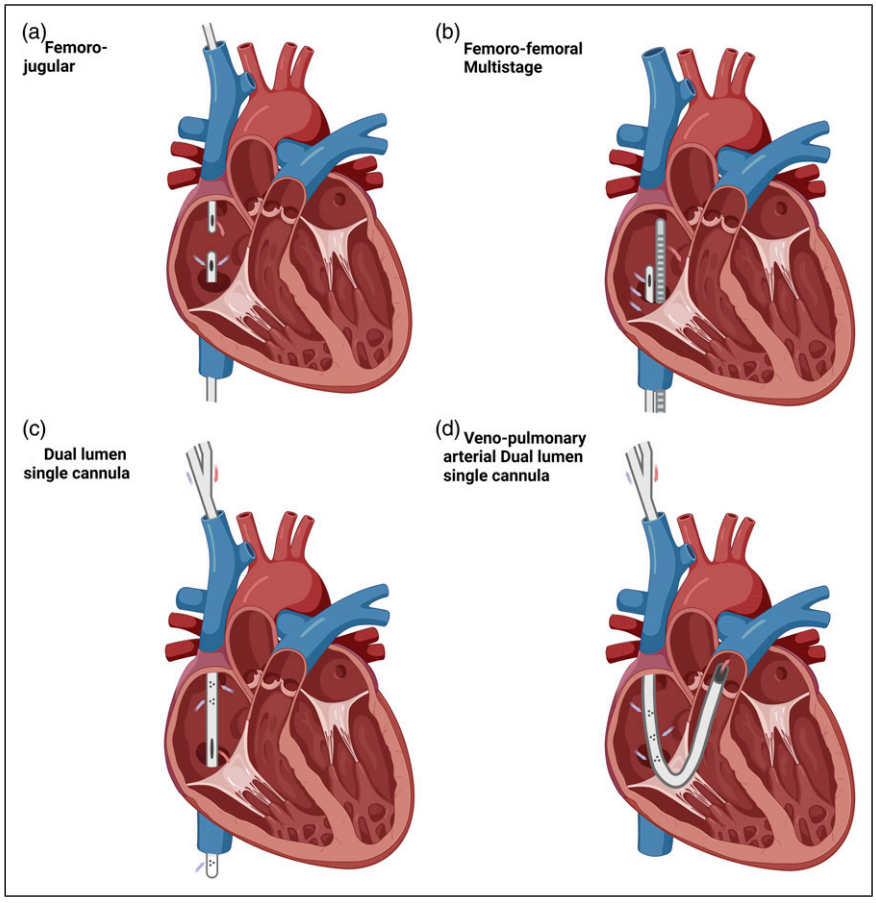

Figure 1. V-V ECMO configurations.

The benefit of this configuration is that it provides mechanical support to the RV, which may be pertinent in ARDS, where cor pulmonale is common and independently associated with increased mortality during ECMO.[37] In addition, this configuration facilitates rehabilitation in awake, extubated patients.[38]

However, insertion mandates the use of transoesophageal echocardiography or ideally fluoroscopy, and its use might be associated with a risk of pulmonary edema in patients with left heart failure, or pulmonary haemorrhage if direct non-pulsatile PA flow is > 4 L/min.[39] For this reason, some centers have reported using a dual return flow to the right atrium and pulmonary artery to limit direct PA flow.[40]

Additional possible downside of V-Pa ECMO is the position of the access in the right atrio-caval junction and its smaller diameter, which limits maximal ECBF to 4.5–5 L/min.[38,41]

Other. Many variations with the addition of a third cannula, or addition of a dual lumen cannula to an existing configuration have been described,[2] with the intent of enabling higher ECBF, lower recirculation or adaptation to new right ventricular failure.

Generation of flow in the extracorporeal circuit

Like the systemic circulation, the ECMO circuit is preload dependent and afterload sensitive, especially with the modern generation of centrifugal pumps.[42] As detailed later, V-V ECMO returns flow into the low-pressure venous system, therefore its afterload is mainly determined by the resistance offered by the membrane lung or the return cannula. As issues of preload ("access insufficiency") predominate in clinical practice, we will first focus on this subject.

Preload dependence. The extracorporeal blood flow (ECBF) must always equal the venous return through the access cannula,[42,43] which, according to the Poiseuille's law, can be calculated as:

$$ECBF = \frac{(P_V - P_A) \cdot \pi \cdot r^4}{8 \cdot \eta \cdot L} \quad (1)$$

Where P_V is the pressure in the vein where the cannula is sited, P_A is the access pressure created by the pump, while the resistance of the access cannula is described as a function of its radius (r), length (L), and blood viscosity (η).

Equation (1) explains why (1) more negative access pressure generated by higher revolutions per minute (RPM) is required to obtain the desired flow in cannulae with higher resistance (e.g., longer and/or with lower diameter),[44] (2) in multistage cannulae, flow is higher at the proximal ports (away from the tip) where the cannula offers lower resistance,[45] and (3) increasing P_V by fluid administration is common, especially on ECMO initiation, to achieve the desired flow with lower access pressure (i.e., lower RPM).[46]

Interestingly, P_V has been reported to be similar from the iliac vein to the superior vena cava across a wide range of airway and abdominal pressures,[47–50] therefore its value reflects the central venous pressure (CVP) irrespective of the position of the access cannula. However, the proportion of venous return flowing through the access vein is different when the tip is located in the IVC, SVC, and right atrium.[7,8] This is important as for P_V to be maintained as upstream pressure to ECMO blood flow (ECBF), the latter can never exceed the proportion of venous return (i.e., of cardiac output) flowing through the access vein, otherwise the latter would collapse. Accordingly, the more the access cannula is pushed to a position that *sees* the entire venous return (e.g., atrial or bicaval position), the higher the ECMO flow that the pump can achieve. The venous (VR) return through the access vein can be calculated as:

$$VR = \frac{P_{ms} - P_v}{R_v} \quad (2)$$

Where P_{ms} is the mean systemic pressure,[51] P_V, is the pressure in the vein where the access cannula is sited, and R_V is the venous resistance. Of note, R_V is not accurately described by the Poiseuille's law only, as veins collapse below a critical closing pressure (known as the Waterfall effect). Vein collapsibility limits the extent to which venous return can increase when the downstream pressure P_V is reduced.[52]

Access insufficiency

Access insufficiency is indicated by a reduction in access pressure and ECBF with constant RPM. Following the reasoning in the previous section, access insufficiency can be schematically divided into conditions with normal or reduced cardiac output (Figure 2).

