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CHEST

Pulmonary Thrombosis and Thromboembolism in COVID-19

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COVID-19, the disease responsible for the devastating pandemic that began at the end of 2019, has been associated with a significantly increased risk of pulmonary thrombosis, even in patients receiving prophylactic anticoagulation. The predilection for thrombosis in COVID-19 may be driven by at least two distinct, but interrelated, processes: a hypercoagulable state responsible for large-vessel thrombosis and thromboembolism and direct vascular and endothelial injury responsible for in situ microvascular thrombosis. The presence of pulmonary thrombosis may explain why hypoxemia is out of proportion to impairment in lung compliance in some patients with COVID-19 pneumonia. Because pulmonary embolism (PE) and COVID-19 pneumonia share many signs and symptoms, diagnosing PE in patients with COVID-19 can be challenging. Given the high mortality and morbidity associated with severe COVID-19 and the concern that aspects of the disease may be driven by thrombosis, many hospital systems have instituted aggressive anticoagulation protocols above standard VTE prophylaxis. In this review, the epidemiologic and pathophysiologic features, diagnosis, and treatment of COVID-19 pulmonary thrombosis and thromboembolism are discussed.

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KEY WORDS: anticoagulation; COVID-19; immunothrombosis; pulmonary embolism; VTE

In late December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood and wet animal wholesale market in Wuhan, China.[1] By early January 2020, a novel coronavirus, SARS-CoV-2, was isolated from these patients with virus-infected pneumonia, and soon after, the clinical syndrome caused by SARS-CoV-2 was labeled as COVID-19 by the World Health Organization.[2] Since then, this highly transmissible and virulent disease has devastated the world, overwhelming hospitals with critically ill patients. A few notable observations about COVID-19 were made early in the course of the pandemic: (1) many patients with COVID-19 demonstrate markedly abnormal coagulation parameters, particularly D-dimer elevation, which correlates with mortality[3]; (2) patients with COVID-19, particularly those in the ICU, show a notably high incidence of thrombotic complications[4]; (3) small autopsy series of patients with COVID-19 have demonstrated a high incidence of both pulmonary macrothrombi and microthrombi, despite the use of prophylactic anticoagulation[5,6]; and (4) many patients with COVID-19 who experience respiratory failure seemed to have hypoxemia that was out of proportion to the impairment in lung compliance, a disconnect that perhaps could be explained by pulmonary thrombosis.[7] Given the high

ABBREVIATIONS: CTPA = CT pulmonary angiography; DIC = disseminated intravascular coagulopathy; PE = pulmonary embolism; PVR = pulmonary vascular resistance; RV = right ventricular

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mortality and morbidity associated with severe COVID-19[8,9] and the concern that aspects of the disease may be driven by thrombosis, many hospital systems instituted aggressive anticoagulation protocols beyond standard VTE prophylaxis, despite the absence of randomized clinical trials supporting such practices.[10,11] In this review, the epidemiologic and pathophysiologic features, diagnosis, and treatment of COVID-19 pulmonary thrombosis and thromboembolism are discussed.

Epidemiologic Features

Accurate assessments of the true incidence of VTE in hospitalized patients with COVID-19 remain elusive, with estimates ranging from 4.8% to 85%.[12] The significant variability in the reported incidence is likely a consequence of multiple factors, including assessment setting (eg, ICU vs non-ICU), type of events counted (eg, symptomatic vs asymptomatic), testing strategies (eg, clinical suspicion vs systematic screening), and degree of thromboprophylaxis. Given infection control concerns and strained resources during peak surge times early in the pandemic, the threshold for diagnostic testing with CT pulmonary angiography (CTPA), compression ultrasonography, or both was high, leading to a low frequency of testing.[13] In a meta-analysis by Jimenez et al[12] comprising 36 studies and more than 11,000 patients, the pooled incidence of VTE in patients with COVID-19 was 17% (12% for DVT, 7.1% pulmonary embolism [PE]).

