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Venovenous extracorporeal membrane oxygenation for COVID-19 associated severe respiratory failure: Case series from a Hungarian tertiary centre

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Abstract

Introduction: Venovenous extracorporeal membrane oxygenation (V-V ECMO) is recommended for the support of patients with severe COVID-19 associated severe respiratory failure (SRF). We report the characteristics and outcome of COVID-19 patients supported with V-V ECMO in a Hungarian centre.

Methods: We retrospectively collected data on all patients admitted with proven SARS CoV-2 infection who received V-V ECMO support between March 2021 and May 2022.

Results: Eighteen patients were placed on ECMO during this period, (5 women, age (mean ± SD) 44 ± 10 years, APACHE II score (median (interquartile range)) 12 (10–14.5)). Before ECMO support, they had been hospitalised for 6 (4–11) days. Fifteen patients received noninvasive ventilation for 4 (2–8) days, two patients had high flow nasal oxygen therapy, for one day each. They had already been intubated for 2.5 (1–6) days. Prone position was applied in 15 cases. On the day before ECMO initiation the Lung Injury Score was 3.25 (3–3.26), the PaO_2/FiO_2 ratio was 71 ± 19 mmHg. The duration of V-V ECMO support was 26 ± 20 days, and the longest run lasted 70 days. Patients were mechanically ventilated for 34 ± 23 days. The intensive care unit (ICU) and the hospital length of stay were 40 ± 28 days and 45 ± 31 days, respectively. Eleven patients were successfully weaned from ECMO. The ICU survival rate was 56%, the in-hospital survival was 50%. All patients who were discharged from hospital reported a good health-related quality of life Rankin score (0–2) at the 5–16 months follow-up.

Conclusions: During the last three waves of the COVID-19 pandemic, we achieved a 56% ICU and a 50% hospital survival rate at our low volume centre.

Keywords

extracorporeal membrane oxygenation, severe hypoxemic respiratory failure, intensive care, respiratory support, COVID-19

Introduction

During the coronavirus (COVID-19) pandemic, after an initial hesitancy, extracorporeal respiratory support became recommended for the management of patients with severe acute respiratory failure due to COVID-19.[1] The first results published from China were disappointing, reporting unfavourable outcomes.[2] Later, survival rates substantially improved, and reached values comparable to pre-COVID data. However, mortality data at different centres show remarkable differences, ranging from 15 to 74%. It was suggested that those centres that had a lower number of cases

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annually showed worse results. Interestingly, survival rates decreased during the later waves of the pandemic.[3]

At our institution, we started to provide V-V ECMO support from 2016 onwards, following a training period at experienced centres. During the subsequent years, the number of annual runs remained low due to financial and organisational issues. At the beginning of the pandemic, we decided against ECMO use due to staff and equipment shortages. Later, in response to the extreme demand, the capacity of Hungarian intensive care units (ICUs) was considerably increased. As a result, after March 2021 we were able to start supporting patients with COVID-19 associated SRF with V-V ECMO.

The aim of this single-centre study was to collect data on the characteristics and outcomes of patients needing V-V ECMO in our ICU.

Methods

This study was approved by the Regional and Institutional Review Board of Human Investigations of University of Szeged (No: 145/2022.SZTERKEB, address: 6725 Szeged, Tisza Lajos krt. 107.I/111. Hungary). Informed consent was waived, given the retrospective nature of the study and the lack of intervention.

In this retrospective analysis we included all severe acute respiratory syndrome coronavirus (SARS CoV-2) positive patients who received V-V ECMO support at our centre between March 2021 and May 2022. The data were collected by manual chart review. During the selection of patients for V-V ECMO support, we followed the updated ELSO recommendations, and the final decisions were made on a case-by-case basis, taking into consideration both the relative contraindications and our actual resources.[4]