Normal cardiac output. If patient's cardiac output is unchanged, access insufficiency occurs either due to a reduction in P_V (the upstream pressure to extracorporeal drainage), or to an increase in the resistance of the access cannula. Reductions in P_V might be due to:

1) *Cannula displacement*: displacement of the access cannula from an atrial or bicaval position to a single IVC or SVC position might reduce the proportion of venous return through the access cannula below the ECBF, therefore eventually reducing P_V with possible collapse of the access vein. For instance, adoption of ultra-lung protective ventilation (ULPV) may result in atelectasis and a shift in the relative position of the diaphragm and cannulae. Repositioning of the cannula may restore access efficiency in this case.
2) *Vigorous respiratory effort*: both high inspiratory and expiratory efforts can cause collapse of the access vein due to reduction in P_V below the critical closing pressure. Specifically, high *inspiratory* efforts would reduce intrapleural pressure and increase abdominal pressure, possibly causing IVC collapse,[53,54] while high *expiratory* efforts, like coughing, would increase both intrapleural and abdominal pressure, with possible collapse of both the IVC and SVC.[42,55] Adjusting mechanical ventilation and sedation might improve access efficiency in these cases, although attention must be paid to the effects of these interventions on cardiac output (see below). Another strategy might be to advance the cannula from an IVC/SVC position to an atrial/bicaval position.
3) *Manoeuvres reducing the central venous pressure (CVP)*: In a non-preload dependent patient, aggressive fluid removal (e.g., during the de-resuscitation phase of septic shock) or significant reductions in mean airway pressure (e.g., on ECMO initiation to ensure lung protection) might reduce CVP (and therefore, P_V) without changing cardiac output. Possible strategies to overcome access insufficiency in these cases are increasing the RPM, and thereby accepting a more negative access pressure (P_A), or giving fluids, and therefore increasing P_V. Risks are of haemolysis and cavitation with the first option,[56,57] congestion and oedema with the second.

Access cannula resistance might increase due to obstruction or kinking. The latter can be managed by repositioning the patient or cannula, while obstruction (e.g., due to thrombosis) by either increasing the

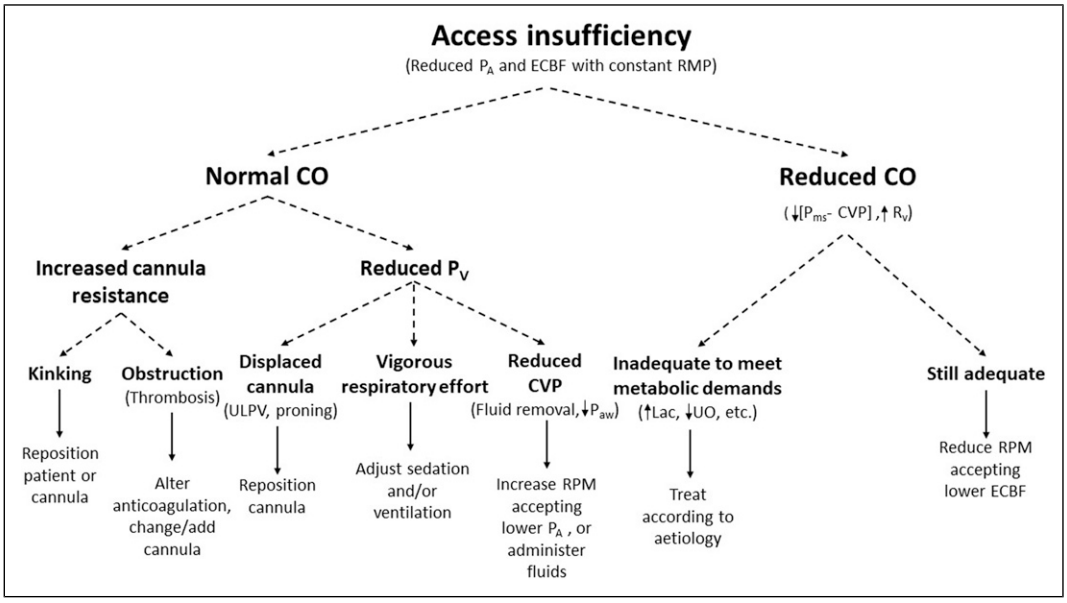

Figure 2. Access insufficiency: access pressure, ECBF: extracorporeal blood flow, RPM: revolutions per minute, CO: cardiac output, Pms: mean systemic pressure, CVP: central venous pressure, [Pms – CVP]: gradient to venous return; RV: venous resistance, PV: pressure in the access vein, ULPV: ultra-protective ventilation, Paw: mean airway pressure, Lac: lactate, UO: urine output.

RPM, and thereby accepting a more negative P_A, or by giving fluids, and therefore increasing P_V. In case of severe obstruction with clotting, altering the anticoagulation regimen and changing or adding a supplementary access cannula might be required.

Reduced cardiac output. Any reduction in cardiac output can decrease the proportion of venous return through the access vein below the ECBF. This would cause collapse of the vein, and therefore loss of the upstream pressure to extracorporeal drainage (P_V). From equation (2), reductions in cardiac output can be due to either a decrease in the gradient to venous return (hypovolemia or vasoplegia decreasing P_{ms}, or cardiac impairment increasing the CVP),[58] or to an increase in R_V (increased airway and/or abdominal pressure, especially in hypovolemic patients).[59–61] Restoring cardiac output with the appropriate treatment would improve access efficiency. However, as detailed in section 4, one should bear in mind that the efficiency of ECMO in terms of oxygenation is tightly dependent on the ratio of ECBF to cardiac output. Therefore, it might be wise to accept lower ECBF rather than aggressively attempt to increase cardiac output if the latter is adequate to meet tissue demands.[62]

One last point worth stressing is that the same condition/manoeuvre might be associated with either improved or worsened blood drainage depending on the underlying status of the patient. For instance, increasing positive end-expiratory pressure (PEEP) might cause access insufficiency if associated with important reductions in cardiac output, while it may improve drainage in a non-preload dependent patient by increasing CVP, and thereby P_V. Similarly, prone position may benefit extracorporeal drainage if it improves cardiac output in ARDS patients with right ventricular failure, but it might also be associated with kinking or displacement of the access cannula causing access insufficiency. In conclusion, an accurate evaluation of the patient is mandatory to troubleshoot and manage access insufficiency (Figure 2).