VTE incidence in patients with COVID-19 is elevated when compared with historical control participants. Using a French National administrative database, Piroth et al[14] compared the 89,530 patients admitted to the hospital with COVID-19 in France over a 2-month period with the 45,819 patients admitted with influenza over a similar 2-month period during the prior year. VTE and PE rates were 4.9% and 3.4%, respectively, for patients with COVID-19, but only 1.7% and 0.9%, respectively, for patients with influenza. Poissy et al[15] noted a PE incidence of 20.6% in 107 consecutive patients with COVID-19 admitted to the ICU during a 1-month period in 2020, which was significantly higher than the 6.1% incidence of PE for the 196 patients admitted to the ICU during the same interval in 2019, despite similar severity of illness scores. Helms et al[16] reported an 11.7% incidence of PE in COVID-19 ARDS compared with a 2.1% incidence of PE in a historical prospective cohort of patients with non-COVID-19 ARDS.

Critically ill patients in the ICU with COVID-19 show significantly higher rates of VTE and thrombosis than patients with COVID-19 on the wards. Klok et al[17] reported a 31% incidence of thrombotic events in 184 critically ill patients, 81% of the thrombotic events being PE. Piazza et al[18] reported that 35.3% of ICU patients experienced major arterial or VTE, whereas the rate was only 2.6% for patients on the wards. Notably, 77% of the DVTs reported in this study were associated with a catheter or device. In attempts to minimize recurrent health care team exposure, many institutions undertook high use of central venous catheters early in the pandemic, especially in the ICU.[19] Helms et al[16] noted that 28 of 29 patients with COVID-19 in the ICU who received continuous renal replacement experienced premature circuit clotting.

A significant percentage of the VTEs in patients with COVID-19 are diagnosed early in the hospital presentation. Mouhat et al[20] reported a PE incidence of 27% in 349 hospitalized patients with COVID-19, of whom 20% were diagnosed at admission. Lodgiani et al[13] noted a 21% cumulative rate of thromboembolic events, half occurring within the first 24 h of hospital admission. For patients hospitalized with COVID-19, rates of PE developing after hospital discharge are low, reported to be 2% within the first 6 weeks after discharge.[21] COVID-19 hospitalization does not seem to increase the risk of VTE after discharge compared with hospitalization as a result of other acute medical illnesses.[22]

Systematic screening for VTE has been known to increase detection rates in patients without COVID-19.[23] Voicu et al[24] reported that 36% of mechanically ventilated patients with COVID-19 were diagnosed with DVT within 3 days after intubation when screened with compression ultrasonography. In patients with COVID-19 on the wards, Santoliquido et al[25] demonstrated a DVT incidence of 12% with systematic screening, although the rate was 2.4% when counting only proximal DVT. Mirsadraee et al[26] performed systematic whole-body CT scanning on 72 patients with COVID-19 on admission to the ICU, noting that 34 patients (47%) demonstrated PE, which had been suspected clinically in only 7%.

The presence of VTE in hospitalized patients with COVID-19 is associated with greater disease severity and increased mortality. Patients with PE more frequently require mechanical ventilation and ICU admission and have increased overall hospital length of stay.[27] In more than 3,000 consecutive hospitalized patients with COVID-19 in a New York City hospital, after multivariate adjustment, both venous and arterial thrombosis were associated with increased mortality

(adjusted hazard ratio, 1.82).[28] It is unclear whether thrombosis is a direct cause of these worse outcomes or merely a marker of more severe disease.

Pathophysiologic Features

Considering that VTE rates in patients hospitalized with COVID-19 are significantly higher than in historical control participants, likely other thrombotic mechanisms beyond the classic VTE risk factors of immobility and severe illness are a factor.[29] The predilection for thrombosis in COVID-19 is driven by at least two distinct, but interrelated, processes: a hypercoagulable state responsible for large-vessel thrombosis and thromboembolism and direct vascular and endothelial injury responsible for in situ microvascular thrombosis (Fig 1).[30]