Interventions

For ECMO support either the Cardiohelp System (Getinge AB, Göteborg, Sweden) with HLS Set Advanced, or the Novalung Heart and Lung Therapy System (Fresenius Medical Care, Bad Homburg, Germany) with Xlung patient kit was used. The access and the return cannula were inserted percutaneously, guided by vascular ultrasound and transesophageal echocardiography under deep sedation and muscle relaxation either at our ICU or at the referring hospital ICU. For access, we mostly used 25 Fr 38 cm long cannula, for return, 19–25 Fr 15 or 55 cm long cannula, depending on the configuration. During the first days of V-V ECMO support all patients were deeply sedated targeting Richmond Agitation and Sedation Score of −5, receiving intravenous sufentanil and propofol, supplemented with midazolam when necessary, and all of them were administered neuromuscular blocking agents. The extracorporeal blood flow (ECBF) was adjusted to reach an SaO_2 greater than 88–90%, and the sweep gas flow to reach a normal pH. The ventilator was set to Pressure Control mode, with low FiO_2 (40%), PEEP between 10 and 15 cmH_2O, driving pressure of 10 cmH_2O and respiratory rate of 10/min to allow lung rest. We targeted negative fluid balance if the patients were hemodynamically stable. Regarding COVID-19 specific therapy, all patients received remdesivir, corticosteroid and vitamin D, four of them were given tocilizumab and three convalescent plasma. Five patients had pulmonary embolism and were provided with systemic thrombolytic therapy with alteplase before or during ECMO support. For anticoagulation, unfractionated heparin was used, monitored by activated clotting time (ACT) or activated partial thromboplastin time (aPTI). The target level of anticoagulation was ACT 160–180 s or aPTI 46–55 s, modified as necessary during complications. We started ECMO weaning when the static compliance (Cstat) improved and on rest ventilator settings tidal volumes reached 4–6 mL/PBW (predicted body weight). From that point on, we gradually decreased ECBF to 3 L/min, and the sweep gas flow to zero. During the weaning period, the analgosedation level was also reduced, allowing the patients to wake up.

Measurements

Collected data included baseline demographics, disease severity scores (Acute Physiology and Chronic Health Evaluation (APACHE II), Lung injury score (LISS) and Respiratory ECMO prediction score (RESP)); time intervals to the initiation of the ECMO run from the first positive SARS CoV-2 real time polymerase chain reaction (rt-PCR) test, from hospital admission and from intubation; pre-ECMO management (high flow nasal oxygen, non-invasive ventilation, COVID-19 specific therapy, prone positioning) and respiratory as well as blood gas parameters (PaO_2, FiO_2, $PaCO_2$, arterial pH, PEEP, pressure control level, tidal volume per (PBW) and Cstat. We gathered data relating to ECMO configuration, the duration of the ECMO run, the duration of IMV from the initiation of ECMO support, complications (clinically significant bleeding, circuit thrombosis, deep vein thrombosis (DVT), pneumothorax, nosocomial infections including blood stream infection (BSI), urinary tract infection (UTI) and

ventilator-associated lower respiratory tract infection (LRTI). We chose LRTI because of the difficulties to establish the diagnosis of ventilator-associated pneumonia in this population. Ventilator-associated LRTI was defined as an increased amount of purulent respiratory secretions with positive culture from tracheal aspirates, with or without procalcitonin elevation developing in patients already receiving invasive mechanical ventilation (IMV) for more than 48 h. Clinically significant bleeding was defined as life-threatening bleeding or bleeding that required blood transfusion or intervention.

Outcome

The outcome variables were ICU and in-hospital survival rates, the duration of ECMO runs, the duration of IMV, ICU and in-hospital length of stay. In addition, we analysed the different complication rates. A follow-up assessment was performed in July 2022. A 6-min walk test, Rankin score determination and health-related quality of life assessment (RAND 36-Item Short Form Survey, SF-36) were performed.

Statistical Analysis

The data were collected in a preformatted table, which was used for further analysis. For statistical analysis, Excel for Windows 365 was used. All calculations were undertaken by means of descriptive statistics. Continuous variables were expressed as mean ± SD or median and interquartile range (IQR), as appropriate.

Results

Demographics, baseline characteristics

Eighteen patients were placed on ECMO during this time (Table 1). They were admitted from either our own COVID-ICU, or from other hospitals from the region. Five patients were retrieved to our department on mobile ECMO. None of the patients had any known serious comorbidity in their previous medical history, except one, who had psoriasis. Three women were in the immediate postpartum period. Three patients already had sepsis due to nosocomial infection and one patient suffered from *Clostridium difficile* infection. During their hospitalisation, fifteen patients received

Table 1. Demographics and pre-ECMO characteristics.