Afterload during V-V ECMO

As the return lumen is placed within the low-pressure venous system, afterload distal to it is generally not clinically significant during V-V ECMO, although it has been suggested that cough may increase V-V ECMO afterload as well as decrease preload.[54] Consequently, changes in pump afterload are generally due to increasing resistance of the membrane lung[63] or the return cannulae. This may occur due to fibrin, lipids, or other molecules accumulating in these structures.[64,65] The resulting increased resistance is reflected by a decrease in flow for the same RPM, or by a rise in the transmembrane pressure (the difference between the pressure before and after the membrane) when RPM are increased to maintain flow. Other consequences of fibres clotting are worsening extracorporeal gas exchange and

haemolysis. In these situations, membrane lung failure requiring a circuit change is associated with increased length of ECMO and adverse events.[63]

Oxygenation and decarbonation through the membrane lung

Once blood has been drawn from the venous circulation, it passes through the membrane lung for extracorporeal gas-exchange.

Membrane lung structure

The membrane lung oxygenator contains a structure of interwoven hollow fibres constructed from polymethylpentene.[66] Modern oxygenators contain micropores for improved exchange and have a hydrophobic layer which reduces plasma infiltration of gas channels. The lattice of perpendicular channels which carry sweep gas and blood facilitates passive gas exchange across the membrane. Additionally, there are fibres for the heat exchange system to prevent hypothermia and facilitate temperature control. The perpendicular 'cross flow' arrangement provides a greater cross-sectional area and induces a more turbulent flow of blood which improves gas exchange by greater mixing.[66] However, the membrane for gas exchange is much thicker than in the native lung. Furthermore, the overall surface area of the membrane lung is much smaller than that of the native lung. These two factors mean that gas exchange is much less efficient in the membrane lung than in the healthy native lung. In general, a larger surface area for gas exchange improves efficiency and this sets the 'ceiling' at which exchange of oxygen and carbon dioxide can occur for a given system when blood and sweep gas flow are maximal.

Next, we will review the most important titratable parameters at the bedside: the fraction of oxygen contained in the sweep gas (FdO_2), the sweep gas flow (SGF) and the extracorporeal blood flow (ECBF).

FdO_2

The sweep gas is to the membrane lung as the alveolar gas is to the native lung. By increasing the FdO_2, the concentration gradient for oxygen transfer across the membrane increases. As might be expected, higher $FdO_2$2 results in higher oxygen partial pressures, saturation and content in the return blood with resulting improvements in the arterial saturations of the patient.[67] Although the Haldane effect[68] would imply that altering the FdO_2 might also affect the CO_2 clearance from ECMO, this has not yet been demonstrated in clinical studies.[67] Extracorporeal gas exchange at high FdO_2 may also lead to changes in blood and alveolar nitrogen: just as ventilation of the native lung with an FiO_2 of 1.0 will lead to denitrogenation and absorption atelectasis, extracorporeal gas exchange with a low fraction of nitrogen in the sweep gas (for example, an FdO_2 of 1.0) can induce the same changes in blood and alveolar nitrogen.[69,70] Although, in clinical practice many centres opt to maintain the FdO_2 at 1.0 during V-V ECMO, physiologically it may be ideal to set the FdO_2 as close as possible to the ventilator FiO_2 while maintaining acceptable systemic arterial gases.

SGF and its interactions with FdO_2

The sweep gas flow rate in the membrane lung is analogous to the minute ventilation of the native lung. As the sweep gas flow rate is increased, bulk transfer of CO_2 is increased due to the maintained concentration gradient across the membrane. Conversely, due to the affinity of haemoglobin for oxygen, the SGF rate has almost no effect on the oxygen transfer from ECMO (until the rate of flow is practically zero). The effects of SGF rate upon nitrogen have not been investigated but it is likely that an increase in SGF will accelerate the development of the new steady state conditions determined by the FdO_2 and FiO_2.

ECBF and its interactions with SGF and FdO_2

With a well-functioning oxygenator and adequate FdO_2, almost all the haemoglobin exiting the membrane lung is fully saturated. Therefore, increasing the ECBF is a key intervention to increase oxygen transfer- so that a greater number of haemoglobin molecules become saturated. Indeed, the partial pressure of oxygen makes a small contribution to the overall blood oxygen content (multiplied by a small solubility constant of 0.003 mL/mmHg) compared to the haemoglobin concentration and its saturation.

Although in a perfect system almost all the metabolically produced CO_2 could be removed extracorporeally with blood flows <0.5 L/min,[71] in practice no such system exists and regardless of membrane lung surface area, with a given sweep gas flow increasing the ECBF increases CO_2 removal (logarithmically with a plateau determined by the membrane lung surface area).[72] There is also a relationship between the ratio of SGF to ECBF and CO_2 clearance, again with a logarithmic pattern which plateaus for a given membrane lung surface area.[73,74]

Effect of different pre-oxygenator blood gas content

Independently of V-V ECMO settings, the total O_2 added and CO_2 removed by the membrane lung will be influenced by the pre-oxygenator blood O_2 or CO_2 content. For example, if a patient develops fever with consequent increase in O_2 extraction and CO_2 production from the tissues, the pre-oxygenator blood's oxygen content will fall, and CO_2 content will rise. This will result in a greater oxygen transfer under the same conditions of ECBF and FdO_2 (e.g., the difference in pre-oxygenator blood oxygen content between a central venous saturation ($ScvO_2$) of 60% and post-oxygenator blood saturation of 100% is greater than if the $ScvO_2$ of aspirated blood is 70%). Similarly, the greater the inlet blood's CO_2 content, the higher the concentration gradient for extracorporeal CO_2 removal and so the higher the VCO_2ML at a given ECBF and SGF. This does not necessarily mean that a patient's arterial O_2 and CO_2 will remain unchanged under different metabolic conditions, only that the VO_2ML and VCO_2ML will vary as the inlet blood's gas content changes.

