Interactive Cardiovascular and Thoracic Surgery (2021) 1–5
doi:10.1093/icvts/ivab087

ORIGINAL ARTICLE

Cite this article as: Natanov R, Wiesner O, Haverich A, Kühn C. Mechanical circulatory support in coronavirus disease-2019-positive patients with severe respiratory failure. Interact CardioVasc Thorac Surg 2021; doi:10.1093/icvts/ivab087.

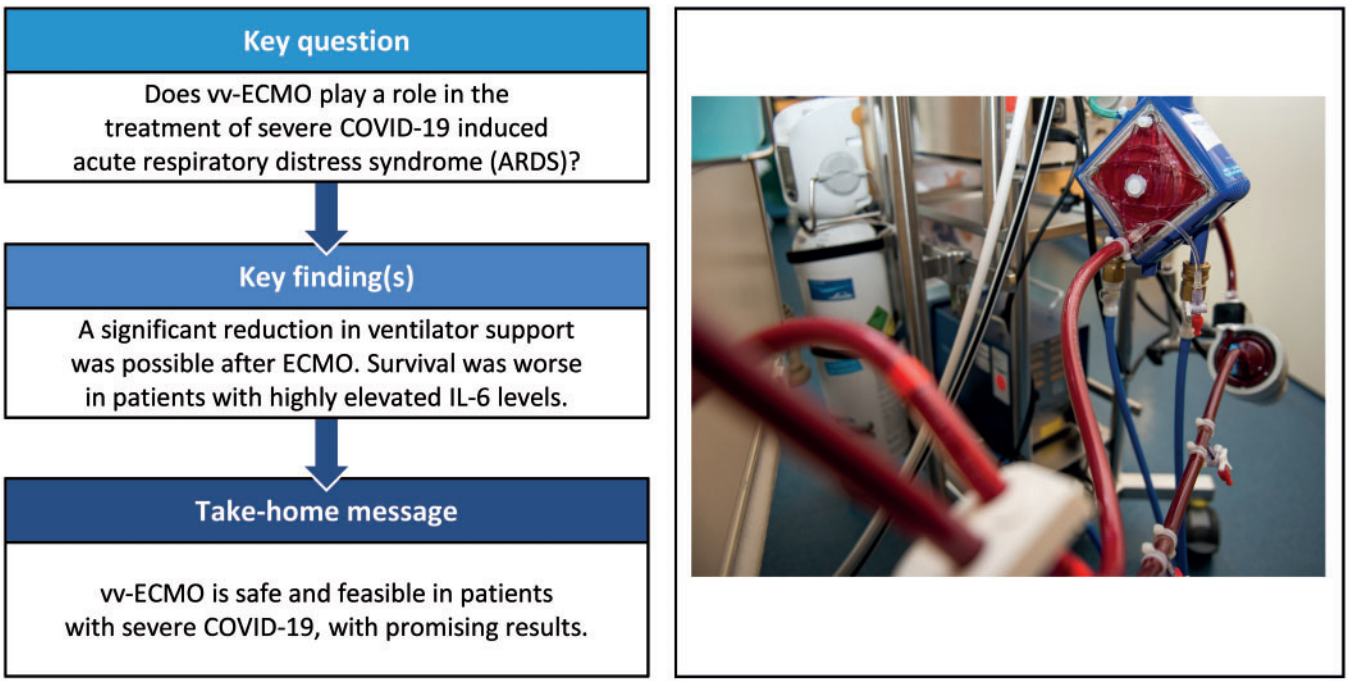
Mechanical circulatory support in coronavirus disease-2019-positive patients with severe respiratory failure

Ruslan Natanov [a,*], Olaf Wiesner[b], Axel Haverich[a] and Christian Kühn[a]

[a] Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany
[b] Department of Pneumology, Hannover Medical School, Hannover, Germany

* Corresponding author. Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany. Tel: +49-511-5322782; fax: +49-511-5325404; e-mail: natanov.ruslan@mh-hannover.de (R. Natanov).

Received 8 December 2020; received in revised form 18 January 2021; accepted 5 February 2021



Abstract

OBJECTIVES: Treatment of severe acute respiratory distress syndrome (ARDS) induced by severe acute respiratory syndrome coronavirus 2 has been heavily debated. Our goal was to describe our findings in patients with severe ARDS due to severe coronavirus disease 2019 (sCOVID-19) treated with venovenous extracorporeal membrane oxygenation (vv-ECMO).

