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Proposed Algorithm for Treatment of Pulmonary Embolism in COVID-19 Patients

There is mounting evidence that COVID-19 patients may possess a hypercoagulable profile that increases their risk for thromboembolic complications, including pulmonary embolism (PE). PE has been associated with an increase in morbidity, mortality, prolonged ventilation, and extended ICU admissions. Intervention is warranted in some patients who develop acute massive and submassive PEs. However, the development of PE in COVID-19 patients is often complicated by such factors as delay of diagnosis, confounding medical conditions, and strict isolation precautions. In addition, depleted cardiopulmonary reserve and prone positioning can make management of PE in these patients especially challenging for the physician. In this article, we review current understanding of PE in COVID-19 patients, summarize consensus data regarding the treatment of PE, and propose an algorithm to guide the management of COVID-19 patients with PE.

INTRODUCTION

Since its early diagnosis in December 2019 in Wuhan, China, the novel enveloped RNA betacoronavirus (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been emerging as a global pandemic affecting lives, societies, and turning the entire world upside down. The lack of prior immunity to COVID-19 has resulted in exponential increase in numbers of infected patients across the globe and uncertainty regarding management of the complications that may arise in the course of that viral illness.

COVID-19 implications on the cardiovascular system include myocardial injury, myocarditis, acute myocardial infarction, heart failure, and dysrhythmias.[1]

In addition, COVID-19 infection purportedly causes a hypercoagulable state that results in an increased risk for embolic and thrombotic vascular complications. Among these, there is an elevated risk for pulmonary embolism (COVID-PE), with an incidence potentially as high as 20−30%.We propose a model for guiding the management of COVID-19 patients with intermediate-risk (submassive) pulmonary embolism (PE).

This article is an attempt to summarize a broad consensus and to propose an algorithm to treat COVID-PE patients.

Pathophysiology

The aerosol viral transmission to the lung and the direct contact between the proteinoids spikes on the COVID-19 surface and alveoli will lead to edema, proteinaceous exudate, reactive hyperplasia of pneumocytes, and multinucleated giant cells. This overwhelming infection is associated with stormy coagulation cascade including increase in procoagulant factors, cytokine, fibrinogen, and D-dimer (DD) levels.[2] Severe cases have been associated also with increase in disseminated intravascular coagulopathy (DIC).[2–4] Interestingly, no bleeding diathesis was reported in COVID hypofibrinolytic consumptive DIC.

The most consistent hemostatic abnormalities include mild thrombocytopenia and an increased in level of DD. In addition, these values have been associated with higher risk of mechanical ventilation (MV), ICU admissions, and mortality.[2,4,5]

In COVID-19, there is a flare-up in thromboembolic pathology which contributes to microvascular pulmonary thrombosis and DIC.[5] Thrombotic phenomenon may occur in both venous and arterial circulations because of excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[6]

In one report of 107 COVID-19 patients admitted to the ICU for pneumonia, risk of PE was 22.6%. Delayed diagnosis of COVID-PE was associated with poor outcomes.[7]

Applying What We Know about COVID-PE

An intermediate-risk or submassive acute PE is one that does not result in sustained hypotension, profound bradycardia, or cardiac arrest but does show signs of right ventricular (RV) dysfunction and/or myocardial necrosis. These signs may include the following:

1) RV dysfunction
   a. RV dilation (RV/LV > 0.9) on echo or CT
   b. RV systolic dysfunction on echo
   c. Elevated BNP (>90 pg/mL) or N-terminal pro-BNP (>500 pg/mL)
   d. ECG changes

i.
New complete or incomplete RBBB

The authors have nothing to declare or disclose.

Ann Vasc Surg 2021; 70: 282–285
https://doi.org/10.1016/j.avsg.2020.08.088

Published online: 4 September 2020

ii.
Anteroseptal ST elevation or depression

iii.
Anteroseptal T-wave inversion

2) Myocardial necrosis
   a. Elevated troponin I (>0.4 ng/mL)
   b. Elevated troponin T (>0.1 ng/mL)

These markers, in the presence of an acute PE and in the absence of shock, warrant consideration for catheter-directed therapy. In addition, per CHEST guidelines, any patient initially treated with conservative management (anticoagulation) who subsequently deteriorates clinically may be considered for catheter-directed therapy if deemed not a candidate for systemic thrombolysis.

