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Veno-venous Extracorporeal Membrane Oxygenation support in COVID-19 respiratory distress syndrome: initial experience

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Abstract

SARS-CoV-2 may cause severe respiratory failure due to massive alveolar damage. Currently, no adequate curative therapy for COVID-19 disease exists. By considering overall impact of COVID-19 pandemic outbreak, an increased need of Extracorporeal Membrane Oxygenation (ECMO) support becomes evident.

We report on our preliminary institutional experience with COVID-19 patients receiving veno-venous ECMO support.

Key Words: COVID-19; Pandemic; ARDS; Extracorporeal Membrane Oxygenation.
Introduction

A new betacoronavirus, named SARS-CoV-2, which causes a severe acute respiratory syndrome, designated as COVID-19, emerged in China in December 2019 [1-8]. The virus has been designated as a pandemic by the World Health Organization (WHO), on March 11st, 2020 [1]. As of April 5th 2020, COVID-19 has been confirmed in 208 countries and currently involves 1133,758 cases globally with 62,784 deaths [1]. The majority of infections has been reported initially in China followed by Italy, Spain, Iran and the United States of America (USA) [1].

WHO interim guidelines for the management of suspected COVID-19 recommend administering veno-venous (VV) ECMO to eligible patients with COVID-19-related acute respiratory distress syndrome (ARDS) in expert centres [1,2,6-8].

We report on our preliminary institutional experience with COVID-19 patients receiving veno-venous ECMO support (tables 1-3).

Study population

COVID-19 infection was confirmed by usage of polymerase chain reaction tests on either nasopharyngeal and/or lower respiratory tract swab samples ordered at intensive care unit (ICU) admission.

Consideration of ECMO was based on the presence of severe respiratory failure (Murray score >3.0 and/or pH <7.20 under protective ventilation [2,6-8]) with sustained clinical deterioration despite optimal conventional treatment and refractory prone positioning. This has been in accordance to Extracorporeal Life Support Organizzazione (ELSO) guidelines document for the adult patient with COVID-19 [2,6-8].

Diffuse bilateral lung injury by SARS-CoV-2 was confirmed by chest X-ray and/or computed tomography (CT) scan in all patients [3-5,7] (figure 1).

Aggressive mechanical ventilation (peak or plateau airway pressure >30 cm H2O or fraction
of inspired oxygen [FiO2] >0.8) for more than 7 days, uncontrolled active bleeding, severe comorbidity, multiple organ failure, sepsis, disseminated intravascular coagulation, age >65 years, and neurological damage were used as contraindications for VV ECMO institution [2,7,8].

Patients have been considered for ECMO by a multidisciplinary team consisting of experts from Anaesthesiology and Intensive Care, Cardiac Surgery, Cardiology and Infectious Diseases.

The study has been approved by our institutional review board. Informed consent was not required for ECMO treatment, as the use of mechanical support was considered a rescue therapy in all patients.

**ECMO support setting**

The ultracompact Cardiohelp (Getinge, Maquet-Cardiopulmonary AG, Rastatt, Germany) has been adopted as ECMO system. For inflow, the right femoral vein was cannulated percutaneously using the Seldinger technique with a 38-cm-long, 21Fr to 23Fr heparin-coated cannula (Bio-Medicus NextGen, Medtronic Inc., Minneapolis, MN). For reinfusion (outflow), a 15-cm-long, 15Fr to 17Fr heparin-coated cannula (Bio-Medicus NextGen, Medtronic Inc., Minneapolis, MN) was used, implanted into the right internal jugular vein.

All the components of the ECMO system and tubings were heparin coated (Bioline® coating; Getinge, Maquet-Cardiopulmonary AG, Rastatt, Germany), and systemic anticoagulation was maintained using unfractionated heparin to a partial thromboplastin time of 1.5 normal [2,6,7].

