VA-ECMO and VV-ECMO in COVID-19: Severe ARDS or Cardiogenic Shock?

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Abstract

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, on December 2019. Since then, it has spread worldwide, causing an unforeseen global crisis. Respiratory involvement ranging from a mild flu-like illness to potentially lethal acute respiratory distress syndrome (ARDS) is the predominant clinical manifestation of SARS-CoV-2. However, cardiovascular complications can also result in severe morbidity and mortality. Although ARDS appears to be the most common trigger for intensive care unit (ICU) admission, cardiac injury and shock are also frequent. In patients with ARDS and/or cardiogenic shock, the Extracorporeal Membrane Oxygenation (ECMO) is often required to provide respiratory and cardiac support. Nevertheless, evidence on ECMO in COVID-19 patients remains controversial. This review sought to analyse the use of veno-venous-ECMO and veno-arterial-ECMO in SARS-CoV-2 positive patients, of whom age (p-value 0.89), previous medical history, presenting complaints, echocardiography, indication for ECMO, duration of support (p-value 0.31), and status at discharge (mortality p-value 0.75) were analysed. It has to be acknowledged that a multidisciplinary approach and a frequent reassessment of response to mechanical circulatory support are fundamental for the SARS-CoV-2 population requiring cardiac and/or respiratory support.

Keywords: VA-ECMO;VV-ECMO;ECLS;COVID-19;SARS-CoV-2;cardiogenic shock;ARDS

Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, on December 2019. Since then, it has spread worldwide, causing an unforeseen global crisis.


Respiratory involvement ranging from a mild flu-like illness to potentially lethal acute respiratory distress syndrome (ARDS) is the predominant clinical manifestation of SARS-CoV-2 [1]. However, cardiovascular complications can also result in severe morbidity and mortality [2]. The existing literature demonstrates that 5-25% of patients hospitalized with COVID-19 had acute myocardial injury, which is defined as a rise and fall in cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit, with a higher prevalence in those admitted to intensive care units (ICU), and those who died [3, 4].

The mortality of SARS-CoV-2 has been reported to be as high as 13.9% in all patients [5]. Risk factors include older age, hypertension, diabetes mellitus and previous cardiovascular events [6]. Although ARDS appears to be the most common trigger for intensive care unit (ICU) admission with an incidence of 32.8%, cardiac injury and shock are also frequent (incidence 13.0% and 6.2%, respectively) [5].

In patients with ARDS and/or cardiogenic shock, extracorporeal membrane oxygenation (ECMO) is often required to provide respiratory and cardiac support. Nevertheless, evidence for ECMO in COVID-19 patients remains controversial. The immunological side effects of ECMO can further compromise the already debilitated immune system fighting COVID-19 [7]. Moreover, the mortality rate in adult patients with ARDS from SARS-CoV-2 pneumonia is 50-82% [8, 9]. Finally, one potential challenge still to be overcome is discriminating between a cardiac or respiratory aetiology of symptoms, as dyspnoea is a common symptom among them. It is, therefore, critical to recognize when cardiac and pulmonary involvement co-exist. This will allow to fully understand the indication for ECMO, particularly for VA-ECMO.

This review sought to analyse the use of extracorporeal membrane oxygenation in SARS-CoV-2 positive patients. The main focus would be to try and establish the type of support, the indication and the duration in regards to ECMO, and any in-hospital mortality as a result of it.
Methods

Authors searched for papers indexed in PubMed using the keywords “VA-ECMO”, “VV-ECMO”, “ECLS”, “COVID-19”, “SARS-CoV-2”, “cardiogenic shock”, and “ARDS”. All authors contributed to paper research and selection. Inclusion criteria consisted of retrospective studies, prospective studies, case reports, and original research work. Papers excluded were: systematic reviews, narrative reviews, and non-original research work. No language restrictions were applied. The initial search resulted in 175 papers, after refining them through the inclusion and exclusion criteria, 18 papers were finally selected.

The focus of this review was the use of VV-ECMO and VA-ECMO in COVID-19 patients. Within these patients the following aspects were analysed: age, previous medical history, presenting complaints, echocardiography, indication for ECMO, duration of support, and status at discharge. Age and length of ECMO support were expressed in mean and interquartile range. These variables were then compared using the unpaired t-test. Mortality rates were expressed in percentage and compared using the Pearson’s Chi-square ($\chi^2$). A p-value below 0.05 was considered statistically significant.