Gas exchange requirements and monitoring

Oxygen consumption (VO_2) at rest in health is ~3 mL/kg/min- equating to around 250 mL. In practice, the average O_2 transfer from the membrane lung (VO_{2ML}) per litre of ECBF has been found to be 25–50 mL, thus during V-V ECMO high ECBF are required- for example, an ECBF of ≥5 L/min in patients with a native shunt fraction of 1.0 (e.g., no native gas exchange capacity). Oxygen consumption by cellular metabolism generates CO_2 in a ratio determined by the nutritional substrate- the respiratory quotient (RQ). With a normal RQ of 0.8 this equates to 200 mL/min (2.4 mL/kg/min) of CO_2 to be cleared to maintain eucapnia. As CO_2 is more soluble and diffusible than O_2, with an SGF/ECBF ratio of 1 at typical V-V ECMO ECBFs the expected extracorporeal CO_2 removal (VCO_2ML) usually exceeds the VO_2ML[74,75] and is adequate to manage the metabolically produced CO_2.

In reality, the gas exchange requirements of patients in whom ECMO is implanted may not be normal, extracorporeal gas exchange may be inefficient due to the effects of recirculation and ventilation perfusion abnormalities in the membrane lung, and native lung function may variably affect gas-exchange, as detailed elsewhere in this review.

Reinfusion of oxygenated blood into the central circulation

Mixing of oxygenated and deoxygenated blood

Pulmonary arterial oxygen saturation (SvO_2) is equal to the weighted average of the oxygenated blood coming from the ECMO circuit and the deoxygenated blood that has not undergone extracorporeal gas-exchange ($ScvO_2$).

$$S_vO_2 = \left(\frac{ECBF}{CO} \cdot S_{out}O_2\right) + \left(\frac{CO - ECBF}{CO} \cdot S_{cv}O_2\right) \quad (3)$$

Where $S_{out}O_2$ refers to the post membrane oxygen saturation.

In a totally non-functional lung (i.e., 100% shunt), the oxygen saturation in the arterial circulation (SaO_2) equals the SvO_2 (no additional gas exchange taking place in the native lung), i.e., $SvO_2 = SaO_2$.

The equation shows how the SaO_2 is dependent on both $ScvO_2$ and the ECBF to CO ratio. For instance, a venous oxygen saturation ($ScvO_2$) of 75% and a ratio of ECBF to cardiac output (CO) equal to 0.6 with a FdO_2 of 1 ensure a SaO_2 of 90%. This is the rationale behind maintaining an ECBF/CO ratio around 0.6 in ECMO patients.[67] Obviously, a higher ratio will be required in patients with lower $ScvO_2$ (Figure 3) (Table 1).

In hyperdynamic states as septic shock with especially high CO, the ECBF/CO ratio might decrease, resulting in a reduction in the arterial oxygen saturation. If the ECBF cannot be increased due to access insufficiency or intrinsic limits imposed by the pump, some authors consider the administration of beta-blockers to lower cardiac output (CO) and restore an adequate the ECBF/CO ratio.[76] The downside of this approach is a reduction in DO_2 to an unpredictable degree. As tissue oxygenation is a function of DO_2, it might be wiser to accept lower oxygen saturations with higher CO in these situations, especially where accurate monitoring of CO is not available.[77] Indeed, monitoring of $ScvO_2$, lactate and perfusion can be helpful in deciding on the best strategy. A more interesting strategy to improve DO_2 might be transfusion: with higher haemoglobin concentration (Hb) patients have higher tolerance to a reduction in ECBF/CO ratio below 0.6.[67]

Effects of oxygen consumption on ECMO efficiency

Resting VO_2 in ECMO patients is approximately 2.5–3 ml/kg/min[78] and can be calculated as the sum of native lung VO_2 (VO_2NL), e.g., from indirect calorimetry, and VO_2 of the membrane lung (VO_2ML).[78,79]

$$VO_{2\,TOT} = VO_{2\,NL} + VO_{2\,ML} \quad (4)$$

$$VO_{2\,ML} = (C_{out}O_2 - C_{in}O_2) \cdot ECBF \cdot 10 \quad (5)$$

Where the subscripts "in" and "out" refer to pre and post membrane values, respectively.

In the critical ill patient sedation, therapeutic paralysis, mechanical ventilation, and cooling are often

