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Review Article

Pulmonary Embolism in Patients with COVID-19

Scarduelli Cleante[1*], Scarduelli Sara[2] and Borghi Claudio[2]

[1]Pulmonology and Sleep Breathing Disorders Center Suzzara Hospital SPA Mantova

[2]Internal Medicine Department of Medical and Surgical Sciences, University of Bologna

***Corresponding Author:** Scarduelli Cleante, Pulmonology and Sleep Breathing Disorders Center Suzzara Hospital SPA Mantova.

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Abstract

Infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) and the resulting syndrome, COVID-19, have been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrinogen, fibrin degradation products and D-dimers. In some studies, elevations in these markers have been associated with worse clinical outcomes.

Several studies have demonstrated a high prevalence of venous thromboembolism (VTE), and pulmonary embolism (PE), particularly in patients admitted to the intensive care unit (ICU), even in those receiving prophylactic anticoagulation.

The high rate of thrombosis in COVID-19 is driven by at least two 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 PE and pulmonary thrombosis may explain why hypoxemia is out of proportion to impairment in lung compliance in some patients with COVID-19 pneumonia. Diagnosing PE in patients with COVID-19 pneumonia may be challenging, because the two pathologies share many signs and symptoms.

It has been 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.

Given the antithrombotic, anti-inflammatory and possibly antiviral properties of heparins, it has been hypothesized that anticoagulation with heparin administered at doses higher than conventionally used for venous thromboprophylaxis may improve outcomes. In non-critically ill patients hospitalized with COVID-19, therapeutic-dose anticoagulants with heparin (most commonly, low-molecular-weight heparin) increased the probability of survival until hospital discharge with a reduced need for ICU-level organ support at 21 days as compared with usual-care thromboprophylaxis.

In Critically ill patients with confirmed COVID-19, therapeutic-dose anticoagulation did not increase the probability of survival to hospital discharge or the number of days free of cardiovascular o respiratory organ support and had a 95% probability of being inferior to usual-care pharmacologic thromboprophylaxis.

Currently, randomized trials evaluating the use of tissue plasminogen activator and Tenecteplase in patients with COVID-19 ARDS are underway.

Key Words: anticoagulation; COVID-19; heparins; pulmonary embolism; VTE

Introduction

In December 2019, a novel coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), quickly began to spread across Wuhan, China. Coronavirus disease (COVID-19) then triggered a global pandemic [1-4]. Since then, this highly transmissible and virulent disease has devastated the world, overwhelming its healthcare systems. By November 16, 2021, there were 252.826.527 patients diagnosed with COVID 19 in the world with 5.092.761 deaths [5].

The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Most patients (81%) with COVID-19 present with mild symptoms (such as fever, cough, chills, muscle pain, and a loss of taste or smell, no pneumonia or mild pneumonia), about 14% are severe (defined as dyspnea, respiratory frequency ≥30 breath/min, oxygen saturation [SpO2]

≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO2/FiO2]< 300 mmHg, and/or lung infiltrates > 50% within 24 to 48 hours), and 5% are critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure) [6]. A significant proportion (10–29 %) of hospitalized patients develop severe respiratory failure (SRF) and acute respiratory distress syndrome (ARDS) requiring admission to the intensive care unit (ICU) [1,2]. Venous thromboembolism (VTE) is now recognized as one of the predominant cardiovascular hazards in patients with COVID-19 [6-18]. Many patients with COVID-19 have markedly abnormal coagulation parameters, particularly D-dimer elevation which correlates with mortality [7].

In this review the epidemiology, pathophysiology, diagnosis and treatment of COVID-19 pulmonary thrombosis and thromboembolism are discussed.

Epidemiology

Accurate assessment of the true incidence of VTE in hospitalized patients with COVID -19 remain elusive, with estimates ranging from 4,8% to 85%. [16]

The significant variability in the reported incidence is likely the consequence of multiple factors: assessment setting (ICU vs non-ICU), type of event counted (symptomatic vs asymptomatic), testing strategies (eg clinical suspicion vs systematic screening), and degree of thromboprophylaxis. [17]

Several studies have demonstrated a high prevalence of VTE in patients with COVID-19 admitted to ICU, particularly lower leg deep vein thromboses (DVTs) in 25 % of 81 patients and pulmonary embolisms (PEs) in 20.6 % of 107 patients. [10-15] The frequency of symptomatic VTE in patients in ICU with COVID-19 has been reported to be 27 %. [10].