Discussion

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is an acute diffuse, inflammatory lung injury, which presents with severe dyspnoea, hypoxaemia and bilateral radiographic opacities. It is associated with an increased venous admixture, increased physiological dead space, decreased lung compliance, increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue [10]. ARDS typically causes respiratory failure. Diagnostic criteria include

- (a) diffuse bilateral pulmonary infiltrates on chest X-Ray (CXR);
- (b) $\text{PaO}_2$ (arterial partial pressure of oxygen in mmHg)/$\text{FiO}_2$ (inspired oxygen fraction) ≤ 200 mmHg; and
- (c) absence of elevated left atrial pressure (pulmonary capillary wedge pressure ≤ 18 mmHg). The severity of ARDS is classified according to the Berlin classification [10]:
  - Mild: 200 mmHg < $\text{PaO}_2$/FiO$_2$ ≤ 300 mmHg with PEEP (positive end-expiratory pressure) or CPAP (continuous positive airway pressure) ≥ 5 cmH$_2$O
  - Moderate: 100 mmHg < $\text{PaO}_2$/FiO$_2$ ≤ 200 mmHg with PEEP ≥ 5 cmH$_2$O
  - Severe: $\text{PaO}_2$/FiO$_2$ ≤ 100 mmHg with PEEP ≥ 5 cmH$2$O

As mentioned previously, ARDS appears to be the most common trigger for ICU admission in SARS-CoV-2, with an incidence of 32.8% [5]. Therefore, several treatment options and their effectiveness have been assessed and used in this patient population. However, when mechanical ventilation and prone positioning are unsuccessful, ECMO is a useful alternative.

Cardiogenic Shock

Cardiogenic shock is defined as severe left ventricle (LV) failure with hypotension (systolic blood pressure < 90 mmHg) and elevated PCW (pulmonary capillary wedge pressure). It usually presents with oliguria (< 20 mL/h), peripheral vasoconstriction, dulled sensorium, and metabolic acidosis.

Cardiogenic shock (CS) of undetermined aetiology was demonstrated in up to 12% of COVID-19 patients [11]. This may be a result of a combination of myocardial virus localization and acute myocardial injury/type II myocardial infarction (MI) [12, 13]. Clinical outcome in CS appears to be worse in concomitant SARS-CoV-2 infection compared with isolated CS (30–40% vs. 45–50% survival) [14].

Extracorporeal Membrane Oxygenation

In patients with ARDS and/or CS, ECMO is often required to provide respiratory and cardiac support. Veno-venous ECMO (VV-ECMO) is primarily used to support the lungs. This is achieved via a single or double venous system with the ECMO circuit connected in series to the heart and lungs. Conversely, veno-arterial ECMO (VA-ECMO) provides both haemodynamic and respiratory function. The ECMO circuit is conducted in parallel to the heart and lungs, resulting in a complete bypass of both.

Respiratory indications for ECMO are [15]:
- Murray score >3
- $\text{PaO}_2$/FiO$_2$ <100 (mm Hg) despite high PEEP (10 - 20 cmH$_2$O) on FiO$_2$ >80%
- Intrapulmonary right-to-left shunt (Qs/QT) >30%
- Total thoracopulmonary compliance (CTstat) <30 ml/cmH$_2$O
- Severe hypercapnia with $\text{PaCO}_2$ >80 on FiO$_2$ >90% or pH <7.20
- Maximal medical therapy >48 h
- Cardiac indications for ECMO are [15]:
  - Cardiac index <2 L/min/m$^2$
  - Lactate level >50 mg/dl or 5 mmol/L or Central Venous Oxygen Saturation - ScVO$_2$ <65% with maximum medical management
  - Systolic blood pressure less than 90 mmHg

Low cardiac output

Pathological processes which would be suitable for respiratory (VV- and VA-ECMO), and cardiac support (VA-ECMO only) are listed on Table 1 [16]. Absolute contraindications for the
The use of ECMO are shown on Table 2 [15].

The World Health Organization (WHO) guidance document includes a statement to consider referring patients with refractory hypoxemia despite lung-protective ventilation in settings with access to expertise in ECMO support [8].

An international Consensus on extracorporeal life support during COVID-19 highlights the importance of established ECMO centres, as well as international cooperation in order to maximize benefits [17].

