Chapter

VV-ECMO in Respiratory Insufficiency

Muhammad K. Hayat Syed, Shehabaldin Alqalyoobi, Hillary Vaughan and Salim Surani

Abstract

Extracorporeal membrane oxygenation (ECMO) has advanced significantly in the last few decades. Although not FDA-approved in the United States for respiratory insufficiency, it is widely used to support cardiac and pulmonary function via Venoarterial (VA) and Venovenous (VV) ECMO, respectively. In the patient with worsening respiratory failure VV-ECMO is considered a salvaging therapy that gives patients' lungs time to heal or as a bridge to lung transplant. Clinicians use tools like the Murray score to initiate a referral for VV-ECMO using indices like oxygen requirement, pulmonary compliance, and bilateral opacities. Early referral for VV-ECMO within 7 days of intubation has shown better results. Important factors that are considered in ECMO candidacy are patients' age, comorbid conditions, and chronic conditions that would affect patients' overall longevity. Extracorporeal life support organization (ELSO) gets data from ECMO centers worldwide and has general recommendations for centers guiding treatment and management. During the COVID pandemic, there was a huge surge in acute respiratory distress syndrome (ARDS) and rampant use of VV-ECMO for COVID-ARDS. Data from various centers have helped us understand the appropriate use of VV-ECMO for ARDS and other causes of hypoxic and hypercapnic respiratory failure. Early referral and careful screening for the patient for ECMO are of paramount importance for a better outcome.

Keywords: VV ECMO, ARDS, interstitial lung disease, IPF, AE IPF, ELSO, ECMO

1. Introduction

Extracorporeal membrane oxygenation (ECMO) has allowed treatment for severe cardiac and pulmonary failure using the concept of a heart-lung bypass pump used in cardiothoracic surgeries. ECMO provides mechanical cardiopulmonary support using a circuit consisting of a pump and membrane oxygenator as key components. Venovenous ECMO, known as VV-ECMO, supports patients with severe respiratory failure. It requires the insertion of cannulae and circulating blood through an extracorporeal circuit where it is oxygenated and then returned to the patient. In VV-ECMO, it will be drained from and returned to the venous side of the systemic circulation. In this chapter, we will cover the basic VV-ECMO circulations and cardiac and respiratory physiology. **Figure 1** is showing VV-ECMO Circuit.