METHODS: We retrospectively examined all patients treated with vv-ECMO for severe ARDS due to acute respiratory syndrome coronavirus 2.

RESULTS: In total, 13 patients were treated with vv-ECMO in our medical centre. The mean patient age was 48.1 years. Most patients were obese (69%) and male (85%). All patients were mechanically ventilated before ECMO. The mean time from intubation to proning was 16.6 h; the time from start of prone therapy to vv-ECMO implantation was 155.1 h. The mean total ECMO run time was 358 h. Significant reduction of positive end-expiratory pressure ($P = 0.02$), peak pressure ($P = 0.001$) and minute volume ($P = 0.03$) could be achieved after implantation of vv-ECMO. All patients showed an inflammatory response. Overall mortality was 30.7%: 1 patient died of mesenteric ischaemia; 3 patients died of multiple organ failure. A worse prognosis was seen in patients with highly elevated concentrations of interleukin-6.

Presented at the 34th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Barcelona, Spain, 8–10 October 2020.

CONCLUSIONS: The use of vv-ECMO in patients with sCOVID-19-induced ARDS is safe and associated with improved respiratory ventilation settings. The rate of immune system involvement plays a pivotal role in the development and outcome of sCOVID-19.

Keywords: ECMO • COVID-19 • Mechanical ventilation • ARDS • Immune system

ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
ICU	Intensive care unit
PEEP	Positive end-expiratory pressure
sCOVID-19	Severe coronavirus disease 2019
vv-ECMO	Venovenous extracorporeal membrane oxygenation

INTRODUCTION

Treatment of acute respiratory distress syndrome (ARDS) and respiratory failure due to severe coronavirus disease-19 (sCOVID-19) have been heavily discussed in the past few months. Conservative therapy such as noninvasive ventilation has been proposed for mild forms of COVID-19. Patients with mild COVID-19 usually present with dyspnoea, coughing and fever. Severe COVID-19 may, however, lead to respiratory failure with rapid development of ARDS, hypoxaemia and death. For this patient population, invasive ventilation, high positive end-expiratory pressure (PEEP) and prone positioning have been proposed as the therapy of choice [1]. Despite the early start of aggressive therapy, patients admitted to the intensive care unit (ICU) with sCOVID-19 are prone to high mortality rates [2, 3]. As an ultima ratio, the use of venovenous extracorporeal membrane oxygenation (vv-ECMO) was proposed for the critically ill [4–6]. Although previous experience in patients with severe ARDS showed beneficial results for patients on ECMO therapy, early reporting on vv-ECMO use in sCOVID-19 showed devastatingly high mortality rates. Due to the high complication and mortality rates, the use of vv-ECMO in sCOVID-19 patients was initially discouraged [7]. Recent data, however, showed improvement in survival rates of patients with sCOVID-19 treated with ECMO. Survival rates of patients with sCOVID-19 treated with ECMO compared to those of patients with severe ARDS of other causes showed similar results [8, 9]. These results suggest the possibility of vv-ECMO implementation during severe COVID-19-induced ARDS. Because there are limited data on the use and efficacy of vv-ECMO in this population, our goal was to present our findings on the treatment with vv-ECMO of patients with sCOVID-19.

PATIENTS AND METHODS

This retrospective study was performed in our tertiary medical facility. The ethics committee at our institution (Hannover Medical School, Hannover, Germany) waived the need for patient consent for this study. All data were retrieved by retrospective review of patient records.

Patients

This retrospective study was done using medical records of patients treated with vv-ECMO for severe COVID-19 at our medical centre. All patients >18 years were included. COVID-19 was confirmed using polymerase chain reaction analysis of tracheal swabs. All patients were sedated using propofol/sufentanil; inhalation anaesthetics (isofuran) were delivered as per house standard. All patients were intubated and mechanically ventilated before the implementation of mechanical circulatory support. Implementation of vv-ECMO was considered when patients met the criteria outlined in the Extracorporeal Life Support Organization guidelines [10]. In brief, patients were evaluated for vv-ECMO when the Horowitz index was <80 mmHg for > 6 h or <50 mmHg > 3 h due to severe respiratory failure under lung-protective ventilation. The Horowitz index was determined as the $\text{PaO2/FiO2 ratio (mmHg)} = \frac{\text{Partial pressure of oxygen PaO2 (mmHg)}}{\text{Fraction of inspired oxygen FiO2 (\%)}}$. Furthermore, prolonged hypercapnic acidosis (pH< 7.25 due to PaCO2 > 60 mmHg for >6 h) was also considered an inclusion criterion for vv-ECMO evaluation.

