COVID-19 and Venous Thromboembolic Disease: Where Are We Today?

What is currently known about the pathophysiology of the SARS-CoV-2 virus, prevalence of venous thromboembolism in COVID-19 patients, and the current approach to anticoagulation.

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The devastating impact of COVID-19 on global health care delivery, especially intensive care medicine, has been unparalleled. A substantial contributor to this impact is the predilection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus for the respiratory tract, which in turn leads to an elevated transmission rate along with a propensity for lung infection and severe hypoxemia frequently requiring intensive care unit (ICU) level of care. Early in the pandemic, numerous reports emphasized an increased incidence of venous thromboembolism (VTE) in the setting of SARS-CoV-2 infection, prompting many to suggest a change in VTE prophylaxis for these patients.[1] In addition, autopsy reports suggested multiple thrombi present in the lungs of COVID-19 patients, raising the specter of a viral-induced coagulopathy and/or vasculitis.[2] By coupling this concept with the well-described "cytokine storm"[3] induced by this coronavirus, the lungs have the potential to be damaged on all levels, further escalating the challenge in caring for these patients.

PATHOPHYSIOLOGY OF SARS-CoV-2

At the basic level, SARS-CoV-2 relies on the angiotensin-converting enzyme 2 (ACE 2) and transmembrane serine protease 2 (TMPRSS2) receptors for cell entry.[4] These critical host entry receptors are both heavily concentrated within the pulmonary vascular endothelium and in alveolar epithelial cells, which explains in part the tremendous pulmonary pathophysiology seen with COVID-19. The vascular endothelium is a dynamic system, and its activation triggers a cascade of inflammation via numerous cellular mechanisms. The cytokine storm phenomenon ensues, with elevated levels of biomarkers including fibrinogen, interleukin-6, von Willebrand factor, tumor necrosis factor-α, C-reactive protein, D-dimer, and others. Additionally, the endotheliopathy induced by SARS-CoV-2 infection can induce a hypercoagulable state, leading to an increase in the incidence of thromboembolism

(including arterial thrombosis), also termed as "CAC" or COVID-19–associated coagulopathy.[5] In a landmark early autopsy study of COVID victims, the lungs showed diffuse alveolar damage, severe endothelial injury, and a unique preponderance of widespread thrombosis with microangiopathy in the vascular beds.[2] This hypercoagulable state along with a high prevalence of traditional risk factors for VTE among COVID-19 patents, such as immobility, central venous catheters, and critical illness, has further spurred interest into how to prevent these vascular events.

PREVALENCE OF VTE IN COVID-19 PATIENTS

The true prevalence of VTE in patients with COVID-19 is unclear and varies widely among studies. This is due to the tremendous difficulty in performing CTA on many patients due to fear of spread, as well as the critically ill, severely hypoxemic nature of these patients precluding their safe transport outside of the ICU. Evidence for this most recently came from a single-center study at a New York academic hospital examining the number of pulmonary embolism response team (PERT) activations during the pandemic. In this study, Finn and colleagues reported a much lower use of CTA for the definitive diagnosis of pulmonary embolism (PE) in COVID-19 patients compared to historical controls (58.1% vs 92.3%; *P* = .001), likely leading to an underdiagnosis of PE in these patients.[6] The literature is also fraught with the confounders of various strategies of anticoagulation used in these patients, which makes the true incidence unknown to date. Kollias et al recently demonstrated a pooled prevalence of PE and deep vein thrombosis of 32% (95% CI, 25%-40%) and 27% (95% CI, 21%-34%), respectively, across 47 studies performed through the end of September 2020.[7] Although the true prevalence is unknown and the numbers vary by study, all reported studies show a higher incidence of VTE in COVID-19 patients compared to those without COVID-19 based on historical data. Even in view of potential selection bias in clinical studies, the numbers are high.

