Mini-review

Hemostasis Pathophysiology Associated With Increased Risk of Thrombosis in Acute COVID-19 Infection

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The aim of this mini review is to understand how COVID-19 contributes to thrombotic events in patients. The recent and ongoing coronavirus 19 pandemic (COVID-19) has presented tremendous challenges to healthcare, with approximately 219 million cases worldwide and 4.5 million deaths associated with infection to date. Patients experience a significant immunological response to the virus, and this is often followed by a state of acute respiratory distress syndrome (ARDS). It has become increasingly evident that hemostatic dysregulation and thrombotic events are prevalent complications of acute COVID-19 infection and may persist chronically in the manifestation of "long-COVID." Current anticoagulant therapies are insufficient in mitigating the risk of thrombosis in COVID-19 patients and further understanding regarding the pathophysiological mechanisms of hemostatic dysregulation following COVID-19 infection is critical to improve clinical management. This manuscript endeavors to summarize the current understanding based on the recent clinical literature and to identify potential future research directions to best inform clinicians on how to optimize patient outcomes.

Key words: COVID-19, hemostasis, thrombosis

Introduction

One of the largest public health crises in the modern era is associated with the pathophysiological mechanisms that follow infection with the globally disseminated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly referred to as COVID-19. It is well understood that COVID-19 can induce ARDS in patients following a marked immunological response to the virus. A markedly increased inflammatory response increases the probability of thrombosis as there is a direct link that can be established when studying the molecular mechanisms of hemostasis and subsequent thrombosis. This can be reflected in the observation of increased predisposing thrombotic markers such as D-Dimer and other procoagulant changes in patients suffering from severe COVID-19 infection, along with reports of increased arterial and venous thrombotic events. This minireview endeavors to investigate and summarize the current clinical literature describing the possible mechanisms and to comment on further impacts on clinical outcomes that occur because of thrombosis in COVID-19 infections. To adequately investigate the thrombotic mechanisms that occur through COVID-19 infection, a baseline understanding of hemostasis must be present.

Accepted: March 25, 2022

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Background

Hemostasis

Hemostasisis the process of arresting the loss of blood and maintaining it as a fluid in its compartments. It is highly regulated and physiologically involved, as hemostatic dysregulation can often lead to thrombotic events when disproportionally upregulated, or bleeding disorders when disproportionally downregulated. An understanding of the processes that occur in the body to induce hemostasis is highly clinically relevant. Clinical intervenetions (such as prophylactic heparin) can be conducive to hemostatic dysregulation or may not be feasible due to an underlying presence of pre-existing hemostatic dysfunction.

Hemostasis occurs in three primary stages within the body, the first stage being agonistic blood vessel activity combined with platelet adhesion to form a mechanical primary plug. The second stage of hemostasis is secondary activation of a cascade of coagulation proteins commonly referred to as coagulation factor interactions that contribute to clot formation and significant strengthening of the formed primary plug. The final stage is activation of the fibrinolytic system to regulate hemostatic activity by breaking down fibrin to dissolve the clot after healing has taken place, as demonstrated in Figure 1.