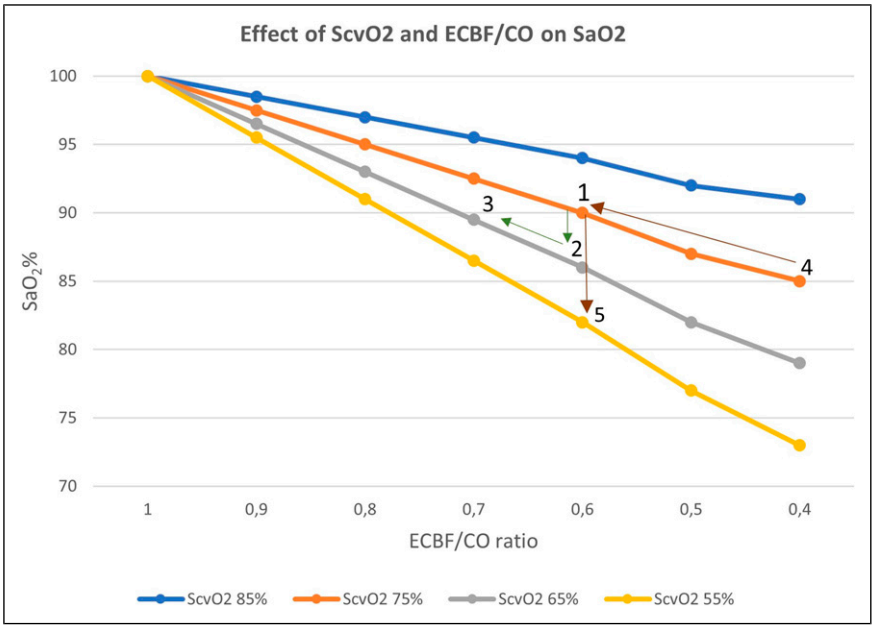

Figure 3. The effect of $ScvO_2$ and ECBF/CO ratio on SaO_2: Assuming a totally non-functional lung with Qp/Qs of 100% we can calculate how different ScvO2 and ECBF/CO ratio can affect the SvO2 and thus SaO2. (1) A ScvO2 of 75% with an ECBF/CO ratio of 0,6 and a FdO2 of 1 ensure a SaO2 90% (2) If the ScvO2 drops to 65% maintaining the same ECBF/CO ratio of 0.6 will ensure a SaO2 86%. (3) In this situation it is advisable to increase the ECBF/CO ratio to 0,7 to achieve a SaO2 around 90% (89,5%). (4) In hyperdynamic states CO increases up to 8–10 L/min reducing ECBF/CO ratio: in this situation a ScvO2 of 75% with an ECBF/CO ratio 0.4 produce a SaO2 of 85%. Increasing ECBF and thus ECFB/CO ratio can be a solution to get back to point 1. (5) Another solution could be the use of a beta-blocker, which by reducing CO could restore the ECBF/CO ratio to point 1, but an eventual reduction in ScvO2 linked to the reduction in CO and thus DO2 may eventually lead to a reduction of Sao2.

Table 1. The effect of ScvO2 and ECBF/CO ratio on SaO2 : Assuming a totally non functional lung with Qp/Qs of 100% and a FdO2 of the ML of 1, we can calculate how different ScvO2 and ECBF/CO ratio can affect the SvO2 and thus SaO2.

	ScvO2 85%	ScvO2 75%	ScvO2 65%	ScvO2 55%
ECBF/CO 1	100	100	100	100
ECBF/CO 0,9	98,5	97,5	96,5	95,5
ECBF/CO 1,8	97,0	95,0	93,0	91,0
ECBF/CO 1,7	95,5	92,5	89,5	86,5
ECBF/CO 1,6	94,0	90,0	86,0	82,0
ECBF/CO 1,5	92,0	87,0	82,0	77,0
ECBF/CO 1,4	91,0	85,0	79,0	73,0

employed to maintain an appropriate DO_2/VO_2 ratio. Indeed, in critical patients lowering body temperature and using a fever prevention strategy led to a reduction in VO_2 of 9% per degree Celsius.[80,81] Similarly, the reduction of sympathetic system activity and the abolition of stress as indirect effect of sedatives is responsible for a reduction in VO_2 of 10-15% depending on the sedative agent used .[82] Moreover, in patients with cardiorespiratory disease the oxygen cost of breathing has been reported to increase markedly, being as high as 25% of total oxygen consumption compared to normal values of 1–3%. Paralysis, together with mechanical ventilation, are responsible for a reduction of up to 30% in oxygen consumption[83] where paralysis alone accounts for 8.7 %.[84] With the strategies above, it is possible to reduce VO_2 in the critical patient, thus ensuring a higher $ScvO_2$ which can be important in situations with an altered ECBF/CO ratio (septic shock) as discussed in the previous paragraph.

Recirculation and its determinants

Recirculation occurs when fully oxygenated blood is aspirated into the drainage cannula resulting in a reduction in the effective ECBF (Total ECBF – Recirculation flow (Q_R)). Recirculation fraction (R_f) is defined as $R_f = Q_R/ECBF$, and effective ECMO flow can be calculated as $Q_{eff} = ECBF\ (1-R_f)$.

The main determinants of Q_R are the type and position of the cannulae, and the ECBF itself. Indeed, Q_R worsens with increasing ECBF, to a point where the Q_{eff} might paradoxically decrease, and oxygenation worsen.[85] Therefore, in the presence of recirculation it is more appropriate to consider (ECBF-Q_R)/CO ratio instead of ECBF/CO ratio (Figure 4).

$$SvO_2 = \left(\frac{ECBF - Q_R}{CO} \cdot S_{out}O_2\right) + \left(1 - \frac{ECBF - Q_R}{CO}\right) \cdot ScvO_2 \qquad (6)$$

Several techniques have been described to quantify the Q_R:

$$Recirculation\ (\%) = \frac{(S_{in}O_2 - SvO_2)}{(S_{out}O_2 - SvO_2)} \qquad (7)$$

Where $S_{in}O_2$ and $S_{out}O_2$ refer to the saturation pre- and post-oxygenator respectively, while SvO_2 is the mixed venous oxygen saturation as it would be in the absence of ECMO. There are two methods that allow calculation of SvO_2: the first relies on obtaining SvO_2 form a central vein felt to be relatively unaffected by recirculation (for example, from a long femoral line with its tip in the IVC when the ECMO return lumen is at the SVC-RA junction). However, this may not reliably reflect the true mixed venous saturation and thereby can be inaccurate. The second method is the most reliable and consists in turning off the sweep gas flow and adjusting the ventilation and FiO_2 to obtain the peripheral oxygen saturation the patient had during extracorporeal support. The saturation of blood from the return cannula can be considered a true (e.g., not influenced by recirculation) central or mixed venous oxygen saturation. Then, SGF is restarted and calculation of Q_R can be performed. However, interrupting ECMO support for this purpose is not generally advisable.[86]

1. Equation (7)

2. Recirculation can be measured through dilutional ultrasound that relies on the detection of velocity changes through an ultrasound (US) probe positioned in the circuit. A bolus of saline is injected in the return cannula and will cause a change in blood velocity (due to viscosity changes) that will be detected by an US probe in the access cannula.[87]
3. Thermodilution has been proposed to assess recirculation in animal[88] and in-vitro[89] models, though in-vivo validity in humans remains to be demonstrated. Although interesting, neither ultrasound nor thermodilution can be strongly recommended for clinical use at present. In practice it is reasonable to judge the degree of recirculation qualitatively by monitoring the changes in the pre-oxygenator and peripheral