Pressures on the ECMO circuit, blood gas analysis, general laboratories, and complete blood coagulation study were also monitored daily. Echocardiography was not performed routinely.
Patient management and weaning from ECMO

After cannulation, patient management was optimized to minimize further ventilator-induced lung injury [2,6-8]. Regarding oxygenation, ECMO blood flow was maximized to reduce the fraction of inspired oxygen (FiO2) less than 0.6 and maintain hemoglobin saturation more than 85%. Positive end-expiratory pressure (PEEP) was maintained above 8 cmH2O. If severe hypoxemia (PaO2, <60 mmHg) still subsisted, the threshold for red blood cell transfusion was elevated from 7.0 to 9.0 g/dL. The threshold for prophylactic platelet transfusion was 35,000/μL, whereas the targeted post-transfusion goal was 100,000/μL in the presence of active bleeding. Regarding CO2 removal, sweep gas flow was maximized to allow a normal pH, small tidal volumes (<6 mL/kg per predicted body weight), and plateau pressures less than 25 cmH2O. Paralysis and sedation were maintained.

After improvement of native lung function (FiO2 <0.5, PEEP <10 cmH2O, peak inspiratory pressure in pressure controlled ventilation [PIP] <25 cmH2O), ECMO flow was gradually reduced to 2.0 L/min [2,6-8]. Sweep gas flow was then tapered and finally shut off for 40 minutes. If blood gases remained stable for more than 6 hours, the ECMO system was removed, and decannulation was carried out.

Statistical analysis

Variables are reported as median and interquartile ranges. For statistical analysis, we used SPSS 24.0 (SPSS, Inc, Chicago, Ill).

Results

As of March 1st 2020, during COVID-19 pandemic outbreak, 59 consecutive adult patients with confirmed infection were admitted at our Cardio-Thorac-Vascular Department (out of >300 confirmed cases throughout S. Orsola University Hospital, Bologna) (tables 1, 2).
All patients suffered severe respiratory failure and were admitted at our ICU. Four of them were referred for ECMO establishment (table 1). Our ECMO population had no severe co-morbidities.

The clinical course consisted of rapid in-hospital deterioration with early ICU admission for ventilatory support. The Murray score [2,6-8] was used to evaluate respiratory failure severity before VV ECMO implantation. In all of patients, alternative rescue therapies such as prone position and inhaled nitric oxide (NO) were used before ECMO referral.

ICU survival has been 75% (table 3). Three patients were weaned from VV ECMO (75%). CT scan and chest X-ray typical ground-glass features and consolidations decreased (figure 1). However, the first weaned patient suffered acute recurrence of pneumonia and eventually died on day 9 after VV ECMO removal. The second weaned patient has been successfully extubated and fully mobilized thus joining a rehabilitation care. The third weaned patient is still intubated and on inhaled NO with a slight resolution of the pulmonary disease.

The remaining patient suffered severe gastrointestinal bleeding, while on ECMO, with high transfusion requirements, namely, of red blood cells (RBC/day 0.57 [0.30-0.10]) and platelets (PLT/day 0.45 [0.10-0.70]), which resulted to be fatal (table 3).

Neither oxygenator failure nor ECMO circuit failure occurred. No neurological complications occurred.

In all patients, lung protective ventilation was sustained during ECMO support and maintained in the 3 weaned patients on the first day after ECMO cessation. The level of PEEP was gradually decreased during weaning from ECMO and afterward during weaning from mechanical ventilation. Percutaneous tracheostomy was performed in 3 patients.

All patients received Tocilizumab and Hydroxy-Cloroquine (table 3) [3,4].
Lopinavir/Ritonavir antiviral therapy was used in two patients. Piperacillin/Tazobactam antibiotic prophylaxis was used in all patients while azithromycin was adopted, additionally, in one [3,4,7]. Corticosteroids were used in a single case while on ECMO.

Low dosage of vasoactive drugs (norepinephrine) infusion and consecutive positive fluid balance was frequently needed during VV ECMO support (table 3) [2,7,8]. Low dosage of corticosteroids have been used as anti-inflammatory agents after ECMO removal.

Conclusions

SARS-CoV-2 may cause severe respiratory failure due to massive alveolar damage [2-7]. The rate of ARDS ranges from 15 to 30% among patients who require hospitalization [1,2,7]. Currently, no adequate curative therapy for COVID-19 disease exists [3-7]. By considering overall impact of COVID-19 pandemic outbreak, an increased need of Extracorporeal Membrane Oxygenation (ECMO) support becomes evident [2,6-8]. So far, the ELSO registry accounts 143 COVID-19 respiratory ECMO running systems worldwide, mostly being in Europe and USA [2,8]. As of April 4th 2020, Euro COVID-19 survey/study showed 253 ongoing VV ECMO patients while 52 have been successfully weaned from ECMO support [2,8].

