Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Critical Care 60 (2020) 10–12

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

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

C. Le Breton, MD [a], S. Besset, MD [a], S. Freita-Ramos, MD [a], M. Amouretti, MD [a], P.A. Billiet, MD [a,b], M. Dao, MD [a], L.M. Dumont, MD [a,c], L. Federici, MD [a], B. Gaborieau, MD [a,d], D. Longrois, MD, PhD [c,e], P. Postel-Vinay, MD [a], C. Vuillard, MD [a], N. Zucman, MD [a,c], G. Lebreton, MD, PhD [f], A. Combes, MD, PhD [g,h], D. Dreyfuss, MD [a,b,c,1], J.D. Ricard, MD, PhD [a,c,d,1], D. Roux, MD, PhD [a,c,d,*]

[a] Médecine Intensive-Réanimation, AP-HP, Hôpital Louis Mourier, F92700 Colombes, France
[b] Common and Rare Kidney Diseases, French National Institute of Health and Medical Research, INSERM UMR_S 1155, Sorbonne Université, Paris, France
[c] Université de Paris, Paris Nord Medical School, F-75018 Paris, France
[d] IAME, INSERM UMR1137, Université de Paris, F-75018 Paris, France
[e] Département d'Anesthésie, AP-HP, Hôpital Louis Mourier, F92700 Colombes, France
[f] Cardio-Thoracic Surgery Department, AP-HP, Pitié-Salpétrière Hospital, Paris, France
[g] Sorbonne Université, INSERM, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, F-75013 Paris, France
[h] Service de médecine intensive-réanimation, Institut de Cardiologie, APHP, Hôpital Pitié–Salpêtrière, F-75013 Paris, France

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.[1] 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_2/FiO_2 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_2O. Despite the application of a low tidal volume, median plateau pressure was 32 cmH_2O and median driving pressure 20 cmH_2O. All patients were hypercapnic (median 65 mmHg, range 59 to 96). Implantation of ECMO allowed for implementation of lung ultraprotective ventilation. Indeed, plateau pressure was set below 25 cmH_20, with a positive end-expiratory pressure between 8 and 12 cmH_20. 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, intraperitoneal 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.

* Corresponding author at: Réanimation, Hôpital Louis Mourier, 178 rue des renouillers, 92700 Colombes, France.
E-mail address: damien.roux@aphp.fr (D. Roux).
[1] DD and JDR contributed equally.

https://doi.org/10.1016/j.jcrc.2020.07.013

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

	Demograhic 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_2O)	Driving pressure (cmH_2O)	Arterial pH	Arterial PaCO2 (mmHg)	SOFA*	Other treatment
Patient #1	M/41	Diabetes mellitus	8	77	NA	NA	31	19	NA	59	11	PP/inhaled NO/NMB
Patient #2	M/64	Arterial hypertension	9	74	5.25	24	32	20	7.36	64	12	PP/inhaled NO/NMB
Patient #3	F/56	Arterial hypertension	7	61	4.36	22	32	20	7.13	96	8	PP/inhaled NO/NMB
Patient #4	M/43	Past smoking	4	54	4.56	24	30	18	7.30	72	8	PP/inhaled NO/NMB
Patient #5	F/53	Arterial hypertension	3	34	6.49	22	32	20	7.24	64	11	PP/inhaled NO/NMB
Patient #6	M/45	Diabetes mellitus/Arterial hypertension	4	56	5.27	20	32	22	7.36	61	8	PP/inhaled NO/NMB
Patient #7	F/41	–	3	44	5.91	22	33	23	7.33	59	12	PP/inhaled NO/NMB
Patient #8	M/55	–	3	59	4.59	22	31	17	7.19	77	13	PP/inhaled NO/NMB
Patient #9	M/58	Past smoking	6	52	4.74	28	31	17	7.37	67	9	PP/inhaled NO/NMB
Patient #10	M/50	Past smoking	5	61	5.84	20	31	19	7.24	81	8	PP/inhaled NO/NMB
Patient #11	M/46	–	6	94	4.2	24	32	26	7.24	96	8	PP/inhaled NO/NMB
Patient #12	M/51	Diabetes mellitus/Past smoking	6	54	5.39	22	32	20	7.35	65	9	PP/inhaled NO/NMB
Patient #13	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).

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 28th, 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).

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
Patient #1	HCQ/CTS	no	no	*	no	no	3	13	dead
Patient #2	CTS	NE	no	no	no	no	13	35	alive
Patient #3	CTS	RRT/NE	yes	yes	no	yes	28	72	alive
Patient #4	HCQ/CTS	NE	no	no	no	no	13	26	alive
Patient #5	HCQ/CTS/Tocilizumab	no	no	no	no	no	8	20	alive
Patient #6	CTS	NE	yes	no	no	no	14	28	alive
Patient #7	HCQ/CTS/Tocilizumab	NE	yes	no	no	no	13	26	alive
Patient #8	CTS	RRT/NE	no	yes	no	yes	19	29	dead
Patient #9	CTS/Tocilizumab	no	no	no	no	no	4	27	alive
Patient #10	CTS/Tocilizumab	no	yes	no	yes	no	16	32	alive
Patient #11	HCQ/Tocilizumab	NE	yes	no	no	no	17	39	alive
Patient #12	CTS/Tocilizumab	NE	yes	no	no	no	7	29	alive
Patient #13	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.

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 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.

Guarantor statement

DR takes responsibility for the content of the manuscript, including the data.

Funding

None.

Author 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.

Declaration of Competing Interest

AC reported receiving grants and personal fees from Getinge and Baxter; he was president of EuroELSO and is a member of the executive and scientific committees of the International ECMO Network (ECMONet). JDR received travel support form Fisher and Paykel Healthcare. DR received personal fees from Astellas. The other authors have no conflict of interests.

Acknowledgments

We thank Dr. Esther Samba, M.D., Dr. Laurène Caubert, M.D., from Nantes, France, and the nursing teams for their invaluable help in the care of COVID-19 patients. We thank Dr. Jimmy Mullaert, M.D., Ph.D., and Mrs Sonya Makhlouf for their implication in the administrative process of the project.

References

[1] Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378:1965–75. https://doi.org/10.1056/NEJMoa1800385.

[2] Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. JAMA 2018;320:2251–9. https://doi.org/10.1001/jama.2018.14276.

[3] Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. Lancet Respir Med 2020;8:e24. https://doi.org/10.1016/S2213-2600(20)30119-3.

[4] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81. https://doi.org/10.1016/S2213-2600(20)30079-5.

[5] Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol Off Publ Pan Am Soc Clin Virol 2020;127:104364. https://doi.org/10.1016/j.jcv.2020.104364.

[6] Zeng Y, Cai Z, Xianyu Y, Yang BX, Song T, Yan Q. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: a retrospective case series. Crit Care 2020;24:148. https://doi.org/10.1186/s13054-020-2840-8.

[7] Li X, Guo Z, Li B, Zhang X, Tian R, Wu W, et al. Extracorporeal membrane oxygenation for coronavirus disease 2019 in Shanghai, China. ASAIO J Am Soc Artif Intern Organs 1992 2020;66:475–81. https://doi.org/10.1097/MAT.0000000000001172.

[8] Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med 2020;8:518–26. https://doi.org/10.1016/S2213-2600(20)30121-1.