Hemodynamic Monitoring during Veno-Venous Extracorporeal Membrane Oxygenation: A scoping review

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Anson Wang
Abstract

Background

Optimizing cardiovascular monitoring and support during veno-venous Extracorporeal Membrane Oxygenation (V-V ECMO) is essential to ensure overall adequacy of end-organ perfusion and proper titration of extracorporeal support. Despite an increasing V-V ECMO use, guidelines on monitoring of cardiovascular function during mechanical support are lacking, with current approaches mostly based on clinicians’ experience rather than evidence-based recommendations. This scoping review focused on basic and more advance methods for hemodynamic monitoring during V-V ECMO in adult patients.

Methods

Databases (PubMed, EMBASE and Cochrane CENTRAL) and reference lists of relevant articles were searched from inception until November 2021. We included studies of any methodology that addressed the a priori key questions relating to hemodynamic monitoring during respiratory extracorporeal support.

Results

Overall, 465 articles were screened, and 106 articles were included for detailed analysis. Protocolized hemodynamic monitoring and lines of evidence were not found and in particular the main body of the literature was concentrated on cardiocirculatory support. Tools recommendations regarding the available monitoring techniques are described, with an overview of basic, prognostic/diagnostic and advanced methods. While these strategy does not influence time to wean, the application of care bundles and multidisciplinary team approaches could be associated with reduced complications and improved outcomes.

Conclusions

Patients undergoing respiratory support with V-V ECMO experience complex interactions among the patient’s and extracorporeal circulation, individual’s lung function and related circulatory changes. The critical needs for multidisciplinary teams, specified trainings, new research directions, and an accurate monitoring aiming to improve outcomes are essential for optimal decision-making.

Background

Over the past decade, the use of veno-venous extracorporeal membrane oxygenation (V-V ECMO) for refractory respiratory failure has widely increased\(^1\)–\(^3\). However, despite international guidelines and recommendations\(^4\),\(^5\), considerable variability exists in V-V ECMO management and outcomes across centers.\(^6\) While there has been an evolution of care to improve the assessment of lung function and recovery, less attention has been given to the potential intercurrent cardiopulmonary abnormalities occurring during extracorporeal respiratory support\(^7\). Indeed, V-V ECMO directly impacts cardiovascular function by decreasing pulmonary vascular resistance, reducing right ventricular (RV) afterload and potentially improving RV function. This is achieved by resolving severe hypoxemia and hypercapnia as well as by decreasing the intrathoracic pressure (i.e. reduced tidal volume and driving pressure),\(^7\) with also positive consequences on left ventricular (LV) filling pressures. Conversely, concomitant cardiac dysfunction,
pulmonary deterioration, increased metabolic demand, the ratio of ECMO flow to native cardiac output (CO), and the
degree of recirculation could affect the extracorporeal efficiency or promote a wide range of cardiocirculatory
compromise in these patients (Fig. 1). The heart-lung-ECMO interaction has also direct consequences on systemic
oxygen delivery (DO₂). Furthermore, in particular after the COVID-19 experience, it has been recognized that some
etiologies of pulmonary failure might also severely impact cardiac function, triggering different degrees of acute right
and/or left heart failure (HF) or even cardiac arrest8–14.

For this reason, a focused and comprehensive cardiovascular monitoring strategy should be considered in V-V ECMO
adult patients, including basic “mandatory” monitoring tools, as well as more “advanced” techniques, which should
be adjusted to patients’ needs, the underlying disease, possible cardiovascular changes over time or the occurrence
of some complications.

Given the limited volume and heterogenous nature of the literature published on this topic, the scoping review
methodology was most suited to the objectives of this review

Methods

This scoping review aimed to map the literature and provide the key concepts identified by the COVID-19 Critical Care
Consortium (COVID-Critical) on this topic. The specific research questions were:

1. To report the existing evidence on hemodynamic monitoring techniques in VV ECMO patients
2. To propose a possible multi-step approach in clinical practice

Studies that focused on patients on veno-arterial (V-A) ECMO support were excluded, studies that did not involve
patient as subjects (i.e. medical devices tested in ex-vivo settings) were only included if they addressed research
questions relevant to the patient population in the inclusion criteria.

