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.

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REFERENCES

1. Doyle AJ, Hunt BJ, Sanderson B, et al: A comparison of thrombosis and hemorrhage rates in patients with severe respiratory failure due to coronavirus disease 2019 and influenza requiring extracorporeal membrane oxygenation. *Crit Care Med* 2021; 49:e663-e672
2. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975
3. Pham T, Combes A, Rozé H, et al; REVA Research Network: Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013; 187:276–285
4. Descamps R, Moussa MD, Besnier E, et al: Anti-Xa activity and hemorrhagic events under extracorporeal membrane oxygenation (ECMO): A multicenter cohort study. *Crit Care* 2021; 25:127
5. Vignoli A, Marchetti M, Balducci D, et al: Differential effect of the low-molecular-weight heparin, dalteparin, and unfractionated heparin on microvascular endothelial cell hemostatic properties. *Haematologica* 2006; 91:207–214

The authors reply:

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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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In context of previous studies, the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) study did not have standardized imaging practice for ICH and was dependent upon approaches taken by individual centers (3). At our center, cranial computer tomography is used universally at initiation of ECMO hence event rates may be higher. A meta-analysis by Sutter et al (4) showed lower rates of ICH at 5%. They acknowledged that some centers including ours had higher rates at 10–16% (5, 6). These centers performed imaging at initiation of ECMO, whereas other centers performed cranial imaging with the development of clinical neurologic signs, associated with subsequent higher mortality rates.

Risk factors associated with ICH during ECMO are a rapid decrease in Co_2 levels within the first 24 hours, thrombocytopenia, hypofibrinogenemia, anticoagulation use, and acute kidney injury (4–7). Conversely, severe COVID-19 infection is typified by hyperfibrinogenemia, platelet activation, and preserved platelet counts. Therefore, focal cerebral hypoperfusion and vasoconstriction with subsequent changes in cerebral blood flow following ECMO initiation may be a universal mechanistic event for ICH development in COVID-19 and other respiratory conditions (4, 7).

We agree that anticoagulation to maintain circuit patency, to treat system thrombotic complications and to reduce major bleeding risk, should be individualized during ECMO. As such, we encourage the use of imaging to assess for these and guide its management. We also support the development of prospective studies to establish anti-Xa targets during ECMO to reduce bleeding complications as suggested by Stahl et al (1).

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

REFERENCES

1. Stahl K, Seeliger B, Hofmaenner DA, et al: The Janus Face of Coronavirus Disease 2019–Associated Coagulopathy. *Crit Care Med* 2021; 49:e1049–e1050
2. Doyle AJ, Hunt BJ, Sanderson B, et al: A comparison of thrombosis and hemorrhage rates in patients with severe respiratory failure due to coronavirus disease 2019 and influenza requiring extracorporeal membrane oxygenation. *Crit Care Med* 2021; 49:e663-e672
3. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975
4. Sutter R, Tisljar K, Marsch S: Acute neurologic complications during extracorporeal membrane oxygenation: A systematic review. *Crit Care Med* 2018; 46:1506–1513
5. Lockie CJA, Gillon SA, Barrett NA, et al: Severe respiratory failure, extracorporeal membrane oxygenation, and intracranial hemorrhage. *Crit Care Med* 2017; 45:1642–1649
6. Arachchillage DRJ, Passariello M, Laffan M, et al: Intracranial hemorrhage and early mortality in patients receiving extracorporeal membrane oxygenation for severe respiratory failure. *Semin Thromb Hemost* 2018; 44:276–286
7. Hunsicker O, Beck L, Krannich A, et al: Timing, outcome, and risk factors of intracranial hemorrhage in acute respiratory distress syndrome patients during venovenous extracorporeal membrane oxygenation. *Crit Care Med* 2021; 49:e120–e129