Archives of Anesthesiology and Critical Care (Spring 2022); 8(2): 144-150.

Available online at http://aacc.tums.ac.ir

Review Article

Vascular Pathophysiological Changes in Patients with COVID-19: A Review Article

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ARTICLE INFO

Article history:
Received 11 October 2021
Revised 02 November 2021
Accepted 16 November 2021

Keywords:
COVID-19;
Vascular injury;
Pathophysiological changes

ABSTRACT

In the last days of 2019, a novel strain of coronaviruses reported in Wuhan and spread rapidly all over the world which called 2019 novel coronavirus (2019- nCoV). Almost a few months later in the early 2020 (January 2020), the WHO declared the outbreak of COVID-19 a Public Health Emergency which Compared with the other SARS-CoV, has a stronger transmission capacity.

Although respiratory problems are the main clinical symptoms of COVID-19, some patients also experience other conditions and injuries, such as severe vascular damage. Therefore, it can be said that understanding the damage caused by this infection to the vascular system and its underlying mechanisms is of great importance.

SARS-CoV-2, which has become a major global infectious agent in recent years, is a member of the coronavirus family that is covered by a positive single-stranded linear RNA [1]. It is containing four below essential structural proteins (Figure 1).

The RBD of SARS-COV-2 must bind to ACE2 to enter cells, which this membrane fusion and virus entry into host cells dependent on host proteases including TMPRSS2. Cathepsin L is a lysosomal protease involved in cell entry through endocytosis [2].

SARS-CoV-2 with 96.2% genomic similarity, is very closely related to the intermediate horseshoe bat RaTG13 coronavirus [3]. Other studies reported evidence of the incidence of a coronavirus equivalent to SARS-CoV-2 in Malayan pangolins. Therefore, it can be said that, the Pangolin-CoV is the second closest relative coronavirus to SARS-CoV-2 [4].

Infection caused by this virus causes different levels of damage to the host body. Although the highest and most severe form of this type of risk is due to the development of ARDS, however, following infection with SARS - COV-2 and severe inflammation in patients with many other organs such as heart, kidney, gastrointestinal tract [5]. The nervous and vascular systems are also associated with pathological changes [6-9]. Among these, many factors such as the amount of specific receptor for the virus on the cell surface of the organ and the physiology of the organ affect the type and severity of pathological manifestations [10]. The vastness of the vascular system and the volume of tissue interactions of this system with other organs create a high potential for the risks of infection with this infection.

The authors declare no conflicts of interest.

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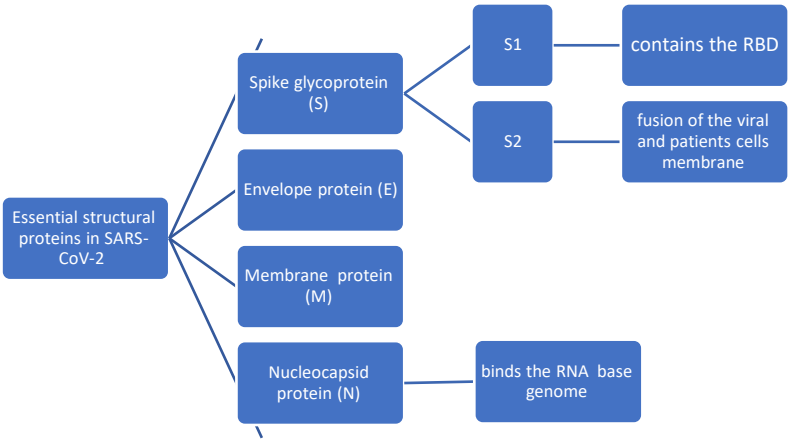
Figure 1- Essential structural proteins in SARS-CoV-2



ACE2: Functional Receptor for SARS-CoV-2

ACE 2 is an anti-regulatory enzyme of RAAS and the angiotensin II hydrolysis catalyst to angiotensin that binds to cell membranes [11-19]. Like SARS-COV, SARS-COV-2 begins to enter the host cell by binding to the ACE2 receptor on the surface of alveolar pneumocyte cells. This receptor plays the role of RBD for the SARS-COV-2 spike protein [18,20]. This receptor is expressed in different cells (Figure 2). However, according to studies, 83% of ACE2 protein is expressed in type 2 alveolar epithelial cells, so these cells are the main host of viral invasion. Besides, ACE2 mRNAs are expressed in humans in almost all organs, including the kidneys, blood vessels, heart, and testes, and this may increase the likelihood of infection of other organs by this infectious agent [21-23].

