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**Title: Extracorporeal membrane oxygenation for refractory COVID-19 acute respiratory distress syndrome**

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Recent studies suggest a survival benefit from extracorporeal membrane oxygenation (ECMO) in patients with severe acute respiratory distress syndrome (ARDS) [1,2]. However, the role of ECMO remains uncertain for COVID-19-related ARDS [3].

This stems from the fact that very high mortality rates have been reported in COVID-19 patients treated with ECMO. In a study on 52 critically-ill patients with SARS-CoV-2 pneumonia, six patients received ECMO of whom five died and one was still on ECMO at the time of publication [4]. In another study on 48 patients, ten patients received ECMO. At the time of publication, three patients had died whereas five out of seven were still on ECMO [5]. In another study describing 12 critically-ill COVID-19 patients treated with ECMO, five patients died [6]. Finally, in a report on eight patients treated with ECMO, only three were weaned from the device but were still mechanically ventilated at the time of publication whereas four died and one was still receiving the technique [7].

These results tend to suggest that patients treated with ECMO during severe COVID-19 related ARDS have a poor prognosis. This in turn questions the role of this invasive and expensive treatment.

Our experience markedly differs as we observed a much better prognosis for patients placed on veno-venous (VV) ECMO during the Covid-19 pandemic in a retrospective analysis. The ethics committee of Paris University Hospitals approved this study (CEERB Paris Nord. IRB 00006477).

We treated 83 patients for SARS-CoV-2 pneumonia between March 8, 2020 and April 18, 2020. Thirteen required VV-ECMO (femoro-jugular cannulation) for very severe refractory hypoxemia and alteration of lung mechanical properties despite prolonged prone positioning, neuromuscular blockade and inhaled nitric oxide administration in all patients. All patients met inclusion criteria of the recently published EOLIA study and all implantations were

decided in consultation with the reference center of Paris area.<sup>1</sup> Of note, the most severe patients in our ICU, who also presented the highest values of proinflammatory and prothrombotic biomarkers, received therapeutic anticoagulation. Patient characteristics are described in **Table 1**. Median SAPS2 score on admission was 58 (range 31 to 79). All patients had both bilateral diffuse ground-glass opacities and alveolar confluent opacities on chest X-ray. Median duration of mechanical ventilation before ECMO implantation was 6 days. Median value of PaO<sub>2</sub>/FiO<sub>2</sub> ratio before ECMO initiation was 59. Median tidal volume was 5.25 ml/kg of predicted body weight and median positive end-expiratory pressure 12 cmH<sub>2</sub>O. Despite the application of a low tidal volume, median plateau pressure was 32 cmH<sub>2</sub>O and median driving pressure 20 cmH<sub>2</sub>O. All patients were hypercapnic (median 65 mmHg, range 59 to 96). Implantation of ECMO allowed for implementation of lung ultrprotective ventilation. Indeed, plateau pressure was set below 25 cmH<sub>2</sub>O, with a positive end-expiratory pressure between 8 to 12 cmH<sub>2</sub>O. This resulted in a median tidal volume of 2.14 ml/kg of predicted body weight. The median output of ECMO was 5 l/min after implantation with a median sweep gas flow rate of 4.0 l/min.

Seven major adverse events occurred in four patients (**Table 2**). Three major hemorrhagic events (hemothorax – patient #13, intra-peritoneal hemorrhage - patient #8, diffuse hemorrhage from cannulas and oropharynx – patient#3) required massive transfusion. Two *Enterococcus faecalis* bacteremia (one complicated by mitral endocarditis) resulted from infection at a cannula-insertion site (patients #10 and #13). Two circuit changes were required: one for device thrombosis and pump dysfunction (patient #8) and one because of severe circuit-related thrombocytopenia (patient #3).