Myocardial pump function was monitored using transthoracic echocardiography throughout the patient's stay in the ICU.

Extracorporeal mechanical circulatory support

Patients meeting vv-ECMO criteria due to respiratory failure were taken off mechanical circulatory support. While the patient was in the ICU, guidewires were placed percutaneously in the common femoral vein and jugular vein. Prior to cannulation, a bolus of 5000 IE unfractionated heparin was given intravenously. Subsequently, a continuous intravenous heparin infusion was given, and the infusion rate was adjusted according to the activated clotting time. The activated clotting time goal was set at 160–180 s according to the ECMO standard at our medical centre. Venous blood was drained via Seldingeŕs technique into the femoral vein using a 55-cm long HLS cannula with BIOLINE coating (Maquet, Rastatt, Germany), size 21, 23 or 25 Fr, depending on the patient's weight and size. The optimal position for the outflow cannula was the entrance of the inferior vena cava to the right atrium. The position of the cannula was optimized using an ultrasound examination. A similar technique was used for the inflow cannula, a 15-cm long HLS cannula coated with BIOLINE, size 13, 15 or 17 Fr, which was placed in the jugular vein. In 1 patient, the inflow cannula was placed in the contralateral femoral vein. After successful cannulation, the cannulas were connected to our mobile ECMO system, the CardioHelp pump (Maquet), and to an HLS Set Advanced oxygenator (Maquet). The patient was weaned from vv-ECMO as soon as pulmonary function was restored. Ventilation parameters such as FiO2, peak pressure, PEEP and driving pressure were used to determine the reduction of vv-ECMO support. Implementation of ECMO removal occurred after pulmonary gas exchange was sufficiently restored: spontaneous breathing, Horowitz index $\geq$150 mmHg, PEEP $\leq$15 mbar and tidal volumes $\geq$4–6 ml/kg of predicted body weight. After weaning, the percutaneously placed cannulas were extracted using 0/0 skin sutures.

RESULTS

Between January and August 2020, a total of 13 patients (11 male; 85%) presented to our tertiary centre with sCOVID-19 in need of ECMO therapy. The mean patient age was 48.1 (range 19–71) years. Patient characteristics are presented in Table 1.

Medical therapy consisted of fluid substitution and antibiotic treatment using predominantly ß-lactam antibiotics. Furthermore, antiviral treatment was initiated using remdesivir. Although elevated levels of interleukin 6 were measured, no clear signs of a cytokine storm were seen. Therefore, we did not use cytokine filters. All patients were treated with a dilative tracheostomy in the ICU ward.

As previously noted, transthoracic echocardiography was used to determine myocardial dysfunction. No significant myocardial dysfunction was noted during the in-hospital stays. Furthermore, there were no signs of right ventricular strain indicating pulmonary embolisms.

Prone therapy was used in 12 (92%) patients prior to vv-ECMO. Proning was done 3 times for 12 h and was repeated when needed. All patients were treated with vv-ECMO; classical cannulation was done in 12 (92%) patients as previously described. One of the externally cannulated patients was cannulated via both femoral veins.

Extracorporeal membrane oxygenation and outcome

After initiation of ECMO therapy, mechanical ventilation pressures were significantly reduced, allowing for lung-protective ventilation (Table 2). Patients treated with prone positioning continued to do so after the initiation of ECMO. Management of the vv-ECMO was based on the clinical presentation: Patients were maintained with a mild negative fluid balance; vv-ECMO blood flow was kept at 4–5 l/min. There were no complications due to prone ventilation in patients on vv-ECMO treatment. As previously stated, patient anticoagulation was done using heparin. Clinical parameters for coagulation monitoring are shown in Table 3. Due to deteriorating oxygenator function over time, an ECMO system exchange was needed in 3 patients. There were no signs of thrombotic material in the oxygenator upon macroscopic examination. There were no clear signs of hypercoagulability when a system exchange was done on day 9 in 1 patient; the second patient's system was changed on day 8 and the third patient's system, on day 11. Of the 3 patients in need of an ECMO system exchange, 1 died of multiorgan failure.