### Table 1: Pathological processes for respiratory and cardiac support

<table>
<thead>
<tr>
<th>Respiratory support (VV- and VA-ECMO)</th>
<th>Cardiac support (VA-ECMO only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td>Extracorporeal assistance to provide lung rest (airway obstruction, pulmonary contusion, smoke inhalation)</td>
<td>Post cardiomyopathy (unable to wean from cardiopulmonary bypass)</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>Post heart transplant</td>
</tr>
<tr>
<td>Lung hyperinflation (status asthmaticus)</td>
<td>Chronic cardiomyopathy</td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>Bridge to transplant</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td></td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Absolute contraindications to ECMO

1. Age > 75 years
2. Irreversible cardiac or pulmonary disease
3. Metastatic malignancy
4. Current intracranial haemorrhage
5. Significant brain injury
6. Prolonged Cardiopulmonary Resuscitation without adequate tissue perfusion
7. Aortic dissection
8. Severe aortic valve regurgitation
9. Major pharmacologic immunosuppression

### VV- and VA-ECMO in COVID-19

The existing literature regarding the use of VV- and VA-ECMO for SARS-CoV-2 positive patients consists of case reports and small cohort studies. It is critical to recognize when cardiac and pulmonary involvement coexist, and, therefore, fully understand the indication for support via VA-ECMO. Furthermore, two recognised complications of ECMO are haemorrhage and thrombosis, which could be fatal in the already deranged coagulation pattern of COVID-19 patients. This has been reported by two case series of intra-cranial haemorrhage and upper airway bleeding [18, 19].

A recent survey conducted by the Euro Extracorporeal Life Support Organization verified the use of ECMO for COVID-19 in Europe: nine in England, two in Germany, three in Belgium, 18 in France, 10 in Spain, one in Sweden, one in Poland, one in Czech, and 14 in Italy [20].

Characteristics of COVID-19 patients requiring VV- and VA-ECMO support are highlighted on Table 3 [21-25] [8] [26-30] and Table 4 [30-33], respectively. Mean age was 54.95 years (IQR 28.5) for VV-ECMO and 53.75 (IQR 10.75) for VA-ECMO, p-value 0.89.

Previous medical history included hypertension, cardiovascular disease, cerebrovascular events, malignancy, chronic kidney disease and obesity. A variety of presenting complaints were also reported, ranging from mild cold symptoms to dyspnoea and cough, as well as pleuritic chest pain. Patients requiring VV-ECMO had a normal Left Ventricle Ejection Fraction (LVEF) on echocardiography, whereas those who required VA-ECMO always had a severely reduced LVEF, which is as expected. The length of support was 19.19 days (IQR 17.25) for VV-ECMO and 9.67 days (IQR 6) for VA-ECMO, p-value 0.31. Finally, the former group reported 6 deceased patient out of 18 (33.3%), compared to 1 deaths out of 4 (25%) patients in the latter group, p-value 0.75.

A closer look at the use of VA-ECMO revealed that patients presented with a mixed picture of ARDS and cardiogenic shock. Therefore, consequently respiratory and cardiac support was not required simultaneously, which led to conversion from VV- to VA-ECMO and vice versa. These results were confirmed by two further studies. Fried highlighted the importance of multisciplinary approach and frequent reassessment of response to mechanical circulatory support. Their case presented with ARDS and profound hypoxia, necessitating treatment with VV-ECMO. The cardiac involvement only became evident after the initiation of VV ECMO, which was eventually converted to a veno-arterial-venous-ECMO [31]. Beitzenn reported the first case of induced refractory cardiogenic plus vasoplastic shock in a patient with moderate ARDS and a positive SARS-CoV-2 polymerase chain reaction test. A peripheral ventricular assist device (p-VAD) was initially implanted for a cardiac output of 1.8 L/min/m²; this was followed by VA-ECMO due to persistent vasoplastic shock. The VA-ECMO eventually switched to VV-ECMO after 3 days. Cardiac support was needed for 17 days in total, whereas ARDS persisted longer [30].