All 13 patients were weaned from ECMO after a median of 13 days (range 3 to 34). Two patients died while still on mechanical ventilation. One was a 41-year-old Jehovah's Witness (patient#1). This fact was unknown at the time of implantation. It was later found that the

patient had expressed his refusal of transfusion in a written document. His spouse (trusted person) repeatedly refused that her husband be transfused. Severe bleeding and hemolysis caused by ECMO resulted in a hemoglobin level of less than 5 g/dl. Given the repeated refusal of blood transfusion, decision to withdraw ECMO was done in the hope that the respiratory condition has sufficiently improved to allow for ECMO withdrawal. Catastrophic hypoxemia and lung mechanical properties alteration recurred, and he died three days later. Improved lung properties and oxygenation allowed for weaning in another patient (patient#8) but he died from cardiogenic shock with massive right ventricular failure seven days later. A diagnosis of pulmonary embolism was suspected but could not be ascertained.

As of June 28<sup>th</sup>, 2020 all surviving patients were weaned from the ventilator after a median duration of mechanical ventilation of 29 days (range 20 to 51) and were discharged alive from the ICU (Table 2) after a mean stay of 34 days (range 23 to 55).

Despite the retrospective nature of our study and the relatively small number of patients, these results are very encouraging. Indeed, a high percentage of patients survived until ICU discharge and a limited number of severe complications was observed in these extremely fragile COVID-19 patients. These results are at striking contrast with previous reports [4–7]. This may be due in part to an adequate selection of patients as highlighted in a recent position paper [8]. ECMO should be integral part of intensive care for properly selected COVID-19 patients without life-threatening comorbidities and established multiple organ failure who develop refractory hypoxemia and severely altered lung mechanical properties despite optimal conventional treatment including lung protective ventilation, prone positioning and inhaled nitric oxide administration.

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**Individual contributions:** CLB and DR designed the study. CLB and DR collected and interpreted the data. All authors participated to patient care and ECMO management. CLB, DD, JDR and DR wrote the manuscript. All authors critically read and modified the manuscript.

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**Table 1. Characteristics of COVID-19 patients before implementation of VV-ECMO.**

|                    | Demographic data/medical history |   | Characteristics of Mechanical Ventilation before ECMO implementation |                 |                          |                               |                                       |                                       |             |                                   |       |                   |
|--------------------|----------------------------------|---|--|-----------------|--------------------------|-------------------------------|---------------------------------------|---------------------------------------|-------------|-----------------------------------|-------|-------------------|
|                    | Gender/Age                       | Medical history                         | Duration of MV before ECMO (days)                                    | P/F before ECMO | Tidal volume (ml/kg PBW) | Respiratory rate (per minute) | Plateau pressure (cmH <sub>2</sub> O) | Driving pressure (cmH <sub>2</sub> O) | Arterial pH | Arterial PaCO <sub>2</sub> (mmHg) | SOFA* | Other treatment   |
| <b>Patient #1</b>  | M/41                             | Diabetes mellitus                       | 8  | 77              | NA                       | NA                            | 31                                    | 19                                    | NA          | 59                                | 11    | PP/inhaled NO/NMB |
| <b>Patient #2</b>  | M/64                             | Arterial hypertension                   | 9  | 74              | 5.25                     | 24                            | 32                                    | 20                                    | 7.36        | 64                                | 12    | PP/inhaled NO/NMB |
| <b>Patient #3</b>  | F/56                             | Arterial hypertension                   | 7  | 61              | 4.36                     | 22                            | 32                                    | 20                                    | 7.13        | 96                                | 8     | PP/inhaled NO/NMB |
| <b>Patient #4</b>  | M/43                             | Past smoking                            | 4  | 54              | 4.56                     | 24                            | 30                                    | 18                                    | 7.30        | 72                                | 8     | PP/inhaled NO/NMB |
| <b>Patient #5</b>  | F/53                             | Arterial hypertension                   | 3  | 34              | 6.49                     | 22                            | 32                                    | 20                                    | 7.24        | 64                                | 11    | PP/inhaled NO/NMB |
| <b>Patient #6</b>  | M/45                             | Diabetes mellitus/Arterial hypertension | 4  | 56              | 5.27                     | 20                            | 32                                    | 22                                    | 7.36        | 61                                | 8     | PP/inhaled NO/NMB |
| <b>Patient #7</b>  | F/41                             | -                                       | 3  | 44              | 5.91                     | 22                            | 33                                    | 23                                    | 7.33        | 59                                | 12    | PP/inhaled NO/NMB |
| <b>Patient #8</b>  | M/55                             | -                                       | 3  | 59              | 4.59                     | 22                            | 31                                    | 17                                    | 7.19        | 77                                | 13    | PP/inhaled NO/NMB |
| <b>Patient #9</b>  | M/58                             | Past smoking                            | 6  | 52              | 4.74                     | 28                            | 31                                    | 17                                    | 7.37        | 67                                | 9     | PP/inhaled NO/NMB |
| <b>Patient #10</b> | M/50                             | Past smoking                            | 5  | 61              | 5.84                     | 20                            | 31                                    | 19                                    | 7.24        | 81                                | 8     | PP/inhaled NO/NMB |
| <b>Patient #11</b> | M/46                             | -                                       | 6  | 94              | 4.2                      | 24                            | 32                                    | 26                                    | 7.24        | 96                                | 8     | PP/inhaled NO/NMB |
| <b>Patient #12</b> | M/51                             | Diabetes mellitus/Past smoking          | 6  | 54              | 5.39                     | 22                            | 32                                    | 20                                    | 7.35        | 65                                | 9     | PP/inhaled NO/NMB |
| <b>Patient #13</b> | M/38                             | -                                       | 6  | 68              | NA                       | NA                            | NA                                    | NA                                    | NA          | 61                                | 11    | PP/inhaled NO/NMB |

