Multi-factorial Mechanism Behind COVID-19 Related Thrombosis

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ABSTRACT

Background: Thrombosis plays a crucial role in the morbidity and mortality of coronavirus disease-19 (COVID-19). About one-third of COVID-19 patients experience a thrombotic event, most commonly pulmonary embolism. Based on published data, the mechanism of thrombosis in COVID-19 patients seems to be multi-factorial. Methods: In this article, we reviewed the published data concerning with thrombosis in COVID-19 and summarized the predisposing factors and the mechanisms behind COVID-19 related thrombosis. Results: Inflammatory response to SARS-CoV-2 and the consequent hyperviscosity thought to cause endothelial damage and initiate coagulation. Furthermore, inflammation promotes platelet activation and exerts a pathogenic effect on endothelial cells. The presence of anticardiolipin and anti-β2-glycoprotein antibodies in some patients with COVID-19 suggests that SARS-CoV-2, like many other viral infections, induces the formation of antiphospholipid antibodies, which provoke hypercoagulability. Thrombophilic mutations, mainly factor V Leiden and prothrombin G20201A mutations, can be a contributing factor in the development of thrombosis in COVID-19 patients, and they are associated with increased disease severity and pulmonary embolism. However, the research concerning with the association of thrombophilic mutations with COVID-19 related thrombosis showed conflict results. Conclusion: The mechanism of thrombosis in COVID-19 patients seems to be multifactorial. Endothelial damage, antiphospholipid antibodies, inflammation, hyperviscosity, and thrombophilic mutations are the main factors that predispose COVID-19 patients to thrombosis.

Keywords: COVID-19, Thrombosis, Inflammation, Hyperviscosity, Antiphospholipid antibodies, thrombophilia.

1. INTRODUCTION

Today, thrombotic events are known to occur frequently in patients with COVID-19. About one-third of patients with COVID-19 suffer from a form of thrombosis, which is commonly a pulmonary embolism (1). The new coronavirus disease (COVID-19) predisposes patients to a thrombotic disease, and lung-centric coagulopathy plays a major role in the degree of severity and mortality of COVID-19 (2, 3). A study by Tang et al. (2020) revealed that most COVID-19 patients (71.4%) who died met the criteria of disseminated intravascular coagulation (DIC) assigned by the International Society of Thrombosis and Haemostasis (ISTH), whereas only 0.6% of the survivors met these criteria (4). Furthermore, the D-dimer level, which is a thrombotic marker, was found inversely correlated with the overall survival of COVID-19 patients, and patients with a markedly increased D-dimer level at admission eventually needed intensive care support (3).

2. MECHANISM OF THROMBOSIS IN COVID-19 PATIENTS

The mechanism of thrombosis in COVID-19 patients seems to be multifactorial. In this review, we summarized the reported predisposing factors and how these factors trigger the haemostatic system.

2.1. Endothelial damage

Vascular endothelial cells (ECs) line the inner surface of blood vessels, providing a critical barrier between the vasculature and organ systems. Activation of endothelial cells is thought to be the primary driver for the increasingly recognised complication of thrombosis. ECs represent an important target for infection in most human viruses. Infection of the endothelium has profound implications for both the virus and the host. For the virus, infection of ECs can provide a gateway for dissemination to organs and a reservoir for long-term persistence. For the host, the virus replication and the ensuing immune response at the endothelium increase tissue permeability and
inflammation, contributing to vascular and pulmonary diseases and to the severity of viral disease (5).

Viral inclusion bodies have been identified in endothelial cells in a variety of organs in patients with COVID-19 (6). Elevated levels of endothelial damage markers in plasma such as the Von Willebrand factor (VWF), plasminogen activator inhibitor-1 (PAI-1), syndecan-1, and soluble thrombomodulin have been reported in COVID-19 patients at intensive care units with respiratory and multiorgan failure, liver injury, and death (7).

The elevated levels of endothelial damage markers and presence of viral inclusion bodies in the endothelial cells suggesting a role for endothelium damage and activation in the development of thrombosis in COVID-19 patients.

2.2 Antiphospholipid antibodies

Antiphospholipid syndrome is a rare systemic autoimmune disease, characterized by the presence of antiphospholipid antibodies (anticardiolipin, anti–β2-glycoprotein, and lupus anticoagulant), and it is associated with susceptibility to both venous and arterial thrombosis (8). Although the mechanism by which antiphospholipid antibodies provoke hypercoagulability and lead to thrombosis is not well understood, several mechanisms have been proposed including the inhibition of prostacyclin production - which is an inhibitor of vasoconstriction and platelet aggregation - by the vascular endothelium, modulation of protein C/S anticoagulation pathway, impairment of fibrinolysis, and a direct procoagulant effect on platelets (9-11). It has been proposed that antiphospholipid antibodies play a role in the thrombosis related to COVID-19. Zhang et al. described three confirmed cases of COVID-19 presenting with multiple cerebral infarctions, all of them were aged more than 65 years old had a history of thrombotic events. On investigations, all of them tested positive for anticardiolipin and anti–β2-glycoprotein but negative for lupus anticoagulant (12).