Figure 2- Tissues and cells that have an ACE 2 receptor.

The high affinity of ACE 2 for SARS-COV 2 compared to SARS -COV 1 S glycoprotein may explain the greater transmission and infectivity of this pathogen in the present conditions [24]. Critical exclusivity of ACE2 receptor cause the hypoxia-inducibility regulated by hypoxia-inducible factor-1. SARS-CoV-2 loading was low in samples of deceased people with hypoxia, despite this, increased ACE2 expression in endothelial cells

increases the possibility of SARS-CoV-2 binding in distant organs [24-27].

Vascular Injury in patients with COVID19

Reports of histological studies in patients infected with new infectious virus reveal marked vascular pathological changes (Table 1). Many of the pathophysiological mechanisms observed in COVID-19 are associated with vascular injury (28-30).

- Expression of ACE 2 receptor at the surface of vascular cells
- The vascular cell infection due to the SARS-CoV-2
- The repeated angiocentric mixed inflammatory
- The relief of interstitial exudates linked to increased vascular
- The presence of numerous microvascular microthrombi

Table1- Vascular pathological changes in COVID19 [28-29,31-32]

Lumen blockage
Focal hemorrhage
Increase the thickness of the vessel wall
Increased lymphocytes in and around blood vessels
Congestion
Vascular hyperplasia
Microthrombi

Observation of SARS-COV-2-induced viral particles in endothelial cells and subsequent apoptosis of endothelial cells throughout the vascular beds of various organs in patients with COVID-19 is a valuable indication of the virus's ability to infect endothelial cells and surrounding cells [33]. This virus can directly infect engineered human blood vessel organoids in vitro, thereby inducing apoptosis due to vascular damage and endothelitis, which may partly explain the systemic dysfunction of microcirculation in the vascular beds of organs [34].

COVID 19 causes an increase in serum levels of pro-inflammatory factors such as IL-8, IL-7, IL-6, IL-22, IL-17, IL-10, IL-1, and TNF-α, which in turn resulting in overactivation of T cells, Th17 skewing, and increased cytotoxicity of CD8 T cells [35-36]. However, as a result of these immune complexes, the association of an immunoglobulin and a viral antigen can lead to the activation of complement and inflammatory cell vasculitis. Indeed, the fact that histopathologic changes in rhesus-inoculated but suppressed macular degeneration of the MERS-CoV immune system underscore the role of the destructive immune response in diseases caused by the coronavirus [37-39].

The significant pathological pattern of vascular injury is COVID-19 development in children and juveniles which resulting from endothelial damage and microthrombi, initially reported as “acute acro-ischemia” of the extremities [40]. These skin ulcers usually present as multiple and have variable [38-42]:

- Pain
- Variably sized
- Erythematous reddish-purple irregular round lesions
- Itching
- Burning
- Fever
- Muscle pain
- Headache

MIS-C is another complication of severe vascular involvement at all ages. This complication, along with Acro ischemia, is associated with vascular inflammation and injury, the formation of microtubules, and the release of cytokines produced, which in turn leads to a severe immune response in people with SARS-CoV-2 infection [43].

Cell death and increased vascular permeability (capillary leakage syndrome) are other complications of COVID 19, which can be seen following irregular inflammatory responses and overproduction of proinflammatory cytokines [44]. What is certain is that the binding of SARS-CoV-2 to ACE2, in addition to disrupting its activity, also activates the kallikrein-bradykinin pathway, thereby increasing vascular permeability [45].