TABLE 1. SUMMARY OF THE NATIONAL PERT CONSORTIUM® POSITION STATEMENTS ON THE DIAGNOSIS AND TREATMENT OF PE IN COVID-19 PATIENTS
PERT Consortium® Position Statements on COVID-19 and PE
• A multidisciplinary approach to diagnose and treat patients with PE is encouraged.
• Carefully assess the contribution of COVID-19 lower respiratory tract involvement to the presenting hemodynamic and gas exchange abnormalities and whether these abnormalities are out of proportion and require exploration for an alternative explanation such as PE.
• Because patients with COVID-19 may exhibit a hypercoagulable state, the index of suspicion for concurrent PE should be high. In patients with clinical and imaging findings not entirely explained by COVID-19, evaluation for PE should be strongly considered.
• Elevated D-dimer, in and of itself, should not be used to diagnose suspected PE.
• PERT consultation should take into account COVID-19 testing and results as a means of risk stratification and to protect allied health care providers from risk of viral transmission.
• For patients with mild COVID-19 symptoms and low-risk PE, outpatient treatment or early discharge may be considered, with close follow-up.
• Indications and contraindications for thrombolysis remain unchanged.
• Consider systemic thrombolysis as a viable alternative in certain COVID-19 patients who are appropriate for advanced therapy but in whom an invasive approach may not be available because of limited resources or concerns about viral transmission.
• The risk-benefit ratio of medical and interventional therapy may require adjustment in patients with concurrent COVID-19 and PE.
• PERT consultation provides a mechanism for evaluation of complex interventional options by a multidisciplinary group of PE experts.
• Transfer of care for a patient with PE and COVID-19 should be requested when needed services are not available at the originating institution and are necessary for best care of the patient.
• The potential benefit versus risk should be carefully considered on a case-by-case basis via direct communication between physicians from transferring and receiving institutions. PERTs can aid in this decision.
• Follow-up assessment of patients with COVID-19 and PE is critical to address issues surrounding anticoagulation, follow-up testing, recovery and persistent symptoms, and psychologic well-being.
• When possible, follow-up visits should be virtual. If persistent symptoms or concern for right ventricular failure exist, long-term follow-up visits may be best evaluated in person.
• Monitoring and collection of data obtained during follow-up visits will help the medical community understand the unique impact of concurrent COVID-19 and PE. Facilities caring for patients with COVID-19 and PE are encouraged to join the complimentary PERT Consortium® COVID-19/PE registry, which provides important data on presentation, assessment, and management of patients with COVID-19 and PE and helps shape real-time decision-making and patient-level care as this pandemic unfolds.
• In all care of patients infected with COVID-19, exposure should be limited, without compromising the medical information necessary to make critical evidence-based management decisions.
• Digital platforms for information exchange enable reduced exposure and facilitate real-time decision-making by a multidisciplinary team such as a PERT.
• Careful and thoughtful advanced planning for interventional or operative procedures, particularly regarding required personnel and equipment, will expedite procedures and minimize staff exposure.
Abbreviations: PE, pulmonary embolism; PERT, pulmonary embolism response team. Reprinted from Chest, 158, Rosovsky RP, Grodzin C, Channick R, et al. Diagnosis and treatment of pulmonary embolism during the coronavirus disease 2019 pandemic: a position paper from the National PERT Consortium, 2590-2601, 2020, with permission from Elsevier.

ANTICOAGULATION IN COVID-19 PATIENTS

The higher prevalence of VTE in COVID-19 patients has prompted numerous studies evaluating various levels of aggressiveness of prophylactic anticoagulation in an attempt to effectively prevent this potentially fatal complication. Most recently, the INSPIRATION randomized trial, conducted at 10 centers in Iran, showed no difference between intermediate-dose (enoxaparin, 1 mg/kg daily) and standard prophylactic dose (enoxaparin, 40 mg daily) anticoagulation in 562 COVID-19 patients admitted to the ICU on the composite endpoint of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days.[8] However, in this trial, mortality in each group was > 40% (ie, much higher than at most United States academic hospitals treating a large number of COVID-19 patients), and thus it is unclear if these results can be extrapolated to United States centers. Several multicenter randomized trials (ACTIV-4a,[9] ATTACC,[10] PROTHROMCOVID,[11] REMAP-COVID[12]) evaluating various anticoagulant dosing

strategies for VTE prophylaxis in hospitalized COVID-19 patients have been conducted. The preliminary report for those patients with severe COVID-19 enrolled in the REMAP-CAP, ACTIV-4a, ATTACC open-label, adaptive, multiplatform, randomized, anticoagulation trials (> 400 sites worldwide in total) has been released,[13] but the final report should offer useful insight.

These and other trials involving various permutations of antithrombotics, antiplatelets, and other strategies to combat VTE in these patients have been recently summarized.[14] At present, there is no single risk score that has been proven to effectively predict which patients with COVID-19 are at the highest risk for VTE nor the optimal prophylaxis or treatment for these patients. Currently, clinicians must use the available data combined with clinical judgment regarding patient-specific risk factors for both VTE and bleeding. When all of the clinical trial data are ultimately available for analysis, we must rigorously and critically analyze them, taking into account the various forms of bias that are present in most and use them to the best of our abilities.

PERT Consortium® Consensus Recommendations

The pandemic has also provided a unique forum for the creation and expansion of PERTs across the globe. Born from a multidisciplinary approach to VTE, The National PERT Consortium® is the largest organization in the world specifically dedicated to improving outcomes in acute PE. The PERT Consortium® has provided consensus recommendations for the diagnosis, treatment, and follow-up of patients with acute PE[15] and recently provided an update for COVID-19 patients.[16] The position statements are summarized in Table 1. The PERT Consortium® emphasizes the need for a multidisciplinary approach in those patients who may have two simultaneous critical cardiopulmonary conditions (COVID-19 and PE) while being limited in diagnostic testing abilities, all in a setting designed to optimize patient outcomes while protecting health care personnel from viral transmission.

CONCLUSION

The complexity of care required to optimize outcomes in critically ill patients with COVID-19 is staggering. Standardized treatment protocols based on the most recent literature must constantly evolve, and this requires a true multidisciplinary team. No one specialty can offer the medical literature vigilance nor the expertise required in such a constantly changing clinical environment; thus, clinicians should consider the creation of COVID-19 teams with expertise in pulmonary, critical care, cardiology, hematology/oncology, vascular medicine,[17] vascular

surgery, cardiothoracic surgery, radiology, and pharmacy to ensure the development of order sets that are as standardized as the available evidence base will permit to successfully prevent and treat VTE in critically ill COVID-19 patients. Sound clinical judgment by these expert teams will still be required in this complex and continuously changing area of medicine. ■

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