

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

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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.<sup>1,2</sup> 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.<sup>3</sup> Venovenous extracorporeal membrane oxygenation (ECMOv) has been successfully used in ARDS during the flu swine epidemic of 2009,<sup>4</sup> 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 ECMOv in patients with severe ARDS, 14% of patients experienced cannula thrombosis.<sup>5</sup> Severe COVID-19 infection appears to be associated with hypercoagulation and an increased risk of thromboembolism.<sup>6</sup> 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 ECMOv 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.<sup>7</sup>

We present preliminary data (Table 1) for 12 patients treated with ECMOv 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<sup>-1</sup> 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 ECMOv treatment. Among

**Table 1** Patient characteristics and clinical data.

Variables	Population study ( $n=12$ )
Age (yr)	62 (56–66)
BMI (kg m <sup>-2</sup> )	29.5 (29.3–32.4)
Male/female ( $n$ )	10/2
SOFA score before ECMO	11 (10–14)
<b>Ventilator settings before ECMO</b>	
Tidal volume (ml kg <sup>-1</sup> )	6.1 (5.8–6.2)
Respiratory rate (bpm)	30 (30–31)
PEEP (cm H <sub>2</sub> O)	14 (12–15)
Plateau pressure (cm H <sub>2</sub> O)	28 (26–28)
Driving pressure (cm H <sub>2</sub> O)	14 (12–15)
Compliance (ml cm H <sub>2</sub> O <sup>-1</sup> )	31 (23–32)
<b>Laboratory data before ECMO</b>	
pH	7.3 (7.22–7.37)
P <sub>a</sub> O <sub>2</sub> (kPa)	9.3 (8.1–10.5)
P <sub>a</sub> O <sub>2</sub> /FiO <sub>2</sub> (kPa)	9.3 (8–10.5)
P <sub>a</sub> CO <sub>2</sub> (kPa)	8.1 (7.2–8.5)
Lactate (mmol L <sup>-1</sup> )	2.5 (2–3)
White blood count (mm <sup>-3</sup> )	10.900 (9525–11875)
Lymphocyte count $\times 10^6$ L <sup>-1</sup>	616 (397–900)
Platelet count $\times 10^9$ L <sup>-1</sup>	240 (151–329)
C-reactive protein (mg L <sup>-1</sup> )	280 (214–345)
Procalcitonin ( $\mu$ g L <sup>-1</sup> )	2.6 (1.7–7)
aPTT	1.4 (1.3–1.5)
PT (%)	60 (52–70)
Anti-Xa UFH assay (IU ml <sup>-1</sup> )	0 (0–0.2)
Fibrinogen (g L <sup>-1</sup> )	7 (6–9)
D-Dimer ( $\mu$ g ml <sup>-1</sup> )	8.3 (4.7–24)
Fibrinogen degradation product ( $\mu$ g ml <sup>-1</sup> )	51 (3–76)
Sepsis-induced coagulopathy score	3.5 (2–4)

Continued

Table 1 Continued

Variables	Population study (n=12)
<b>Laboratory data during ECMO therapy on Day 2</b>	
Platelet count $\times 10^9$ L <sup>-1</sup>	200 (124–327)
aPTT	1.6 (1.4–2.8)
PT (%)	70 (63–80)
Anti-Xa UFH assay (IU ml <sup>-1</sup> )	0.3 (0.1–0.5)
Fibrinogen (g L <sup>-1</sup> )	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)
<b>ECMO initiation</b>	
In ECMO centre	2 (17)
Out of ECMO centre	10 (83)
<b>DVT before ECMO</b>	
Jugular	1 (8)
Femoral	5 (41)
Anticoagulation therapy before ECMO	6 (50)
<b>Thrombotic complications</b>	
Cannula thrombosis	2 (17)
Oxygenator thrombosis	1 (8)
Massive PE	1 (8)
Death related to thrombotic complication	2 (17)
<b>Outcome</b>	
Still on ECMO	8 (66)
ECMOv 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; ECMOv, veno-venous extracorporeal membrane oxygenation; MV, mechanical ventilation; PE, pulmonary embolism; PT, prothrombin time; UFH, unfractionated heparin.

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 ECMOv 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<sup>-1</sup> (214–345 mg L<sup>-1</sup>), fibrinogen 7 g L<sup>-1</sup> (6–9 g L<sup>-1</sup>) D-dimer 8.3  $\mu$ g L<sup>-1</sup> (4.7–24  $\mu$ g L<sup>-1</sup>), and fibrinogen degradation product 51  $\mu$ g ml<sup>-1</sup> (3–76  $\mu$ g ml<sup>-1</sup>). 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. Studies have assessed long-term thrombotic complications during EMCO therapy, but data on the incidence of thrombotic complications during cannula insertion are scarce.<sup>8</sup> 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 ECMOv parameters given the hypercoagulable status of COVID-19 patients.<sup>9</sup> Moreover, in our centre we decided to rinse cannulae with heparin before starting ECMOv. 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.