A multicentre analysis in France compared the outcomes of ARDS in COVID-19 and non-COVID-19 patients. The former

<table>
<thead>
<tr>
<th>Age</th>
<th>PMH</th>
<th>Clinical presentation</th>
<th>Echocardiography</th>
<th>Duration of support</th>
<th>Status at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>41♀</td>
<td>Nil</td>
<td>Cough, dyspnoea, chest tightness, flu-like</td>
<td>LVEF 60-65% with moderate PH</td>
<td>4 days</td>
<td>Dead</td>
</tr>
<tr>
<td>51♀</td>
<td>HTN</td>
<td>“mild cold symptoms” and “pink and frothy” secretions</td>
<td>Normal LVEF</td>
<td>11 days</td>
<td>Alive</td>
</tr>
<tr>
<td>44♂</td>
<td>HTN, Hyperlipidemia</td>
<td>Dyspnoea and fever</td>
<td>Normal LVEF</td>
<td>7 days</td>
<td>Alive</td>
</tr>
<tr>
<td>76♂</td>
<td>DM, HTN, Glaucoma</td>
<td>Sore throat, cough and fever</td>
<td>-</td>
<td>11 days</td>
<td>Alive</td>
</tr>
<tr>
<td>62♀</td>
<td>HTN, COPD, Ex-smoker, OSA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>64♂</td>
<td>HTN</td>
<td>-</td>
<td>-</td>
<td>40 days</td>
<td>Alive</td>
</tr>
<tr>
<td>81♂</td>
<td>HTN, Cardiovascular disease</td>
<td>-</td>
<td>-</td>
<td>47 days</td>
<td>Dead</td>
</tr>
<tr>
<td>62♂</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>47 days</td>
<td>Alive</td>
</tr>
<tr>
<td>75♂</td>
<td>Bladder cancer</td>
<td>-</td>
<td>-</td>
<td>37 days</td>
<td>Dead</td>
</tr>
<tr>
<td>65♂</td>
<td>HTN, DM, CVA, CKD</td>
<td>-</td>
<td>-</td>
<td>22 days</td>
<td>Alive</td>
</tr>
<tr>
<td>25♂</td>
<td>Nil</td>
<td>-</td>
<td>-</td>
<td>8/10 days</td>
<td>Dead</td>
</tr>
<tr>
<td>45♂</td>
<td>HTN, DM, Asthma</td>
<td>Cough, dyspnoea and fever</td>
<td>Normal LVEF</td>
<td>11 days</td>
<td>Alive</td>
</tr>
<tr>
<td>73♂</td>
<td>HTN, Dyslipidemia</td>
<td>Dyspnoea, cough and fever</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>72♂</td>
<td>CKD stage IV, DM, Obesity</td>
<td>Fever and dyspnoea</td>
<td>Normal LVEF</td>
<td>6 days</td>
<td>Alive</td>
</tr>
<tr>
<td>34♂</td>
<td>HTN, Hyperlipidemia</td>
<td>DKA</td>
<td>-</td>
<td>12 days</td>
<td>Alive (still in-patient)</td>
</tr>
<tr>
<td>31♂</td>
<td>HTN</td>
<td>Respiratory distress</td>
<td>-</td>
<td>14 days</td>
<td>Alive (still in-patient)</td>
</tr>
<tr>
<td>34♀</td>
<td>Asthma, Migraine, Chronic gastritis</td>
<td>Intubated outside hospital</td>
<td>-</td>
<td>23 days</td>
<td>Alive (still in-patient)</td>
</tr>
<tr>
<td>54♂</td>
<td>-</td>
<td>Fever</td>
<td>LVEF 67%</td>
<td>5 days</td>
<td>Alive</td>
</tr>
</tbody>
</table>

accounted for 150 cases, age 63 [median 53; IQR 71], the latter for 233, age 74 [median 63; IQR 81]. In the SARS-CoV-2 positive group, 12 (8.1%) patients required ECMO (11 VV-ECMO and 1 VA-ECMO for ARDS + CS) for a duration of 7 days [median 4.3; IQR 11], versus 10 (4.3%) (p-value 0.124) for a duration of 8 days [median 5.3; IQR 10.8] (p-value 0.642) in the other cohort [34].

Regarding the choice of cannulation, the International Consensus on extracorporeal life support during COVID-19 recommends that either the femoro-femoral or femoro-internal jugular configuration should be used for VV-ECMO. Alternatively, they recommend a femoro-femoral configuration for VA ECMO with a distal limb perfusion catheter to reduce the risk of limb ischemia [17]. In accordance with that, the femoro-jugular approach was the preferred cannulation site for VV-ECMO Table 5, and the femoro-femoral for VA-ECMO (Bemtgen).