Search methodology

An electronic search was conducted of three key databases (PubMed, EMBASE and Cochrane CENTRAL) from
inception through to November 2021. The keywords used were "cardiovascular monitoring" or “hemodynamic
failure” or "respiratory failure" and "veno-venous extracorporeal membrane oxygenation" We also searched using
individual terms such "oxygenation", "lung-heart interplay", "cardiovascular insuiciency", "extracorporeal support". The
search was not limited but mainly focused on English language studies. The reference lists of included articles
were also searched for additional potential studies. Titles and abstracts were screened independently by two authors
(MEDP and SM) and conflicts regarding the inclusion or exclusion of studies were resolved by consensus with a third
investigators (RL). Data extracted included first author’s surname, year of publication, settings, aim or objectives,
study population and size (if applicable), study design (if applicable) and key findings. Analysis was descriptive and
was performed according to the PRISMA extension for scoping review (Additional File S1).

Results

Search Results

Electronic searches conducted retrieved 465 citations; following the removal of duplicates and application of study
criteria, 106 articles were included in the final analysis. Most of the identified articles addressed one hemodynamic
monitoring techniques. The key findings were categorized in: a) basic; b) diagnostic and prognostic; c) advanced monitoring tools (Table 1).
Table 1
Cardiocirculatory Monitoring during veno-venous extracorporeal membrane oxygenation

<table>
<thead>
<tr>
<th>Modalities</th>
<th>Invasive</th>
<th>Consideration</th>
<th>Frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic Monitoring</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>Sensor</td>
<td>No</td>
<td>Valid</td>
<td>Continuous</td>
</tr>
<tr>
<td><strong>Pulse Oxymetry</strong></td>
<td>Sensor</td>
<td>No</td>
<td>Usually Valid</td>
<td>Continuous</td>
</tr>
<tr>
<td><strong>Urine Output</strong></td>
<td>Catheter</td>
<td>Yes</td>
<td>Usually Valid</td>
<td>Hourly</td>
</tr>
<tr>
<td><strong>Capnography</strong></td>
<td>Sensor</td>
<td>No</td>
<td>Usually Valid</td>
<td>Continuous</td>
</tr>
<tr>
<td><strong>Capillary Refill Time</strong></td>
<td>Manual pressure</td>
<td>No</td>
<td>Usually Valid</td>
<td>Daily + after significant clinical variation</td>
</tr>
<tr>
<td><strong>Mottling Score</strong></td>
<td>Clinical evaluation</td>
<td>No</td>
<td>Usually Valid</td>
<td>Daily + after significant clinical variation</td>
</tr>
<tr>
<td><strong>Arterial Blood Pressure</strong></td>
<td>Sensor</td>
<td>No</td>
<td>Usually Valid</td>
<td>Continuous</td>
</tr>
<tr>
<td><strong>Blood Gases</strong></td>
<td>Blood samples</td>
<td>No</td>
<td>Usually Valid</td>
<td>QID + after ventilatory and ECMO changes</td>
</tr>
<tr>
<td><strong>Venous Blood Oxygen Saturation</strong></td>
<td>Blood samples (pre-oxy)</td>
<td>No</td>
<td>Usually Valid</td>
<td>BID + after significant clinical variation</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td>X-ray</td>
<td>No</td>
<td>Valid</td>
<td>Daily + after significant clinical variation</td>
</tr>
<tr>
<td><strong>POCUS</strong></td>
<td>Echocardiography</td>
<td>No</td>
<td>Usually Valid</td>
<td>Daily + after significant clinical variation</td>
</tr>
<tr>
<td><strong>NIRS</strong></td>
<td>Sensor</td>
<td>No</td>
<td>Usually Valid</td>
<td>Continuous</td>
</tr>
<tr>
<td><strong>Lactate</strong></td>
<td>Blood samples</td>
<td>No</td>
<td>Potentially valid</td>
<td>QID + after ventilatory and ECMO changes</td>
</tr>
<tr>
<td><strong>ECMO parameters (BF, Pressure)</strong></td>
<td>Sensor</td>
<td>No</td>
<td>Usually Valid</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

BID: twice a day; BNP: Brain natriuretic peptide; NT-pro-BNP:N-terminal-brain natriuretic peptide; ECG: Electrocardiogram; ECMO: Extracorporeal membrane oxygenation; IL: Interleukin; NIRS: near-infrared spectroscopy; POCUS: Point of care ultrasound; TTE: Transthoracic echocardiography; TEE: Transesophageal echocardiography; QID: four time a day
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<th><strong>Modalities</strong></th>
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<th><strong>Consideration</strong></th>
<th><strong>Frequency</strong></th>
<th><strong>Comment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECMO components circuit</strong> (cannula, tubing, pump, oxygenator) and Recirculation</td>
<td>Visual</td>
<td>No</td>
<td>Usually Valid</td>
<td>Daily</td>
</tr>
</tbody>
</table>