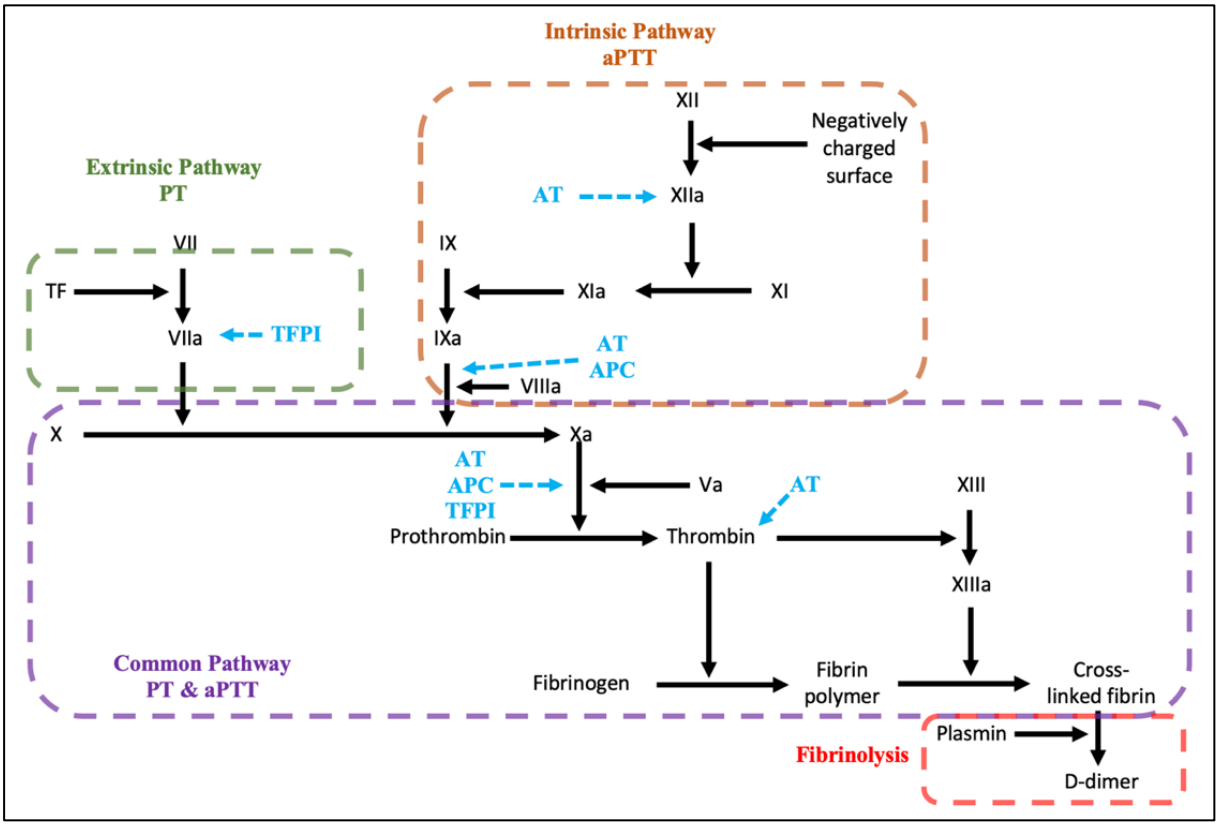

Figure 1: Coagulation Cascade Depiction

Blood coagulation cascade involving an amplification system in which activation of various coagulation factors occurs in sequence leading to a cascade or domino effect. Each reaction is promoted by the preceding reaction. If there is a deficiency of any one of the factors, the following may result: The rate of blood coagulation is slowed, initiation of the next reaction in the sequence is delayed, the time taken to form a clot is prolonged and bleeding from an injured blood vessel is not effectively arrested. Hyperactivation of these procoagulant factors would conversely result in a hypercoagulable state and present risk of uncontrolled clot formation and eventual thrombosis, as is being demonstrated in COVID.

Figure based on (adapted) information in Rodak's hematology textbook: Keohane EM, Otto CN, Walenga JM. Rodak's Hematology: Clinical Principles and Applications. 6th ed. St. Louis, Missouri: Elsevier; 2020.

Discussion

Hemostasis in COVID-19

A high prevalence of increased thrombotic events and prothrombotic pathophysiology has been observed through the infection of COVID-19, due to dysregulation of the coagulation cascade caused by an imbalance between procoagulation and anticoagulation.[1, 2] This imbalance in the coagulation system is evidenced by the finding of both microvascular and macrovascular thrombosis and embolism in COVID-19 patients in multiple organ systems.[3] There are many hypotheses regarding the reason for the dysfunctional coagulation seen in COVID-19, including a cytokine storm, which consequently leads to a hyperinflammatory state.[1] The study by Pretorius, Vlok showed hypercoagulation induced by inflammation along with hypofibrinolysis in COVID-19 affected patients.[2] A particularly high proportion of thromboembolic complications have been reported to arise in hemodialysis circuits and in young, otherwise healthy patients with no underlying predispositions to hypercoagulation despite the administration of prophylactic anticoagulant medications. This would suggest that COVID-19 induces mechanisms which increase the risk of thrombosis in not only patients with underlying medical conditions, but also young and healthy patients. Furthermore, thromboembolism has been reported in acute care and in weeks following illness, suggesting that the mechanisms of hypercoagulation in COVID-19 infection may not only lead to a transient increase of risk for thrombosis, but may last several weeks or longer after hospitalization.[4] This would warrant further study into the pathophysiology of COVID-19 and long COVID.

It has been previously mentioned that a direct link can be observed in the physiological mechanisms between inflammation and hemostasis; however, there is still a significant gap in the literature and a further understanding of this potentially causal link that would suggest anti-inflammatory prophylaxis and therapeutic treatment could mitigate the risk of thrombosis in COVID-19. If there is no causal link, the use of targeted anti-coagulation medication would likely be more favorable in reducing the risk of thrombosis, as anti-inflammatory medication would not have clinical utility. This could also be described as being a significant gap in the current literature, as an understanding of the exact mechanisms of action of COVID-19 infection that give rise to a pathophysiological increased level of hypercoagulation which has been demonstrated in healthy and ill patients would provide a basis for the development of preventative therapies that could appropriately target the cause of thrombosis post infection and potentially reduce rates of mortality and morbidity as a result of COVID-19 infection.