Demographics (mean ± SD, median, (IQR))	Patients (n = 18)
Age (years)	44 ± 10
Male sex	13
Apache II score	12 (10–14.5)
LISS score	3.25 (3.0–3.26)
RESP score	5 (2–7)
Pre-ECMO time intervals (days) (mean ± SD, median, IQR)	
From first positive SARS CoV-2 rt-PCR	9 (7–15)
From hospital admission	6 (4–11)
Time on NIV	4 (2–8)
From intubation	2.5 (1–6)
Pre-ECMO respiratory parameters (mean ± SD, median, IQR)	
FiO_2 (mmHg)	100 (100–100)
PEEP (cmH_2O)	9 ± 2
Driving pressure (cmH_2O)	21 ± 5
Vt/PBW (mL/kg)	7.6 ± 1.9
Cstat (mL/cmH_2O)	27 ± 10
Pre-ECMO blood gases (mean ± SD, median, IQR)	
PH	7.33 (7.28–7.39)
$PaCO_2$ (mmHg)	65 ± 15
PaO_2 (mmHg)	67 ± 14
PaO_2/FiO_2 (mmHg)	71 ± 19

ECMO: Extracorporeal membrane oxygenation; Apache II score: Acute Physiology and Chronic Health Evaluation score; LISS score: Lung Injury Score; RESP score: Respiratory ECMO prediction score; SARS CoV-2 rt-PCR: Severe acute respiratory syndrome Coronavirus real-time polymerase chain reaction; NIV: Non-invasive ventilation; FiO2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; Vt/PBW: the ration of tidal volume and predicted body weight; Cstat: static compliance; PaCO2: partial pressure of arterial carbon dioxide tension; PaO2: partial pressure of arterial oxygen tension; PaO2/FiO2: the ratio of partial pressure of arterial oxygen tension and fraction of inspired oxygen.

non-invasive ventilation, two patients high flow nasal oxygen therapy. After intubation, 15 patients were put to prone position. The demographics, pre-ECMO management, respiratory and blood gas parameters on the day before ECMO initiation are summarized in Table 1.

Overall outcome

Femoro-jugular configuration was applied in 17 cases, and femoro-femoral configuration in 3 cases. Two patients had a second ECMO run because of the deterioration of gas exchange, 2 and 9 days after the initial decannulation. One patient was turned prone three times for 16–20 h while on ECMO because no improvement of lung function occurred for 2 weeks. For the 20 ECMO runs, 31 oxygenators were used; 7 oxygenators were changed because of clot formation, increased membrane pressure drop and decreased oxygen transfer capacity.

The duration of V-V ECMO support was prolonged, the longest run lasted 70 days. Eleven patients were successfully weaned from ECMO and decannulated. The patients were also mechanically ventilated for an extended period, and in 15 cases we performed dilatational percutaneous tracheostomy. Average ICU and hospital length of stay were around 6–7 weeks. ICU and in-hospital survival rates were 56% and 50%., respectively. The surviving patients were discharged to another acute care or rehabilitation facility. The outcomes are summarised in Table 2.

Table 2. Outcomes and complications (mean ± SD).

Duration of ECMO support (day)	26 ± 20
Duration of IMV (day)	34 ± 23
ICU LOS (day)	40 ± 28
Hospital LOS (day)	45 ± 31
ICU survival *n* (%)	10 (56%)
Hospital survival *n* (%)	9 (50%)
Complications (patients)	16
Bleeding *n* (%)	9 (50%)
PTX *n* (%)	5 (28%)
DVT *n* (%)	6 (33%)
Nosocomial infections (patients)	16
LRTI *n* (%)	14 (77%)
BSI *n* (%)	11 (61%)
UTI *n* (%)	7 (39%)
Other *n* (%)	8 (44%)

ECMO: Extracorporeal membrane oxygenation; IMV: invasive mechanical ventilation; ICU LOS: intensive care unit length of stay; hospital LOS: hospital length of stay; PTX: pneumothorax; DVT: deep vein thrombosis; LRTI: lower respiratory tract infection; BSI: blood stream infection; UTI: urinary tract infection.

Complications

Complications occurred in 16 patients. Clinically significant bleeding affected half of the patients. The most serious one was a vascular injury during cannulation, leading to hemothorax and fatal exsanguination. The other sites of major bleeding were the upper airways, the upper and lower gastrointestinal tract, intrapleural and intraabdominal bleeding. There was no intracranial bleeding. Minor bleedings occurred at cannulation sites in almost all patients.

Two patients had severe COVID-related coagulopathy affecting the perfusion of the fingers and one of them also had pulmonary embolism, celiac trunk thrombosis, spleen and pancreas infarcts and ischemic liver injury. In these two patients we also suspected heparin induced thrombocytopenia (which was not proven later) and switched to argatroban anticoagulation. After decannulation, six patients had DVT in the cannulated veins.

