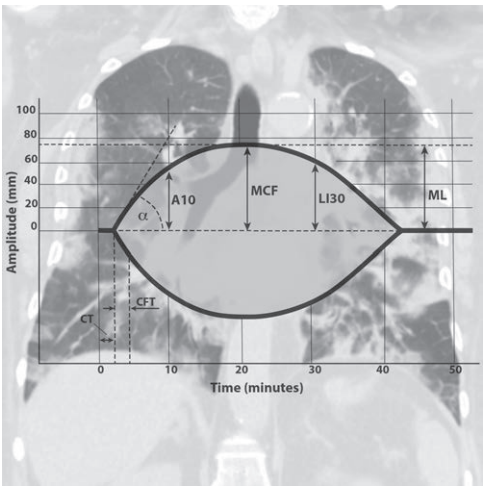
Hypoxia and Hypercoagulability in COVID-19: Chicken or the Egg?

David J. Douin, M.D., Ana Fernandez-Bustamante, M.D., Ph.D.

The presence of coagulation abnormalities in acute respiratory distress syndrome (ARDS) has been identified and studied for decades,[1] and these investigations have increased substantially during the coronavirus disease 2019 (COVID-19) pandemic. Hypercoagulability in response to severe acute respiratory syndrome coronavirus-2 infection is a well documented phenomenon characterized by increased plasma concentrations of D-dimer, fibrin, fibrin degradation products, and fibrinogen,[2] contributing to thromboembolic events, multiorgan failure, and death.[3] However, the relationship between quantitative measures of hypercoagulability, hypoxemia, and clinical outcomes in patients with COVID-19 has not been fully elucidated.



"[What is] the potential value of hypercoagulability assays in the management of patients with hypoxemia and ARDS?"

In this issue of Anesthesiology, Corey *et al.*[4] report a prospective observational single-center study investigating the association between respiratory failure and hypercoagulability in patients with extreme respiratory failure caused by severe acute respiratory syndrome coronavirus-2 infection. The authors studied 55 critically ill patients with COVID-19, of which 89% were receiving invasive mechanical ventilation and 16% were receiving extracorporeal membrane oxygenation (ECMO) at the time of enrollment. A total of 13 patients (23%) from the study cohort died during the hospitalization. The authors analyzed hypercoagulability profiles during the intensive care unit stay using various coagulation-specific laboratory values, including viscoelastic rotational thromboelastometry (ROTEM). They looked at the association between these hypercoagulability profiles with the primary outcomes of mortality, major thrombotic events, and ARDS severity. The presence of hypercoagulability was reported by biomarker concentrations in blood and ROTEM parameters and involved all phases of clot formation, including fibrinolysis inhibition. Hypercoagulability profiles were more common in patients with severe ARDS requiring ECMO, in nonsurvivors, and in patients who experienced significant thromboembolic events (independent of ECMO status). ROTEM measurements of clot firmness and fibrinolysis inhibition were the primary assessments by which the investigators reported hypercoagulability. Viscoelastic coagulation assays are already widely used in complex coagulopathy scenarios, such as those that occur during trauma, liver transplantation, and cardiac surgery. Incorporating them into clinical practice for ARDS patients appears to be a novel and provocative opportunity. Of course, these findings will need to be validated, but the authors present a compelling case for expanding the scope of ROTEM, or other viscoelastic measures of coagulation, for patients with COVID-19 ARDS.

Patients with COVID-19 often present with extreme pulmonary capillary microthrombi and endothelial damage.[5] These maladaptive responses contribute to profound hypoxia by increasing intrapulmonary shunting and ventilation/perfusion mismatch. It is known that microvascular thrombi, in the lung and other organs, lead to endothelial injury, hypoxia, and inflammation by activating hypoxia-inducible factors and releasing inflammatory cytokines as part of the organ ischemic-protection response.[6,7] Interestingly, hypoxia-inducible factors target pathways in the endothelial cells that control coagulation, including prothrombotic tissue factor and fibrinolysis-inhibiting plasminogen activator inhibitor 1. Further, hypoxia by itself may facilitate thrombotic formation by promoting inflammation and platelet and endothelial activation, mediated by increased expression of hypoxia-inducible factors,

Image: J. P. Rathmell

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David J. Douin, M.D.: Department of Anesthesiology, University of Colorado School of Medicine, Aurora, Colorado.

Ana Fernandez-Bustamante, M.D., Ph.D.: Department of Anesthesiology, University of Colorado School of Medicine, Aurora, Colorado.

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inflammatory cytokines, endothelial integrins that promote cellular adhesion, and neutrophil extracellular traps.[8–10]

Corey *et al.*[4] report elevated concentrations of plasminogen activator inhibitor 1 that were associated with the severity of COVID-19 ARDS. This is interesting because plasminogen activator inhibitor 1 is an accepted early marker of endothelial dysfunction and plays a role in the development of both pulmonary dysfunction and thromboembolic events.[11] In COVID-19 patients, plasminogen activator inhibitor 1 is thought to play a central role in coagulation cascade initiation, inhibition of fibrinolysis, and overall morbidity in severe disease presentations.[12] Not surprisingly, Corey *et al.*[4] demonstrated significant elevations of plasminogen activator inhibitor 1 in patients with severe COVID-19 ARDS and a significant association between elevated plasminogen activator inhibitor 1 concentrations, thromboembolic events, and mortality. Although their single-center cohort is relatively small and limited by a variety of prophylactic and therapeutic anticoagulation regimens received by study patients, these results are promising. The specific inhibition of plasminogen activator inhibitor 1 is currently being explored to mitigate the endothelial and thromboembolic events associated with COVID-19, such as the STOP Severe COVID trial (NCT04634799), which aims to evaluate the safety and efficacy of a novel plasminogen activator inhibitor 1 inhibitor known as TM5614.

We applaud the authors for their clinically relevant investigation of ROTEM and procoagulant markers, particularly plasminogen activator inhibitor 1, and their association with severe pulmonary dysfunction and major thrombotic events in COVID-19 patients. The time course and cause–effect relationship between hypercoagulability and hypoxemia in COVID-19 are still unclear and represent the classic "chicken or the egg" phenomenon. We should encourage rigorous trials with reproducible methodology to investigate the potential value of hypercoagulability assays in the management of patients with hypoxemia and ARDS.

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Competing Interests

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Correspondence

Address correspondence to Dr. Fernandez-Bustamante: ana.fernandez-bustamante@cuanschutz.edu

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