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HOT TOPIC

The Role of Anticoagulation in COVID-19-Induced Hypercoagulability

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Abstract

Purpose of Review We aim to provide a comprehensive analysis of hypercoagulability in individuals affected by COVID-19. Our goal is to describe the hypercoagulable state related to the infection and provide guidance regarding the possible benefits of anti-coagulation with the support of evidence from current literature.

Recent Findings The incidence of thrombotic disease in individuals affected by COVID-19 is reported as high as 31%. A significant mortality benefit has been observed with the use of therapeutic anticoagulation in high-risk individuals. Literature supports the use of scoring systems, such as the sepsis-induced coagulopathy score, to risk-stratify individuals who might benefit from anticoagulation.

Summary COVID-19-induced hypercoagulability has been demonstrated to play a significant role in overall COVID-19 outcomes. Current literature shows promising evidence with the use of therapeutic anticoagulation in high-risk individuals. Further studies are needed to better analyze the risks and benefits of anticoagulation in this specific patient population.

Keywords COVID-19 · SARS-CoV-2 · Hypercoagulability · Anticoagulation

Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19's impact on multiple organ systems, most notably the respiratory tract, has led to an increasing number of morbidity and mortality worldwide. As our knowledge regarding the novel virus continues to evolve, we are noticing the significance of the virus outside of the respiratory tract. Recent articles have described hypercoagulability in COVID-19-affected patients [1, 2]. While mortality in COVID-19 can be largely attributed to hypoxemia secondary to acute respiratory distress syndrome (ARDS), there is growing suspicion that thromboembolic events could also be contributing to the overall picture, as described in the article published by Cui S et al. [3].

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Pathophysiology of Procoagulability in COVID-19

While the pathophysiology behind the hypercoagulable state in COVID-19 is still under investigation, several proposed mechanisms have been described. Disseminated intravascular coagulation (DIC), properties of the virus itself, antiphospholipid syndrome, activation of the complement cascade, and endothelial dysfunction induced by the infection have been described in the possible pathophysiology [4–7]. The New England Journal of Medicine recently published a case series in which three affected patients tested positive for anticardiolipin anti-IgA, anti-B2 glycoprotein IgA, and IgG, which hypothesizes antiphospholipid syndrome (APS) as a possible etiology [4]. The authors highlighted that viral infections are associated with the development of reactive antiphospholipid antibodies, which could predispose to hypercoagulability [5]. A recent article by Campbell et al. noted that severe COVID-19 infection is consistent with excessive complement activation, with evidence of patients having elevated LDH, D-dimer, bilirubin, decreased platelets, mild anemia, renal and cardiac injury, and diffuse thrombotic microangiopathy, hypothesizing the benefit of therapy with complement inhibitors as an addition to anticoagulation [7]. Unfortunately, a limited understanding of the hypercoagulable mechanism has limited our treatment techniques. This leads to the question if therapeutic anticoagulation is the right choice in regard to optimal management of COVID-19 patients.

The infectious mechanism of SARS-CoV-2 relies on binding to the ACE2 receptor. The spike (S) protein of SARS-CoV-2 binds to the TMPRSS2 receptor, which facilitates viral entry using the ACE-2 receptor [8]. This mechanism may be similar to SARS-CoV-1. In vitro studies of SARS-CoV-1 show increased gene expression of fibroblast growth factor (FGF), fibrinogen gamma chain (FGG), and serin protease proteases (SERPIN), leading to upregulation of coagulation cascade factors, including factor II, III, and X, ultimately leading to a procoagulable state [9]. See Fig. 1.

SARS-CoV-2 mortality has been linked to a dysregulated inflammatory reaction, likely from a cytokine storm or macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistocytosis. McGonagle et al. asserts that the tropism of SARS-CoV-2 towards angiotensin-converting enzyme 2 (ACE2), mostly present in type II pneumocytes, leads to an inflammatory cascade causing a generalized pulmonary hypercoagulable state [8]. The secondary lymphohistiocytosis triggers expression of tissue factor in the endothelial cells, macrophages, and neutrophils, inducing activation of the coagulation cascade [9]. Beyond the hypercoagulable state this generates, a study of bronchoalveolar lavage showed that both severe pneumonia and acute respiratory distress syndrome (ARDS) are associated with thrombin generation and fibrin deposition within the bronchoalveolar system. Given the MAS-like disease of COVID-19 pneumonia and the associated procoagulable state, guided therapy with anti-cytokine therapy and anticoagulation is an interesting possibility.

The immune factors leading to pulmonary intravascular coagulopathy include diffuse alveolar damage and inflammation, diffuse interstitial inflammation, extensive pulmonary macrophage activation, dysregulation of pulmonary innate immune responses, activation of innate immunity with older age, and mechanical ventilation forcing viral immunostimulatory molecules into microvasculature leading to increased propensity towards immuno-thrombosis [10].