Goals of catheter-directed thrombolysis (AHA guidelines) are as follows:

1) to rapidly reduce pulmonary artery pressure, RV strain, and pulmonary vascular resistance;
2) to increase systemic perfusion;
3) to facilitate RV recovery.

Potential Complications

- PA perforation or dissection → massive pulmonary hemorrhage;
- Increased risk in <6 mm vessels;
- RA/RV perforation → cardiac tamponade;
- Arrhythmias.

Available Recommendations and What We Can Apply for COVID-PE

The CHEST guidelines[8,9] recommend administering systemic thrombolytic therapy for the treatment of massive PE in patients without contraindications (grade 2B) and recommend against such treatment in patients who are hemodynamically stable (grade 1B). For patients who have a massive PE and high bleeding risk, rapid clinical deterioration, or failed systemic thrombolytic therapy, the CHEST guidelines suggest consideration for catheter-directed therapy (2C).

The Inari FlowTriever device is currently the only device the FDA has approved for percutaneous mechanical PE thrombectomy.[10] The FLARE study[11] found a 25% reduction in RV/LV ratio and only 1% incidence of major bleeding in patients with submassive PE treated with the FlowTriever device. Of note, the inclusion criteria in this study included hemodynamic stability.

The EkoSonic Endovascular System (''EKOS'') was the first device approved by the FDA for catheter-directed treatment of PE. The device directly delivers thrombolytics via catheter while utilizing ultrasound technology to assist in the destruction of thrombus. The ULTIMA and SEATTLE II trial[12] demonstrated improved RV function without an increased risk of bleeding after treatment with EKOS for submassive PE. The OPTYLASE trial showed that this device could be effectively used employing low doses of thrombolytics and short infusion durations.[13]

Available observational data reported that up to 10% of COVID-19 patients who required MV had acute PE/deep venous thrombosis (DVT). Clearly, the incidence of PE is high in those with history of DVT. Clinicians should be cognizant that chance of PE is high in those with acute DVT. Other symptoms that may be encountered are hypotension, tachycardia, hypoxia, and low-grade fever, which all tend to be associated with COVID-19. Hemoptysis has been reported in 13% of COVID-PE cases.[14] Signs of COVID-PE may include right-sided heart failure,[15,16] respiratory rate ≥30 breaths/min, arterial oxygen saturation ≤93% and at rest, $PaO_2/FiO_2 \leq 300$ mm Hg.[17] Being highly sensitive, recent studies[18–20] have indicated early utilization of DD in COVID-19 patients to guide therapy and to rule out PE/DVT. An elevated DD value does not affirm the presence of DVT/PE and more cross-sectional imaging tools such as echocardiography, point-of-care ultrasonography, or computed tomography angiography are needed to affirm the diagnosis as COVID-PE.[19,20] Yet, there is uncertainty regarding management of possible complications that arise in the course of this viral illness. Therefore, having common ground for a possible approach to treat COVID-PE is highly recommended.

Challenges with COVID-PE

1. The overlap in the signs and symptoms of COVID-19-associated acute respiratory distress syndrome (ARDS) and COVID-19 with concurrent PE creates a diagnostic challenge.
2. COVID-PE in pregnancy.[21]
3. Safety measures and changing the paradigm of computed tomography.[22]
4. Maintaining COVID-19 safety measures for general personal protective equipment in accordance with local guidelines and availability before entering the scene or patient room, minimize the number of clinicians performing examination; use a negative pressure room whenever possible; keep the door to the room closed.
5. Prone position and the possible need to access popliteal or jugular veins for interventions.[23] In popliteal vein access, the length of the catheter needs to be determined, and 135 cm may be considered.
6. The patient may have other contraindications to systemic thrombolysis, warranting catheter-directed therapy even in high-risk patients

COVID-PE Recommendations (Fig. 1)

