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Chemical and Histopathologic Effects of COVID-19 on Virchow's Triad

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ABSTRACT

Although COVID-19 is known primarily as a respiratory disease, infected patients have been known to experience COVID-19-associated coagulopathy from overactivation of immune response resulting in cytokine storm. As a fundamental principle of venous thromboembolism, Virchow's triad – consisting of stasis, hypercoagulability, and endothelial injury – remains the foundation for increased clotting risk which can often precipitate life-threatening complications, such as pulmonary embolism, if left untreated. We conducted a literature search using PubMed for evidence to explain the increased coagulopathy in COVID-19 positive patients in relation to the three pillars of Virchow's triad. Hypercoagulability in COVID-19 patients is increased due to cytokine-induced fibrin clot formation. Infected patients also have decreased ADAMTS13, which leads to endothelial injury. Lastly, the increased blood viscosity combined with patient immobility promotes vascular stasis. These factors put COVID-19 patients at an increased risk of acquiring blood clots. In conclusion, we have defined a plausible mechanism by which COVID-19 may induce venous thrombosis using the three components of Virchow's triad. Due to the fatal nature of vascular complications, it is important to consider prophylactically treating these patients with a low molecular weight heparin regimen in order to mitigate the effects of hypercoagulability.

Keywords: COVID-19, Virchow's triad, venous thromboembolism, hypercoagulability, endothelial injury, venous stasis, anticoagulation

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared novel coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), herein labeled COVID-19, to be a global pandemic (*1*). Although bats are the primary vector for SARS-CoV-2, this is an RNA virus that is easily transmitted via respiratory droplets between humans (*2*). Although the clinical course of COVID-19 is most commonly associated with fever, viral pneumonia, and acute respiratory distress syndrome (ARDS), this disease has an additional relevance to the field of vascular surgery due to its adverse effects on coagulation (*3*). The prothrombotic state acquired due to COVID-19 demonstrates that its effects extend beyond the realm of pulmonology and must be understood by specialists in cardiovascular and hematologic fields, as well.

Around the world, multiple medical centers have noted that arterial and venous clotting may complicate the disease course of COVID-19. Helms, et al. noted that in a French hospital, 28 out of 29 dialysis patients with COVID-19 experienced thrombosis, which obstructed dialysis filter function thus compromising renal replacement therapy in critically ill patients (*4*). In the United States, a study of over 3,000 hospitalized COVID-19 patients revealed a rate of thrombotic complications over 10% for non-ICU patients and almost 30% for ICU patients (*5*). Since the venous thrombosis rate in COVID-19 patients is higher than that in uninfected individuals (21% vs. 0.5%), it is crucial to investigate the underlying mechanisms of pathologic thrombosis due to COVID-19 (*6,7*). A deeper understanding of the vascular pathophysiology could potentially guide clinical solutions for affected patients.

Virchow's triad is a well-recognized axiom in venous thromboembolism (VTE). Rudolf Virchow was a 19th century German physician who defined clotting as the combination of three factors: hypercoagulability, endothelial injury, and stasis. Kushner et al. define hypercoagulability as a condition in which blood is at a greater propensity to clot often due to oral contraceptive use, chemotherapy drugs, or thrombophilia. Any insult to the wall of the blood vessel can produce an endothelial injury, promoting activation of the clotting cascade for vessel repair and disruption of laminar blood flow, which can initiate thrombosis. Lastly, stasis is a reduction of flow, which permits blood to pool and clot (*8*). As earlier studies have demonstrated increased thrombosis in COVID-19 patients, we sought to explain these findings as they relate to Virchow's triad. Hypercoagulability and endothelial injury are directly affected by the coronavirus due to its usage of spike (S) protein to infiltrate (*9*). We reason that stasis is a contributing factor to thrombosis in COVID-19 patients likely due to prolonged bed rest and immobility. In this paper, we will explore the pathology of COVID-19 at the cellular and biochemical level, with a focus on Virchow's triad and shed light on possible treatments for patients.

METHODS

A literature search was performed to investigate the effects of COVID-19 on Virchow's triad. Using PubMed, we conducted individual searches on the components of Virchow's Triad. The inclusion criteria used were as follows: 1) published within the last year to ensure relevance, 2) written in English, and 3) full-text must be available. The primary exclusion criterion was case report articles, as these were not considered to be adequate evidence for evaluating widespread effects on Virchow's Triad. The search terms "COVID-19" and "hypercoagulation" resulted in 411 articles. These were then screened by two of the investigators (JN, AM) based on their pertinence to elucidating biochemical mechanisms and/or histopathology. Articles without this focus were removed from our search. This yielded 9 studies describing the mechanism of action for hypercoagulability in COVID-19. We repeated this process with the other two components of Virchow's triad, yielding 132 articles involving "endothelial injury" and 5 articles each involving "cytokine injury" and "stasis". However, we chose to expand this search to "COVID-19" and "stasis" in order to yield greater results. We had a total of 16 results after expanding the search and included 7 of these stasis-related studies after applying the screening criteria. Altogether, we compiled a total of 21 articles regarding the components of Virchow's Triad.