**Diagnostic/Prognostic Monitoring**

| **Bilirubin** | Blood sample | No | Potentially valid | Daily | Serial assessment |
| **BNP, NT-pro-BNP** | Blood sample | No | Potentially valid | On start + serial exams after clinical variation | Serial assessment |
| **Troponin T and I** | Blood sample | No | Potentially valid | On start + serial exams after clinical variation | Serial assessment |
| **IL-6** | Blood sample | No | Potentially valid | Daily | |

**Advanced Monitoring**

| **TTE** | Echocardiography | No | Usually valid | Serial exams | Operator-dependent, limitations related to thoracic impedance (obesity, emphysema, high Peep, fluid overload, dressing) |
| **TEE** | Echocardiography | Yes | Valid | Serial and closer exams in RV dilatation/dysfunction, increased sPAP | Operator-dependent |
| **Pulmonary Artery Catheter** | Injection indicator (thermal, lithium) | Yes | Lacks validity | Daily | Valid at low BF rates |
| **Pulse Contour stroke volume** | Sensor in arterial line | No | Lacks validity | Continuous | Depending on correct detection of arterial waveform |
| **Transpulmonary thermodilution** | Injection indicator (thermal) | Yes | Lacks validity | Daily | Compromise by small Vt, reduced lung compliance, ventricular dysfunction |

BID: twice a day; BNP: Brain natriuretic peptide; NT-pro-BNP: N-terminal-brain natriuretic peptide; ECG: Electrocardiogram; ECMO: Extracorporeal membrane oxygenation; IL: Interleukin; NIRS: near-infrared spectroscopy; POCUS: Point of care ultrasound; TTE: Transthoracic echocardiography; TEE: Transesophageal echocardiography; QID: four time a day
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<th>Frequency</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sublingual Microcirculation</td>
<td>Sensor</td>
<td>Yes</td>
<td>Usually Valid</td>
<td>Daily + after significant clinical variation</td>
</tr>
</tbody>
</table>

BID: twice a day; BNP: Brain natriuretic peptide; NT-pro-BNP: N-terminal brain natriuretic peptide; ECG: Electrocardiogram; ECMO: Extracorporeal membrane oxygenation; IL: Interleukin; NIRS: near-infrared spectroscopy; POCUS: Point of care ultrasound; TTE: Transthoracic echocardiography; TEE: Transesophageal echocardiography; QID: four time a day

### Basic hemodynamic monitoring

Basic hemodynamic monitoring include physical examination, blood pressure, heart rate, pulse-oximetry, daily chest X-rays and urine output.\(^{15}\)

### Capillary Refill time (CRT)

CRT is a useful and rapid metric in determining the intravascular volume status, is an easily performed and interpreted examination. The performing examiner applies manual pressure to the ventral surface of distal phalanx of fingers until the nailbed is blanched. This pressure is maintained for ten seconds and then released. The amount of time, in seconds, that transpires before reperfusion stated the conditions; the upper limit of normal time to reperfusion is less than 3 seconds. As demonstrated by the ANDROMEDA-SHOCK trial\(^{16}\), its utility extends beyond diagnostic purposes and may be used to guide fluid resuscitation strategies in unstable patients.

### Mottling score

Alongside macro-hemodynamic parameters abnormalities, microcirculation blood flow impairment has been remarkably pronounced in the most severely ill patients. The microvascular disorders have been associated with mortality as well as their persistence despite resuscitation. These abnormalities could persist even if macro-hemodynamics parameters have been normalized, suggesting a dissociation between micro and microcirculatory compartments.

Mottling, defined as patchy skin discoloration, is a common sign of cutaneous hypoperfusion. Blood flow reduction may be due to local vasoconstriction and endothelial dysfunction. The Mottling score provides a semi quantitative evaluation of mottling based on skin area extension on legs\(^{17}\).