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>PMH</th>
<th>Clinical presentation</th>
<th>Echocardiography</th>
<th>ARDS/CS</th>
<th>Duration of support</th>
<th>Status at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemtgen et al</td>
<td>52♂</td>
<td>Dilated cardiomyopathy</td>
<td>Dyspnoea and fever</td>
<td>-</td>
<td>Moderate ARDS + CS and vasoplegic shock (then switched to VV-ECMO)</td>
<td>17 days</td>
<td>Alive (still inpatient)</td>
</tr>
<tr>
<td>Fried et al</td>
<td>38♂</td>
<td>DM.</td>
<td>Cough, pleuritic chest pain and dyspnoea</td>
<td>LVEF 20-25%</td>
<td>Severe ARDS (VV-ECMO) → CS (switched to VAV-ECMO)</td>
<td>7 days</td>
<td>Alive (still inpatient)</td>
</tr>
<tr>
<td>Tavazzi et al</td>
<td>69♂</td>
<td>-</td>
<td>Dyspnoea, cough and weakness</td>
<td>LVEF 34% → dropped to 25%</td>
<td>CS → switched to VAV-ECMO for persistent hypoxaemia</td>
<td>5 days</td>
<td>Dead</td>
</tr>
<tr>
<td>Yousefzai et al</td>
<td>56♂</td>
<td>HTN. Current smoker</td>
<td>Dyspnoea, cough and chest pain</td>
<td>Severely ↓LVEF</td>
<td>ARDS (VV-ECMO) → RV rupture (switched to VA-ECMO)</td>
<td>-</td>
<td>Alive (still inpatient)</td>
</tr>
</tbody>
</table>

Table 5: VV-ECMO cannulation

<table>
<thead>
<tr>
<th>Femo-jugular</th>
<th>Femo-femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firstenberg</td>
<td>■</td>
</tr>
<tr>
<td>Hartman</td>
<td>■</td>
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<tr>
<td>Ikuyama</td>
<td>■</td>
</tr>
<tr>
<td>Li</td>
<td>■</td>
</tr>
<tr>
<td>Nakamura</td>
<td>■</td>
</tr>
<tr>
<td>Takahashi</td>
<td>■</td>
</tr>
<tr>
<td>Taniuchi</td>
<td>■</td>
</tr>
<tr>
<td>Zhan</td>
<td>■</td>
</tr>
<tr>
<td>Bemtgen</td>
<td>■</td>
</tr>
<tr>
<td>Fried</td>
<td>■</td>
</tr>
</tbody>
</table>

Conclusions

Since December 2019, the world has experienced an unforeseen crisis due to the spread of the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The predominant clinical manifestation of COVID-19 includes respiratory involvement, with a wide range of presentations from mild flu-like illness to potentially lethal acute respiratory distress syndrome (ARDS). However, cardiovascular complications such as cardiogenic shock can also result in severe morbidity and mortality.

In patients with ARDS and/or cardiogenic shock, Extracorporeal Membrane Oxygenation (ECMO) is often required to provide respiratory and cardiac support. Due to the events being very recent, there is still on-going debate regarding the effectiveness of ECMO in COVID-19 patients. This review tried to highlight multiple factors such as age range, previous medical history, presenting complaint, and the length of ECMO support that may play a role in mortality rates. No statistically significant difference was detected between the two types of support with regards to age, duration and mortality. Mixed presentations of ARDS and cardiogenic shock with consequent conversion between VA- and VV-ECMO (and vice versa) were also reported, highlighting the importance of a multidisciplinary approach and frequent reassessment to check the response to mechanical circulatory support.

In conclusion, clinical judgment along with thorough understanding of risks to benefit ratio is required to establish if ECMO would be effective in a patient with COVID-19.
Limitations

This study includes some unavoidable limitations which merit consideration. Firstly, the majority of papers included in this review were either case reports or small cohorts; therefore, further studies with larger patient groups are required to produce significant results. Secondly, it is important to stress that there is some diversity in the study designs, patient selection and outcomes between studies. Lastly, due to this being an on-going pandemic, a consistent amount of literature is published in a preprint form, prior to full peer review.

Disclosure

Authors declare no conflict of interest.

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