Hypercoagulable State

It became evident early in the pandemic that patients with COVID-19 showed abnormal hemostasis profiles, elevated D-dimer being the most frequent abnormality.[3] In a study of 2,377 hospitalized patients with COVID-19 in a New York hospital, 76% showed elevated D-dimer at presentation.[31] D-dimer is a degradation product of fibrinolysis, and although a multitude of inflammatory processes can influence D-dimer levels, to some extent its elevation likely reflects intravascular thrombosis in patients with COVID-19.[32,33] Elevated D-dimer has been shown to correlate with rates of thrombosis in COVID-19.[20,27,28] Mouhat et al[20] reported that a D-dimer of > 2,590 ng/mL was associated with a 17-fold increase in adjusted risk of PE in patients hospitalized with COVID-19. Li et al[34] noted that a > 50% increase in D-dimer level during hospitalization was the strongest independent predictor of symptomatic VTE in patients with COVID-19. Elevated D-dimer levels also are associated independently with more severe disease and increased mortality in COVID-19.[9,35]

The biochemical coagulation phenotype in COVID-19 likely differs from disseminated intravascular coagulopathy (DIC) and sepsis-induced coagulopathy. DIC and sepsis-induced coagulopathy are consumptive coagulopathies characterized by low platelet counts, decreased plasma levels of clotting factors, and prolongation of prothrombin time.[36] In contrast, neither platelet nor clotting factor consumption are common features in COVID-19, suggesting a different mechanism of coagulopathy in COVID-19.[37] For example, Huang et al[38] reported that in hospitalized patients with COVID-19, only 8% of patients in the ICU and 4% of patients not in the ICU showed platelet counts of $< 100 \times 10^9$/L on admission. Helms et al[16] reported that although > 95% of patients with COVID-19 in the ICU showed elevated D-dimer and fibrinogen levels, none demonstrated a positive International Society of Thrombosis and Haemostasis DIC score. Table 1 summarizes and compares the main coagulation parameters of DIC and COVID-19 coagulopathy.

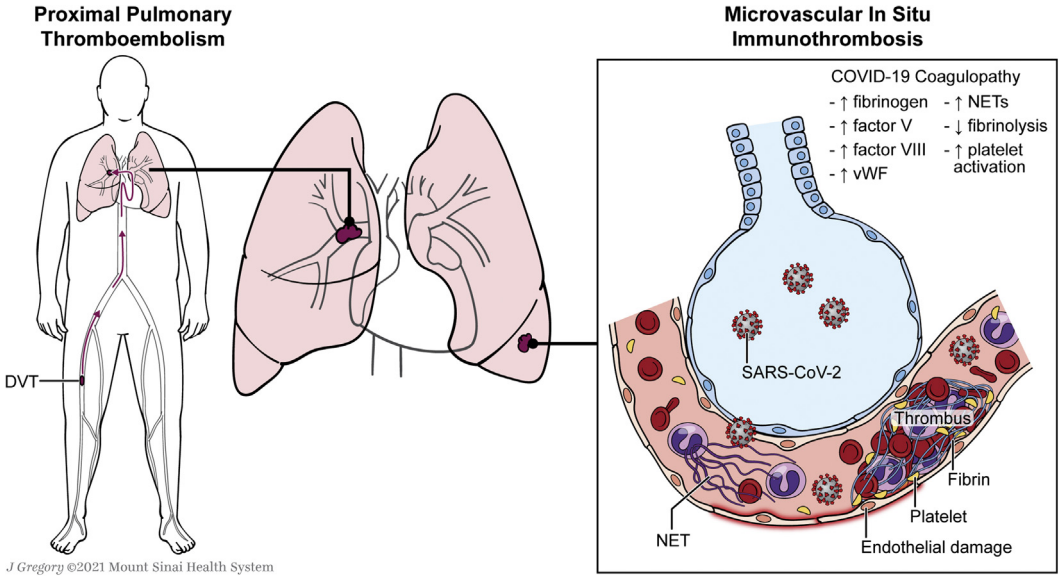

Figure 1 – *Illustrations demonstrating two different mechanisms for pulmonary thrombosis in COVID-19, which include large-vessel occlusion resulting from thromboembolism and microvascular in situ immunothrombosis resulting from direct vascular and endothelial injury. NET = neutrophil extracellular trap; vWF = von Willebrand factor.*

TABLE 1] Alterations of Hematologic Parameters in COVID-19 Coagulopathy and DIC

Hematologic Parameter	COVID-19 Coagulopathy	DIC
D-dimer	↑	↑
Platelets	↔	↓
PT, aPTT	↔	↑
Fibrinogen	↑	↓
Thrombin	↑	↑
Factor VIII, factor V	↑	↓

aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; PT = prothrombin time.