During ECMO therapy, complications were noted in 6 (46%) patients. Five (38%) patients had renal failure with the need for renal replacement therapy. Gastrointestinal complications occurred in 1 patient; mesenteric necrosis due to occlusion of the mesenteric vasculature was determined post-mortem. Pulmonary complications were seen in 3 (23%) patients: 2 patients developed pulmonary haemorrhages and 1 patient developed a pneumothorax on the contralateral side of the cannulation. Although there were no cerebral complications due to bleeding or ischaemia in our population, all surviving patients developed severe postanaesthesia delirium. The mean ECMO runtime was 358 h (72–1224 h). Three patients were cannulated at another hospital and transferred to our medical centre. Weaning from ECMO was possible for 9 (69%) patients; 4 patients (31%) died while on ECMO. As stated previously, 1 patient died of mesenteric ischaemia. The other 3 patients died of multiple organ failure. With the exception of the patient with mesenteric ischaemia, relatives of the remaining non-surviving patients did not allow post-mortem examinations.

Table 1: Characteristics of patients on venovenous extracorporeal membrane oxygenation due to severe coronavirus disease-2019

Patient characteristics	$n = 13$	100%
Age in years	48,1	(19–71)
Male sex, *n* (%)	11	85%
Body mass index in kg/m^2	32	(22–47)
Proning, *n* (%)	12	92%
COPD	1	8%
DM II	3	23%
Cardiovascular disease	1	8%
Renal disease	1	8%
Arterial hypertension	5	38%
Smoking	1	8%
Obesity	9	69%

Data are shown as mean value (interquartile range).
COPD: chronic obstructive pulmonary disease; DM II: diabetes mellitus type II.

Table 2: Mechanical ventilator settings showing a significant decrease in mechanical ventilator pressures after implantation of venovenous extracorporeal membrane oxygenation

	Before ECMO	During ECMO	*P*-value
FiO2 (%)	100 (1.7)	93.6 (1.2)	0.03
PEEP (mbar)	18 (0.6)	16 (0.2)	0.02
Peak pressure (mbar)	36.5 (1.8)	31.9 (0.3)	0.001
Driving pressure (mbar)	15.8 (1.2)	15.9 (0.3)	n.s.
Minute ventilation (l/min)	16.2 (1.1)	11.5 (0.5)	0.03

All values are given in mean (standard error of the mean).
ECMO: extracorporeal membrane oxygenation; FiO2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; n.s.: not significant.

Table 3: Anticoagulation during extracorporeal membrane oxygenation therapy was managed using unfractionated heparin

Clinical parameters during ECMO therapy	
ACT (s), mean ± SD	156 ± 32
Fibrinogen (g/l), mean ± SD	4.28 ± 2.18
Thrombocyte count (1000/µl), mean ± SD	147 ± 86
APTT (s), mean ± SD	44.7 ± 17.6
Intubation–proning (h), median (IQR)	17 (0–72)
Intubation–ECMO (h), median (IQR)	172 (0–912)
Proning–ECMO (h), median (IQR)	155 (0–840)

Clinical parameters during ECMO therapy were monitored to adjust the infusion rate and prevent bleeding.
ACT: activated clot time; APTT: activated partial thromboplastin time; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range; SD: standard deviation.

Criteria for vv-ECMO weaning included improved pulmonary gas exchange function. After ECMO removal, all patients were breathing spontaneously with PEEP <15 mmHg, Horowitz >150 mmHg and tidal volumes >4–6 ml/kg predicted body weight.

All ECMO-weaned patients were transferred to a respiratory weaning centre for further recovery; no patients were readmitted due to respiratory failure. Follow-up computer tomography examinations of the surviving patients showed no signs of pulmonary emboli. Compared to the patients who survived, the patients who did not survive showed no significant difference in time from intubation to prone positioning. Also, no significant difference was seen in time from proning to ECMO implantation or from time from presentation to ECMO implantation. However, concentrations of interleukin-6 were significantly higher in the non-surviving population prior to ECMO implantation ($P = 0.005$) (Table 4). Other inflammatory parameters, such as C-reactive protein and procalcitonin, did not significantly differ between surviving and non-surviving population prior to ECMO implantation. During the ECMO treatment, a significantly worse Horowitz index was seen in the non-surviving population ($P < 0.001$). Furthermore, non-surviving patients needed significantly more norepinephrine support ($P = 0.009$), had higher procalcitonin concentrations ($P = 0.012$) and had more haemolysis because lactate dehydrogenase levels were significantly higher ($P = 0.015$). Interestingly, interleukin-6 concentrations were similar during ECMO treatment in both groups.