### Arterial blood waveform

The arterial waveform provides a real-time signal of arterial blood pressures and pulse pressure variation (PPV). When appropriately measured and interpreted, it is a minimally invasive predictor of fluid responsiveness\(^{18}\). However, PPV strongly depends on the waveform that could be damped for peripheral vasoconstriction, low tidal volume (Vt), low lung compliance, dysrhythmias, and intra-abdominal pressure. These are all conditions frequently encountered in patients with Acute Respiratory Distress Syndrome (ARDS) and particularly in patients with protective strategy ventilation on V-V ECMO. No randomized controlled trial has compared PPV-based fluid management with standard care, but its dynamic response during simple tests such as the Vt challenge, conducted by transient increasing Vt for 2 minutes, may overcome limitations.
Another dynamic index of fluid responsiveness is Passive Leg Raising (PLR) based on preload-redistributing maneuver not limited by the use of Vt, high respiratory rates or low pulmonary compliance. PLR mimic fluid expansion by shifting blood from lower limbs and splanchnic compartment and a variation > 10% was predictive of fluid responsiveness and may be helpful in reliably identifying patients who will benefit from fluid loading.

**Arterial and venous blood gas analysis**

An arterial line is also essential for the direct measurement of arterial oxygen content (CaO$_2$), partial arterial pressure of oxygen (PaO$_2$), and carbon dioxide (PaCO$_2$). The CaO$_2$ is controlled by the ECMO blood flow, which influences the oxygen exchange in the membrane lung and the oxygen-carrying capacity related to the hemoglobin concentration. ECMO mainly controls the PaCO$_2$ through sweep gas flow and blood flow and patient-related factors such as minute ventilation. During ECMO support, blood flow from the extracorporeal circuit mixes with blood that follows the normal pattern of circulation, and the PaO$_2$ depends on the ratio between blood flow and CO. Consequently, PaO$_2$ reflects the relative amount of oxygenated blood from the circuit and deoxygenated venous blood. The site of blood sampling for arterial blood gas analysis is less relevant in V-V ECMO.

The venous analysis should be considered complementary to the arterial one and represents the mixture of venous blood from all body regions. In a normal, non-ECMO patient, a venous blood gas can be performed using a mixed venous blood sample drawn from the pulmonary artery by using a pulmonary artery catheter (PAC) or a central venous blood sample using a central venous catheter placed in the internal jugular vein or subclavian vein. V-V ECMO-related hemodynamics and cannula configuration (jugular-femoral, femoro-jugular, femoro-femoral, double-lumen) significantly impact the anatomical point where the mixture of venous blood occurs. Therefore, the venous sample should be drawn before the membrane lung. However, several assumptions must be verified:

- a stable ECMO circuit flow and oxygenation without variations in blood drainage (or fluctuations in metabolic demand, such as shivering)
- a stable patient’s CO, especially RV function
- the percentage of recirculation (affected by cannula configuration and positioning, ECMO blood flow, changes in intra-thoracic, intra-cardiac and intra-abdominal pressures)
- ventilator adjustments, blood transfusion, and vasoactive medication use

**DO$_2$, VO$_2$, and PCO$_2$ gap**

The simultaneous sampling of arterial and venous blood allows the calculation of three parameters that reflects tissue perfusion: DO$_2$, oxygen consumption (VO$_2$), and DO$_2$/VO$_2$ ratio. However, these samples can only give indirect indications of oxygen supply adequacy if CO is available and require to be repeated whenever the patient condition changes.

The PCO$_2$ gap, calculated as the difference between venous and arterial PCO$_2$, is proportional to the CO$_2$ production (VCO$_2$) and reflects the adequacy of the microcirculation. A PCO$_2$ gap > 6 mmHg implies inadequate CO. Persistent elevation of PCO$_2$ gap has been associated with worse prognosis as a reflection of venous return from poor capillary bed with inadequate microcirculation. Variations of the PCO$_2$ gap, easily measured via point-of-care analyzers, occur faster than changes in lactate and are an earlier sign of CO impairment.

**Serum Lactate Measurement**
Lactate is one of the metabolic products of anaerobic glycolysis and may reflect inadequate DO₂. High lactate values are induced by increased production due to administration of catecholamines or decreased hepatic clearance and represent a late marker of hypoperfusion, less sensitive than SvO₂ or PCO₂ gap. Dynamic serial lactate measurements and lactate clearance are a surrogate for the magnitude and duration of global tissue hypoxia, are more reliable for risk stratification than absolute level present in most prognostic ECMO scores.