RESULTS

Hypercoagulability

SARS-CoV-2 belongs to a family of coronaviruses that infect human host cells. However, these family members differ in virulence and have unique thrombotic activity. Based on initial investigations, Gabutti et al. postulate that the S protein for SARS-CoV-2 has a higher affinity for human angiotensin converting enzyme 2 transmembrane receptor (ACE-2R) than the previous SARS-CoV reported in 2002 (*10*). Although the specific differences between SARS-CoV-2 and SARS-CoV S proteins are still under investigation, it is known that the higher ACE-2R affinity for the current virus has allowed for lower viral loads to produce symptoms in the host (*10*). Despite the differences between the two strains, SARS-CoV-2 spike protein shares approximately 75 percent amino acid sequence homology with the SARS-CoV spike protein (*11*).

Similar to its predecessor, SARS-CoV-2 uses a transmembrane protease, serine 2 (TMPRSS2) enzyme as a primer for the surface unit of its S protein, which binds to the ACE-2R and achieves viral entry into host respiratory epithelium (*12*). Since SARS-CoV-2 shares a high degree of amino acid sequence homology with SARS-CoV, it is logical that there are similarities in biological pathogenesis (*13*). SARS-CoV-2 causes tissue damage and vascular leakage due to cytotoxic T cell and neutrophil activation, coupled with upregulation of pro-inflammatory cytokines interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β), and C-C motif chemokine ligand 2 (CCL2) (*12*). Furthermore, COVID-19 increases activation of pro-fibrotic genes transforming growth factor beta 1 (TGFβ1), connective tissue growth factor (CTGF), and platelet derived growth factor subunit A (PDGFA). The combination of pro-inflammatory cytokines and pro-fibrotic genes leads to the coagulation cascade cleavage of prothrombin to thrombin and subsequent transformation of fibrinogen to fibrin (*12*). The cytokine-induced cascade of fibrin clot formation generates the abnormal hypercoagulation associated with COVID-19, which is similar to chronic (compensated) disseminated intravascular coagulation (DIC), with rapid consumption of endogenous coagulation factors promoting blood clots (*14*). It is important to note that COVID-19-associated coagulopathy (CAC) is a preliminary stage, which could further progress to DIC (15). The primary notable difference between CAC and sepsis-induced DIC is that initially, fibrinogen remains elevated in CAC as an acute phase response. Eventually, as CAC progresses, fibrinogen decreases to low levels in DIC (*15*). The underlying mechanism of this difference is not yet well understood. Additionally, platelet aggregation and abnormal thrombus formation rapidly causes tissue hypoxia (*16*). Vascular events predominantly reported in COVID-19 patients with severe infection include VTE and pulmonary embolism (PE). Patients have developed rare complications such as venous gangrene of the extremities, which can lead to critical limb ischemia, but the more common and potentially worrisome event of VTE is a PE presenting with dyspnea, syncope and/or palpitations (*17*). Rapid deterioration has been noted and if left untreated, is fatal (*18*).

Endothelial Injury

Weibel-Palade bodies (WPB) stored in endothelial cells contain P-selectin and ultra-large Von Willebrand Factor (ULVWF) (*19*). Based on current knowledge of the mechanisms of COVID-19-induced cytokine storms, IL-8 and TNFα have particular importance due to their impact on endothelial cells. Specifically, their activation causes the release of P-selectin and ULVWF from WPBs, thereby accelerating clotting and contributing to the development of VTE (*20*). P-selectin plays a vital role in the leukocyte adhesion cascade by binding to P-selectin Glycoprotein Ligand-1 (PSGL-1) on neutrophils (*21*). With regards to coagulation, ULVWF is known to initiate clotting by promoting the glycoprotein Ib receptor to bind to glycoprotein IIa receptors on platelets (*22*). This step of clotting is known as platelet aggregation, in which platelets can connect to one another.

Homeostatic autoregulation of the clotting process is facilitated by the ADAMTS13 enzyme, which works by cleaving endothelial-bound ULVWF into smaller components such that thrombi do not form (*22*). Deficiencies in ADAMTS13 can present as thrombotic thrombocytopenic purpura, which produce microthrombi dispersed throughout the body (*22*). In COVID-19 infection, IL-6 generation downregulates ADAMTS13, thus increasing the propensity for ULVWF to aggregate and create thrombi (*22*). Similar to IL-6, activated neutrophils have adverse effects on ADAMTS13 activity. Activated neutrophils and neutrophil extracellular traps (NETs) produce reactive oxygen species (ROS) in the process of fighting viral infections such as COVID-19. Increases in ROS levels prevent ADAMTS13 from cleaving ULVWF along the endothelium (*23*). The subsequent cytokine storm propagates endothelial dysfunction and hypercoagulation, two of the three components of Virchow's triad, and serves as a plausible framework to understanding the presentation of VTEs in COVID-19 patients.