In COVID-19 patients the initial pulmonary pattern is not similar to ARDS, as hypoxia is prevalent and pulmonary compliance is generally high [3-7]. The main finding is hypoxic vasoconstriction. The lungs are inflated and increasing PEEP or prone positioning do not help. Lung CT scans in those patients confirm that there are not significant areas to recruit. Moreover, high PEEP levels may compromise right cardiac filling and an increase of the need for fluid intake and/or norepinephrine [5-7].

Ventilator induced lung injury (VILI), volutrauma, barotrauma, oxygen toxicity should be avoided and ‘lung protective ventilation’ is the recommended strategy for COVID-19 patients [2,5-7].
In addition to viral pneumonia, consequently, those patients likely have had self-inflicted ventilator induced lung-injury, due to diffusely initial type ICUs management and misunderstanding with subsequent decrease in compliance and edema in the lower lobes [4-7]. Those patients present a pattern similar to ARDS and they benefit of PEEP and prone positioning.

If the conservative treatment is not effective, VV ECMO support might be considered [2,6-8]. Unfortunately, ECMO infrastructures and resources are limited, globally [7,8].

Our small sample of COVID-19 ECMO patients presented young age and showed no severe co-morbidities but severe ARDS occurred in all of them. Thus, warm caution and thoughtful approaches for timely detection and treatment should be taken for people who are currently living in high density COVID-19 infected areas [1] to preserve life.
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**Figure Legend**

**Figure 1.** COVID-19 respiratory disease. Computed Tomography (CT) scan axial view (upper, medium and lower pulmonary lobes sections). Panel A; Pre-Extracorporeal Membrane Oxygenation (ECMO) pulmonary involvement (evidence of multilobular and subpleural ground-glass opacities, and consolidation). Panel B; Post-ECMO pulmonary involvement (evidence of resolution).
| Patient | Age (y) | Gender | City of origin | Region        | Hospital admission | ICU admission | ECMO implantation |
|---------|---------|--------|---------------|---------------|-------------------|--------------|------------------|
| 1       | 44      | Male   | Guastalla (RE)| Emilia-Romagna| 03/01/2020        | 03/02/2020   | 03/02/2020       |
| 2       | 38      | Male   | Bologna (BO)  | Emilia-Romagna| 03/13/2020       | 03/15/2020   | 03/19/2020       |
| 3       | 61      | Male   | Piacenza (PC) | Emilia-Romagna| 03/13/2020       | 03/20/2020   | 03/23/2020       |
| 4       | 53      | Male   | Bologna (BO)  | Emilia-Romagna| 03/14/2020       | 03/21/2020   | 03/21/2020       |