Five patients had pneumothorax, either spontaneous or iatrogenic, which required the insertion of chest drains. In two cases, the air leakage was so significant that we were unable to ventilate them at all, therefore we switched off ventilators. During this period, when they were totally dependent on ECMO, we further deepened sedation and applied mild hypothermia to decrease the oxygen consumption. In one case, we were able to ensure adequate oxygen delivery, and after 11 days could restart IMV, and after 70 days stop extracorporeal support. That patient survived and was discharged home.

Nosocomial infections were frequent, occurring in 16 patients. The most common were LRTI, BSI and UTI. Other infections developed in 8 patients, including sinusitis in 5, purulent keratitis in 1, and intraabdominal infection in 1 case. One woman had puerperal fever (Table 2). These infections were often caused by multidrug-resistant pathogens, especially *Acinetobacter Baumanii* and *Pseudomonas aeruginosa*.

Other organ failures in addition to respiratory failure included circulatory failure in 10 patients (8 septic and 4 hemorrhagic shock), 5 acute kidney injury (3 patients were treated with continuous renal replacement therapy) and one acute liver failure.

Follow-up

Nine patients were discharged home after rehabilitation. At the follow-up that occurred between 150 to 489 days after ICU admission, we assessed their functional recovery and health-related quality of life. The results of 6-min walk tests showed that none of them was able to

walk the distance expected for age, gender, height, and body weight; they reached 36–74% of predicted values. The Rankin score was 0 in three, 1 in three and 2 in three patients, corresponding with no symptoms at all; no significant disability despite symptoms; or slight disability. The RAND SF-36 Survey showed that the mean scores in all eight categories were above 70, corresponding with good health related quality of life, except role limitation due to physical health, which received a slightly lower score (Table 3).

Discussion

In this case series of SARS CoV-2 positive patients receiving V-V ECMO support we achieved ICU and in-hospital survival rates of 56% and 50%, respectively. However, most of these patients required very long ECMO runs, a long duration of IMV with extended ICU and hospital stay. Complications were frequent; the most common ones were nosocomial infections, clinically significant bleeding, and pneumothorax. At the 5–16 month follow-up assessment, all survivors reported good health-related quality of life.

At the beginning of the pandemic, there was uncertainty about the role of extracorporeal respiratory support in the management of patients suffering from severe respiratory failure as a consequence of COVID-19. Early studies from China reported an unacceptably high, 94% mortality rate.[2] However, later, even during the first wave of the pandemic, considerably better results were reported. The Paris-Sorbonne ECMO-COVID investigators found 36% mortality at 60 days.[5] Of note, Pitie-Salpetriere is one of the largest ECMO centres in Europe with a long-established expertise. They organised and centralised ECMO support in the Greater Paris region, including 17 ICUs with a common referral system, protocols and mobile ECMO teams. They published 46% survival at 90 days that was even better, 60% among the patients cared for at the 3 high volume centres. They concluded that a shorter time on invasive ventilation before ECMO initiation, younger age, lower pre-ECMO renal component of Sequential Organ Failure Assessment score and treatment at centres managing at least 30 V-V ECMO cases annually were independently associated with 90-day survival.[6] These survival rates are similar to data from the pre-COVID era, supporting the recommendation that experienced centres should consider V-V ECMO support for COVID-19 associated SRF.

Several observational studies were published during the pandemic, reporting data from large registries and from single centres, and the outcomes show great variability. The Extracorporeal Life Support Organization (ELSO) Registry contains data from 213 hospitals in 36 countries. During the first wave, 90-day mortality was 38% in patients supported by V-V ECMO.[7] EuroELSO also initiated near real-time prospective data collection from centres in Europe and Israel including both V-A and V-V ECMO cases. They published the first results from the EuroECMO COVID-19 Survey of 1531 patients, who had 55% chance of survival.[8] The best outcomes so far were published by Mustafa.[9] They used a single-access, dual-lumen right atrium-to-pulmonary artery cannula. That configuration, besides ensuring gas exchange, also supports the right ventricle. In addition, they tried to wake up and extubate the patients while on ECMO support and achieved only 15% in-hospital mortality.[9] However, there are several studies reporting significantly higher mortality. In Germany, throughout the first three waves of the pandemic, in-hospital mortality was 68%.[10] In a similar nationwide analysis from the same country, Friedrichson reported 65.9% in-hospital mortality for V-V ECMO support. It is remarkable that CPR was performed in 16.4% of the V-V ECMO-supported patients and patients in these cohorts were older compared to others. Another contributor could be that the use of ECMO in Germany is not centrally regulated.[11] In Poland, the ICU mortality rate was high as well, 74.1% for patients requiring ECMO support.[12] In a recent systematic review and meta-analysis, Ramanathan included 22 observational studies and 1896 patients and found 35.7% in-hospital mortality in those patients who received V-V ECMO support.[13]

These data support that high-volume centres with previous expertise in V-V ECMO and those with early centralised referrals, organised transport and protocolized management achieved better result. These ICUs had the infrastructure, equipment, and

Table 3. Follow-up (mean ± SD, median; IQR).

