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EDITORIAL

Extracorporeal Membrane Oxygenation Without Systemic Anticoagulation—Are We There Yet?

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Extracorporeal membrane oxygenation (ECMO) has been successfully used to support patients with refractory cardiopulmonary failure since 1971 (1). Pumping blood through an extracorporeal circuit, however, leads to a complex pathophysiological response that is incompletely understood despite decades of research, activating the coagulation and inflammatory cascades and promoting thrombosis (2). Systemic anticoagulants are administered to reduce thrombosis and the consequent risks of embolization or circuit malfunction, but this significantly increases the chances of bleeding (3, 4). Various approaches such as anti-thrombotic circuit coatings have been used to mitigate these complications, but none of them have yet displayed sufficient reliability or utility as to become a consistent standard of care (2, 5).

In this issue of *Critical Care Medicine*, Suzuki et al (6) report on a cohort of ECMO patients managed without systemic anticoagulation. The authors used a registry from 24 centers in Japan to analyze the outcomes of 695 patients supported on venovenous ECMO for acute respiratory distress syndrome (ARDS), 54 of whom did not receive anticoagulation. The authors observed no differences in the primary outcome of 28-day survival (85.8% vs. 81.5%; $p = 0.5$). Other outcome measures included 60-day survival, ECMO duration, circuit exchanges, bleeding complications, and transfusion volumes, again with no apparent difference in outcomes.

There are some obvious limitations to the study (6), many of which were acknowledged by the authors. First and most importantly, anticoagulation was withheld not by protocol but at the discretion of the treating physicians. It is unknown on what basis these decisions were made because they were not captured by the registry, that is, anticoagulation administration was not standardized. It seems likely, however, that those in whom anticoagulation was withheld were at higher risk of bleeding, given the greater transfusion volumes administered in the no-anticoagulation group after initiation of ECMO. There were also differences in other patient characteristics, such as a higher prevalence of hypertension, diabetes, and lung disease in the anticoagulation group, which may have affected outcomes. Those who received anticoagulation also had higher concentrations of hemoglobin (12.5 vs. 11 g/dL), platelets (184 vs. $116 \times 10^3/\mu L$), and fibrinogen (509 vs. 365 mg/dL). Second, no details were provided about the ECMO circuitry used, in particular, the circuit coating, which may have influenced the complication rates (2). Third, 28-day survival is a very limited outcome measure

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in ECMO patients. Historically, many ARDS patients had care withdrawn if there was no lung recovery after 2 weeks but this is no longer the case (7). Months of venovenous or venopulmonary ECMO support for ARDS is no longer unusual and the longest documented period of successful support without recourse to lung transplantation is 605 days (8), highlighting the obvious limitations of focusing on 28-day survival. Last, anticoagulation was only captured as a binary variable (i.e., yes or no), and it is unclear whether medications other than unfractionated heparin were used, what proportion of the ECMO run was anticoagulation-free, how successfully anticoagulation was managed (e.g., what proportion of time patients were in a therapeutic range), or even the targeted therapeutic range in those who received anticoagulation.

Before clinicians try and adopt anticoagulation-free ECMO, a number of important factors need to be considered. Adult patients receiving venovenous ECMO for ARDS are probably the safest population in whom to apply this strategy. The smaller the patient, the lower the net ECMO blood flow rates, which are more likely to promote thrombosis according to the principles articulated in Virchow's Triad. Although the authors (6) were unable to demonstrate an association between ECMO circuit blood flow rates and survival, this may have been because all of the patients were adults. Those who care for small children on venoarterial ECMO know that the risks of thromboembolism increase substantially with the lower circuit flows used in this population, particularly in premature infants. Similarly, the impact of thrombotic complications is different between venovenous and venoarterial ECMO patients, the latter of whom are at considerably greater risk.

Despite the limitations of the study by Suzuki et al (6), the idea of utilizing ECMO without systemic anticoagulation is not a pipe dream (9). Novel circuit coatings or using nitric oxide in the sweep gas hold the promise of substantially reducing the risks of thromboembolism during ECMO (10, 11). Even if these emerging strategies prove unsuccessful, other approaches such as administering IV direct thrombin inhibitors titrated to ecarin clotting times or using novel factor XI or XII inhibitors may be effective.

The effects of ECMO on the clotting cascade are extremely complex and it is small wonder that we do not fully understand them. One recent study identified over 2000 different proteins deposited on the surface of the circuit, only 933 of which were common to every patient (12). While awaiting further research to clarify the most effective way forward in specific patient populations (13), anticoagulation-free ECMO should be regarded as the exception, not the rule. It may be safe in some adult patients on venovenous ECMO with relatively high circuit blood flows, but the study by Suzuki et al (6) should be regarded as hypothesis-generating, not practice-changing. Extrapolating this concept to other patient populations, such as adult venoarterial ECMO patients or small children, would be ill-advised. Nonetheless, the authors (6) demonstrate that highly selected patients can be managed on venovenous ECMO for ARDS without systemic anticoagulation and without an apparent increase in complications.

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Dr. MacLaren has disclosed that he is the Past President of the Extracorporeal Life Support Organization.

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