Table 1. Demographics and origin of patients with confirmed SARS-CoV-2 infection requiring ECMO support. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; y, years.
|               | n   | %   |
|---------------|-----|-----|
| **Age (y)**   | 49  | (38-61) |
| **Male**      | 4   | 100  |
| **BMI (kg/m²)** | 28.3 | (24.1-38.2) |
| **BSA (m²)**  | 2.1 | (1.9-2.4) |
| **Obesity**   | 1   | 25   |
| **Hypertension** | 1        | 25   |
| **Diabetes mellitus** | 1     | 25   |
| **Other comorbidities** | 0     | -    |
| **Bilateral lung involvement (CT scan)** | 4 | 100  |
| **LV EF >50%** | 4  | 100  |
| **HR**        | 109 | (90-125) |
| **SBP (mmHg)** | 120 | (105-130) |
| **DBP (mmHg)** | 68  | (65-72) |
| **Inotrope score [2,7,8]** | 2.5 | (2.0-4.5) |
| **Temperature (°C)** | 37.1 | (36.1-38.5) |
| **Murray score [2,7,8]** | 3.5 | (2.7-3.8) |
| **Arterial blood gas analysis** |       |       |
| **pH**        | 7.35| (7.21-7.45) |
| **paO₂ (mmHg)** | 46.7 | (33-56) |
| **paCO₂ (mmHg)** | 70.5 | (43-100) |
| **SaO₂ (%)**  | 82  | (73-89) |
| **Lactates (mmol/L)** | 3.2 | (2.5-3.7) |
| **Mechanical ventilation** |       |       |
| **Minute ventilation (L/min)** | 11.5 | (8.5-12.0) |
| **Tidal volume (mL)** | 607.5 | (420-750) |
| **Tidal volume/PBW (mL/kg)** | 7.5 | (6.0-9.0) |
| **PEEP (cmH₂O)** | 15  | (10-18) |
| **FiO₂ (%)**  | 95  | (80-100) |
| **PaO₂/FiO₂** | 50.2| (33-70) |
| **Plateau pressure (cmH₂O)** | 31  | (27-35) |
| **Driving pressure (cmH₂O)** | 16  | (12-19) |
| **Compliance (mL/cmH₂O)** | 33.5 | (21-41) |
| **Laboratory** |       |       |
| **WBC (x10⁹/L)** | 10.2 | (4-15) |
| **Neutrophils (%)** | 86.5 | (79-91) |
| **Lymphocytes (%)** | 9.6 | (6-18) |
| **Monocytes (%)** | 3.1 | (1-6) |
| **Hct (%)**    | 43.8| (36-52) |
| **PLT (x10⁹/L)** | 194.5 | (94-313) |
| **Glucose (mg/dL)** | 171 | (103-221) |
| **Creatinine (mg/dL)** | 1.2 | (0.8-1.6) |
| Test       | Value   | Range     |
|------------|---------|-----------|
| BUN (mg/dL)| 72      | (30-121)  |
| GFR (mL/min)| 81     | (47-112)  |
| LDH (U/L)  | 547     | (293-867) |
| CPR (mg/dL)| 18.7    | (5.7-28.6)|
| PCT (ng/mL)| 1.6     | (0.1-3.5) |
| IL-6 (pg/mL)| 1509   | (86-3541) |