6MWT (Percentage of expected (%))	60 ± 13
SF-36	
Physical functioning	75 (70–94)
Role limitation due to physical health	58 ± 42
Role limitations due to emotional problems	100 (67–100)
Energy/fatigue	73 ± 14
Emotional well-being	92 (82–96)
Social functioning	82 ± 13
Pain	83 ± 20
General health	68 ± 12

6 MWT: 6 min walking test; SF-36: RAND 36-Item Short Form Survey.

qualified personnel, and coukld therefore cope with the very high demand. Our centre was in a unique position. We started to provide ECMO support before the pandemic, though we managed only 16 cases during a 4-year period including V-V and veno-arterial (V-A) runs.[14] However, we had equipment, trained physicians and nurses, previous experience and management protocols. The multidisciplinary involvement, including cardiac surgeons, perfusionists, occasionally pulmonologists, physiotherapists, psychologists also helped to achieve an acceptable survival rate.

An important factor influencing survival is the duration of non-invasive and especially IMV before ECMO initiation; in general, the longer it lasts, the worse the outcome is.[6] Interestingly, results from the first wave seem to be better than the ones achieved later, which may be associated with timing. Braaten found a significantly worse survival after October 2020, and, of note, the median interval from hospital admission to V-V ECMO initiation was longer in that cohort (10 days vs 6 days) and it was associated with 60-day mortality.[15] The pooled mean duration of IMV prior to ECMO initiation was 4.4 days in Ramanathan's metaanalysis, but it was not associated with mortality.[13] In our case series, the median length of IMV before ECMO was 2.5 days, but because of the small number of patients we could not compare survivors with non-survivors.

During the pandemic it was impossible to compare outcomes with V-V ECMO or IMV alone in a randomized study. Whebell used propensity score matching to compare hospital mortality of patients receiving ECMO at specialist centres with a cohort of patients referred for ECMO but managed conventionally. In the United Kingdom, a centralised national referral system was established early on during the pandemic. This multicenter retrospective cohort study was conducted at two national ECMO centres, the Guy's and St Thomas' Foundation Trust and the Royal Brompton and Harefield Trust. They found an absolute in-hospital mortality reduction of 18.2%, from 44% in conventionally treated patients to 25.8% for patients supported with ECMO in a specialist centre.[16]

STOP-COVID investigators in the United States and COVID-ICU investigators in France, Belgium and Switzerland performed emulated target trial analyses during the first half of 2020. Shaefi examined clinical features and outcome of patients supported with ECMO using data from the STOP-COVID multicenter study. One hundred and thirty patients receiving ECMO support were compared with 1,167 who did not. During a median follow-up of 38 days, 34.6% of the ECMO group and 47.4% of the non-ECMO group died (HR 0.52, $p < 0.001$).[17] Hajage investigated the effect of ECMO support on 90-day mortality compared to IMV only. The ECMO strategy resulted in higher 90-day survival if it was performed in a high-volume centre or where an organized ECMO network was set up and when initiated within the first 4 days of IMV.[18]

The duration of ECMO support was longer in our cohort than the 15.8 days or 18 days reported by Lorusso and Ramanathan.[8,13] We had two very long runs (65 and 70 days), and both patients survived, which is in line with previous data.[19] The ICU length of stay was longer, too, which is partly the result of the low number of high dependency beds at our hospital, and the fact that even most of the HDU personnel worked at the ICU with us during the pandemic. The long ICU stay was associated with unexpectedly high rate of nosocomial infections.

This single centre analysis has certain limitations. It is a retrospective analysis involving a relatively small number of patients, from a low-volume centre. In addition, as probably in every similar case, the level of surge capacity continuously changed with the ever-changing management system, which made it more difficult to maintain high quality care.

In conclusion, during the last three waves of COVID-19 pandemic, at our low volume centre we achieved 56% ICU and 50% hospital survival rates. The ICU and hospital lengths of stay were very long.

Author Contributions

ÉZ conceived the study, participated in data collection, conducted the analysis, and drafted the manuscript. All authors participated in data collection. All authors helped to revise the draft of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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