Other commonly noted coagulation abnormalities in COVID-19 include dramatically increased thrombin production[39] and elevated concentrations of both von Willebrand factor and factor V.[16,40] Factor VIII, one of the more potent triggers of hypercoagulability, has been shown to be increased significantly in COVID-19.[41] Thromboelastography studies of severe COVID-19 demonstrate rapid clot formation with impaired fibrinolysis.[41] Additionally, platelets from patients with COVID-19 are activated more efficiently than are platelets from both healthy control participants and patients with non-COVID-19 ARDS.[42]

Immunothrombosis

Elevated markers of systemic inflammation, particularly C-reactive protein and IL-6, are observed commonly in patients with COVID-19.[43] Extensive cross talk occurs between the immune and coagulation systems to provide effective host defense.[44] Immune cells and inflammatory cytokines incite the development of immunothrombi, which consist of fibrin, monocytes, neutrophils, and platelets. By creating a sterile barrier against further pathogen invasion, these physiologic thrombi initially serve a protective purpose.[45,46] However, dysregulation of thrombosis and inflammation can devolve into an injurious vicious cycle, leading to exuberant thrombosis with consequent organ dysfunction.[33,47] The immune and coagulation systems also are linked via neutrophil extracellular traps, weblike structures of DNA decorated with antimicrobial proteins. Neutrophil extracellular traps are expelled from neutrophils to capture and immobilize pathogens physically and also can activate immunothrombosis.[48] Neutrophil extracellular trap levels have been shown to be elevated in patients with COVID-19 when compared with control participants and also to correlate with disease severity.[49]

Endothelial Injury

Autopsy studies early during the pandemic revealed diffuse endothelial inflammation in many organs, including the lung, heart, liver, and kidney, with evidence of direct viral infection of endothelial cells by the SARS-CoV-2 virus.[50] Because in vivo biosynthesis of von Willebrand factor is restricted to endothelial cells and megakaryocytes, high plasma von Willebrand factor concentrations in patients with COVID-19 suggest significant endothelial cell derangement.[40,41] Immune cell arteritis was found in the lungs of nearly half of those who had died of COVID-19 in one autopsy series.[51] Endothelial injury, particularly in the context of a hypercoagulable milieu, likely is responsible for the high rates of microthrombosis noted in the pulmonary vasculature. Although pulmonary microthrombosis has been noted previously in classical ARDS,[52] the extent evident in COVID-19 is significantly greater. Ackerman et al[6] noted that autopsies from patients with COVID-19 showed nine times more alveolar capillary microthrombi compared with autopsies from patients with ARDS secondary to H1N1 influenza. The high rates of microthrombosis are not limited to the lungs; they also have been reported in the heart[53] and skin.[54] Imaging studies demonstrate that thrombotic lesions in COVID-19 are smaller and more peripherally located compared with those in non-COVID acute PE, suggesting that some filling defects on CTPA, particularly isolated subsegmental PE, may reflect in situ pulmonary thrombosis instead of the typical embolization of thrombi originating from peripheral DVT.[12,55] Mirsadraee et al[26] reported that of the critically ill patients with COVID-19 found to have pulmonary thrombosis via screening CTPA, 77% did not have radiologic evidence of peripheral DVT.

Gas Exchange vs Lung Compliance

Early in the pandemic, Gattinoni et al[7] noted that although many patients with COVID-19 technically fulfilled the Berlin criteria for ARDS, many showed marked hypoxemia and elevated shunt fraction with only minimally affected lung compliance, particularly early in the course of disease. Chiumello et al[56] noted that venous admixture was unrelated to the fraction of nonaerated lung tissue in COVID-19 ARDS, yet was correlated to the fraction of nonaerated lung tissue in a historical cohort of patients with non-COVID ARDS who were matched for both Pa_{O_2} to F_{IO_2} ratio and compliance. Additionally, many nonintubated patients with COVID-19 demonstrate dramatic hypoxemia, yet

lack proportional signs of respiratory distress, a condition coined *happy hypoxemia*.[57] Some have hypothesized that the presence of pulmonary thrombi, both microthrombi and macrothrombi, may help to explain the disconnect between gas exchange and lung compliance in severe COVID-19.[58]