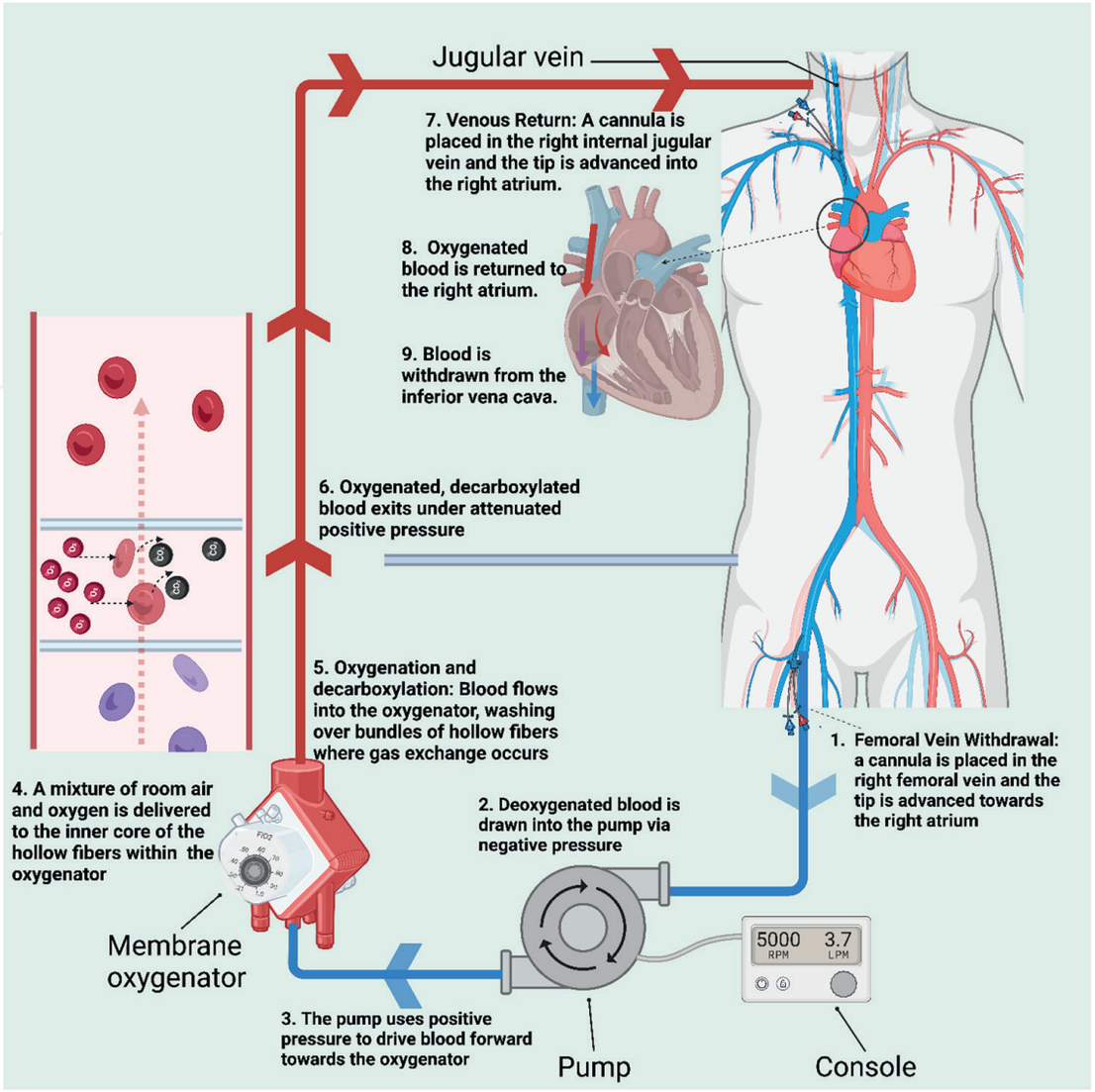

Figure 1.
VV ECMO circuit showing drainage of blood and return to body on venous side after passing through the membrane oxygenator and the pump.

1.1 Oxygen content

Alveolar oxygen partial pressure (PAO_2) is slightly lower than the atmospheric air O_2 ~ 100 mmHg due to the humidification and water content. The arterial oxygen partial pressure (PaO_2) is ~90 mmHg. On the VV-ECMO machine, the venous blood will pass through the gas chamber of the oxygenator (PO_2 ~ 550–600 mmHg, PCO_2 = 0). The oxygen will diffuse from the gas chamber to the blood, while CO_2 will diffuse out. The CO_2 will leave the oxygenator from the outlet. PaO_2 and PCO_2 pre and post-membranes can be analyzed by collecting blood gasses pre and post-membranes [1].

The amount of oxygen in the blood is determined by two main factors: oxygen bound to hemoglobin (98.5%) and dissolved in plasma (1.5%). The total oxygen content of blood is calculated using this equation [2] (CaO_2 arterial oxygen content) as shown in **Table 1**.

CaO_2 = Hb (gm/dl) × 1.34 ml O_2/gm Hb × SaO_2 + (PaO_2 × 0.003 ml O_2/mm Hg/dl) CaO_2 = 15 x 1.34x 1.00 + (90 x 0.003) = 20.37 g/dl
CaO_2 ~ 20 g/dL for a human with normal hemoglobin (15 g/dL), PaO_2 of 90 mmHg, and saturation of 100%. The solubility coefficient of oxygen in plasma is 0.003.
CvO_2 = 15 × 1.34 × 0.75 + (40 × 0.003) = 15.195 g/dl
The CvO2 ~ 15 g/dL for a human with normal hemoglobin (15 g/dL), PvO2 of 40 mmHg, and a saturation of 75%.
DO_2 = CO × CaO_2 DO_2 = HR × SV × CaO_2
The oxygen delivery (DO_2, mL/kg/min) is the amount of oxygen delivered to the tissue (in mL/kg) per unit of time (in min). Normal oxygen delivery equals ~15–25 mL/kg/min (at a normal cardiac output of 5 LPM and arterial oxygen content of 20 g/dL.
O_2 ER = DO_2:VO_2
OThe oxygen extraction ratio of VV-ECMO under normal physiologic conditions is 20–25%.
O_2 ER: Oxygen Extraction Ratio; DO_2: Oxygen Delivery; VO_2: Oxygen consumption, CO: Cardiac output; SV: Stroke volume; HR: Heart Rate.