Risk factors associated with poor outcomes in COVID-19 are well known (e.g., hypertension, obesity, diabetes mellitus, coronary heart disease, stroke, chronic obstructive pulmonary disease, and chronic kidney disease). Interestingly, Hong-Long Ji et al. described an association between patients with the aforementioned comorbidities and an elevated serum plasmin level. These authors hypothesized that plasmin may cleave furin sites in the spike "S" protein of SARS-CoV-2, enhancing its infectivity by promoting entry, duplication, and release of viral particles in respiratory cells [11]. This novel hypothesis led to the theoretical concept of measuring serum plasmin, plasminogen, and D-dimer levels to assess disease severity. Of note, elevated D-dimer levels observed in patients with COVID-19 could be secondary to elevated serum plasmin levels [12]. Therapies targeting plasmin such as antiplasmin compounds may become a promising treatment option for patients at risk of thrombotic complications.

Anticoagulation

Expert recommendations for the use of anticoagulants have already been published, reflecting the recognition of clotting dysregulation on this entity.

Klok et al. reported a cohort of 184 patients in the Netherlands, admitted to the ICU with proven COVID-10 pneumonia and assessed the thrombotic events, with thrombotic incidence of 31%. All patients received at least standard doses of thromboprophylaxis. VTE was reported in 27% of the patients, arterial thrombotic events in 3.7%, and PE was the most frequent thrombotic complication in 81%. Age and coagulopathy, defined as spontaneous prolongation of the prothrombin time > 3 s or activated partial thromboplastin time > 5 s, were independent predictors of thrombotic complications. The authors recommend thrombosis prophylaxis in all COVID-19 patients admitted to the ICU and suggest an increasing to high-prophylactic doses, even in the absence of randomized evidence [13].

Lin et al. asserts that the rise of inflammatory factors and D-dimer on days 7–14 of the disease could support anticoagulation with low molecular weight heparin