**Near infrared spectroscopy (NIRS)**

Near infrared spectroscopy (NIRS) generates data on the regional oxygen saturation (rSO₂), evaluates the interaction between the macro-circulation and organ-specific auto-regulatory mechanisms, and indicates peripheral DO₂ of the total vascular bed. Generally, a decreased rSO₂ reflects a decreased global perfusion and can be used to indicate low DO₂. Although NIRS estimates the regional hemoglobin oxygen saturation, it cannot distinguish between changes due to reduced oxygen availability versus increased consumption. Usually, hypoperfusion is diagnosed when rSO₂ < 50% or there is a drop > 20% from the baseline. Serial measurements, instead of absolute numbers, timely detect altered hemodynamics. In ECMO patients, NIRS is usually applied to detect the cerebral hypoxic-ischemic injury. NIRS can assess cerebral vasoconstriction due to an abrupt alteration in the CO₂ equilibrium in the brain, particularly in the first 24 hours, and represents an important tool to facilitate a slow PaCO₂ removal reducing the time-consuming frequent blood gas analysis.

**Point-of-care ultrasound (POCUS)**

POCUS is now used in almost every branch of critical care medicine and enables frequent goal-directed, dynamic evaluation. Imaging data with thoracic ultrasound could detect bilateral B pattern, non-uniform distribution, pleural lines abnormalities, reduced lung sliding and C pattern. Moreover, POCUS can assist in V-V ECMO by evaluating vessel patency, cannula position, RV and LV structures, function, intravascular volume status, lung aeration, and causes of shock.

**ECMO circuit monitoring**

Variations in ECMO blood flow may indicate a need for volume resuscitation. Signals of hypovolemia or significant vasodilatation include excessive negative pressure in the drainage side of the circuit, “chattering” of the drainage cannula due to the collapse of the inferior vena cava around the drainage cannula secondary to either excessive negative pressure or patient hypovolemia or both. Therefore, a regular circuit check of the critical components of the circuit (cannulas, pump, tubing, oxygenator) can be considered part of the basic monitoring during V-V ECMO to maintain circuit integrity and patient safety.

In particular, in V-V ECMO, the crucial determinants of oxygen saturation are the oxygen fraction of the circuit, the ratio of ECMO flow to native CO, metabolic demand, native lung function and recirculation.

Recirculation is defined as the fraction of oxygenated blood infused into the right atrium and is then aspirated back into the venous line of the ECMO circuit. In V-V settings, gas transfer efficiency is reduced in direct proportion to the amount of recirculation. Native CO is one of the factors influencing the amount of recirculation with higher recirculation levels in case of RV failure and low CO. Increasing over time of the recirculating fraction might indicate a decline in RV function when excluding negative effects of factors such as pump speed, ECMO blood flow rates, intrathoracic, intracardiac and intra-abdominal pressures, cannula type, size, and position.
Diagnostic and Prognostic Cardiovascular Monitoring

Bilirubin and liver enzymes

Hepatic injury may be caused by changes in hemodynamics, venous congestion, and decreased DO$_2^{34}$. It might be detected through markers of hepatocyte injury (aminotransferases), markers of hepatic clearance/biliary secretion capacity (bilirubin), and measures of synthetic capacity (prothrombin time, albumin). Hypoxic hepatitis can cause sharp increases in aminotransferases in the setting of respiratory failure, shock, or cardiac failure$^{35}$. Its pathogenesis comprises hepatic ischemia and venous congestion due to elevated central venous pressure and RV failure$^{36}$. Furthermore, many medications used for ARDS (antibiotics, corticosteroids, catecholamines) are potentially hepatotoxic. Increased values are frequently observed in ECMO patients and are associated with disease severity, increased inflammation but also with ECMO-induced hemolysis. Particularly, high bilirubin is a common finding (incidence: 20–40%), mainly related to systemic hypoperfusion and cardiac failure$^{37}$. As a marker of hepatic dysfunction, it is incorporated in scoring algorithms to assess prognosis in critically ill patients$^{38}$. Therefore, a regular dosage is advised, and changes over time might indicate the development of cardio-circulatory compromise when other causes of hepatotoxicity can be excluded.

BNP, NT-pro-BNP and Troponin

Biomarkers of cardiac myocyte stretch, such as brain natriuretic peptide (BNP) and N-terminal-natriuretic-peptide (NT-proBNP), are well established in the diagnosis and prognosis of HF$^{39}$. Myocardial disease is not the predominant cause of elevated NT-proBNP, elevated values (> 800 pg/mL), correlates with infection, organ failure, and increased disease severity and represents a strong independent predictor of mortality. Furthermore, Troponin-T and Troponin-I could have prognostic value in pulmonary diseases such as pneumonia and chronic obstructive pulmonary disease$^{40}$. A serial assessment can identify factors predicting cardio-circulatory damage or mortality in ECMO but with a lower prognostic value compared to lactate$^{39,41}$.