Table 1.
Arterial and venous oxygen content (CaO_2, CvO_2) and oxygen delivery (DO_2).

These equations apply to the oxygenator on VV-ECMO to calculate the pre-membrane and post-membrane oxygen content. Using the same principle, we can calculate the CvO_2. **Table 1** DO_2 is determined by the oxygen content and the cardiac output (CO) [3] as shown below:

On the other side, oxygen consumption (VO_2, mL/min) is the difference between the arterial and venous oxygen content multiplied by the cardiac output.

1.2 Equation (naive circulation) (oxygen consumption)

The oxygen consumption is approximately 3–5 mL/kg/min. The ratio of DO_2: VO_2 [1] is the oxygen extraction ratio (O_2 ER). Under normal physiologic conditions, O_2 ER is 20–25%. The DO_2 during the ECMO circuit is the product of the oxygen content of the post-oxygenator blood multiplied by the circuit blood flow.

1.3 Equation ECLS (oxygen delivery)

The total DO_2 equals the DO_2 of the naive circulation plus the DO_2 of the ECLS machine. The two circulations are connected in series. In VV-ECMO, usually, the cardiac output of the patient is higher than the ECMO circuit.

$$\text{Equation Total } DO_2 = \text{ECLS } DO_2 + \text{Naive circulation } DO_2 \qquad (1)$$

To determine the contribution of the VV-ECMO circulation to the oxygenation of the naive circulation, we divide the blood flow of the circuit by the naive circulation circuit. For example, if the ECMO circuit flow is 3 LPM and the patient's cardiac output is 5 LPM, then 60% of the patient's blood is being oxygenated by the ECMO circuit, and the patient's diseased lung oxygenates 40%.

The carbon dioxide (CO_2) clearance in the ECLS circuit is determined by the sweep gas flow rate (typically between 1 and 11 L). Due to the high solubility of CO_2, it transfers 6 times faster across the membrane faster than oxygen.

2. Indications and contraindications for VV ECMO

The major indication for VV ECMO a severe but potentially reversible respiratory failure without significant heart failure like ARDS. The decision to initiate an ECMO circuit is refractory hypoxemia and/or hypercapnia after maximizing the standard of care. The term "maximizing" care includes prone positioning, the use of neuromuscular agents, and high positive end-expiratory pressure (PEEP) strategy. It might be appropriate to consider inhaled pulmonary vasodilators and recruitment maneuvers. The concept is to provide adequate oxygenation and ventilation in a patient with severe ARDS and, at the same time, rest the lung to promote healing and prevent mechanical Ventilation-Induced lung injury (VILI).

After considering the above measures, if the PaO_2:FiO_2 ratio is <80 mmHg for >6 hours, the PaO_2:FiO_2 ratio is <50 mmHg for >3 hours, or PCO_2 is >60 mmHg (and pH < 7.25) and no contraindications, then ECMO should be considered if the underlying disease process if potentially reversible (i.e., pneumonia) or the ECMO done as a bridge to a pre-planned surgery or intervention (i.e., lung transplant) [1, 4].

These are relative to the ECMO center and patient characteristics and specific situations. Generally, patients should have a reversible condition like an infection or ARDS or should have a destination plan for a lung transplant, and ECMO is used as a bridging therapy. The absolute contraindication for VV-ECMO is the presence of irreversible pathology and patients who are not a candidate for a lung transplant. Relative contraindications include multiorgan failure, irreversible neurologic injury, uncontrolled bleeding or thrombocytopenia or other bleeding tendencies, metastatic cancer, prolonged mechanical ventilation, and advanced age (greater than 65–70).

3. VV-ECMO for COVID-19 ARDS

ECMO played a significant role in the COVID-19 Pandemic. Overall, the approach to select patients and manage VV-ECMO for COVID-19-related respiratory failure is the same as other etiologies of ARDS.