Several studies have found increases in factor VIII and the presence of ultra-large von Willebrand factor (UL-VWF) multimers in COVID-19 patients.[5-8] Under normal circumstances, UL-VWF multimers are cleaved into smaller, functional units, which allows platelet adhesion in the required conditions, such as an active bleed. The increased factor VIII and UL-VWF may produce or augment the hypercoagulable state seen in COVID-19. Currently, the implication of conventional preventative therapies is largely unreliable in reducing thrombotic events due to COVID-19 infection, and treatments generally target the effects on organ systems that occur because of thrombosis and / or embolism. This may be due to the unique pathophysiological processes of COVID-19. The most reported cases of thrombotic events in COVID-19 are deep vein thrombosis and subsequent pulmonary embolism.[9]

Thrombotic Events in COVID-19

Pulmonary embolism has been shown to be extremely prevalent in patients experiencing COVID-19 infection, with about a 20-30% incidence in critically ill patients.[10] Pulmonary embolism (PE) is a pathology where a thrombus has formed generally in a deep vein of the leg, known as a deep vein thrombosis (DVT), dislodged into the vascular circulation

(embolized) and occluded a pulmonary artery. The occlusion of pulmonary vessels causes pulmonary infarction, meaning the death of tissue (tissue necrosis) as a result of a lack of blood supply. The dissemination of micro-thrombi formation throughout the pulmonary vasculature has been hypothesized to contribute to the extremely high incidence of thrombosis overall, PE and the unique presentation and physiology associated with ARDS following COVID-19 infection. Ackermann *et al.,* compared autopsies of lung specimens from 7 patients who died because of COVID-19 with 7 patients who died because of H1N1 influenza ARDS complications.[11] Alveolar capillary microthrombi were found to be approximately 9 times as prevalent in COVID-19 patients when compared to influenza patients, supporting the hypothesis that the COVID-19 virus contributes to thrombotic mechanisms through its unique pathophysiology. Marked increase in endothelial injury in addition to intracellular virus could also be observed in areas of increased microthrombus formation, also supporting the hypothesis that there is a causal link between inflammatory response and thrombus formation. It has also emerged recently that a condition of reduced platelet count in the peripheral blood can be induced by vaccine administration, called vaccine-induced immune thrombotic thrombocytopenia (VITT) in rare cases.

Anticoagulation in COVID-19

Currently, there is insufficient literature to identify and describe the role, significance, and appropriate use of anticoagulant therapies on a large clinical scale in the mitigation of hypercoagulation in COVID-19 afflicted patients. The enormous prevalence of this virus and the high rate of mortality resulting from thrombosis following infection should sufficiently motivate clinical studies in this area to ascertain the true mechanisms of action and therefore develop appropriate therapies. There is currently no targeted strategy for treating the hypercoagulative state observed in COVID-19 infection and the current guidelines suggest thromboembolism prophylaxis for all patients in the absence of significant contraindications. Recent clinical trials have shown conventional thromboprophylaxis was ineffective in reducing inappropriate coagulation due to COVID-19.[12] Low molecular weight heparin has also been demonstrated to be ineffective in recent studies.[13] This would suggest that the hypercoagulation demonstrated in COVID-19 cases are most probably linked to inflammatory pathophysiology.

Conclusion

The emergence and persistence of the COVID-19 pandemic has propelled widespread investigations into the complex pathophysiological mechanisms interacting between multiple organ systems to lead to an increase in patient outcomes; particularly in the management of ARDS frequently developed in hospitalized patients infected with the virus. The aim of this manuscript was to review the current state of literature to ascertain the current level of understanding of these mechanisms, specifically regarding the induction of hypercoagulation in patients infected with COVID-19, to infer possible gaps in the current literature and to form an educated proposal for future directions.

Recent studies demonstrate that a direct link can be observed in the physiological mechanisms between inflammation and hemostasis, but it has not yet been determined whether this is a causal relationship, or if the illness simply induces simultaneous pathophysiological pathways in parallel.[14] This is a significant gap in the literature and a further understanding of this potentially causal link would suggest that anti-inflammatory prophylaxis and therapeutic treatment could mitigate the risk of thrombosis in viral infection from COVID-19. If there is no causal link, the use of targeted anticoagulation medication would likely be more favorable in reducing the risk of thrombosis, as anti-inflammatory medication would not have clinical utility. The presence or

lack thereof a link between these mechanisms should be addressed in future studies.

Currently, there is insufficient literature to identify and describe the role, significance, and appropriate use of anticoagulant therapies on a large clinical scale in the mitigation of hypercoagulation in COVID-19 afflicted patients. The enormous prevalence of this virus and the high rate of mortality resulting from thrombosis following infection should sufficiently motivate clinical studies in this area to ascertain the true mechanisms of action and therefore develop appropriate therapies.

Overall, there is a rising comprehension of the mechanisms of COVID-19 and how these contribute to thrombotic events in patients, however, the current literature is insufficient in establishing standardization of care and appropriately informing clinicians on how to manage cases of COVID19 infection to optimize patient outcomes.

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