Advanced cardio-circulatory monitoring

Transthoracic and transesophageal echocardiography

Echocardiography (transthoracic and transesophageal) has a growing role in management of V-V EMO patients, mainly because of the strict interactions between the lung (and ventilation) and the RV and pulmonary circulation. These two techniques are not completely interchangeable. The choice is usually made on the acoustic windows or challenging anatomy$^6$ as well as on the clinical needs (Fig. 2). According to the existing evidence a screening to timely identify variations in the right and left cardiac function (Table 2) should be measured in all V-V ECMO patients.$^{42-44}$ Serial echocardiographic monitoring of RV function are needed to assess the effect of lung rest ventilation on RV function and to clarify whether RV dysfunction in ARDS is a marker of a more severe underlying disease or an independent risk factor for mortality. In addition, the COVID-19 pandemic has highlighted the importance of echocardiography monitoring amongst patients with respiratory failure$^{45,46}$.
<table>
<thead>
<tr>
<th>Measurements</th>
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<tbody>
<tr>
<td><strong>Left Ventricle</strong></td>
</tr>
<tr>
<td>Systolic function</td>
</tr>
</tbody>
</table>
| Diastolic function | E/A ratio E/e' ratio at mitral annulus 
TR velocity 
LA volume index |
| **Left Atrium** | Size and volume |
| **Valvular assessment** | Diagnosis and quantification of potential aortic/mitral regurgitation/stenosis |
| **Right Ventricle** |
| Morphology | RV end-diastolic area/LV end-diastolic area Triangular shape versus rounded shape of apex RV wall thickness McConnell's sign |
| Systolic function | TAPSE tissue doppler at tricuspid annulus, S wave Fractional area of change Pulse wave doppler through pulmonary |
| Diastolic function | E/A trans-tricuspid flow |
| Interventricular septum | Presence of paradoxical septum Eccentricity index |
| Tricuspid regurgitation | Estimation of RV systolic pressure |
| **Valvular assessment** |
| **Right atrium** | Size and volume |
| **Other** |
| Patent foramen ovale | Colour flow doppler, bubble study |
| IVC/SVC (if TEE) | Size and respiratory variation |
| Right atrium | Dilated coronary sinus Chiari network |
| **Vascular** | Thrombosis/stenosis/aortic dissection/severe atheroma |

E/A early diastolic peak velocity/diastolic ventricular filling with atrial contraction; E/e' early diastolic peak velocity/early diastolic tissue Doppler velocity; FAC fractional area change; IVC inferior vena cava; LV left Ventricle; LVOT left ventricular outflow tract; RV right ventricle; SVC superior vena cava; TAPSE tricuspid annular plane systolic excursion; TEE transesophageal echocardiography

**Pulmonary Artery Catheter (PAC)**
Advanced hemodynamic monitoring involves PAC. PAC provides measurements including right atrial pressure, RV pressure, pulmonary artery pressure, pulmonary artery occlusive pressure, and mixed venous saturation. Systemic and pulmonary vascular resistances are calculated from these variables, and CO is measured using a thermodilution method. Information from PAC can be central to evaluating the adequacy of ventricular support and diagnosing potential ECMO complications, including thrombosis. However, CO measurement with thermodilution might be influenced by the presence of ECMO flow itself, cannulas position, intrinsic RV contractility, systemic and pulmonary vascular properties, and any coexisting valvular lesions. Pulmonary pressure is always reliable, except in the case of intracardiac shunt defects. CO reliability is dependent on recirculation and drainage cannula position. All pressure measured must be interpreted according to intrathoracic pressure. Consequently, PAC measurements should be carefully considered during V-V ECMO, and trends might be more clinically significant than absolute values. Moreover, placement of PAC can be associated with the risk of tachy-dysrhythmia, pulmonary artery rupture, knotting, carotid artery damage, arterio-venous fistula, tricuspid valve damage, and infection.

Despite the frequent use of right heart catheterization in patients undergoing mechanical circulatory support, such as V-A ECMO or left ventricular assist device, its routine use in V-V settings has declined over the past decade, and there is no consensus on its systematic use47.

**Pulse contour wave analysis**

Pulse contour analysis of CO is based on the principle that stroke volume can be continuously estimated by analyzing the arterial pressure waveform. Calculations are based on the area under the curve of the systolic portion of the arterial waveform, which can be influenced by stroke volume, vascular compliance, aortic impedance, and peripheral vascular resistance. This technique provides dynamic analysis for the assessment of fluid responsiveness, such as stroke volume variation and systolic pressure variation between the inspiratory and expiratory phase of mechanical ventilation48. Currently, different devices measure CO based on the pulse contour analysis, and all of them use a similar PAC thermodilution technique. Cardiovascular arrhythmia, right HF, spontaneous breathing activity, low Vt, drainage cannula position can affect its reliability. Particularly, methods that rely on diluting an indicator injected into a venous system could produce ambiguous results due to the loss of indicator into the ECMO circuit. However, when ECMO flows are very low, thermodilution can retain accuracy.