The two major differences in COVID-19-related infections are cardiovascular and other systemic involvement and outcomes. Respiratory involvement has been the major indication for VV-ECMO. However, 20% of COVID-19 patients have experienced cardiac involvement, [3] and about 4% required VA-ECMO configuration [5]. Different mechanisms like thrombosis, pulmonary embolism, direct damage to the cardiac myocytes, severe inflammatory response, and cardiac arrhythmias [6] have resulted in cardiac failure during COVID-19 infection. The short-term outcomes in COVID-19-related ARDS requiring ECLS have evolved during different waves [5]. During the first wave (prior to May 2020), the mortality was 36% and then increased to 52% in the second wave (between May 2020 and December 2020) [5, 7]. Changes in the virus virulence, the introduction of immunosuppressive medications, and the presence of additional bacterial pneumonia might explain this increase in mortality [8]. A cohort of 1035 patients with COVID-19 ARDS patients managed

with VVECMO showed an estimated cumulative hospital mortality of 37% [5] and some COVID-19 patients with high D-dimer and low static compliance phenotype had mortality as high as 56% [9]. These COVID-19 phenotypes might benefit from VVECMO.

4. Extracorporeal carbon dioxide removal ($ECCO_2R$) for hypercapnic respiratory failure

The technology behind $ECCO_2R$ overlaps with the VV-ECMO circuit. The major difference is the absence of an oxygenator integrated into the membrane lung. This can be achieved with a smaller cannula like a 14–18 Fr. The blood flows from the venous patient site to the pump (flow range: 0–8 L/min) and then to the membrane lung. The membrane lung has two chambers (blood on one side and sweep gas on the other side). The chamber is separated by a semipermeable membrane. CO_2 diffusion across the membrane is gradient dependent. CO_2 removal is more efficient than oxygenation, and a 1–3 lit/min flow is enough to fully remove CO_2 produced by patients, but this flow might not be enough for oxygenation.

The baseline arterial CO_2 is a product of tissue production and lung ventilation. The higher the blood flow, the greater the CO_2 removal. Similarly, the higher the sweep flow, the greater the CO_2 removal. Maintaining the CO_2 gradient ensures the CO_2 diffusion from the blood to the gas chamber in the membrane lung [10, 11]. The determinants of CO_2 removal are baseline arterial CO_2 content, sweep gas flow, blood flow, blood pH, membrane area, and time of transit.

ARDS and chronic obstructive lung disease (COPD) are the major potential indications for $ECCO_2R$ use. In ARDS, the protective mechanical ventilation strategy (low tidal volume, 6 ml/kg of ideal body weight) reduces the risk of VILI, and Respiratory acidosis is a common side effect of this strategy. $ECCO_2R$ can be used to assist in ventilation, allowing ultra-protective ventilation (4 ml/kg of ideal body weight) in ARDS patients [12]. This means the damaging [13] plateau pressure, driving pressure, and mechanical power can be kept in an acceptable range [14].

COPD is another potential indication for $ECCO_2R$ use. The standard of care suggests the use of noninvasive mechanical ventilation (NIV) to reduce the rate of invasive mechanical ventilation (IMV). However, up to 25% of patients with COPD exacerbation will fail NIV [15]. In this patient population, $ECCO_2R$ is considered an additional intervention to prevent IMV.

5. VV ECMO configuration, cannulation and site selection

5.1 Configuration and cannulation site

For VV ECMO, deoxygenated blood is drained from the venous side of the circulation, and oxygenated blood is returned to the venous side or directly into the right atrium and sometimes in the right ventricle (helpful in right heart failure patients). Dual site cannulation IJ-Fem or Fem-Fem with one catheter in Internal Jugular and the other in the Femoral or both in Femoral Veins, respectively. These are more invasive, limiting patient ambulation. Single site dual lumen catheter is accessed via the right IJ vein and is designed to have drainage ports (proximal and distal) to be positioned in IVC and SVC. A return port is in the middle of the catheter that is directed toward

	Cannulation Configuration	Drainage Site	Return Site
1	Single Site Dual Lumen Catheter	IVC and SVC	Right atrium
2	Dual Site Single Lumen	Internal Jugular Vein/ Subclavian	Femoral Veins
3		Femoral Vein	Femoral Vein

Table 2.
Cannulation configuration types.

