BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

CORRESPONDENCE

Extracorporeal membrane oxygenation for COVID-19-associated severe acute respiratory distress syndrome and risk of thrombosis

Christophe Beyls*, Pierre Huette, Osama Abou-Arab, Pascal Berna and Yazine Mahjoub

Amiens, France

*Corresponding author. E-mail: beyls.christophe@chu-amiens.fr

Keywords: acute respiratory distress syndrome; anticoagulation; COVID-19; extracorporeal membrane oxygenation; hypercoagulability; thrombosis

Editor—Infection by severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) has spread globally since the first cases appeared in Wuhan in China.[1,2] Most COVID-19 patients present with mild or moderate symptoms, but the number of severe cases with acute respiratory distress syndrome (ARDS) requiring ventilation support rapidly increased during the past few weeks.[3] Veno-venous extracorporeal membrane oxygenation (ECMOvv) has been successfully used in ARDS during the flu swine epidemic of 2009,[4] however, there is very little reported experience regarding the use of ECMO for COVID-19-related ARDS. Thrombosis is a major concern for ECMO management. In the ECMO to rescue lung injury in severe ARDS (EOLIA) trial, an international randomised clinical trial evaluating the effect of early initiation of ECMOvv in patients with severe ARDS, 14% of patients experienced cannula thrombosis.[5] Severe COVID-19 infection appears to be associated with hypercoagulation and an increased risk of thromboembolism.[6] This hypercoagulable state may be enhanced by inflammation and platelet aggregation related to the circuit during ECMO therapy. To date, there are no data regarding an increased risk of thrombosis in patients treated with ECMO for refractory ARDS attributable to COVID-19 infection.

In this preliminary report, we summarise our early experience regarding thrombotic complications during ECMOvv treatment of patients with COVID-19. We intend to alert frontline ECMO teams about a probable increased thrombotic risk related to COVID-19 infection in severe ARDS. Written informed consent was waived by the Amiens University Hospital Institutional Review Board (Comite de Protection des Personnes Nord-Ouest II CHU—Place V. Pauchet, 80054 AMIENS Cedex 1) in accordance with French law on clinical research for non-interventional studies.[7]

We present preliminary data (Table 1) for 12 patients treated with ECMOvv therapy for severe ARDS attributable to COVID-19 infection between March 1, 2020 and April 4, 2020. Median age was 62 (56—66) yr and 80% were male (n=10). ECMO was started early after intubation (4 [1.5—7.5] days) mainly for severe hypoxaemia (9.3 [8.1—10.5] kPa) despite prone positioning sessions (n=2 [1.2—3]). An initial bolus of unfractionated heparin (Heparine Choay®, Sanofi-Aventis, Amiens, France) of 50—100 IU kg^{-1} i.v. was given with an activation coagulation time target of 150—220 s (Hemochron Signature Elite®, Werfen, Spain). Four thrombotic complications (33%) were encountered during percutaneous cannula insertion for ECMOvv treatment. Among these, two (17%) led to death: one as a result of a massive pulmonary embolism during insertion of the femoral cannula and one as a result of major oxygenator thrombosis several minutes after starting the ECMOvv therapy. We also had two cases of cannula thrombosis (17%): one (8%) required urgent cannula change. Five (42%) patients had documented DVT at cannula sites despite heparin treatment. We observed an inflammatory and hypercoagulable state for all patients with high concentrations of C-reactive protein 280 mg L^{-1} (214—345 mg L^{-1}), fibrinogen 7 g L^{-1} (6—9 g L^{-1}) D-dimer 8.3 μg L^{-1} (4.7—24 μg L^{-1}), and fibrinogen degradation product 51 μg ml^{-1} (3—76 μg ml^{-1}). Because of the limited sample size, we were not able to identify any specific risk factor of thrombosis.

A hypercoagulable state in COVID-19-infected patients with the presence of DVT at cannulation sites appears to be associated with an increased risk of major thrombotic events.

Table 1 Patient characteristics and clinical data.