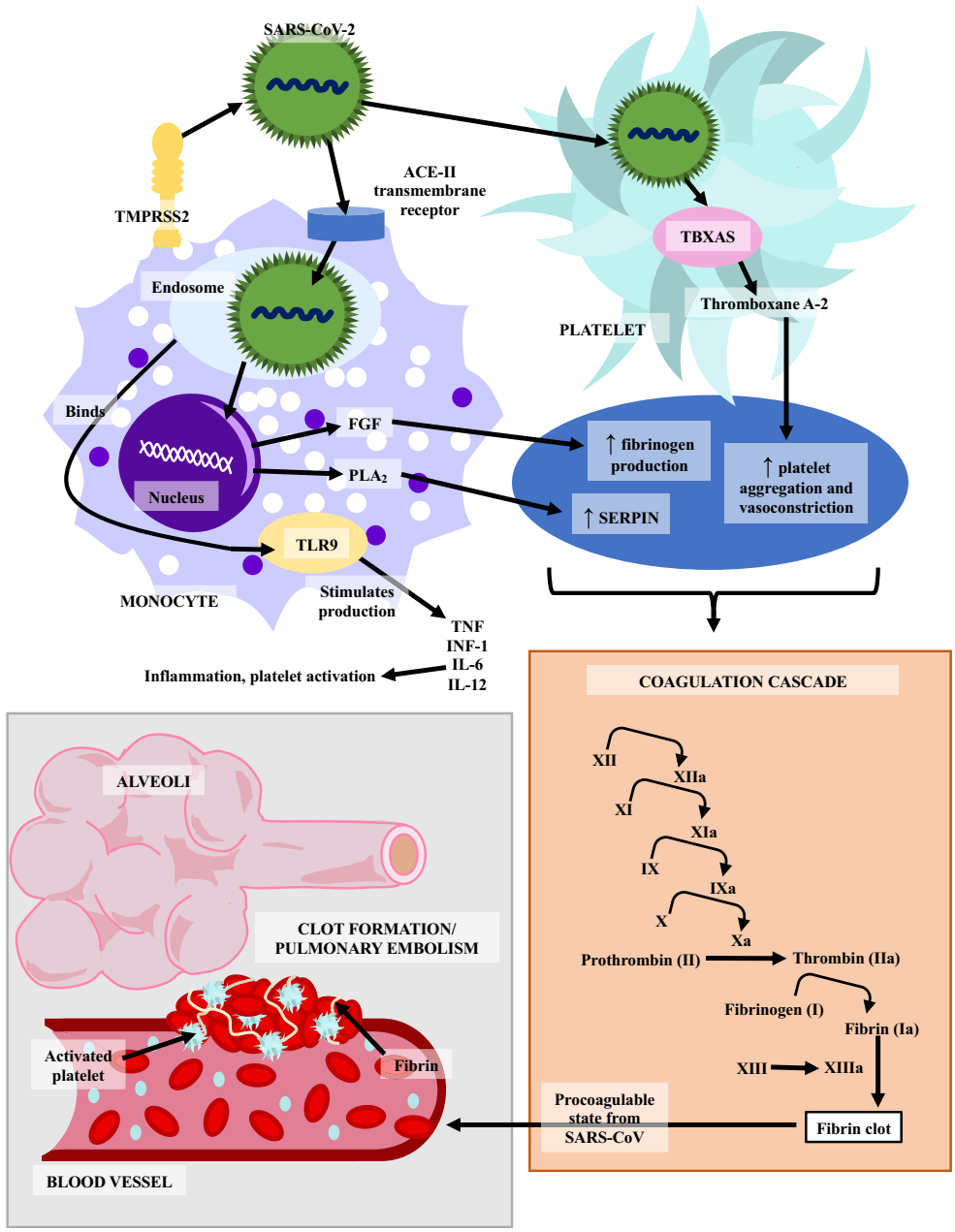

Figure 1 SARS-COV-induced hypercoagulable state model. This model was hypothesized based on SAR_COV-1 known intracellular interactions to stimulate clot formation. It also integrates the known infectious pathways of SARS-COV-2 to enter the cell and induce inflammation. This is a hypothetical model based on the behavior of both microorganisms. SARS-COV starts by binding the TMPRSS2 utilizing the Spike protein, enabling the virus to enter the cell, in this case the monocyte, via transmembrane ACE-2 receptor. Many other cells can be infected, particularly if they have the ACE-2 receptor (e.g., pneumocyte type 2, myocardiocytes) (top left). Once inside, it induces the production of FGF and PLA_2, leading to fibrinogen production and SERPIN expression. Simultaneously, SARS-COV binds the TLR9, which stimulates the production of TNF, INF-1, IL-1, IL-6, and IL-12. SARS-COV also enters the platelet and activates the TBXAS, which catalyzes the conversion of prostaglandin H_2 (not included in the figure) to Thromboxane A-2, leading to platelet aggregation and vasoconstriction (top right). These cytokines, thromboxanes, and inflammatory mediators lead to activation of the coagulation cascade (bottom right). Coagulation cascade steps are shown below (intrinsic and common pathway), leading to fibrin production. Ultimately, fibrin will accumulate and bind platelets, leading to hypercoagulability and clot formation. Clots may be present in the lungs, causing hypoxemia and contributing to shunt development and ventilation/perfusion mismatch, resulting in ARDS (bottom left). Abbreviations: ACE-2 angiotensin converting enzyme-2, ARDS acute respiratory distress syndrome, FGF fibroblast growth factor, IL interleukin, INF-1 interferon type 1, PLA_2 phospholipase A_2, SARS-COV severe acute respiratory distress-coronavirus, SERPIN serine protease, TBXAS thromboxane a synthase, TLR9 toll-like receptor 9, TMPRSS2 transmembrane serine protease 2, TNF tumor necrosis factor

(LMWH) as a therapeutic strategy [14]. Given the risk of sepsis-induced disseminated intravascular coagulation (DIC), the authors recommend anticoagulation for COVID-19 patients with D-Dimer levels above four times the upper limit of normal (ULN), except for those with contraindications to anticoagulation. They recommended a subcutaneous dose of 100 IU/kg of LMWH twice a day, for at least 3–5 days [14].

Similarly, the European Society of Cardiology recently proposed an anticoagulation algorithm [15]. For high thrombotic risk patients, defined as those with dyspnea, respiratory rate > 24, oxygen saturation < 90%, elevated C reactive protein, rising D-dimer levels, and elevated fibrinogen levels, anticoagulation strategies should be considered [15]. In the ICU setting, a parenteral heparin drip protocol should be started with close follow-up and an active prothrombolastin time goal of 60–85 s. For non-ICU patients, they recommend the use of subcutaneous enoxaparin 1 mg/kg twice a day or consideration of the same heparin protocol used for ICU patients. In addition, they recommend the use of point of care ultrasound for deep venous thrombosis. If deemed to be positive, continuation of therapeutic anticoagulation is recommended. If negative, de-escalation to subcutaneous enoxaparin 40 mg B.I.D is be recommended [15].