In a meta-analysis comprising 36 studies and more than 11000 patients the pooled incidence of VTE in patients with COVID-19 was 17% (12% for DVT and 7,1% for PE). [14]

In a recent Spanish, retrospective, case-control, multicenter study, PE incidence in COVID-19 patients at emergency department presentation was approximately ninefold (310 pe 100000 person-year) than that observed in the non COVID-19 population (35 per 100000 person-year) [18]

A Study using a French National database compared 89530 patients admitted to the hospital with COVID-19 in France over a 2-month period with 45819 patients admitted with influenza over a similar 2-month period during the prior year. [19]

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. [19]

Poissy et al. 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. [15]

Systematic screening for VTE has been shown to increase detection rates in patients without COVID-19. Voicu et al. [20] reported that 36% of mechanically ventilated patients with COVID-19 were diagnosed with DVT within 3 days after intubation when screened with compression ultrasonography. Mirsadraee et al. 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 was suspected clinically in only 7%. [21]

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. [22]

In more than 3000 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. [23] It is unclear whether thrombosis is a direct cause of worse outcome or merely a marker of more severe disease. [17]

Pathophysiology

Considering that VTE rates in patients hospitalized with COVID-19 are significantly higher than in historical control participants, probably other thrombotic mechanisms, beyond the classic VTE risk factors, contribute. [24]

The high rate of thrombosis in COVID-19 is driven by at least two interrelated processes: a hypercoagulable state responsible for large-vessel thrombosis and thromboembolism and direct vascular and endothelial injury responsible for in situ microvascular thrombosis. [25]

Early in the pandemic it became evident that patients with COVID-19 showed a high release of inflammatory mediators, increased levels of factor VIII, von Willbrand factor, fibrinogen and local fibrinolysis with increased D-dimer. [7] A study of 2,377 hospitalized patients with COVID-19 showed that 76% of them had elevated D-dimer at presentation. [26]

Although a multitude of inflammatory processes can increase D-dimer levels, to some extent its elevation is a sign of excessive activation of coagulation and hyperfibrinolysis. Thus D-dimer levels are often used to detect the presence of an active thrombus, despite having a high sensitivity but a low specificity. [11]

It has been reported that a D-dimer cut-off value of 3000 ng/ml has a sensitivity, specificity, and negative predictive value for PE of 76,9%, 94,9%, and 92,5%, respectively. [11]

Other authors 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. [27]

Elevated D-dimer levels also are associated independently with more severe disease and increased mortality. [28,29]

COVID-19 coagulopathy is characterized by increased levels of D-dimer, fibrinogen, thrombin, Factor VIII, Factor V, von Willebrand factor, and neutrophil extracellular traps. [17]

Additionally, platelets from patients with COVID-19 are activated more efficiently than are platelets from both healthy controls and patients with non-COVID-19 ARDS. [17]

In patients with COVID-19, are commonly observed elevated markers of systemic inflammation, particularly C-reactive protein and IL-6. [30]

Immune and coagulation systems cross talk to provide effective host defense. [31]

Immune cells and inflammatory cytokines promote the development of immunothrombi consisting of fibrin, monocytes, neutrophils, and platelets, which create a barrier against further pathogen invasion. [32] However excess inflammation and thrombosis can lead to exuberant thrombosis and organ dysfunction. [33] Neutrophil extracellular traps are expelled from neutrophils to capture and immobilize pathogens and also can activate immunothrombosis. [34]

Autopsy studies have shown diffuse endothelial inflammation in many organs, including lung, heart, liver, and kidney, with evidence of direct viral infection of endothelial cells by the SARS-COV2 virus. [35] Endothelial injury, particularly in the context of a hypercoagulable condition, likely is responsible for the high rates of microthrombosis observed in the pulmonary vasculature. [35]

It has been 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. [36]

High rates of microthrombosis have also been reported in the heart and skin. [17]

Imaging studies have shown that thrombotic lesions in COVID-19 are smaller and more peripherally located compared with those in non-COVID-19 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 from peripheral DVT. [14,21]

Early in the pandemic it has been reported 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. [37]

Many non-intubated patients with COVID-19 demonstrate dramatic hypoxemia but lack proportional signs of respiratory distress, a condition coined "happy hypoxemia". [38]

It has been hypothesized that the presence of pulmonary microthrombi and macrothrombi, may explain the mismatch between gas exchange and lung compliance in severe COVID -.19. [39]

Surprisingly, patients with COVID-19 requiring mechanical ventilation are characterized by low, not high pulmonary vascular resistance (PVR). [40] 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. [41]