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## Obesity as a risk factor for poor outcome in COVID-19-induced lung injury: the potential role of undiagnosed obstructive sleep apnoea

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**Editor—**As the severe acute respiratory syndrome-coronavirus disease 2019 (SARS-COVID-19) pandemic is unfolding around the world, reports are being published identifying risk factors for severe and critical disease.<sup>1–3</sup> In this context, published observations suggest that the presence of comorbidities associated with the metabolic syndrome, such as diabetes, are commonly present in this patient population.<sup>4</sup> Although not addressed extensively in the published literature at this time, physician groups are increasingly concerned about the high incidence of severe and critical COVID-19 in patients who are overweight, obese, or both. In this context, an over-proportional prevalence of obesity has been anecdotally reported by clinicians around the world. As defined by the WHO, overweight is a BMI  $\geq 25$ , and obesity is a BMI  $\geq 30$ .

This study was determined to be exempt from Institutional Review Board consideration under United States Health and Human Services code 45 CFR 46.104(d). In an analysis of all critically ill patients receiving mechanical ventilation with respiratory failure as a result of COVID-19 across three randomly selected ICUs at our institution, the average BMI was: males, 28.3 [SD 5.3] ( $n=41$ ) and females, 30 [6.3] ( $n=16$ ); collectively, 20/60 (33%) had a BMI  $\geq 30$ . Similarly, in patients severely ill with respiratory failure (i.e. those not in an ICU and therefore not requiring mechanical ventilation) in three randomly selected in-patient care units, the average BMI was: males, 29 [6.1] ( $n=35$ ) and females, 33.5 [12.1] ( $n=21$ ), with approximately the same proportion classified as obese (17/47, 36.2%) as in the ICU population. These numbers are greater than the reported prevalence of New Yorkers who are overweight (34%) or obese (22%) as provided by the New York City Department of Health (<https://www1.nyc.gov/site/doh/health/health-topics/obesity.page>). Additional details regarding basic patient characteristics of this population can be found in Table 1.

A mechanism explaining the co-presence of obesity, metabolic syndrome, and severe to critical COVID-19, however, remains elusive. Evidence, which is largely non-clinical in nature, suggests that obesity is associated with a proinflammatory state that potentially predisposes patients to lung injury.<sup>5</sup> While this theoretical concept may not be sufficient to explain a potential

link between COVID-19-associated propensity to develop acute severe or critical lung disease based on the concept of a 'double hit phenomenon', it is well known that obesity is highly correlated with the presence of obstructive sleep apnoea (OSA).<sup>6</sup> Amongst these individuals, OSA remains undiagnosed in the vast majority,<sup>7</sup> and thus remains untreated. The low incidence of diagnosed OSA in a high-risk patient population, such as described here, is congruent with underdiagnosis of this disease.<sup>7</sup>

Research suggests that when controlling for obesity, the presence of OSA is associated with decreased lung function, decreased lung-transfer factor for carbon monoxide, and, importantly, increased lung inflammation.<sup>8</sup> These conditions may therefore explain, at least in part, why patients with OSA are at increased risk for pneumonia in general.<sup>9</sup> Further supporting our hypothesis that OSA is an additional risk for the development of severe disease in patients with COVID-19 is the observation that patients with OSA are at increased risk of developing adult respiratory distress syndrome following noncardiac surgery.<sup>10</sup> These observations therefore may provide for the possibility of increased severity in disease in the setting of COVID-19. In this context, the pathophysiology associated with untreated OSA may not just present a predisposing factor for developing severe or critical disease in COVID-19, but once infection has occurred, repeated airway obstruction with generation of negative intrathoracic pressure and associated shear forces may actually lead to worsening in lung injury. It is of interest that reports from Jiangsu province in China suggest that when proning non-intubated patients with COVID-19, oxygenation and pulmonary heterogeneity can be improved.<sup>11</sup> Although speculative, this intervention—in addition to the known benefits of improved clearance of secretions and perfusion, reduction of lung ventilation/perfusion mismatch, and promoting recruitment of non-aerated dorsal lung regions of the lung—also reduces the risk and rate of airway obstruction.<sup>12</sup> The latter effect might be especially beneficial in patients with respiratory compromise<sup>13</sup> attributable to COVID-19 infection, and this should be explored in more detail.

In conclusion, preliminary evidence suggests that COVID-19 seems to lead to a more morbid course amongst the