Hemodynamic Perturbations

Pulmonary emboli increase pulmonary vascular resistance (PVR) and pulmonary artery pressure, with higher thrombotic burden correlating with higher PVR and pulmonary artery pressure.[59] With sufficiently elevated right ventricular (RV) afterload, pulmonary emboli can induce RV dilation and dysfunction.[60] Somewhat strikingly, patients with COVID-19 requiring mechanical ventilation show invasive hemodynamic profiles that are characterized by low, not high, PVR.[61] This finding is surprising given the high prevalence of PE in patients with COVID-19 in the ICU, as well as the high prevalence of elevated PVR in non-COVID ARDS.[62]

It is possible that the hemodynamic effect of pulmonary thrombosis is mitigated by a primary pulmonary vasodilatory process in some patients with COVID-19. Dual-energy CT imaging has demonstrated pulmonary vessel dilation in COVID-19 pneumonia.[63] Ackerman et al,[6] in addition to demonstrating high rates of pulmonary microthrombosis in COVID-19, also noted high rates of intussusceptive and sprouting angiogenesis. Reynolds et al[64] reported that 83% of mechanically ventilated patients with COVID-19 showed positive bubble study findings as assessed by contrast-enhanced transcranial Doppler imaging, likely indicative of abnormal pulmonary capillary dilation, pulmonary arteriovenous malformations, or both. Additionally, the degree of transpulmonary bubble transit correlated with Pao_2 to FIO_2 ratio, suggesting that these pulmonary vascular dilations may be a significant cause of hypoxemia in COVID-19 ARDS. Whereas pulmonary macrothrombi and microthrombi increase PVR, pulmonary vasodilation decreases PVR; when both processes occur simultaneously, each can "cancel out" the hemodynamic effect of the other (Fig 2).[65] The coexistence of both obliterative and vasodilatory processes in the pulmonary vasculature is reminiscent of what can occur in chronic liver disease, specifically portopulmonary hypertension (obliterative) and hepatopulmonary syndrome (vasodilatory).[66] Ultimately, in COVID-19 ARDS, the obliterative processes may dominate, leading to severe RV failure and cardiogenic shock.[67]

Although the vasodilatory and obliterative processes may offset each other hemodynamically, their coexistence may amplify hypoxemia in COVID-19. Vasodilated regions experience increased blood flow, creating low $\dot{V}/\dot{Q}$ ratios. Microthrombi and vasoconstriction in other areas of the lung reroute additional blood flow to the vasodilated regions and drive down the $\dot{V}/\dot{Q}$ ratio further.[65] Mathematical modeling demonstrates that the large amount of pulmonary venous admixture in the setting of relatively minor parenchymal involvement observed in early COVID-19 can be explained reasonably by a combination of pulmonary thrombosis and vasodilation.[68]

Diagnosis

In the absence of systematic screening, the diagnosis of PE begins with clinical suspicion. Unexplained dyspnea