**Sublingual microcirculation**

The microcirculation is the terminal vascular network of systemic circulation consisting of microvessels responsible for oxygen transfer. It is a compartment of the cardiovascular system of utmost importance since it is in direct contact with the parenchymal cells, which rely on its proper function to maintain their viability to support organ function. Various studies suggest that the assessment of sublingual microcirculation may have a role in guiding clinical decisions during ECMO-treatments49,50. Total vessel density, perfused vessel density and blood flow quality (microvascular flow index), percentage of perfused vessels, and flow heterogeneity index provide information about microcirculatory flow abnormalities that are associated with an increased risk of unfavorable outcome. Over the last decades, important progress has been made in understanding microcirculatory dysfunction, and many technological advances have led to the development of hardware-related hand-held vital microscopes for bedside monitoring and fully automated software51.

The direct visualization of the microcirculation and the point-of-care analysis of functional parameters can identify patients at risk where apparent resuscitation targets have been met based on the normalization of systemic hemodynamic variables and possibly provide new microcirculatory-based resuscitation targets in conjunction with systemic hemodynamic goals.
Multi-step practical approach

It is important to note that hemodynamic responses during V-V ECMO support are complex and vary among patients due to multiple clinical variables. Microthrombi, pulmonary arterial remodeling, vasoconstriction from hypoxia, acidosis, and/or inflammatory mediators, deleterious effects of mechanical ventilation on RV function, sepsis-induced tissue demands could be paired to hemodynamic dysfunction. Moreover, RV failure could be worsened by the loading due to the ECMO itself. Monitoring hemodynamics is essential to optimize perfusion, improve gas exchange, and minimize ventilator lung injury risk.

Three dimensions of hemodynamic monitoring interacting closely and summarized as follow:

1. Basic
Provide valuable information on perfusion state by clinical examination, cold and clammy skin, arterial waveform, oliguria and direct and indirect signs of tissue oxygenation (lactate, blood gases and rSO2). Evaluating ECMO support provides the degree of gas exchange support and by echocardiography analyze the thoracic cardiac side.

2. Diagnostic/Prognostic
Identifying the evolution of disease severity due to a multifactorial explanation including hyper-sympathetic state, administration of exogenous catecholamines, mechanical ventilation, aggressive intravenous resuscitation by cardiac biomarkers and hepatic function.

3. Advanced
Detecting native cardiac function and his derangement guiding the treatment by a more detailed echocardiography, transpulmonary thermodilution techniques and the incoherence between macro- and micro-circulation mainly predominant in septic shock patients.

Challenges in cardio-circulatory monitoring

This practical approach, categorized by theme, have been summarized in Table 1 and Fig. 3.

Besides definite etiologies which might require specific strategies, some conditions demand particular attention.

The prone position is an adjunct therapy often employed in treating ARDS and RV failure. This technique reduces the difference in the ventral-dorsal trans-pulmonary pressure leading to homogeneous perfusion and recruitment of collapsed lung alveoli. It might be beneficial also during ECMO support, by decreasing airway pressure and reducing hypercapnia, offloading the RV, favoring venous return, and, consequently, increasing CO. The prone position is accomplished by having the patient on her stomach with the left arm raised above the head and the right arm resting along the torso. A pillow is positioned under the left arm to slightly elevate the left hemithorax permitting more space for the transducer (Fig. 2).
Another practice that requires meticulous cardiovascular monitoring is the awake-ECMO approach. The patient’s increased work of breathing, discomfort, pain, and anxiety can lead to high oxygen consumption and CO₂ production. Hemodynamic monitoring in awake ECMO patients does not differ from non-awake ECMO patients. The challenge is maintaining the control of the volume status, preload, and venous return that the duration of negative intrathoracic pressure could influence due to the respiratory muscle activity and the metabolic interactions linked by extracorporeal gas exchange.

**Discussion And Recommendations**

There is consensus that hemodynamic monitoring is essential for the early identification and management of critical changes in cardiac function and hemodynamics during ECMO support. Extensive data regarding cardio-circulatory monitoring during V-A settings are available, whereas limited information and suggestions are reported in V-V ECMO management. Herein, we propose a three-step approach to establish an effective and adequate cardio-circulatory monitoring protocol (Fig. 3).