DISCUSSION

We have presented our results for patients on vv-ECMO due to sCOVID-19-induced ARDS and severe respiratory failure. To date, there is no adequate curative option for patients with severe respiratory impairment. Thus, guidelines for the management of moderate-to-severe respiratory impairment due to COVID-19 infection have been proposed [11]. These guidelines recommend the use of vv-ECMO in patients in whom conservative therapeutic options have failed. Our study showed a population with severe COVID-19 and respiratory failure in need of vv-ECMO support. Our population showed no complications during cannulation for vv-ECMO. Furthermore, prone ventilation in patients on vv-ECMO could be done without problems. These findings are consistent with findings reported elsewhere [11–13]. During the vv-ECMO runs, several complications were noted. Renal insufficiency with the need for dialysis was the most frequent complication in our population. Although most authors reported renal failure during vv-ECMO, a comparison is difficult due to the relatively small population sizes provided in the literature [8, 14–16]. Furthermore, other complications such as bleeding and thrombosis have been described [9]. Although all our patients showed signs of severe delirium, no patients had cerebral bleeding or ischaemia, which was in contrast to a series of 10 patients described by Usman *et al.* [15] in which 4 patients developed cerebral haemorrhage during ECMO therapy. This finding may, however, be attributed to the relatively high rate of anticoagulation with unfractionated heparin. Although the development of delirium during sCOVID-19 has been described, few data are available on the effect of ECMO in this patient population [17, 18]. To our knowledge, propofol is the sedative of choice in these patients. After vv-ECMO initiation, a significant reduction in mechanical ventilator support was possible. Interestingly, acute inflammation seems to play a pivotal role in the development and outcome of sCOVID-19-induced ARDS. We saw a clearly elevated interleukin 6 concentration in the non-surviving population. This finding is in accordance with the reports in the literature on cytokine expression during sCOVID-19-induced ARDS. Previous data confirmed worse outcomes in patients with elevated interleukin 6 concentrations [19, 20]. After being weaned from vv-ECMO, all patients were transferred to a respiratory weaning centre for further recovery. Although the role of vv-ECMO in severe ARDS is debated, post hoc Bayesian analysis of the EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) study showed a favourable outcome in the vv-ECMO group [21]. In sCOVID-19-induced severe ARDS, to date, it is too early to determine the protective role of an early vv-ECMO implant on the development of late secondary pulmonary damage. Furthermore, determining the effects of ECMO will be difficult because many centres lack the manpower and resources needed for this therapy.

Table 4: Clinical chemistry prior and post extracorporeal membrane oxygenation implantation

	Survival population ($n = 9$)	Non-surviving population ($n = 4$)	*P*-value
Prior to ECMO			
IL-6 (ng/l)	142 (33)	552 (114)	0.005
CRP (mg/l)	162 (24)	188 (21)	n.s.
Procalcitonin (µg/l)	6.1 (4.3)	7.7 (1.5)	n.s.
During ECMO			
IL-6 (ng/l)	897 (209)	993 (257)	n.s.
Horowitz (mmHg)	153 (4)	120 (5)	<0.001
Norepinephrine (µg/kg/min)	0.173 (0.019)	0.378 (0.073)	0.009
Procalcitonin (µg/l)	5.2 (1.3)	10.9 (1.8)	0.012
LDH (U/l)	828 (36)	2998 (863)	0.015

Significantly higher inflammatory cytokine expression prior to ECMO implantation was associated with worse outcome. Furthermore, a worse Horowitz index, a higher demand for norepinephrine and higher concentrations of procalcitonin and lactate dehydrogenase could be measured in non-surviving patients during ECMO. All data are shown as mean (SEM). The Horowitz index is defined as PaO2/FiO2 ratio in mmHg.

CRP: C-reactive protein; IL-6: Interleukin 6; ECMO: extracorporeal membrane oxygenation; LDH: lactate dehydrogenase; PaO2/FiO2: arterial oxygen partial pressure/fractional inspired oxygen.

CONCLUSION

Our findings show that the implementation of vv-ECMO in patients with moderate to severe ARDS caused by sCOVID-19 infection is safe and associated with improved respiratory ventilation settings. Furthermore, immune system activation seems to play a pivotal role in the development and outcome of sCOVID-19-induced ARDS.

Funding

This work was not supported by external funds.

Conflict of interest: none declared.

Author contributions

Ruslan Natanov: Formal analysis; Investigation; Project administration; Validation; Visualization; Writing—original draft. **Olaf Wiesner:** Data curation; Investigation. **Axel Haverich:** Supervision; Validation. **Christian Kühn:** Conceptualization; Methodology; Validation; Writing—review & editing.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Davide Pacini, Jarle Vaage and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] National Center for Immunization and Respiratory Diseases (NCIRD) Division of Viral Diseases. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Centers for Disease Control and Prevention, 2020.