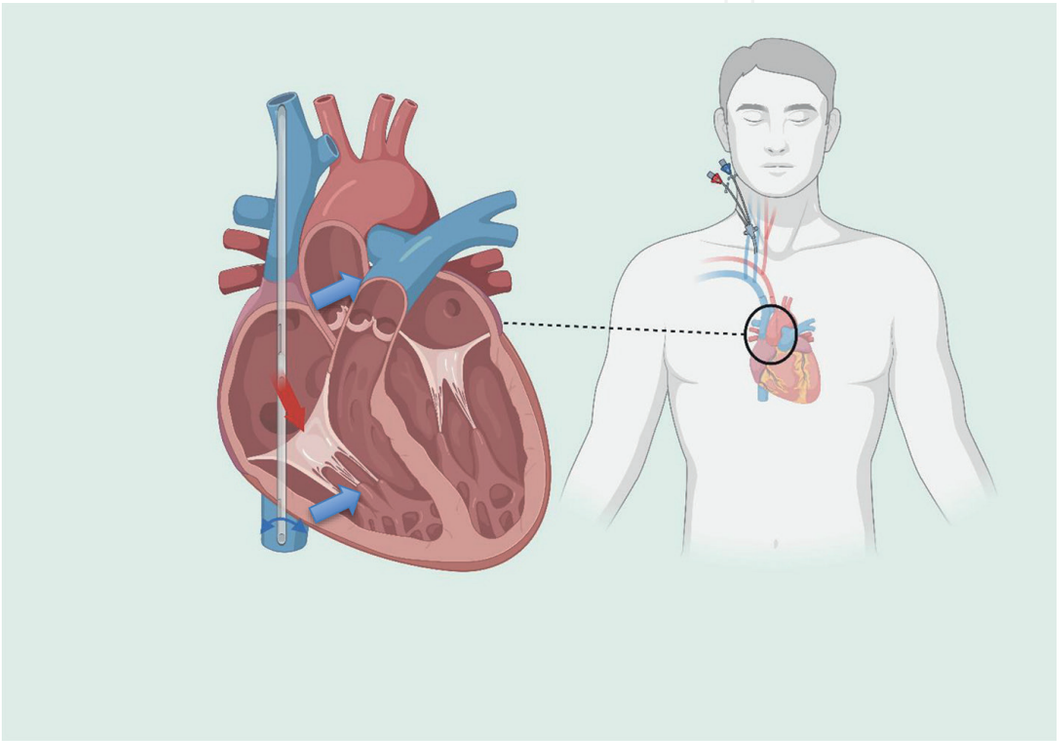

Figure 2.
Single site dual lumen catheter with blue arrows shows drainage of blood to the ECMO circuit and red arrow indicating the return of oxygenated blood into the right atrium.

the tricuspid valve using transesophageal echocardiogram (TEE) and fluoroscopy. Although single-site cannulation is less invasive and allows patient ambulation, the cannula must be sutured and secured carefully, and slight rotation or neck movement can dislodge the ports causing issues. The details of the cannulation configuration types, drainage and return sites are shown in **Table 2**.

5.2 VV ECMO vs. VA ECMO

Single Site Cannulation using Bicaval dual lumen cannula (Avalon) with blue drainage apertures both in SVC and IVC and red return aperture directed toward the tricuspid valve (**Figure 2**).

Two-site cannulation (IJ-Fem) with drainage via femoral access catheter in IVC and return of oxygenated blood to SVC via internal jugular (IJ)/subclavian access (**Figure 3**) [16].