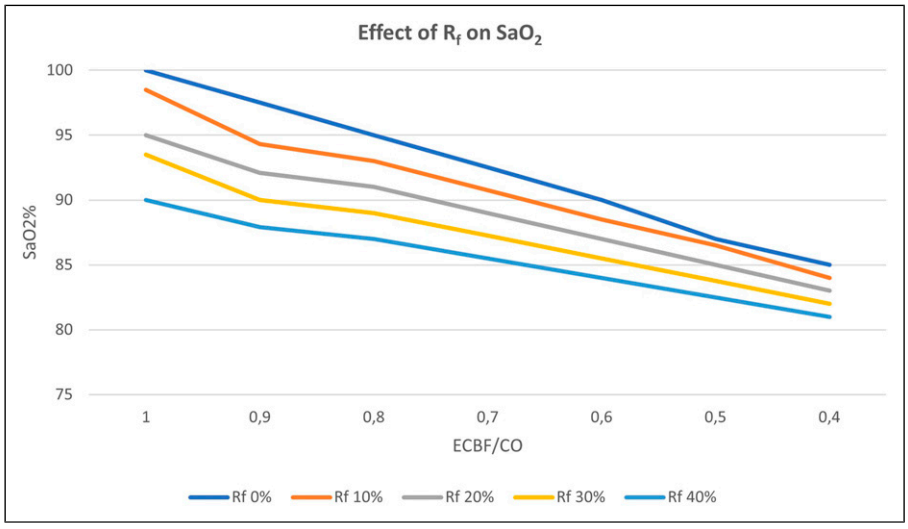

Figure 4. Effect of Rf on SaO_2: Assuming a totally non-functional lung with Qp/Qs of 100% and a ScvO2 of 75%, increasing Rf, will decrease the achieved SaO_2.

oxygen saturations as ECBF is changed. However, in clinical practice, a moderate degree of recirculation is acceptable provided that systemic oxygenation is adequate. When the recirculation fraction is high enough to lower systemic oxygen content below a critical threshold, strategies to reduce recirculation (e.g., manipulation of cannulae position) are recommended.

Effects of ECMO on right ventricular function

The right ventricle (RV) ejects blood into a low resistance-high compliance system allowing large increases in blood flow without significant changes in pulmonary artery pressure (PAP). Increases in RV afterload (i.e., pulmonary vascular resistance, PVR) result in RV dilation with left ventricular diastolic disfunction, RV-LV uncoupling, and eventually acute cor-pulmonale (ACP) with paradoxical septal motion and increased right filling pressures.[90,91] In ARDS, factors such as mechanical ventilation, hypoxic vasoconstriction, hypercapnia, acidaemia, in situ thrombosis, and vascular remodelling contribute to elevated PVR, leading to pre- and capillary pulmonary hypertension.[92–94]

Accordingly, the initiation of V-V ECMO will affect right heart function through multiple mechanisms. First, protective ventilation allows reduction in the transcapillary pressure, and therefore PVR.[95,96] Indeed, a driving pressure < 18 cmH2O has been associated with a lower risk of ACP in ARDS.[94] Additionally, V-V ECMO increases PvO_2 and decreases $PvCO_2$, reducing hypercapnic and hypoxic vasoconstriction and lowering PVR. Moreover, the increase in oxygen delivery to the coronary circulation may increase myocardial contractility. Thus, although lacking direct mechanical support, CO normally improves following V-V ECMO initiation,[67,97,98] and in situations of ACP, RV afterload could be sufficiently reduced to avoid the need for V-A ECMO.

In practice: monitoring the hemodynamic effects of V-V ECMO

During V-V ECMO, hemodynamic monitoring is crucial in at least three conditions:

Cardiac output and RV function. As stated above, improvements in CO and RV unloading are expected upon ECMO initiation. Despite well-known limitations in the intensive care setting,[99] echocardiography remains the gold standard for cardiac output monitoring on V-V ECMO.[95] Indeed, thermodilution techniques overestimate CO, especially at high ECBF and Q_R.[100] Continuous CO monitoring with peripheral pulse wave analysis remains valid on ECMO.[101] Obviously, external calibration with echocardiography should be preferred to internal calibration with thermodilution,[102] the latter being inaccurate.

Despite limitations regarding CO monitoring, PAC remains an excellent and reliable instrument to monitor RV function. Indeed, it allows assessing (1) RV-pulmonary vascular coupling with CVP/WP and RV FAC/sPAP ratios,[97,103] (2) RV response to different afterload conditions with PAPi,[104] and (3) RV diastolic dysfunction through RV pressure waveform monitoring.[105] RV function can also be assessed by echocardiography through LV eccentricity indexes, right ventricular two-dimension fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), tissue doppler-derived tricuspid lateral annular systolic velocity (S′), and right ventricular index of myocardial performance (RIMP). Estimation of PAPs by tricuspid regurgitation peak velocities using the Bernoulli equation are inaccurate during ECMO.[106,107]

Monitoring fluid responsiveness to address access insufficiency. Hemodynamic parameters derived from pulse contour analysis (SVV, PPV), and related assessments of fluid responsiveness are not affected by ECMO,[108] except for ultrasound assessment of the inferior and/or superior vena cava in the presence of cannulae. Changes in central venous pressure remain of clinical relevance in limiting fluid administration.[91]

Monitoring LV function to assess the need for conversion to V-A ECMO. As for the RV, echography is the gold standard in the hemodynamic assessment of LV function, and should be performed when considering conversion to V-A or V-Pa ECMO. Wedge pressure remains a reliable parameter if the patient has a PAC in situ,[109] while extravascular lung water index (ELWI) is inaccurate for the same reason as other thermodilution based methods due to ECBF.[110]

Further gas-exchange through the native lung

Different pathologies may result in severe respiratory failure requiring ECMO,[111] ultimately resulting in increased venous-admixture and dead-space.[112–116] As detailed in this section, not only does the initiation of ECMO and associated ventilatory strategies affect the native lung, but, conversely, changes in native lung function also ultimately influence membrane lung function.