**Table 2.** Clinical features at admission of SARS-CoV-2 patients. BMI, body mass index; BSA, body surface area; BUN, Blood urea nitrogen; CPR, C-reactive protein; CT, computed tomography; GFR, glomerular filtration; DBP, diastolic blood pressure; FIO2, fraction of inspired oxygen; Hct, Hematocrit; HR, heart rate; IL, Interleukin; y, years; LDH lactate dehydrogenase; PLT, Platelets; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PCT, Procalcitonin; SBP, systolic blood pressure; WBC, White blood cells; [2,7,8] as references.
|                        | Pt 1          | Pt 2          | Pt 3          | Pt 4          |
|------------------------|---------------|---------------|---------------|---------------|
| **Ventilatory support**|               |               |               |               |
| Ventilation mode       | VC            | VC            | VC            | VC            |
| **Minute ventilation** | 5.1 (3.8-5.9) | 4.1 (3.8-4.9) | 4.1 (3.4-4.9) | 4.5 (3.9-4.9) |
| Tidal volume (mL)      | 320 (240-380) | 280 (200-300) | 320 (280-370) | 300 (270-340) |
| PEEP (cmH2O)           | 12 (9-13)     | 11 (8-13)     | 11 (8-13)     | 10 (8-12)     |
| FiO2 (%)               | 60 (50-80)    | 50 (50-70)    | 60 (50-70)    | 50 (50-70)    |
| Tidal Volume (mL/Kg)   | 3.1 (2.4-3.5) | 2.9 (2.5-3.4) | 2.8 (2.5-3.6) | 2.7 (2.5-3.5) |
| Plateau pressure (cmH2O)| 19 (18-20)  | 18 (15-20)   | 18 (16-20)   | 18 (16-20)   |
| Driving pressure (cmH2O)| 10 (9-12)     | 10 (7-11)     | 10 (7-12)     | 11 (9-12)     |
| **Compliance**         | 34.1 (33.0-40.2) | 33.2 (30.6-36.1) | 33.5 (31.5-38.7) | 34.1 (32.6-37.3) |
| Neuronal blockers      | yes           | yes           | yes           | yes           |
| Nitric Oxide           | yes           | yes           | yes           | yes           |
| Corticosteroids        | no            | no            | no            | yes           |
| Prone position         | yes           | yes           | no            | yes           |
| **Haemodynamic support**|             |               |               |               |
| Inotrope score [2,7,8] | 8 (2-10)      | 4 (2-6)       | 8 (2-10)      | 8 (2-10)      |
| Norepinephrine (µg/Kg/min) | 0.08 (0.02-0.10) | 0.04 (0.02-0.06) | 0.08 (0.02-0.10) | 0.08 (0.02-0.10) |
| **ECMO**               | VV            | VV            | VV            | VV            |
| ECMO configuration      | Cardiohelp    | Cardiohelp    | Cardiohelp    | Cardiohelp    |
| ECMO system             | Right FV      | Right FV      | Right FV      | Right FV      |
| Inflow line site        | Internal JV   | Internal JV   | Internal JV   | Internal JV   |
| Inflow line size (Fr)   | 23            | 23            | 23            | 23            |
| Reinfection line site   | Internal JV   | Internal JV   | Internal JV   | Internal JV   |
| Reinfection line size (Fr) | 21           | 21            | 21            | 21            |
| ECMO flow (L/min)       | 5.2 (2.0-5.7) | 4.5 (2.0-4.8) | 4.5 (2.0-4.8) | 4.7 (2.0-4.9) |
| ECMO speed (rpm)        | 3200 (2000-3750) | 3050 (2000-3800) | 3100 (2000-3700) | 3170 (2000-3650) |
| Oxygenator              | PLS Quadrox   | PLS Quadrox   | PLS Quadrox   | PLS Quadrox   |
| **Medical therapy**     |               |               |               |               |
| Antiretroviral          | Lopinavir/Ritonavir | Lopinavir/Ritonavir | Lopinavir/Ritonavir | Hydroxy Chloroquine |
| Antibiotics             | Piperacillin/tazobactam | Piperacillin/tazobactam | Piperacillin/tazobactam | Piperacillin/tazobactam |
| Anti-IL-6               | Tocilizumab   | Tocilizumab   | Tocilizumab   | Tocilizumab   |
| **Outcomes**            |               |               |               |               |
| Ventilation time (d)    | 18            | 14            | 27            | 23            |
| Tracheostomy            | yes           | no            | yes           | yes           |
| Bleeding                | no            | no            | no            | yes (GI)      |
| CVVH                    | yes           | no            | yes           | no            |
| Superinfection          | BAL E. Coli+  | no            | BAL Pseudomonas A+ | no |
| ECMO support at 1 week  | ongoing       | ongoing       | ongoing       | ongoing       |
| PaO2/FiO2 at 1 week     | 110 (85-130)  | 150 (100-165) | 133 (95-150)  | 118 (95-160)  |
| ECMO support at 2 weeks | weaning completed | weaning completed | weaning phase | ongoing       |
| PaO2/FiO2 at weaning    | 280 (260-295) | 275 (260-290) | 255 (260-285) | -             |
| Parameter                        | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---------------------------------|--------|--------|--------|--------|--------|
| ECMO duration (d)               | 15     | 11     | 17     | 16     |
| Exitus on ECMO                  | no     | no     | no     | yes    |
| Exitus after ECMO               | yes    | no     | no     | no     |
| Survival on ECMO                | yes    | yes    | yes    | no     |
| Weaned from ECMO                | yes    | yes    | yes    | no     |
| ICU LOS (d)                     | 28     | 21     | 24     | 23     |
| ICU survival                    | yes    | yes    | yes    | no     |
| Hospital LOS (d)                | 29     | 23     | 27     | 28     |
| Hospital survival               | no     | yes    | yes    | no     |

**Table 3.** Mechanical ventilation, ECMO support and pharmacological management plus outcomes of VV ECMO COVID-19 patients. A., Aeruginosa; BAL, bronchoalveolar lavage; CVVH, continuous veno-venous haemofiltration; d, days; ECMO, extracorporeal membrane oxygenation; E., Escherichia; FV, femoral vein; GI, Gastro-intestinal; ICU, intensive care unit; IL, interleukin; JV, jugular vein; LOS, length of stay; PEEP, positive end-expiratory pressure; Pt, patient; rpm, rotations per minute; VC, Volume-Controlled; VV, veno-venous; [2,7,8] as references.