1. Anti-inflammatory effects of heparin/LMWH may offer benefit and antiviral mechanisms have been

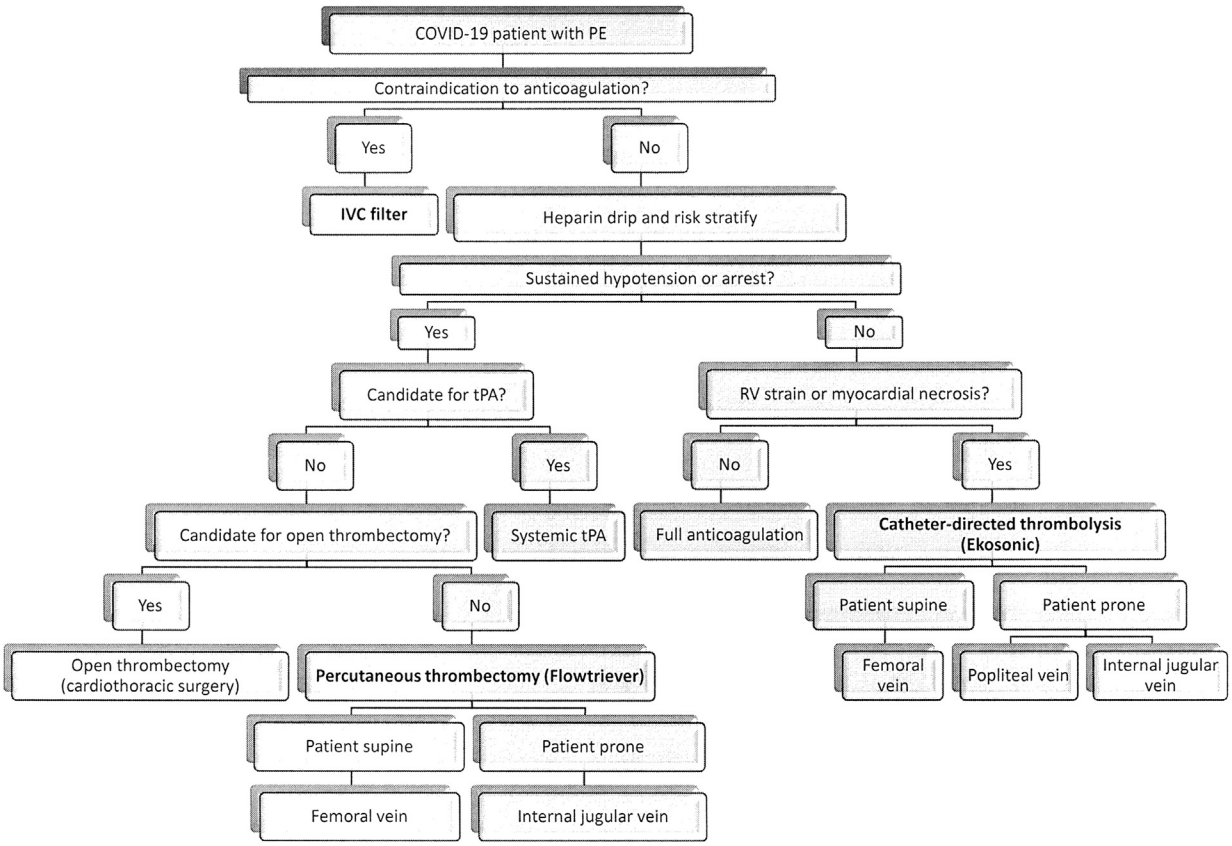

Fig. 1. Proposed algorithm for management of PE in COVID-19 patients.

demonstrated for factor Xa inhibitors in animal studies. Consequently, the use of empiric therapeutic anticoagulation in certain COVID patients who do not have PE/DVT has been advocated in a select group of patients such as those on MV, with a presence of increased level of DD and/or fibrinogen.

2. Full anticoagulation therapy appears to be associated with lower mortality in COVID-19 patients with sepsis-induced coagulopathy criteria or with a markedly elevated DD. Therefore, all hospitalized COVID-19 patients should receive thromboprophylaxis or full therapeutic—intensity anticoagulation if such an indication is present.[24,25]

3. A French guidance document recommends full-therapeutic dose anticoagulation for patient with increase fibrinogen >8 g/l or DD > 3.0 μg/ml.[15]

IN SUMMARY

The COVID-19 patient with acute PE presents a unique and formidable set of challenges to the vascular surgeon. First, the cohort of these patients who develop thromboembolic complications frequently do so as sequelae of the severe form of the disease, which manifests as ARDS and multiorgan failure. These patients have diminished cardiopulmonary reserves, and the development of acute PE is poorly tolerated in this population. In addition, the management of some patients with ARDS due to COVID-19 infection warrants prone positioning, making access for catheter-directed interventions challenging. Finally, the clinical deterioration associated with COVID-19 infection is often swift and unrelenting, requiring the care team to be quick and decisive in their actions. For these reasons, we presented this article as an attempt to both summarize a broad consensus and to propose a simple evidence-based algorithm to guide the management of COVID-19 patients with acute PE.

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