Probably the hemodynamic effect of pulmonary thrombosis is mitigated by a primary pulmonary vasodilatory process in some patients with COVID-19, as demonstrated with dual-energy CT imaging in COVID-19 pneumonia. [42]

In addition together with high rates of pulmonary microthrombosis, high rates of angiogenesis have been described in COVID-19. [36]

Pulmonary macrothrombi and microthrombi increase PVR, whereas pulmonary vasodilation decreases PVR, so when both processes occur simultaneously, each can counterbalance the hemodynamic effect of the other. [43]

The coexistence of vasodilatory and obliterative processes may offset each other hemodynamically, but their coexistence may amplify hypoxemia in COVID-19. [17]

Diagnosis

The diagnosis of pulmonary embolism begins with clinical suspicion. Clinical suspicion of PE in patients with COVID-19 pneumonia is diminished because the signs and symptoms of COVID-19 pneumonia mimic those of PE. Although clinical probability scores, such as Wells score, are helpful in raising clinical suspicion of PE, they have not been validated in patients with COVID-19 and probably underestimate the probability of PE in COVID-19. [44]

D-dimer together with clinical probability assessment, has great usefulness in ruling out PE in patients with low or intermediate probability of PE. D-dimer levels in COVID-19 correlate with rates of thrombosis, but it is not clear whether a particular D-dimer value "rules in" or "rules out" PE. [21]

It has been reported that the D-dimer cut-off value of 3000 ng/mL has a sensitivity, specificity, and negative predictive value for PE of 76.9 %, 94.9 %, and 92.5 %, respectively. [11]

A study in which screening computed tomography pulmonary angiography (CTPA) was performed in patients with COVID-19 on admission to the ICU, D-dimer levels didn't discriminate between patients with and without PE. [21]

CTPA is the first-choice and the gold standard method for PE diagnosis. [45]

The reported rate of positive CTPA in patients with COVID-19 and suspected PE varies widely with estimates ranging from 23% to 50%. [46-49] This significant variability of the rate of positive CTPA in patients with COVID-19 is likely the consequence of multiple factors: -criteria used to request CTPA, assessment setting, patient's clinical status (critically ill patients who are not stable enough for transfer to the radiology department), degree of thromboprophylaxis. [48, 49].

Prophylaxis and Treatment

Several studies have demonstrated a high prevalence of VTE and PE in patients hospitalized with COVID-19, particularly in those admitted to the ICU. [10-15, 20-23]

PE is one of the most common preventable causes of hospital death, and thromboprophylaxis is crucial in the care of hospitalized patients. [50]

A retrospective study 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. [51]

Critically ill patients with COVID-19 are at high risk for thrombosis and PE despite receiving standard-dose thromboprophylaxis. [15,21]

Given the antithrombotic, anti-inflammatory and possibly antiviral properties of heparins, it has been hypothesized that anticoagulation with heparin administered at doses higher than conventionally used for venous thromboprophylaxis may improve outcomes. [23, 52-55]

We studied, retrospectively, 92 patients with COVID-19 and severe respiratory failure, admitted to an Italian respiratory intensive care unit for non-invasive mechanical ventilation, PE was diagnosed by CTPA in 11 (12 %) patients despite treatment with intermediate- to full-dose enoxaparin. [56]

However, the frequency of PE in our patient population was lower than that previously reported in similar patients. [15]

Although our study probably underestimated the real frequency of PE, because only a small portion, (24 %) of patients underwent CTPA, it is possible to assume that the reduced PE incidence may have been due to the use of a higher-than-prophylactic dose of enoxaparin. [49]

Our patients underwent CTPA only if there was a clinical suspicion of PE and/or in the presence of elevated D-dimer levels (> 3000 ng/ml), and if a patient's clinical status allowed for a safe transfer to the radiology department. Considering these assumptions, 50 % of our patients who underwent CTPA had confirmed PE. [49]

Our report had several limitations. First, this was a retrospective, single-center study with a small sample size. Second, our study probably underestimated the actual frequency of PE because only a small portion

(24 %) of patients underwent CTPA, which is the gold standard for PE diagnosis. [45]

In more than 4000 patients with COVID-19 at a New York Hospital with an aggressive anticoagulation protocol it was noted a trend toward a mortality reduction with therapeutic anticoagulation compared with prophylactic anticoagulation, but the difference wasn't statistically significant. [56]