[2] Hu H. T, Xu S, Wang J, Rao X. Respiratory Support in Severely or Critically Ill ICU Patients With COVID-19 in Wuhan, China. Curr Med Sci 2020;40:636–41.

[3] Hazard D, Kaier K, von CM, Grodd M, Bugiera L, Lambert J *et al.* Joint analysis of duration of ventilation, length of intensive care, and mortality of COVID-19 patients: a multistate approach. BMC Med Res Methodol BMC Methodol 2020;20:206.

[4] Ikuyama Y, Wada Y, Tateishi K, Kitaguchi Y, Yasuo M, Ushiki A *et al.* Successful recovery from critical COVID-19 pneumonia with extracorporeal membrane oxygenation: a case report. Respir Med Case Rep 2020;30:101113.

[5] Bemtgen X, Krüger K, Supady A, Duerschmied D, Schibilsky D, Bamberg F *et al.* First successful treatment of coronavirus disease 2019 induced refractory cardiogenic plus vasoplegic shock by combination of percutaneous ventricular assist device and extracorporeal membrane oxygenation: a case report. ASAIO J 2020;66:607–9.

[6] Loforte A, Dal Checco E, Gliozzi G, Benedetto M, Cavalli GG, Mariani C *et al.* Veno-venous extracorporeal membrane oxygenation support in covid-19 respiratory distress syndrome: initial experience. ASAIO J 2020; 66:734–8.

[7] Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020; 383:2451–10.

[8] Schmidt M, Hajage D, Lebreton G, Monsel A, Voiriot G, Levy D *et al.* Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respir Med 2020;8:1121–1131.

[9] Le Breton C, Besset S, Freita-Ramos S, Amouretti M, Billiet PA, Dao M *et al.* Extracorporeal membrane oxygenation for refractory COVID-19 acute respiratory distress syndrome. J Crit Care 2020;60:10–2.

[10] Bartlett RH, Ogino MT, Brodie D, McMullan DM, Lorusso R, Maclaren G *et al.* Initial ELSO Guidance Document: ECMO for COVID-19 patients with severe cardiopulmonary failure. ASAIO J 2020;66:472–4.

[11] Garcia B, Cousin N, Bourel C, Jourdain M, Poissy J, Duburcq T; on behalf of the Lille Intensive Care COVID-19 group. Prone positioning under VV-ECMO in SARS-CoV-2-induced acute respiratory distress syndrome. Crit Care 2020;24:20–3.

[12] Navas-Blanco JR, Dudaryk R. Management of respiratory distress syndrome due to COVID-19 infection. BMC Anesthesiol 2020;20:4–9.

[13] Kasai T, Bunya N, Wada K, Kakizaki R, Mizuno H, Inoue H *et al.*; Japan ECMOnet for COVID-19. Veno-venous extracorporeal membrane oxygenation and prone ventilation for therapeutic management of COVID. Acute Med Surg 2020;7:2–5.

[14] Kon ZN, Smith DE, Chang SH, Goldenberg RM, Angel LF, Carillo JA *et al.* Extracorporeal membrane oxygenation support in severe COVID-19. Ann Thorac Surg 2020;19–21.

[15] Usman AA, Han J, Acker A, Olia SE, Bermudez C, Cucchiara B *et al.* A case series of devastating intracranial hemorrhage during venovenous extracorporeal membrane oxygenation for COVID-19. J Cardiothorac Vasc Anesth 2020;19–21.

[16] Ma X, Liang M, Ding M, Liu W, Ma H, Zhou X *et al.* Extracorporeal membrane oxygenation (ECMO) in critically ill patients with coronavirus disease 2019 (COVID-19) pneumonia and acute respiratory distress syndrome (ARDS). Med Sci Monit 2020;26:e925364.

[17] Kotfis K, Williams Roberson S, Wilson JE, Pun BT, Ely EW, Jeżowska I *et al.* COVID-19: what do we need to know about ICU delirium during the SARS-CoV-2 pandemic? Anaesthesiol Intensive Ther 2020;52: 132–8.

[18] Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Crit Care Critical Care 2020;24:176.

[19] Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020;368:473–4.

[20] Rieder M, Wengenmayer T, Staudacher D, Duerschmied D, Supady A. Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation. Crit Care Critical Care 2020;24:20–1.

[21] 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.