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.

Overcoming bleeding events related to extracorporeal membrane oxygenation in COVID-19

Authors' reply

We thank Hidesaku Asakura and Haruhiko Ogawa for their correspondence on our study on extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome related to COVID-19.[1] They rightfully highlight that apart from heparin overdose, factors such as circuit-associated defibrination and thrombocytopenia, disseminated intravascular coagulation, acquired von Willebrand syndrome, and COVID-19-associated endotheliitis might cause bleeding in patients under ECMO support.

Indeed, in a previous study,[2] we had shown that haemorrhagic stroke in patients receiving venovenous-ECMO was not associated with haemostasis disorders or anticoagulant use. Platelet counts, prothrombin time, activated partial thromboplastin time (aPPT), and fibrinogen concentrations while on ECMO were similar among patients with and without cerebral haemorrhage, and heparin doses in the 3 days preceding cerebral bleeding were low, without overdose. The only factors independently associated with brain haemorrhage were renal failure at intensive care unit admission and acute changes in partial pressure of carbon dioxide ($PaCO_2$) at ECMO initiation. The association with $PaCO_2$ change was confirmed in a 2020 study of a large international registry, in which a greater than 50% decrease in $PaCO_2$ in the first 24 h of ECMO was independently associated with an increased incidence of neurological complications.[3]

To investigate possible reasons for the most severe bleeding complications in our cohort, we have analysed patients who had haemorrhagic stroke (n=4) or who died of haemorrhagic shock (n=4) for haemostasis parameters obtained in the 48 h before the event.[1] First, these bleeding events occurred after a median of 19 days (range 4–36) after ECMO initiation. Thrombocytopenia (platelet count $\leq 100 \times 10^9$ cells per L) occurred in five patients and severe thrombocytopenia (platelet count $\leq 50 \times 10^9$ cells per L) in one patient. Median serum fibrinogen was 2·6 g/L (range 1·3–5·8), with only one patient having a fibrinogen concentration of less than 2 g/L before bleeding. Second, following early reports of frequent thromboembolic events in severe COVID-19 on ECMO, unfractionated heparin doses were adjusted to reach high anticoagulation activity, with a target aPPT of 60–75 s or anti-Xa activity of 0·3–0·5 IU/mL (respective values were 40–55 s or 0·2–0·3 IU/mL in the 2018 EOLIA trial[4]). Notably, no heparin overdose was observed in the eight patients with severe bleeding complications: median aPTT was 74 s (range 50–84), whereas anti-Xa activity was 0·3 IU/mL (range 0·2–0·5). Third, of the four patients with brain haemorrhage, three had a greater than 40% decrease in $PaCO_2$ in the first 24 h after ECMO initiation.[3] Lastly, we collected haemostasis parameters only in the 48 h preceding the event. Therefore, we cannot rule out that a haemostasis disorder might have caused intracranial bleeding several days before it was diagnosed by cranial CT scan, since neurological examination is complex in these patients who require deep sedation and frequent neuromuscular blockade.

In conclusion, our data concur with the hypothesis of Hidesaku Asakura and Haruhiko Ogawa and previous reports suggesting that severe bleeding complications under ECMO are multifactorial, and not frequently associated with heparin overdose.

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*Matthieu Schmidt, Juliette Chommeloux, Corinne Frere, Guillaume Hekimian, *Alain Combes*
alain.combes@aphp.fr

Sorbonne Université, INSERM, Unité Mixte de Recherche 1166, Institute of Cardiometabolism and Nutrition, Paris, France (MS, JC, GH, AC); and Service de Médecine Intensive–Réanimation, Institut de Cardiologie (MS, JC, GH, AC) and Department of Haematology (CF), Assistance Publique–Hôpitaux de Paris Sorbonne University, Pitié-Salpêtrière Hospital, F-75013 Paris, France

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