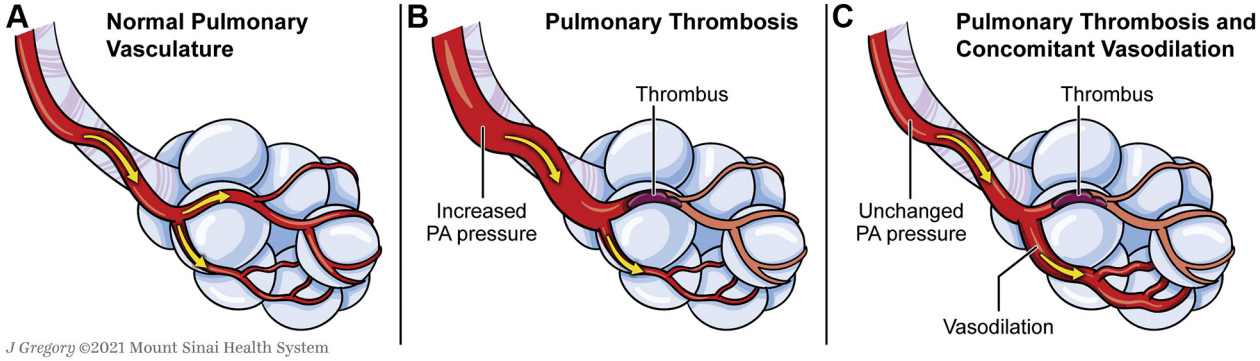

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Figure 2 – *Illustration showing how concomitant vasodilation can mitigate the hemodynamic effects of pulmonary thrombosis. A, Normal pulmonary vasculature. B, Pulmonary thrombosis, which increases pulmonary vascular resistance and leads to increased PA pressure. C, Concomitant pulmonary vasodilation potentially can "cancel out" the increases in pulmonary vascular resistance and PA pressure caused by pulmonary thrombosis. PA = pulmonary arterial.*

and hypoxemia, particularly in the setting of normal chest radiography findings, raises the clinical suspicion for PE.[69] Clinical suspicion of PE in a patient with COVID-19 pneumonia often is diminished because the signs and symptoms of COVID-19 pneumonia mimic those of PE; a patient's dyspnea and hypoxemia may be attributed solely to COVID-19 pneumonia, and further diagnostic testing for potential PE may be deferred. Although clinical probability scores, such as the Wells score,[70] are helpful in raising clinical suspicion of PE in patients, they have not been validated in patients with COVID-19 and likely underestimate the probability of PE in COVID-19.[71]

D-dimer, in conjunction with clinical probability assessment, has great usefulness in ruling out PE in patients with low or intermediate probability of PE, although its usefulness in COVID-19 is unclear.[72] Although D-dimer levels in COVID-19 correlate with rates of thrombosis, it is not clear whether a particular D-dimer value "rules in" or "rules out" PE. In the study by Mirsadraee et al[26] in which screening CTPA was performed for patients with COVID-19 on admission to the ICU, D-dimer levels did not discriminate between patients with and without PE. Li et al[34] developed a three-factor score consisting of admission fibrinogen, admission D-dimer, and D-dimer increment $>$ 1.5 fold, the score performing with a sensitivity of 0.93 and specificity of 0.71 for symptomatic VTE.

CTPA is the first-choice method for the diagnosis of PE because of its high accuracy, wide availability, and ability to assess for other pulmonary pathologic features. Its use may be limited in critically ill patients with COVID-19 who are not stable enough for transfer and in patients with renal failure, a common complication in severe COVID-19.[73] $\dot{V}/\dot{Q}$ scanning can be used for patients in whom CTPA is contraindicated or inconclusive. Scans performed on patients with abnormal chest radiography findings, as is often the case in patients with COVID-19 pneumonia, are more likely to result in false-positive results because the images rarely appear as normal or showing a low probability of PE in such patients. Compression ultrasonography can be performed to assess for DVT when chest imaging is contraindicated or indeterminate; however, the absence of DVT does not imply the absence of pulmonary thrombosis, especially because in situ pulmonary thrombosis is a potential mechanism in COVID-19. A diagnosis of DVT may eliminate the need to evaluate for PE because the indication for therapeutic anticoagulation will have been established. Echocardiography can raise suspicion for the diagnosis of PE with the presence of clot in the right side of the heart or new right heart strain. Although it has limited diagnostic value, echocardiography is most useful for risk stratification of confirmed PE.[74]

Prophylaxis

Considering that PE is one of the most common preventable causes of hospital death, thromboprophylaxis is a crucial component in the care of hospitalized patients,[75] and COVID-19 is no exception. A retrospective study by Rentsch et al[76] demonstrated that the administration of prophylactic anticoagulation within 24 h of admission in patients with COVID-19 was associated with decreased mortality when compared with no prophylactic anticoagulation. Multiple society guidelines recommend prophylactic anticoagulation for hospitalized patients with COVID-19 who do not have a contraindication to treatment.[77,78] However, standard doses of prophylactic anticoagulation likely are insufficient for the prevention of VTE in patients with COVID-19; many VTE events are diagnosed within the first 24 h after admission,[13] and the reported rates of VTE are notably high despite the use of anticoagulant thromboprophylaxis.[15,17,24]

