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There Will be Blood—But Maybe Less with Prostaglandin E_1

Although there may be disputes over its efficacy, there are few people left who do not think that venovenous extracorporeal membrane oxygenation (VV-ECMO) is lifesaving to some extent in patients with acute respiratory distress syndrome (ARDS); this belief has been reflected by a sharp increase in its deployment over the last decade despite lack of clear positive randomized controlled trials (1). The question remains to what extent and for which patients is ECMO lifesaving, as mortality is still close to 50% in observational studies (2). One of the problems is that the benefits in terms of lifesaving are offset by complications of ECMO support itself. Analogously to, for example, the case of patients with hematological malignancies, mortality is in part disease-related, but there is also significant treatment-related mortality.

Exposure of blood to the nonbiologic surfaces of an extracorporeal circuit initiates a complex inflammatory response involving both the coagulation and the inflammatory response pathway. Historically, the most feared complication is a thromboembolic stroke due to extracorporeal system-induced clotting activation, for which systemic anticoagulation, usually with unfractionated heparin with an aPTT (Activated Partial Thromboplastin Clotting Time) target of 2.0–2.5 times baseline, is necessary.

Or is it? Perhaps not, or at least that belief has been challenged by recent data on thromboembolic and hemorrhagic complications in cohort studies. For example, a cohort study in which 61 VV-ECMO patients were treated with a prophylactic dosage of LMWH (Low Molecular Weight Heparin) found fewer bleeding complications and no ischemic strokes, although in 5 patients the pump unexpectedly stopped due to thrombotic occlusion (3). Thus, omitting anticoagulation may be too revolutionary a step; however, severe thromboembolic complications like ischemic stroke seem to occur less often and are far outnumbered by severe hemorrhagic complications including hemorrhagic stroke, which were present up to 21% in autopsy studies in patients with coronavirus disease (COVID-19) who died in spite of being supported with VV-ECMO (4). This is in part explained by improved materials and the use of heparin-coated cannulas. More importantly, there seems to be no relationship between the level of anticoagulation and the occurrence of a rare thromboembolic stroke; however, there is a strong relationship between the level of anticoagulation and the frequent occurrence of bleeding complications (55%) as well as the need for a blood transfusion, both of which are directly related to poor outcome (5). Moreover, fatal hemorrhagic stroke is far more frequent than fatal thromboembolic stroke (6). Taken together, one might postulate that anticoagulation with heparin during ECMO might lead to more problems than benefits. However, there is a paucity of studies evaluating different anticoagulation strategies in patients supported with ECMO and no randomized trials comparing one strategy with another. A comprehensive guideline from Extracorporeal Life Support Organization for the use and monitoring of anticoagulation during ECMO support has been recently published, but this guideline stops short of any mandate, given the lack of evidence in favor of most of the practices reviewed (7). Rigorous evaluations of anticoagulation use in ECMO patients are, therefore, urgently needed (8).

Therefore, we welcome the performance of pharmacological studies in which the primary aim is the optimization of anticoagulation during ECMO support. In this issue of the *Journal* (pp. 170–177), Buchtele and colleagues share the results of a phase-II RCT in which 5 ng/kg/min prostaglandin E_1 (PGE_1) in addition to low dose heparin was compared with heparin alone in patients supported by VV-ECMO (9). Both groups included 24 patients. The hypothesis, based on experiences with renal replacement therapy, was that the addition of PGE_1 could extend the lifespan of the ECMO circuit, but as this was a safety study, the primary outcome was the rate of transfused packed red cells per day of ECMO support. The transfusion rate was similar between groups (0.41 versus 0.39; $P = 0.733$). Fewer patients in the PGE_1 group had any membrane lung clotting (7 versus 16; $P = 0.020$) and the time to first membrane change was longer in patients allocated to PGE_1 (hazard ratio 0.30; 95% confidence interval 0.12–0.75). These findings suggest that the addition of PGE_1 to heparin might extend the lifespan of the ECMO circuit, although it is not clear by how long exactly, without an increase in hemorrhagic complications as reflected by similar blood transfusions in both groups. The secondary endpoints even suggest a reduction in thromboembolic *and* bleeding events with PGE_1 administration, but given the pharmacological features of PGE_1, inhibition of platelet aggregation and arterial vasodilatation, the mechanism by which that would work is obscure. As blood pressure

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was unaffected with this low dose of PGE_1 the mechanism of action is most probably restricted to inhibition of platelet aggregation, which also suggests that platelet aggregation plays a major role in circuit lifespan. This is important, as it has also been postulated that fibrin formation plays a pivotal role in thrombotic complications of the ECMO circuit for which inhibition of platelet aggregation is less effective.

Currently, the main purpose of anticoagulation during ECMO support seems to be the prevention of thromboembolic events other than stroke and preventing the ECMO circuit from clotting, which is also potentially fatal. Circuit exchange might be an objective measure for the study of the latter assuming that the exchange is protocolized; which is complicated, as the decision for exchange is guided by multiple parameters in clinical practice. Determining whether PGE_1 administration would indeed extend the lifespan of circuits when added during VV-ECMO support requires a proper well-powered randomized clinical trial (RCT). In the current phase II study, the number of patients with COVID-19 in the placebo group was substantially higher (17 [71%] compared with only 8 [33%] in the intervention arm). Although a sensitivity analysis was performed, the trial was too small to properly correct for this imbalance and may have caused confounding, as COVID-19 is associated with a high incidence of thromboembolic complications (10).

Although examining the results of the primary endpoint, blood transfusion, yields no concern about safety, 90-day survival was lower, although statistically nonsignificant, in the treatment group; accordingly, mortality should be included in the (combined) endpoint of a definitive phase-III trial. Furthermore, a question remains about whether the next step should be a larger RCT in which PGE_1 is added to heparin, or one in which a lower dose of heparin (or even no heparin) in combination with PGE_1 is compared with the current dose of heparin. That decision is probably better made once the results of the ongoing multicenter Reduced Anticoagulation Targets in Extracorporeal Life Support (RATE) study, that compares low-dose heparin or LMWH with moderate dose heparin, are in hand (11).

In the end, the authors need to be complimented on having performed one of the first double-blind, placebo-controlled medication trials during ECMO support; we welcome their results. We hope this study paves the way for further medication trials to find, in addition to the optimal anticoagulant, drugs such as the optimal inotrope or vasopressor for administration during ECMO support. ■

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