In a joint webinar between the Chinese Cardiology Association and the American College of Cardiology, investigators reported diffuse microvascular thrombi on autopsies reviews of COVID-19 patients. Similar findings of platelet-fibrin thrombi were reported in an Italian case series, where findings of diffuse multiorgan microvascular thrombosis without viral infiltrates were seen in autopsies during the SARS epidemic [16]. Recently, Bikdeli et al. described how a thrombotic state may be a precedent factor or an incidental complication of patients with COVID-19 [2]. The authors state that careful considerations including probability of diagnosis, risk stratification, bleeding risk estimation, and medication of choice should be considered for the preventative and therapeutic use of antithrombotic agents in this high-risk population to mitigate the thrombotic and hemorrhagic events. They also advocate for higher quality data that is prospective, multicentered, and multinational.

The International Society of Thrombosis and Hemostasis (ISTH) proposed a new method in identifying an earlier phase of sepsis-associated DIC, called "sepsis-induced coagulopathy" (SIC) [17–20]. This scoring system was utilized by Tang et al. to risk-stratify patients who should receive anticoagulation (see Table 1) [20]. In this study of 449 patients with severe COVID-19, 99 patients received heparin, mainly low molecular weight heparin (LMWH) for 7 days or more. The 28-day mortality between heparinized (hep+) and non-heparinized (hep−) patients was compared in different risk populations who were stratified by SIC score or D-dimer levels. Overall, no difference was observed in 28-day mortality between hep+ and hep− patients; however, the mortality of hep+ patients was lower than hep− patients with SIC score ≥ 4 or D-dimer > 6-fold of upper limit of normal (ULN) (see Table 1). For SIC score description, the researchers concluded that anticoagulation appears to be associated with better prognosis in severe COVID-19 cases meeting SIC criteria or with markedly elevated D-dimer [20]. Yin et al. used this previous cohort data to evaluate whether patients with elevated D-dimer could benefit from therapeutic anticoagulation. They found that the 28-day mortality of heparin users was lower than non-users in COVID-19 patients with D-dimer > 3.0 μg/mL [21]. In this study, the platelet count of the COVID-19 group was significantly higher than that of the non-COVID group, perhaps due to the reactively increased thrombopoietin following pulmonary inflammation. This might be another factor that promotes hypercoagulability. The authors concluded that although further prospective studies are needed, patients with severe pneumonia induced by SARS-CoV-2 benefited from heparin if D-dimer values were higher than 3-fold of the ULN.

Table 1 International Society of Thrombosis and Hemostasis (ISTH) sepsis-induced coagulopathy (SIC) scoring system [18]

Item	Score	Range
Platelet count ($\times 10^9$/L)	1	100–150
	2	< 100
INR	1	1.2–1.4
	2	> 1.4
SOFA score	1	1
	2	≥ 2
Total score for SIC	≥ 4	

Abbreviations: *INR* international normalized ratio, *SOFA* sequential organ failure assessment

One of the well-described reasons of mortality in COVID-19-affected patients has been the overwhelming inflammatory response that leads to damage in the lungs. There may be benefits other than anticoagulation by which heparin products are beneficial such as anti-inflammatory. Based on the immuno-thrombosis model, which highlights the bidirectional relationship between the immune system and thrombin generation, blocking thrombin formation may dampen the inflammatory response, which is being hypothesized to damage the lung tissue in ARDS. Several publications describe this immuno-modulatory mechanism beneficial by way of binding to inflammatory cytokines, inhibiting neutrophil chemotaxis, leukocyte migration, neutralizing the positively charged peptide complement factor C5a, and sequestering acute phase proteins [22–26]. A meta-analysis study noted that adjunctive treatment with LMWH within the initial 7-day onset of ARDS reduces

the risk of 7-day mortality by 48% and the risk of 28-day mortality by 37%, in addition to significantly improving PaO2/FiO2 ratio [27].

Conclusion

As our understanding of patients with COVID-19 grows, our approach to optimal medical management continues to rapidly evolve. The precise mechanism behind the pro-coagulability of COVID-19 is poorly understood, and further research is needed. As such, anticoagulation in this vulnerable patient population should be considered carefully and addressed appropriately. Our recommendation supports the use of anticoagulation in COVID-19 patients who meet criteria by way of risk stratification using the SIC scoring system and/or D-dimer levels. The data and studies cited in this article demonstrate encouraging results with regard to mortality rates when anticoagulation is used according to proper risk stratification.

Compliance with Ethical Standards

Conflict of Interest Drs. Rico-Mesa, Rosas, Ahmadian-Tehrani, White, and Chilton have nothing to disclose. Dr. Anderson has received honoraria from Novartis, Pfizer, and Relypsa. He is a consultant for Edwards LifeSciences and has received research support from Abbott.

Human and Animal Rights and Informed Consent This manuscript does not contain any studies with human or animal subjects.

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- • Of importance
- •• Of major importance

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