F: female; M: male; PP: prone positioning; NO: inhaled nitric oxide; NMB: neuro-muscular blocker; \*all patients had 4 points from the respiratory failure and 4 points for the Glasgow score; NA: not available (patients were implanted in another unit and then transferred in our ICU)

**Table 2. Patient evolution during VV-ECMO and after weaning.**

|                    | Other therapies     |                     |                | Complications                          |   |                | Evolution           |                       |                  |
|--------------------|---------------------|---------------------|----------------|--|---|----------------|---------------------|-----------------------|------------------|
|                    | Specific therapy    | Other organ support | PP during ECMO | Bleeding requiring massive transfusion | Infection at the cannula-insertion site | Circuit change | Time on ECMO (days) | Duration of MV (days) | Clinical outcome |
| <b>Patient #1</b>  | HCQ/CTS             | no                  | no             | *                                      | no                                      | no             | 3                   | 13                    | dead             |
| <b>Patient #2</b>  | CTS                 | NE                  | no             | no                                     | no                                      | no             | 13                  | 35                    | alive            |
| <b>Patient #3</b>  | CTS                 | RRT/NE              | yes            | yes                                    | no                                      | yes            | 28                  | 72                    | alive            |
| <b>Patient #4</b>  | HCQ/CTS             | NE                  | no             | no                                     | no                                      | no             | 13                  | 26                    | alive            |
| <b>Patient #5</b>  | HCQ/CTS/Tocilizumab | no                  | no             | no                                     | no                                      | no             | 8                   | 20                    | alive            |
| <b>Patient #6</b>  | CTS                 | NE                  | yes            | no                                     | no                                      | no             | 14                  | 28                    | alive            |
| <b>Patient #7</b>  | HCQ/CTS/Tocilizumab | NE                  | yes            | no                                     | no                                      | no             | 13                  | 26                    | alive            |
| <b>Patient #8</b>  | CTS                 | RRT/NE              | no             | yes                                    | no                                      | yes            | 19                  | 29                    | dead             |
| <b>Patient #9</b>  | CTS/Tocilizumab     | no                  | no             | no                                     | no                                      | no             | 4                   | 27                    | alive            |
| <b>Patient #10</b> | CTS/Tocilizumab     | no                  | yes            | no                                     | yes                                     | no             | 16                  | 32                    | alive            |
| <b>Patient #11</b> | HCQ/Tocilizumab     | NE                  | yes            | no                                     | no                                      | no             | 17                  | 39                    | alive            |
| <b>Patient #12</b> | CTS/Tocilizumab     | NE                  | yes            | no                                     | no                                      | no             | 7                   | 29                    | alive            |
| <b>Patient #13</b> | CTS                 | NE                  | yes            | yes                                    | yes                                     | no             | 34                  | 51                    | alive            |

HCQ: hydroxychloroquine; CTS: corticosteroids; NE: norepinephrine; RRT: renal replacement therapy; PP: prone positioning; \*The patient was Jehova's witness and had refused blood transfusion