The association of antiphospholipid antibodies is known with many viral infections including hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), varicella-zoster, Epstein-Barr virus (EBV), adenovirus, and parvovirus B. It can be persistent or transient and disappears within two or three months after the viral infection and in many conditions, it can be associated with a thrombotic event (13).

Antiphospholipid syndrome is categorised into two types: autoimmune and infectious. However, this classification is not absolutely true, as some infectious organisms can induce autoimmunity and lead to the production of antiphospholipid antibodies (14). There are many theories proposed to explain how infectious organisms induce autoimmunity; for instance, viruses can lead to an imbalance of the immune response by destroying a particular subset of T-lymphocyte. Furthermore, some microbes direct the release of some growth, differentiation, and chemotactic factors for various cells and regulate the expression of major histocompatibility complex class I and class II (15).

The presence of negative results for LA in such situations is possible, as LA testing during an acute thrombotic event is known to show variable results; it can initially be negative but change to positive when the test is repeated, and this is attributed to the masking of the antibody by a complex interaction of inflammatory, thrombotic, and fibrinolytic processes. Furthermore, the authors didn't explain if the patients were on anticoagulant therapy or not, as some anticoagulants are known to affect phospholipid-dependent coagulation tests (16). Although these indicate that antiphospholipid antibodies play a role in COVID-19-related thrombosis, this needs further confirmation, as all the three patients had a history of thrombotic events suggesting that antiphospholipid antibodies may have developed before the infection with SARS-CoV-2.

2.3 Inflammation

There is a strong link between inflammation and haemostasis, while inflammation leads to the activation of the haemostatic system, the activation of haemostasis stimulates the inflammatory response, and both function in a positive feedback loop (17). The interactions between inflammatory and haemostatic systems include proinflammatory cytokines, chemokines, adhesion molecules, tissue factor expression, activation of platelet and vascular endothelial cells, and microparticles. Inflammation increases procoagulant factors and inhibits naturally occurring inhibitors of coagulation and fibrinolytic activity, leading to a hypercoagulable state. Furthermore, chronic inflammation causes damage to the blood vessel walls, leading to disturbances of the anticoagulant properties of the vascular endothelium, which further augments hypercoagulability. However, inflammation can induce thrombus formation even if the endothelial damage has not occurred (18).

The inflammatory response to SARS-CoV-2 is an important factor related to disease morbidity and mortality, and it is associated with elevated blood cytokines levels, significant lymphopenia, and considerable mononuclear cell infiltration in the lungs and many other organs (19-22). The study of ultra-structural features of the autopsy lung samples from COVID-19 patients has revealed evidence for a pathogenic link between inflammation and thrombosis (23). Sriram and Insel (2020) presented a framework for the mechanisms of thrombosis in COVID-19 patients. They proposed that thrombosis initially arises from the interaction of SARS-CoV-2 with the angiotensin-converting enzyme 2 (ACE2), leading to the dysregulation of angiotensin signalling and subsequent inflammation and tissue injury, resulting in increased signalling by thrombin and purinergic receptors, which promote platelet activation and exert pathological effects on other cell types including endothelial cells (25).

2.4 Hyperviscosity

Hyperviscosity is thought to cause endothelial damage and is a known risk factor of thrombosis. It can result from an increased concentration of plasma proteins such as fibrinogen and immunoglobulin, which lead to the aggregation of erythrocytes and the sludging of
blood in areas of low shear in the coronary circulation, veins, and microvasculature. A study on 15 clinically ill COVID-19 patients reveals the presence of hyperfibrinogenemia and hypervelocity (> 95% of normal) in all the study subjects. Four of the patients with hyperviscosity > 3.5 centipoises had a documented thrombotic event (25-28). Therefore, these findings suggest a possible link between hyperviscosity and thrombosis in COVID-19 patients.

2.5 Genetic thrombophilia

Thrombophilia is defined as an abnormality of haemostasis predisposing individuals to form blood clots inappropriately. It can be either inherited or acquired, but commonly the predisposition to form clots results from an interaction between genetic and acquired factors (29, 30). Factor V Leiden and prothrombin G20210A mutations are the most common inherited forms of thrombophilia (31).

The studies concerning the association of thrombophilic mutations and novel coronavirus virus pneumonia showed conflicting results. Kiraz et al. (2021) reported no statistically significant difference in the frequency of these polymorphisms in patients with severe COVID-19 pneumonia and the healthy population (32). Conversely, Appenzeller et al. presented a case of a previously healthy 21-year-old male with extensive thromboembolism in the absence of obvious thrombophilic risk factors; the thrombophilia screening revealed the presence of the heterozygous factor V Leiden mutation, and despite the absence of clinical presentations of COVID-19, he tested positive (33). Two studies by Stefely et al. (2020) and Meijenfeldt et al. (2021) reported the increased activity of factor V and predisposition to thrombosis in critically ill and non-critically ill COVID-19 patients (34, 35). Furthermore, Meijenfeldt et al. (2021) also reported a link between prothrombin G20210A polymorphism and DVT and pulmonary embolism (PE) in COVID-19 patients (36).

3. CONCLUSION

The mechanisms of thrombosis in COVID-19 patients seems to be multifactorial. Endothelial damage, inflammation, hyperviscosity, antiphospholipid antibodies, and thrombophilic mutations are the main factors predispose patients to thrombosis.

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