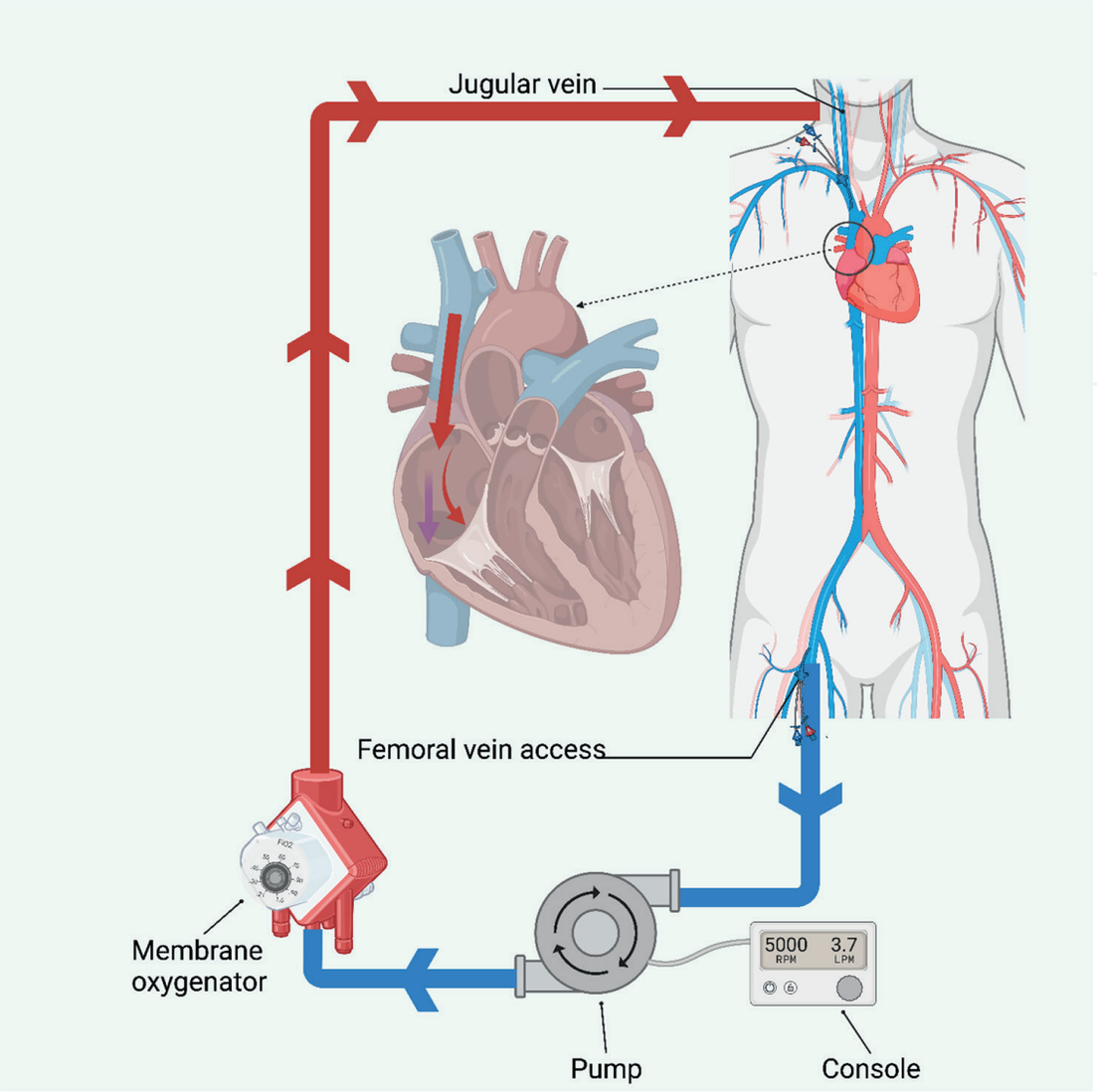

Figure 3.
Dual catheter dual-site configuration.

5.2.1 Difference in indication

VV ECMO is for respiratory failure alone. When we have cardiac failure, we need to use VA ECMO. In VA ECMO, the return cannula is placed in the arterial circulation, i.e., bypassing the heart and lungs. Some commonly used sites are the femoral artery, axillary or subclavian artery. In VV ECMO, the return cannula is placed on the venous side and is pumped by the heart. VV ECMO does not provide any cardiac support directly. However, it may improve hemodynamics by improving hypoxia and acidosis and indirectly improving right and left ventricular function. Placing VA ECMO configuration with normal LVEF will result in complications like north–south syndrome with the heart and ECMO pump forcing blood in opposite directions.

6. Ventilator management on ECMO

While on VV ECMO, the ventilator settings are adjusted to allow lung healing and minimize VILI in the already damaged lung. The goal is to provide oxygenation

via the ECMO circuit and not through native lungs. Data from landmark trials [17, 18] have been used to guide ventilator settings. A commonly used setting is pressure support of 10 cmH_2O, PEEP of ≥10 cmH_2O, respiratory rate of 10, and FiO_2 of 0.3 [4]. Other Modes are also used but keeping the tidal volume low so that plateau pressure < 20–25 cm H_2O.