Stasis

The third element of Virchow's triad is venous stasis. Although current literature does not have a quantitative measure of the degree to which venous stasis is associated with COVID-19 infection, behavioral and physical explanations for a potential association exist. Fatigue is a common clinical presentation of COVID-19, and it is hypothesized that this symptom occurs due to an IL-6 cytokine surge, which is known to influence skeletal muscle fatigability in mice (*24*). In addition, most patients experience respiratory difficulties, such as dyspnea, pleurodynia, cough, and expectoration (*25*). The constellation of symptoms (common to most viral-induced respiratory infections) likely occur due to the viral destruction of lung parenchyma and interstitial inflammation (*25*). COVID-19 is known to cause mast cell degranulation (*26*). As a result, histamines are released, increasing vascular permeability of pulmonary endothelial cells. The subsequent leakage of transudative fluid in the pulmonary interstitium is associated with dyspnea from increased work of breathing and discomfort (*26*). Pulmonary edema reduces the lung's ability to oxygenate blood, resulting in an increased arterial-alveolar gradient. Combining this increased respiratory effort with IL-6-induced systemic fatigue, COVID-19-infected persons are less likely to be mobile. With immobility, venous blood begins to pool due to reduced velocity and decreased muscle activity, which can promote higher risks of venous thromboembolism (*27*). It has been shown in the past that those who are in a stationary position for a prolonged time are at a higher risk of developing blood clots (28). One study by Murugesan et al. mentions that post-operative deep venous thrombosis (DVT) in Caucasian populations occurs in 15-40% of hospitalized patients (*28*). While the exact cause of this is unknown, it can be hypothesized that post-surgical bed rest is a contributing factor, since immobility is a common cause of thrombosis in obese populations and video game users (*29*).

Stasis is also impacted by hyperviscosity, which is strongly associated with COVID-19. A study from Emory University involving a cohort of 15 COVID-19 patients identified blood viscosities exceeding 95% of the normal limit (*30*). One potential explanation for this phenomenon is the correlation between severity of COVID-19 disease course and increased plasma fibrinogen levels, fibrinogen-to-albumin ratio (FAR), and D-dimer levels. Specifically, one cohort study found that patients with severe disease were in a hypercoagulable state with shortened prothrombin time (PT) and activated partial thromboplastin time (aPTT), which stabilized as patients' condition improved (31). As a result, there may be a critical threshold of FAR that can serve as a predictor of the severity of disease (*31*).

Treatments

As of January 2021, the American Society of Hematology and American College of Chest Physicians have provided guidelines stating that all adult patients admitted to the hospital for COVID-19 infection should be placed on prophylactic low molecular weight heparin (LMWH) over unfractionated heparin (UFH) and direct oral anticoagulant, unless contraindicated (*32,33*). Studies in China have shown clinical benefits of this therapy. In a cohort of 449 COVID-19 patients in Tongji hospital, 99 patients were placed on a LMWH regimen. In patients who had a D-dimer score greater than six times the normal limit, a LMWH regimen for at least 7 days improved the 28-day mortality risk (*34*).

In a cohort study with over 2,500 patients at the Mount Sinai Health System, the benefits of systemic treatment-dose anticoagulation for hospitalized patients were evident. The in-hospital mortality rate for patients on mechanical ventilation was 62.7% for patients who did not receive anticoagulation when compared to 29.1% for patients that did (*35*). However, the potential benefits of anticoagulation need to be weighed against the potential risk of major bleeding on an individual patient basis prior to initiating systemic treatment-dose anticoagulation. For those who experience heparin-induced thrombocytopenia, it is beneficial to use non-heparin anticoagulants such as bivalirudin or argatroban as prophylactic treatment over fondaparinux or rivaroxaban (*36*). In more critically ill COVID-19 patients, the use of intermittent pneumatic compression (IPC) is recommended for prevention of VTE with the use of UFH in cases of severe renal impairment (*36*).

CONCLUSION

For each component of Virchow's triad, we have provided a plausible mechanism by which COVID-19 may induce venous and, rarely, arterial thrombosis. Similar to its predecessor, SARS-CoV, the infection caused by SARS-CoV-2 virus is thought to recruit pro-inflammatory cytokines and cause excess stimulation of the coagulation cascade resulting in hypercoagulability. As a result of the cytokine storm response to COVID-19 infection, the production of IL-6 and ROS downregulated ADAMTS13 enzyme allowing ULVWF to contribute to endothelial injury and *in situ* thrombosis. Finally, COVID-19 infection may promote venous stasis, the final component of Virchow's triad, as infected patients experience fatigue and immobilization during hospitalization, which further increases the risk of adverse thrombotic events due to reduced blood flow. Anticoagulation drugs should be considered a front-line therapy for patients requiring hospitalization and empiric therapeutic dosing for those needing ICU admission. In conclusion, COVID-19 patients are at a greater risk of blood clotting due to the mechanisms defined by Virchow's Triad.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: GWL

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