Effects of extracorporeal circulation on native lung function

Extracorporeal oxygenation results in mixed venous 'hyperoxia', which blunts hypoxic vasoconstriction decreasing pulmonary resistance and increasing venous admixture.[117,118] Indeed, hypoxic pulmonary vasoconstriction depends not only on alveolar O_2, but also on pulmonary arterial O_2.[119] Consequently, arterial oxygenation often does not increase as expected, despite a strong increase in oxygen delivery from the membrane lung.[120] This is also the reason for suggesting an initial decrease in FdO_2 during weaning from V-V ECMO, thus allowing time to restore hypoxic pulmonary vasoconstriction[121] prior to weaning off SGF.

Another interesting consequence of extracorporeal gas-exchange on native lung function is that, by removing CO_2, ECMO reduces the VCO_2 of the native lung and therefore the respiratory quotient (RQ_{NL} = VCO_2NL/VO_2NL) might decrease. As evident from the rearranged alveolar gas equation this would reduce the alveolar PO_2 (PAO_2).

$$PAO_2 = PIO_2 - \left(\frac{PaCO_2 \cdot VO_{2NL}}{VCO_{2NL}}\right) \quad (8)$$

Where PIO_2 is the inspired pressure of oxygen calculated as the FiO_2 multiplied by the dry barometric pressure.

This mechanism is more important during ECCO_2R (extracorporeal CO_2 removal), where ECBF is < 1 L/min [71] with limited ability to increase oxygenation, while during V-V ECMO the effect might become evident during a weaning trial.[120] Furthermore, when considering changes in alveolar gas volume during breathing (see extended alveolar gas equation below), one can appreciate that this deleterious effect of reductions in RQ_{NL} on the PAO_2 can be minimized by increasing the FiO_2 of the native lung.[122,123]

$$PAO_2 = PIO_2 - \left(\frac{PaCO_2}{RQ_{NL}}\right) + \left(FiO_2 \cdot PACO_2 \cdot \frac{1 - RQ_{NL}}{RQ_{NL}}\right) \quad (9)$$

Overall, the extent to which this theoretical mechanism worsens native lung gas-exchange during V-V ECMO remains to be demonstrated.

Finally, irrespective of the underlying disease, lung rest strategies adopted during V-V ECMO might result in worsening lung compliance and venous-admixture,[115] further compromising gas-exchange of the native lung.

Interdependence between mechanical ventilation, native and membrane lung function

During V-V ECMO, mechanical ventilation should ideally keep the alveoli open, thus reducing native lung shunt, and avoid alveolar overdistension, therefore minimizing lung injury and dead space.[124] Overall, this is a system in which ECMO, the native lung and mechanical ventilation are interdependent (Figure 5).

As illustrated in Figure 5, the mechanical power of ventilation (MP as defined below) (1) will be reduced thanks to extracorporeal gas exchange; the lower Vt and RR will lead to a decreased VCO_2NL which can increase ECMO efficiency if the inlet blood's CO_2 content rises (2). The effect of the ventilator (1) on the native lung (3) is proportional to MP, defined as the quantity of energy per minute transferred to the native lung to generate the ventilation.[125] This depends on peak and plateau pressure, PEEP, respiratory rate, and tidal volume (Vt).

$$MP = 0.098 \cdot RR \cdot Vt \cdot \left(P_{peak} - \frac{Plat - PEEP}{2}\right) \quad (10)$$

Both excessive and unduly low MP can affect native lung function, either promoting VILI or by derecruitment. Mean airway pressure will affect the mean Pleural pressure ($_mP_{pl}$) which in turn may affect access pressure and ECBF (see section 2).

To better understand the possible interaction between the ECMO circuit (2) and the native lung (3), we could consider the following sequence of events arranged as a "figure of eight" (Figure 6).

As shown, the diseased native lung has reduced volume and increased Vd/Vt (dead space) resulting in lower efficiency (a higher minute ventilation is required to achieve a given VCO_2NL). Adoption of ultra-lung protective ventilation following ECMO initiation will usually result in further derecruitment and increased Vd/Vt. The reduced VCO_2NL will lead to the increase of CO2 content at the inlet of the ECMO circuit ($CinCO_2$) and therefore increase efficiency of membrane lung as the gradient for CO_2 diffusion into the sweep gas will increase.

$$VCO_{2ML} = (C_{out}CO_2 - C_{in}CO_2) \cdot ECBF \cdot 25 \quad (11)$$

Where $C_{out}CO_2$ is the content of blood leaving the membrane lung and $C_{in}CO_2$ is the content of blood at the inlet of the ECMO circuit. Blood flow is measured in L/min and the correction factor (25) is in mL/mmol. If the $C_{out}CO_2$ and ECBF are held constant, increasing $C_{in}CO2$ will lead to an increased VCO_2ML.

Furthermore, extracorporeal gas exchange will decrease the mixed venous CO_2 content ($CvCO_2$), reduce the gradient for diffusion into the alveolar gas in the native lung and so further reduce the VCO_2NL. From this we deduce that for the same ventilation and support of the ECMO circuit this is a self-feeding circuit, in which the native lung will improve the ECMO efficiency while the ECMO could worsen the native lung function by affecting the VCO_2NL and therefore PAO_2, lung volume and Vd/Vt. Indeed, the reduced VCO_2NL and increased VCO_2ML will lower the PAO_2 as described by the alveolar gas equation (Equation (13)) which, together with the loss of alveolar nitrogen will lead to further loss of lung volume and increased Vd/Vt.

In practice: monitoring native lung function on V-V ECMO

Determinants of arterial gas content during V-V ECMO. As detailed above, the arterial gas content depends on both extracorporeal and native gas-exchange. Arterialized blood re-entering the right atrium arrives to the pulmonary circulation where it perfuses some healthy alveoli, therefore providing gas-exchange, and some non-ventilated alveoli (shunted areas).

