Editorial

Hemostatic changes during extracorporeal membrane oxygenation: a commentary

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Veno-venous extracorporeal membrane oxygenation (ECMO) is a technique utilized to support patients suffering from respiratory failure. Historically, ECMO has been used as a last resort life-saving procedure by a restricted group of highly specialized centers of care. Recently, interest in ECMO has risen. Technology advancements have made ECMO safer (1). The CESAR trial showed that Acute Respiratory Distress Syndrome (ARDS) patients might have better outcomes if treated with ECMO rather than conventional strategies (2). The H1N1 experience demonstrated the feasibility of implementation of ECMO even in centers with limited experience (3).

Notwithstanding these progresses, use of ECMO is guided by center-specific experiences rather than by evidence-based guidelines. This is particularly true for coagulation management. Anticoagulation policies vary widely among centers (4) and each ECMO center has elaborated its anticoagulation protocol. Most of these local anticoagulation protocols are founded on the Extracorporeal Life Support Organization (ELSO) clinical indications (5), which are a guide to safe clinical practice, but not a consensus recommendation or an evidence-based blueprint.

These difficulties stem from the lacking of knowledge of the biology of blood compatibility (6). Seminal works have shown activation of coagulation factors and complement factors, platelets consumption and impairment (7-10) leading to bleeding (11) and thromboembolic (12) complications following ECMO connection. Since then, not many studies have focused on coagulation during ECMO. Indeed, few properly performed studies evaluated the clinical impact of technological advances, such as of heparin-coated circuitry (13,14), centrifugal pumps (15) and polymethylpentane oxygenators (16). To the contrary, only recently the interest in studying the effects of veno-venous ECMO upon coagulation has re-grown (17) and provided interesting hints. In particular, Heilmann *et al*. (18) have shown that during ECMO extracorporeal blood undergoes high shear stress, leading to the uncoiling of von Willebrand factor (vWF). This in turns reduces the capabilities of vWF in binding collagen and platelets, resulting in a state of thrombosis, fibrinolysis and impaired platelet function that propagate from the extracorporeal circuit to the patient.

Malfertheiner *et al*. (19) expanded our knowledge on coagulation during ECMO. The Authors randomized a cohort of 54 consecutive adult patients with acute respiratory failure to be treated with three different veno-venous ECMO circuits (i.e., CardioHelp, Maquet Cardiopulmonary, Rastatt, Germany; Dideco ECC.O5, Sorin Group, Mirandola, Italy; Hilite 7000 LT, Medos Medizintechnik, AG, Stolberg, Germany) and extensively assessed the effect of long-term extracorporeal support upon coagulation. Notably, all these systems have polymethylpentene hollow-fiber oxygenator and two (i.e., Maquet and Medos) are heparin-coated while the latter (i.e., Sorin) is phosphorylcholine-coated. Patients were managed by continuous infusion of unfractionated heparin, targeting an activated partial thromboplastin time (APTT) of 50–60 seconds. Factor XIII, thrombin-antithrombin (TAT) complex, prothrombin fragment 1.2 (F1.2), antithrombin were assessed, alongside standard measurements such as platelet count, D-dimers and fibrinogen. Even if differed as regards to priming volume, membrane surface, and coatings,

the ECMO systems had similar effects on coagulation status of the patients. Indeed, regardless of the employed circuitry, connection to the extracorporeal circuit was associated with a progressive consumption of platelets and with the activation of coagulation pathways as demonstrated by the drop in fibrinogen and rise in D-dimers, F1.2, TAT complexes. Interesting, such pathologic condition was reverted by ECMO termination.

As acknowledged by the authors, limitations apply to the work. First, platelet and vWF function were not assessed. Second, the application of different extracorporeal setups (i.e., higher blood flows or smaller cannulas) may expose blood at various shear stresses and thus affect blood coagulation differently. Finally, with increasing duration of ECMO treatment activation of coagulation in the circuit require to exchange the oxygenator or the entire circuit. When circuit exchange became necessary, the activation of coagulation is maximal and likely associated with the higher effects on coagulation factors. Since only the first 5 days of ECMO treatment were studied, the effects of duration of circuit and circuit thrombosis on hemostatic function remain to be investigated.

These limitations pave the way for future research. Following the cell-based model of coagulation, future research efforts should focus on platelets and their primary role in the response of blood to artificial surfaces. Innovative monitoring techniques, such as thromboelastography and aggregometry, allow for the analysis of coagulation as a whole and the evaluation of platelet activation and function, respectively. Despite being validated, these tests are reported inconsistently. We believe that the application of these techniques in the ECMO scenario may allow for a more comprehensive study of the coagulation status and the adjustment of anticoagulant therapy to the varying clinical needs of patients with respiratory failure. The consequences of the application of different extracorporeal blood flows and thus the effects of varying shear stress on coagulation-factors functionality and the uncoiling of vWF needs further analysis. Moreover, more extensive studies of novel drugs capable of the modulation of platelet function (i.e., nitric oxide, prostacyclins), direct inhibition of thrombin, antibody-mediated inhibition of factor XIIa (20) are needed. Similarly, assessment of the effects on coagulation of new polymers and technological solution (i.e., membranes, circuit materials) are warranted.

In conclusion, despite shedding new light on coagulation status during ECMO, the findings of the present work are a small step forward in the knowledge of such neglected huge topic. Influence of long-term ECMO therapy on hemostasis deserves further in-depth experimental as well as clinical evaluations.

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Footnote

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