6.1 Extubation while on VV ECMO

In patients who do not have a shock, multiorgan failure and are somewhat stable on supportive care, planned extubation while on VV-ECMO can be considered. Extubation helps decrease sedative medications, improve patients' communication and physical therapy, and decrease ventilator-associated complications. However, patients should be on minimal vent settings (P/F < 0.4 PEEP ~5), able to protect the airway and clear secretions. After extubation, there is a risk of failure and reintubation along with increased work of breathing, so patients should be closely monitored. Post-extubation sweep gas might need to be adjusted depending on arterial blood gas.

6.2 Tracheostomy

Some patients tolerate extubation on ECMO well. Others may develop tachypnea, causing increased work breathing leading to possible reintubation or lung [19]. Tracheostomy can be considered for the patient on prolonged ECMO >10 days and has failed extubation.

7. Complications of VV-ECMO and management

7.1 Vascular complications

7.1.1 Bleeding

By far, bleeding and thrombosis are the most common complication of ECMO. Bleeding is mainly because of the need for anticoagulation to prevent circuit thrombosis. The most common sites are gastrointestinal, cannulae insertion sites, and intracranial bleeds.

Retroperitoneal bleed can happen when the cannula is inserted at the groin site.

7.1.2 Circuit thrombosis

Thrombosis-resistant circuits decrease the chances of circuit thrombosis, but systemic anticoagulation is mandatory.

7.1.3 Systemic thromboembolism

Venous thrombosis and thromboembolism (VTE) are common in patients with VV-ECMO, with incidences reported as low as 10% [20] to as high as 42% [21] even with full anticoagulation. Locations of VTE include upper and lower extremity VTE, cannulation site, and pulmonary emboli. Factors favoring VTE are longer time on ECMO, low pump speed and low blood flow velocity, cannula malposition, kinks, larger bore cannulae, partial thromboplastin time < 50, elevated D dimers, and patients with COVID-19 infections [22].

7.1.4 Cannulation related complications

A systematic review [23] reports a 7% complication rate during cannulation for VV ECMO in 12,800 patients reported in 33 studies. Other less frequently seen complications include catheter site infection, Aneurysms, and pseudoaneurysms [23].

7.2 Oxygenator dysfunction

As the circuit ages, its oxygenator starts to develop microthrombi, leading to a gradual decrease in its efficacy.

7.3 Recirculation and cannula malposition

Recirculation is the phenomenon when oxygenated blood returning to the body is aspirated back by the drainage cannula without passing through systemic circulation, decreasing the efficacy of ECMO. It more commonly happens in single-site ECMO configurations or where the drainage and return cannulae are in proximity. One way of estimating the recirculation fraction is using SvO_2.

$$\text{Recirculation}(\%) = (\text{SpreO}_2 - SvO_2) / (\text{SpostO}_2 - SvO_2) \times 100 \qquad (2)$$

SvO_2 is central venous oxygen saturation in IVC/SVC. When the recirculation is high enough that it requires higher ECMO support, measures are taken to decrease it. Increasing the distance between drainage and return cannulae, adding an additional drainage cannula at a second site, using dual lumen cannula, adjusting the position of cannula/cannulae, and decreasing the pump speed [16] or upsizing the cannulae french can help reduce the recirculation fraction to an acceptable level.

Cannula malposition may occur during patient turns, skincare, or ambulation. This can lead to increased recirculation, patient desaturation, or increased ECMO support. This requires correction using echocardiography transthoracic (TTE), transesophageal (TEE), and/or fluoroscopy to reposition the cannula to the optimum position.

7.4 Neurologic complications

7.4.1 ICH

Intracranial hemorrhages (ICH) are the most common neurologic complication of VV ECMO with high mortality. The most common types of ICH are subarachnoid hemorrhage and intraparenchymal hemorrhage. Most of these are reported to have occurred earlier, within 6–24 hours of ECMO initiation.

7.4.2 Long-term complications

Post-ECMO patients can experience anxiety, depression, and post-traumatic stress. Cognitive deficits and psychiatric symptoms can affect the quality of life. It is important for ECMO survivors to have neuroimaging post-decannulation and follow-up outpatient to screen for possible neuropsychiatric issues.

1.	Sepsis	26.1%
2.	Acute Renal Injury	24.7%
3.	Multiorgan failure	24.7%
4.	Cannulation complications	6.6%
5.	Neurologic complication	6.9%

Table 3.
Incidence of complications in a meta-analysis of 12,800 VV-ECMO patients [23].