The arterial oxygen content is therefore described by the following formula:

$$CaO_2 = CcO_2 \cdot \left(1 - \frac{Qs}{Qt}\right) + \left(CvO_2 \cdot \frac{Qs}{Qt}\right) \qquad (12)$$

Where CvO_2 is the content of oxygen in pulmonary arteries, C_cO_2 is the content of oxygen in the pulmonary capillary, and Q_s/Q_t represents the shunt fraction according to Riley's model.[126] As CaO_2 is relatively proportional to SaO_2, the formula can be translated into the following.

$$SaO_2 = ScO_2 \cdot \left(1 - \frac{Qs}{Qt}\right) + \left(SvO_2 \cdot \frac{Qs}{Qt}\right) \qquad (13)$$

Therefore, combining equations (3) and (13), we obtain

$$S_aO_2 = S_cO_2 \cdot \left(1 - \frac{Q_s}{Q_t}\right) + \left\{\left(\frac{ECBF}{CO} \cdot S_{out}O_2\right) + \left(\frac{CO - ECBF}{CO} \cdot S_vO_2\right)\right] \cdot \frac{Q_s}{Q_t}\right\} \qquad (14)$$

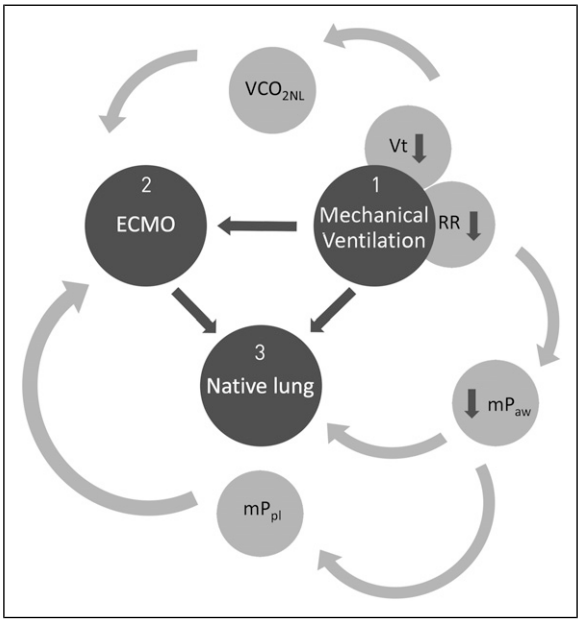

Figure 5. Relationship between ECMO, mechanical ventilation and native lung: The 3 components are affected by each other, with cascading effects. Vt= Tidal volume; RR= respiratory rate; mPaw= mean airway pressure; mPpl= mean pleural pressure; VCO2NL= volume of carbon dioxide produced by native lung.

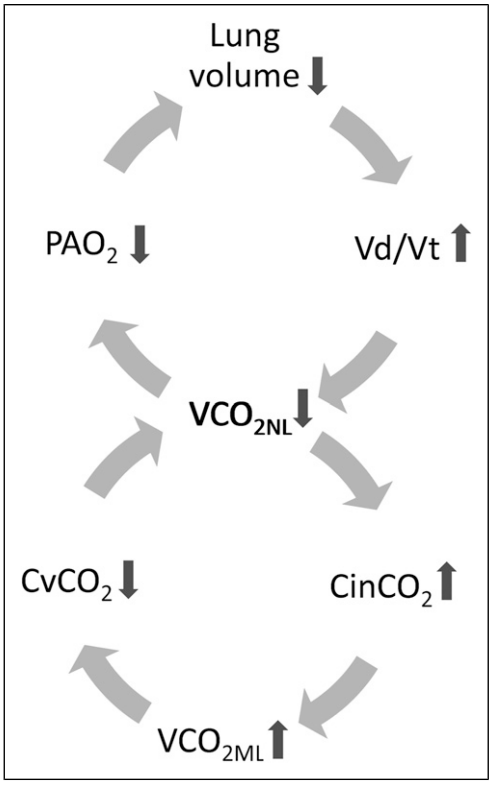

Figure 6. Interaction between ECMO and native lung: PAO2= alveolar pressure of O2; VCO2NL= volume of carbon dioxide produced by native lung; CinCO2= CO2 content at the inlet of the ECMO circuit; CvCO2= CO2 content of mixed venous blood; Vd/Vt= dead space, VCO2ML= volume of carbon dioxide removed by membrane lung.

Similarly, when applying equation (3) to carbon dioxide, the content of CO_2 in the mixed venous blood becomes:

$$C_vCO_2 = \left(\frac{ECBF}{CO} \cdot C_{out}CO_2\right) + \left(\frac{CO - ECBF}{CO} \cdot C_{cv}CO_2\right) \quad (15)$$

Since, from the classic Fick's equation, Cardiac Output (CO) can be estimated as:

$$CO = \frac{VCO_{2NL}}{C_vCO_2 - C_aCO_2} \quad (16)$$

It follows that equations (15) and (16) can be combined to calculate the arterial content of carbon dioxide during extracorporeal circulation as:

$$C_aCO_2 = \left(\frac{ECBF}{CO} \cdot C_{out}CO_2\right) + \left(\frac{CO - ECBF}{CO} \cdot C_{cv}CO_2\right) - \frac{VCO_{2NL}}{CO \cdot 10} \quad (17)$$

Where 10 is a conversion factor required as CO is in L/min while C_aCO_2 is in mL/dL.

These equations demonstrate that the arterial content of both oxygen and carbon dioxide during V-V ECMO can be easily calculated. Notably, in the presence of recirculation, ECBF should be substituted with the *effective* ECBF (i.e., ECBF – Q_R) in equations (14) and (17).

Conclusions

We have reviewed the complex physiology of the patient being supported with V-V ECMO. Until- much needed evidence about the best strategies to care for this group of patients is generated, we use physiology to direct care. However, it is important that this is underpinned by pragmatism. The benefit of extracorporeal gas exchange is in allowing unloading of the native lung with protective ventilation to buy time to heal. It may be wise to tolerate a lower ECBF rather than submit the patient to volume overload, prolonged deep sedation and paralysis or an additional ECMO drainage cannula. The SGF may have to rise to a level inducing alkalosis to provide respite from dyspnoea and reduce patient work. Physiological reasoning can help us devise solutions to a patient's problems, but the patient must be at the centre.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical statement

Ethical approval

Ethical committee approval was not required for this narrative review.

Contributorship

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