In an open label, adaptive, multiplatform, controlled trial, patients hospitalized with COVID-19 and who were not critically ill (defined as absence of oxygen delivery by high-flow nasal cannula, non-invasive or invasive mechanical ventilation, or the use of vasopressors or inotropes) were randomly assigned to receive pragmatically defined regimens of either therapeutic - dose anticoagulation with heparin or usual-care pharmacologic thromboprophylaxis. [57] The trial was stopped when prespecified criteria for the superiority of therapeutic-dose anticoagulation were met. In non-critically ill patients hospitalized with COVID-19, therapeutic-dose anticoagulants with heparin (most commonly, low-molecular-weight heparin) increased the probability of survival until hospital discharge with a reduced need for ICU-level organ support at 21 days as compared with usual-care thromboprophylaxis. [57]

In another open label, adaptive, multiplatform, randomized clinical trial, of the same group, critically ill patients with severe COVID-19 were randomly assigned to a pragmatically defined regimen of either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care. [58] The trial was stopped when the prespecified criterion for futility was met for therapeutic-dose anticoagulation. In this multiplatform, randomized trial involving more than 1000 critically ill patients with confirmed COVID-19, therapeutic-dose anticoagulation did not increase the probability of survival to hospital discharge or the number of days free of cardiovascular o respiratory organ support and had a 95% probability of being inferior to usual-care pharmacologic thromboprophylaxis. [58] It is possible that therapeutic-dose heparin cannot influence the cascade of inflammation, thrombosis, and organ injury in patients with advanced disease. [57] In Contrast in non-critically ill patients with COVID-19 an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival until hospital discharge with reduced use of ICU-level organ support as compared with usual-care thromboprophylaxis. [57]

The mainstay of the treatment of PE in patients with and without COVID-19, to prevent further thrombosis and thromboembolism is Anticoagulation. [45] Initial treatment options include heparin, low-molecular-weight heparin, fondaparinux and in low-risk patients, direct oral anticoagulants. [45] In hospitalized critically ill patients with COVID-19 low-molecular-weight heparin or unfractionated heparin are preferred. [59]

Guidelines about coagulopathy and prevention and management of VTE in patients with COVID-19 have been released by multiple organizations. [59] All guidelines agree that hospitalized patients with COVID-19 should receive prophylactic dose anticoagulation for VTE. [59] Some guidelines report that intermediate dose anticoagulation can be considered for critically ill patients. [59] Several randomized trials have been developed to evaluate the risks and benefits of anticoagulation in patients with COVID-19 (visit ClinicalTrials.gov for the current list of trials). [58]

Risk stratification of patients with PE is the central tool used to identify patients at increased risk of early death, who may benefit from reperfusion therapy, mechanical circulatory support, or both. [45]

As described in European Society of Cardiology Guidelines, high risk PE is characterized by cardiac arrest, systolic BP < 90 mmHg, 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. [45]

If possible, patients with high-risk PE should undergo reperfusion therapy, mechanical circulatory support, or both. [45] Patients with intermediate-risk PE should be monitored closely for signs of clinical deterioration, and selected patients should undergo reperfusion therapy. [45]

Given the potential pathophysiologic role of pulmonary microthrombosis, thrombolysis has been used in small case series of COVID-19 ARDS. [17]

Currently, randomized trials evaluating the use of tissue plasminogen activator and Tenecteplase (ClinicalTrail.gov Identifier: NCT04357730; and Identifier: NCT045055920 respectively) in patients with COVID-19 ARDS are underway. [17]

Conclusions

COVID-19 has been associated with inflammation and a prothrombotic state.

Several studies have demonstrated an high prevalence of VTE, and PE, particularly in patients admitted to the ICU, even in those receiving prophylactic anticoagulation.

COVID-19 is characterized by a hypercoagulable state responsible for large-vessel thrombosis and thromboembolism and direct vascular and endothelial injury responsible for in situ microvascular thrombosis. Diagnosing PE in patients with COVID-19 pneumonia may be challenging, because the two pathologies share many signs and symptoms.

Guidelines released by multiple organizations, agree that hospitalized patients with COVID-19 should receive prophylactic dose anticoagulation for VTE.

In non-critically ill patients hospitalized with COVID-19, therapeutic-dose anticoagulants with heparin increased the probability of survival until hospital discharge with a reduced need for ICU-level organ support at 21 days as compared with usual-care thromboprophylaxis. Several randomized trials have been developed to evaluate the risks and benefits of anticoagulation in patients with COVID-19.

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