In addition to neuroimaging, transcranial dopplers, Pupil index, EEG, and Cerebral infrared spectroscopy can be used to monitor for neurologic complications [24].

Other complications included Infections and Sepsis, likely pneumonia, cannulation site infection, bacteremia, Acute renal failure requiring renal replacement therapy, liver dysfunction, hemolysis, and disseminated intravascular coagulation (DIC). The incidence of complications in a meta-analysis of 12,800 VV-ECMO patients are described in **Table 3** [23].

8. Decannulation/weaning of VV-ECMO

Weaning of VV-ECMO is based on multiple factors like underlying lung pathology, radiographic clearance, lung compliance, other organs' functions, and blood oxygen and carbon dioxide levels. The timing of weaning is a delicate balance between an "optimal" state and "resolution," knowing the risk of ECMO complications.

The basic weaning approach is to gradually reduce the pump flow to a minimum and reassess the patient. One way is to reduce the flow to about 1 L/min in an adult ECMO circuit. Another way is to keep the flow above 3 L/min (to reduce the risk of thrombosis). If the patients remain stable after weaning the sweep gas and FiO_2%, then consideration for a formal weaning trial should be given.

The oxygenation response test is an indicator of lung readiness for weaning of ECMO. This is done by increasing the ventilator FiO_2 to 1.0 and the peripheral saturations to >95%. The sweep gas is weaning as well in response to carbon dioxide levels. It is acceptable to keep the patient in mild respiratory acidosis (pH 7.25–7.35).

After performing the above measure, the formal trial is started by initiating lung protective ventilation. We disconnect the sweep gas from the oxygenator and assess the arterial blood gas every 20–30 mins. The ventilator is adjusted accordingly. The satisfactory arterial blood gas (ABG) means arterial PO_2 > 60 mmHg on lung protective ventilation (TV < 6 ml/kg of IBW, and peak inspiratory pressure < 25 cm/H_2O and FiO_2 < 0.6). If ABG is satisfactory, the blood flow through the circuit is maintained for a period of 2–4 hours to ensure stable organ function. Decannulation is considered if organ function remains stable. If ABG is not satisfactory, then sweep gas should be reconnected, and the patient should be evaluated.

9. Duration of ECMO

Expectations should be set with patients and/or families before initiation of ECMO. This should include a discussion about discontinuing ECMO in case of no

recovery in a reasonable time period or if due to any because there is no chance of meaningful survival [25]. Usually, durations last around 2–4 weeks but may vary in centers and regions based on resources and patient characteristics. The pooled average of ~10 days on VV ECMO and about ~25 days of ICU length of stay [23]. Like any other severe critical care illness, patients who were on VVECMO might develop similar deconditioning and psychosocial problems requiring evaluation and therapy.

10. Evidence-based VVECMO outcomes

Many studies are looking at it [26]. A retrospective analysis found better 6-month survival in ECMO-ARDS out of 90 patients. There was great interest in VV ECMO use during the H1N1 pandemic, and then the Cesar trail [17] in the UK, showed a 63% 6-month survival with VV ECMO as compared to 47% with conventional treatment of ARDS. However, 25% of patients referred to the ECMO centers never received treatment. Data from this trial have convinced physicians to make early referrals to ECMO centers in severe ARDS patients. Severe ARDS itself has a mortality of ~45%. A meta-analysis of 33 VV ECMO studies with 12,800 patients showed single-arm meta-analysis mortality of 41% [23]. A subsequent EOLIA trial was stopped for futility. However, a post hoc Bayesian analysis [27] and a meta-analysis [28, 29] of both EOLIA and CESAR trials supported the use of VV ECMO in expert centers for severe ARDS with persistent hypoxemia after being treated with standard therapy for ARDS.

11. Conclusion

VV ECMO is a great tool that can help select patients with severe respiratory failure as they recover and possibly prevent adverse outcomes and as a bridge to transplant therapy for end-stage pulmonary disease patients' pulmonary fibrosis, cystic fibrosis, COPD, etc., after they have failed conventional, evidence-based ARDS therapies like prone ventilation and low tidal volumes. Early referral for VV ECMO to expert centers and careful selection of patients are key to better patient outcomes.

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Conflict of interests

None were reported by the authors.

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