The Janus Face of Coronavirus Disease 2019–Associated Coagulopathy

Klaus Stahl, MD[1]
Benjamin Seeliger, MD[2]
Daniel A. Hofmaenner, MD[3]
Michael Doebler, MD[4]
Christian Bode, MD[4]
Sascha David, MD[3]

To the Editor:

We congratulate Doyle et al (1) on their exciting and clinically relevant report published in a recent issue of *Critical Care Medicine* comparing thromboembolic complications and bleeding events in coronavirus disease (COVID)–19 acute respiratory distress syndrome (ARDS) with influenza A patients on veno-venous extracorporeal membrane oxygenation (ECMO). The key finding that COVID-19–induced ARDS is associated with higher thromboembolic events despite therapeutic anticoagulation is of high relevance to the community of intensivists. That being said, the reported high rate of both incident intracranial hemorrhages (ICHs) in eight of 51 COVID-19 patients (16%) early after ECMO cannulation and the additional three cases of ICHs (6%) during ECMO support astonishes us. Besides the morbidity attributable to thromboembolic complications, the fact that a total of 22% of COVID-19 patients experienced an ICH during ECMO support is alarming and raises several important questions.

First, is there a reasonable pathophysiologic explanation for this unexpected high rate of ICHs in COVID-19? As a reminder, ICHs were observed only in 2% in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial (2) and 4% in patients with H1N1 influenza associated ARDS (3). General features of bleeding vulnerability such as therapeutic anticoagulation and ECMO-associated hemotrauma should be taken into account together with COVID-19–induced unique features such as a potential endothelial susceptibility in the sense of a vasculitis.

Second, the severity of the ICHs and the clinical response is not elaborated. Did these patients receive heparin-free ECMO support or was heparin dose merely reduced? Were the findings on cranial CT minor or did they require surgical intervention? In light of the global resource-shortness during the COVID-19 pandemic and the assumed unfavorable outcome associated with ICH on ECMO, we would be very much interested in the survival of these ECMO patients.

Third, a broad range of prophylactic (0.3–0.7 U/L) and therapeutic (0.6–1.0 U/L) anti-Xa levels were targeted during ECMO support in this study. Did the authors adjust this target range according to the supposed risk of present or impending thromboembolism and bleeding? One could hypothesize that the theoretical rational regarding endotheliopathy and bleeding vulnerability might justify 1) a narrow and 2) a lower range of anti-Xa. Interestingly, recent evidence supports the notion that target levels above 0.46 IU/mL might represent an independent risk factor for severe bleeding under ECMO support (4). At the same time, hemostaseologists would probably argue that anti-Xa levels do not fully reflect the important effects heparin has on other coagulation enzymes and the expression of tissue factor and tissue factor pathway inhibitor (5).

The complex coagulopathy in light with the endothelialitis found in critically ill COVID-19 patients might literally be "Janus faced" with regard to

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the simultaneous risk of thrombosis together with potentially fatal bleeding events (particularly if additional factors such as an extracorporeal circulation comes into play). Both the associated mortality and the long-term morbidity for thrombosis versus bleeding highlight the utmost importance of a tailored individualized approach to choose the right degree of anticoagulation.

1 Department of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Hannover, Germany

2 Department of Respiratory Medicine, Medical School Hannover, Hannover, Germany

3 Institute of Intensive Care Medicine, University Hospital Zurich, Zurich, Switzerland

4 Department of Anesthesia and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany

The authors have disclosed that they do not have any potential conflicts of interest.

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The authors reply:

Andrew J. Doyle, MBBS[1]

Andrew Retter, MBBS[1,2]

We read with interest the comments from Stahl et al (1) regarding intracranial hemorrhage (ICH) seen in our described cohort of patients requiring extracorporeal membrane oxygenation (ECMO) due to severe coronavirus disease 2019 (COVID-19) pneumonia, as noted in our recently published article (2) in *Critical Care Medicine*. We agree that our results demonstrate high rates of this significant complication. However, rather than ICH being intrinsic to patients with COVID-19, this may be attributable to brain hypo- and reperfusion injury at the time preceding and during ECMO commencement following the development of severe respiratory failure.

We highlight that similar rates of ICH were seen between COVID-19 and influenza at initiation (16% and 14%, respectively; $p = 0.8$). Two of three ICH events after starting ECMO in the COVID-19 cohort were extensions of preexisting ICH as opposed to new events. All ICHs at initiation in COVID-19 and influenza were small volume radiologically with no midline shift or intraventricular hemorrhage. None required neurosurgical intervention, and all were managed with cessation of anticoagulation. We repeated imaging in all patients with ICH after an interval of 3–5 days to assess for resolution or extension to decide when anticoagulation may be reinitiated. We provide information on this anticoagulation strategy in the supplementary protocol of the original article. Additionally, this cohort was analyzed during the first wave of COVID-19 in early 2020. Anticoagulation approaches were not standardized with some referring hospitals using higher doses of anticoagulation owing to the early concerns regarding high rates of thrombosis. We find it reassuring that ICH rates were not higher than those with influenza as a historic comparator group.

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