Variables	Population study (n=12)
Age (yr)	62 (56–66)
BMI (kg m^{-2})	29.5 (29.3–32.4)
Male/female (n)	10/2
SOFA score before ECMO	11 (10–14)
Ventilator settings before ECMO	
Tidal volume (ml kg^{-1})	6.1 (5.8–6.2)
Respiratory rate (bpm)	30 (30–31)
PEEP (cm H_2O)	14 (12–15)
Plateau pressure (cm H_2O)	28 (26–28)
Driving pressure (cm H_20)	14 (12–15)
Compliance (ml cm H_2O^{-1})	31 (23–32)
Laboratory data before ECMO	
pH	7.3 (7.22–7.37)
P_aO_2 (kPa)	9.3 (8.1–10.5)
P_aO_2/FiO_2 (kPa)	9.3 (8–10.5)
P_aCO_2 (kPa)	8.1 (7.2–8.5)
Lactate (mmol L^{-1})	2.5 (2–3)
White blood count (mm^{-3})	10.900 (9525–11875)
Lymphocyte count $\times 10^6$ L^{-1}	616 (397–900)
Platelet count $\times 10^9$ L^{-1}	240 (151–329)
C-reactive protein (mg L^{-1})	280 (214–345)
Procalcitonin (μg L^{-1})	2.6 (1.7–7)
aPTT	1.4 (1.3–1.5)
PT (%)	60 (52–70)
Anti-Xa UFH assay (IU ml^{-1})	0 (0–0.2)
Fibrinogen (g L^{-1})	7 (6–9)
D-Dimer (μg ml^{-1})	8.3 (4.7–24)
Fibrinogen degradation product (μg ml^{-1})	51 (3–76)
Sepsis-induced coagulopathy score	3.5 (2–4)
Laboratory data during ECMO therapy on Day 2	
Platelet count $\times 10^9$ L^{-1}	200 (124–327)
aPTT	1.6 (1.4–2.8)
PT (%)	70 (63–80)
Anti-Xa UFH assay (IU ml^{-1})	0.3 (0.1–0.5)
Fibrinogen (g L^{-1})	7.5 (4.9–9.0)
Duration from ICU admission to ECMO (days)	6.5 (4.2–8.0)
Duration from intubation to ECMO (days)	4 (1.5–7.5)
Prone positioning before ECMO	12 (100)
• Number of sessions	2 (1.2–3)
Nitric oxide treatment	8 (83)
ECMO initiation	
In ECMO centre	2 (17)
Out of ECMO centre	10 (83)
DVT before ECMO	
Jugular	1 (8)
Femoral	5 (41)
Anticoagulation therapy before ECMO	6 (50)
Thrombotic complications	4 (33)
Cannula thrombosis	2 (17)
Oxygenator thrombosis	1 (8)
Massive PE	1 (8)
Death related to thrombotic complication	2 (17)
Outcome	
Still on ECMO	8 (66)
ECMOvv converted to ECMOva	0
Weaned from ECMO and still in hospital	2 (16)
• Weaned from MV	1 (8)
Discharge from ICU	0
Discharge from hospital	0

Data are presented as median (interquartile range) or n (%).
aPTT, activated partial thromboplastin time; BMI, body mass index; ECMOva, veno-arterial extracorporeal membrane oxygenation; ECMOvv, veno-venous extracorporeal membrane oxygenation; MV, mechanical ventilation; PE, pulmonary embolism; PT, prothrombin time; UFH, unfractionated heparin.

Studies have assessed long-term thrombotic complications during EMCO therapy, but data on the incidence of thrombotic complications during cannula insertion are scarce.[8] Based on our experience, we suggest that venous Doppler ultrasonography of jugular and femoral veins should be performed routinely for refractory COVID-19-related ARDS in order to prevent issues in case ECMO therapy is needed. Venous ultrasound may help when starting and adapting anticoagulation therapy and provide insight for cannula insertion. In their interim COVID-19 guidelines, the Extracorporeal Life Support Organisation recommended following existing anticoagulation guidelines, with consideration given to targeting anticoagulation to the higher end of normal ECMOvv parameters given the hypercoagulable status of COVID-19 patients.[9] Moreover, in our centre we decided to rinse cannulae with heparin before starting ECMOvv. We also suggest repeated UFH dosing before cannula insertion. The ECMO team should be aware of this thrombosis risk, and further studies investigating the thrombotic risk in this setting are mandatory.

Declarations of interest

The authors declare that they have no conflicts of interest.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727–33
2. Peng PWH, Ho P-L, Hota SS. Outbreak of a new coronavirus: what anaesthetists should know. *Br J Anaesth* 2020; **124**: 497–501
3. Yang X, Yu Y, Xu J, 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. https://doi.org/10.1016/S2213-2600(20)30079-5. S2213260020300795
4. Choi H, Ko UW, Lee H, Hong S-B, Chung CR. Improved survival rates in patients with H1N1 acute respiratory failure in Korea between 2009 and 2016. *PLoS One* 2019; **14**: e0223323
5. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; **378**: 1965–75
6. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020 May 4. https://doi.org/10.1007/s00134-020-06062-x
7. Toulouse E, Masseguin C, Lafont B, McGurk G, Harbonn A. French legal approach to clinical research. *Anaesth Crit Care Pain Med* 2018; **37**: 607–14
8. Trudzinski FC, Minko P, Rapp D, Fähndrich S, Haake H. Runtime and aPTT predict venous thrombosis and thromboembolism in patients on extracorporeal membrane oxygenation: a retrospective analysis. *Ann Intensive Care* 2016; **6**: 66
9. Ogino Mark T. *ELSO COVID-19 interim guidelines*. ELSO; 2020. Available from, www.elso.org. [Accessed 16 April 2020]

doi: 10.1016/j.bja.2020.04.079