In order to effectively apply this method, creating a multidisciplinary ECMO team that includes perfusionists, nurses, intensivists, pneumologists, cardiac surgeons, and cardiologists with specific skills in cardio-circulatory physiology and pathophysiology, is of paramount importance to manage the heart-lung-ECMO interaction correctly. The COVID-19 pandemic has highlighted the importance of these conditions and competencies to understand and distinguish between the primary hemodynamic effects of a VV device in the absence of any change in native heart or vessels and the development of secondary cardiac or circulatory diseases. The COVID-19 ECMO experience emphasized how it is necessary to establish a routinely cardio-circulatory monitoring approach on VV ECMO with a shift from the severity of hypoxemia as the only predictor of outcome during ARDS to the recognition of RV function and pulmonary vascular system alterations as equally important prognostic factors.

**Gaps of Knowledge and future directions**

This scoping review showed a great variability among monitoring strategies and significant gaps of knowledge, with few articles reporting a clear management policy to evaluate the hemodynamic side in V-V ECMO patients. On a general level some future directions can be defined. First, existing methods on hemodynamic monitoring should be investigated according to a uniform protocol in multiple centers to fill the identified gaps. Second, new methods of hemodynamic monitoring, including dynamic variables and less invasive techniques, are under development and might improve the reliability of measures. Third, artificial intelligence and machine learning algorithms run on valid data might allow for predictive analytics of hemodynamic complications before they occur. In the future, there could be automated feedback loops based on artificial intelligence that may enable titration of ECMO support according to changing physiological needs of the patients. Finally, the effect of interventions should be studied based on newly defined hemodynamic monitoring protocols or guidelines to see whether the interventions have an effect on these surrogate measures and clinical outcome.

**Conclusions**

Understanding the importance of the interplay between ventilation, hemodynamics, and laboratory tests should be paramount in any patients with respiratory failure and V-V ECMO, has been highlighted during the COVID-19 ECMO experience. There are currently no guidelines regarding optimal cardiovascular monitoring in V-V ECMO patients. Accordingly, we propose a sequential approach with basic, diagnostic/prognostic tools that should be implemented
with more advanced strategies to target precise patient-centered metrics. Many questions remain unaddressed and require further investigations. Therefore, ad hoc guidelines and the development of new technologies are warranted to help clinicians and improve outcomes.

**Abbreviations**

V-V ECMO: Veno-venous extracorporeal membrane oxygenation; V-A ECMO: veno-arterial extracorporeal membrane oxygenation; RV: right ventricle; LV: left ventricle; HF: Heart failure; CO: Cardiac output; DO\(_2\) : Oxygen delivery; VO\(_2\) : Oxygen consumption; CRT: Capillary Refill Time; PPV: Pulse pressure variation; Vt: Tidal volume; ARDS: Acute Respiratory Distress Syndrome; PLR: Passive Leg Raising; CaO\(_2\): arterial oxygen content; PaO\(_2\): Partial arterial pressure of oxygen; PaCO\(_2\): Partial arterial pressure of carbon dioxide; PAC: Pulmonary Artery Catheter; SvO\(_2\): venous oxygen saturation; NIRS: Near-infrared spectroscopy; rSO\(_2\): Regional saturation of oxygen; POCUS: Point of care ultrasound; BNP: Brain Natriuretic Peptide; NT-pro-BNP: N-terminal-natriuretic peptide

**Declarations**

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**Consent for publication:** Not applicable

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**References**


Figure 1

Effects of increased lung stiffness and high vascular resistances on extracorporeal membrane oxygenation (ECMO) flow and right ventricular function in patients undergoing veno-venous ECMO. Increased pulmonary vascular resistance leads to right ventricular dilatation as well as reduced contractility. Consequently, the forward ECMO flow towards the pulmonary artery is reduced, and the recirculation fraction is increased.
Figure 2

Example of echocardiographic examination in a patient in prone positioning with a double-lumen cannula for veno-venous extracorporeal membrane oxygenation.
Figure 3

Summary of general principles for recommended hemodynamic monitoring in patients undergoing veno-venous extracorporeal membrane oxygenation. ECG, electrocardiogram; CRT, capillary refill time; ECMO, extracorporeal membrane oxygenation; POCUS, point of care ultrasound; COVID-19, coronavirus disease 2019.

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