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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-value0.31), and status at discharge (mortality p-value0.75) 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.

The World Health Organization declared the pandemic status for the coronavirus disease 2019 (COVID-19) on March the 11th, 2020. As of June 2020, the World Health Organization reported 10,357,662 cases, and 508,055 deaths worldwide.

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 (χ^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) PaO_2 (arterial partial pressure of oxygen in mmHg)/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 < PaO_2/FiO_2 ≤ 300 mmHg with PEEP (positive end-expiratory pressure) or CPAP (continuous positive airway pressure) ≥ 5 cmH_2O

• Moderate: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cmH_2O

• Severe: PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥ 5 cmH2O

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
- PaO_2/FIO_2 <100 (mm Hg) despite high PEEP (10 - 20 cmH_2O) on FiO2 >80%
- Intrapulmonary right-to-left shunt (Qs/QT) >30%
- Total thoracopulmonary compliance (CTstat) <30 ml/cmH_2O
- Severe hypercapnia with $PaCO_2$ >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 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

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

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-value0.31. 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-value0.75.

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 a multidisciplinary 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]. Bemtgen reported the first case of induced refractory cardiogenic plus vasoplegic 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/m^2, this was followed by VA-ECMO due to persistent vasoplegic 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

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Table 3: The use of VV-ECMO in COVID-19. PMH: previous medical history. HTN: hypertension. DM: diabetes mellitus. COPD: chronic obstructive pulmonary disease. OSA: obstructive sleep apnoea. CVA: cerebrovascular accidents. CKD: chronic kidney disease. DKA: diabetic ketoacidosis. LVEF: left ventricle ejection fraction. PH: pulmonary hypertension

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

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-value0.124) 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 4: The use of VA-ECMO in COVID-19. PMH: previous medical history. HTN: hypertension. DM: diabetes mellitus. LVEF: left ventricle ejection fraction. ARDS: acute respiratory distress syndrome. CS: cardiogenic shock. RV: right ventricle

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

Table 5:VV-ECMO cannulation

	Femo-jugular	Femo-femoral
Firstenberg		■
Hartman		■
Ikuyama	■	
Li	■	
Nakamura	■	
Takahashi	■	
Taniguchi	■	
Zhan	■	
Bemtgen	■	
Fried	■	

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 a 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 and 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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