As a result of the high rates of VTE despite standard-dose thromboprophylaxis, many institutions have implemented protocols using higher doses, including an intermediate dose and even a therapeutic dose. Tacquard et al[11] reported in a study of 538 patients with COVID-19 in eight French ICUs that high-dose prophylactic anticoagulation (intermediate or therapeutic dose) was associated with a significant reduction in thrombotic complications (hazard ratio, 0.81) without an increase in bleeding risk. In more than 4,000 patients with COVID-19 at a New York hospital with an aggressive anticoagulation protocol, Nadkarni et al[10] noted a trend toward a mortality reduction with therapeutic anticoagulation compared with prophylactic anticoagulation, a finding that did not meet statistical significance ($P = .08$).

However, recent randomized controlled trials do not support the use of higher than standard doses for prophylactic anticoagulation in critically ill patients with COVID-19. In 600 critically ill patients, intermediate-dose anticoagulation with enoxaparin 1 mg/kg daily was not superior to standard prophylactic anticoagulation with enoxaparin 40 mg daily in reducing the composite outcome of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or

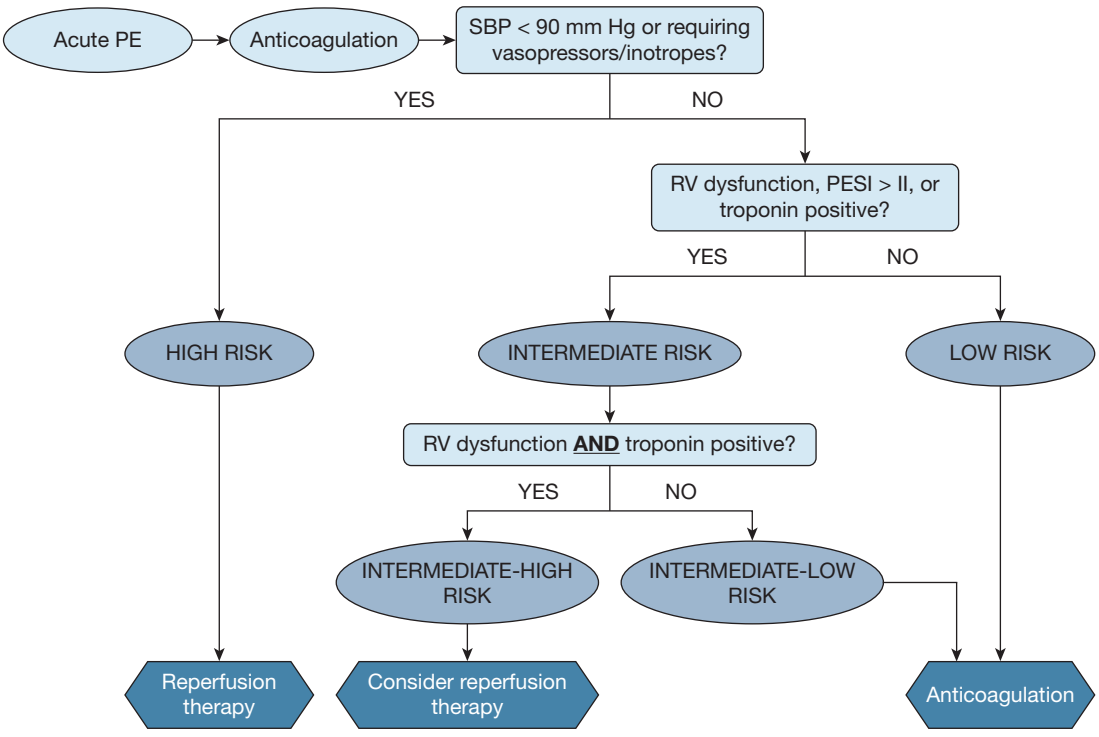

Figure 3 – *Risk-stratification algorithm and treatment strategy, adapted from the European Society of Cardiology Guidelines.*[75] *Reperfusion therapy includes thrombolysis and embolectomy. PE = pulmonary embolism; PESI = pulmonary embolism severity index; RV = right ventricular; SBP = systolic BP.*

mortality within 30 days. Although bleeding events were rare, major and clinically relevant nonmajor bleeding events were nonsignificantly more frequent with intermediate-dose anticoagulation (6.2% for intermediate dose, 3.1% for standard dose; $P = .08$).[79] A large National Institutes of Health multiplatform randomized controlled trial incorporating three global networks (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP], Anti-Thrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], and Accelerating COVID-19 Therapeutic Interventions and Vaccines-4A [ACTIV-4A]) examining the benefit of therapeutic dose vs standard dose prophylactic anticoagulation in more than 1,000 critically ill patients with COVID-19 discontinued enrollment because statistical criteria for futility were met. Importantly, despite therapeutic anticoagulation decreasing major thrombotic events, an 89% probability was found that therapeutic anticoagulation was inferior to standard dose prophylactic anticoagulation in achieving the primary outcome of survival or days free of organ support.[80] The mechanism for this likely harm is unclear, given that major bleeding was increased only mildly with therapeutic anticoagulation (3.1% vs 2.4%). These findings suggest that initiating therapeutic anticoagulation after severe COVID-19 has developed may be too late to alter the clinical course beneficially. In contrast, for moderately ill hospitalized patients with COVID-19, the National Institutes of Health recently announced via press release that therapeutic-dose anticoagulation was superior to standard-dose prophylactic anticoagulation in reducing the need for organ support and mortality.[81] The full results and official publication of these studies are awaited anxiously because they undoubtedly will help to establish the optimal anticoagulation dosing strategies for patients with COVID-19.

Treatment

Anticoagulation is the mainstay of the treatment for acute PE, both for patients with and without COVID-19, to prevent further thrombosis and thromboembolism.[74] Initial treatment options for anticoagulation include unfractionated heparin, low-molecular-weight heparin, fondaparinux, and, in low-risk patients, direct oral anticoagulants. As is the case with non-COVID-19 PE, risk stratification is the central tool used to identify patients at increased risk of early death who may benefit from reperfusion therapy (ie, thrombolysis or embolectomy), mechanical circulatory support, or both. Per the European Society of Cardiology guidelines,[74] high-risk PE is characterized by cardiac arrest, systolic BP $<$ 90 mm Hg, or requiring vasopressors, inotropes,

or both. Intermediate-risk PE is characterized by normotension with signs of RV dysfunction on echocardiography or CTPA, elevated troponin levels, or an elevated PE severity index score. Of note, the role of troponin levels as a prognostic biomarker for PE in COVID-19 is confounded by the fact that troponin frequently is elevated in patients with COVID-19[82]; in that context, it likely reflects myocardial inflammation, cardiac microthrombosis, or both, rather than RV pressure overload. Low-risk PE is characterized by normotension, lack of RV dysfunction, and a low PE severity index score. Figure 3 summarizes the European Society of Cardiology risk stratification algorithm and treatment strategy.

If possible, patients with high-risk PE should undergo reperfusion therapy, mechanical circulatory support, or both. Patients with intermediate-risk PE should be monitored closely for signs of clinical deterioration, with select patients proceeding to reperfusion therapy.[74] Given the risk of viral transmission from transporting patients with COVID-19 to operating rooms and invasive laboratories, the use of procedural-based therapies (eg, surgical embolectomy, catheter-based therapies) may be limited in patients with PE and COVID-19. Ultimately, the use of PE response teams can aid in providing multidisciplinary recommendations and rapid mobilization of resources.[83]

Given the potential pathophysiologic role of pulmonary microthrombosis, thrombolysis has been used in small case series of COVID-19 ARDS. Although these reports note improvement in hypoxemia, dead-space ventilation, and hemodynamics in patients with COVID-19 ARDS, the therapeutic responses seem to be short-lived.[58,84] It is possible that concomitant anticoagulation during the administration of a thrombolytic is necessary to prevent immediate rethrombosis.[58] Currently, randomized trials evaluating the use of tissue plasminogen activator (ClinicalTrials.gov Identifier: NCT04357730) and tenecteplase (ClinicalTrials.gov Identifier: NCT045055920) in patients with COVID-19 ARDS are underway.

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