Coagulation disorders in patients with COVID19

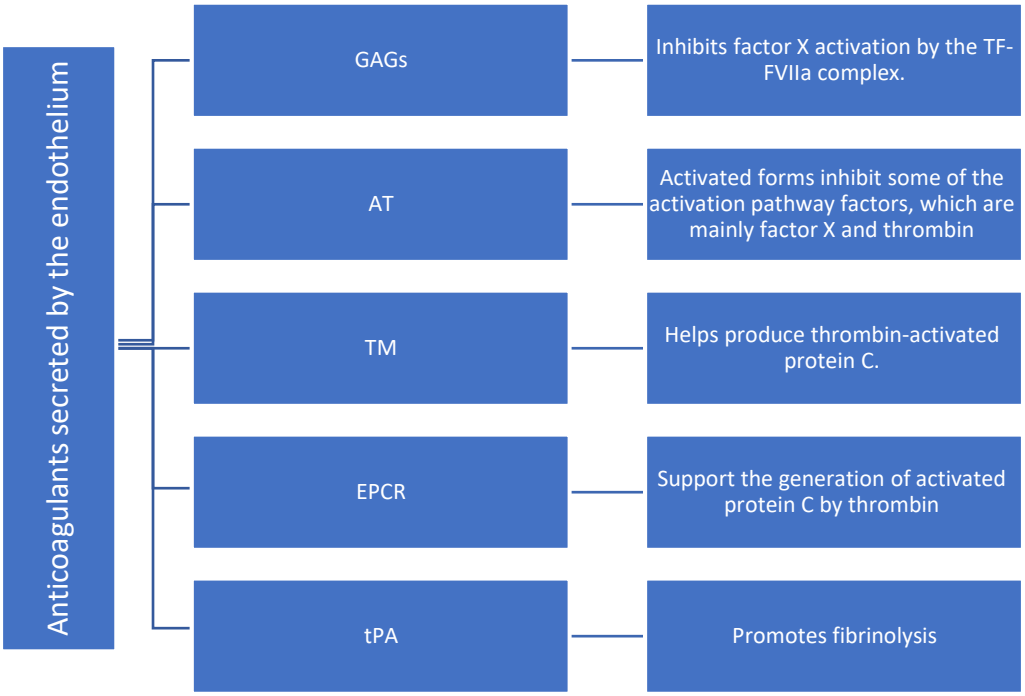
Coagulation abnormalities were identified as an outstanding feature in COVID-19 patients that were outstanding to have an aptitude for developing thrombotic complications. The normal endothelium prevents coagulation by expressing multiple types of molecules (Figure 3) and, in fact, provides an "anticoagulant" resting-state [46-48].

Endothelial damage following a COVID19 viral infection eventually leads to disruption of the normal controlled antithrombotic state, which activates the endothelium in response to inflammatory cytokines and other signals emitted during cell death [49]. Numerous events help to create such a state (Table 2):

Table 2- The events that contribute to prothrombotic state

1-	Lack of precise regulation in the production of GAGs that cause anticoagulant proteins to separate from the endothelial cell surface.
2-	Tissue factor (TF) production increases with thrombin production and subsequent conversion of fibrinogen to fibrin.
3-	Activation of IL-1β and TNF-α endothelial cells, which is ultimately associated with platelet uptake and accumulation.
4-	Activation of platelet activity by some coagulation proteases

Figure 3- Anticoagulants secreted by the endothelium



Microbial infiltration into the organism initiates thrombosis and fibrin deposition and platelet aggregation, which helps the host defense by preventing the spread of infectious microorganisms [50]. Interference between homeostasis and innate immune responses creates the right conditions for the activation of innate immune cells through the formation of "immunotrombs" [51]. Unrestrained stimulation of cytokine release can coincide with the loss of hemostatic agents and an increased risk of bleeding. [52].

It has previously been shown that markers of endothelial inflammation increase in patients with COVID-19 admitted to the ICU [53]. These cases may explain the post-mortem findings of patients with COVID-19 in which micro platelet-rich thrombotic deposits are found. Thrombi formation is a common feature seen in DAD; however, it can be argued that severe COVID-19 can cause separate thrombotic vasculopathy [54].

The incidence of arterial and venous thromboembolism following infection with COVID 19, despite anticoagulant therapy with LMWH, indicates the activity of additional pre-coagulation mechanisms [55]. One of the things that can be mentioned in this regard is the potential pathways that lie in FGL2 [56]. These pathways are involved in thrombotic processes involving the innate immune arm [57].

COVID-19 coagulation abnormalities (Table 3) follow an unusual pattern compared to other coagulation diseases.

Table 3- COVID-19 coagulation abnormalities

Normal or low platelet count
Elevation of d-dimer level
Elevation of fibrinogen level
Microvascular venous and arterial thrombosis

Abnormal coagulation tests (including longer PT, elevated d-dimer, and fibrin degradation (FDP)) at the time of hospitalization is associated with a mild prognosis and an increase in mortality [58].

Conclusion

Processes including vascular injury, inflammation, and thrombosis due to SARS-CoV-2 infection can explain the wide range of pathologies observed in COVID-19 patients.

The nature of COVID-19 infection is such that it can affect blood vessels in various organs, although in severe cases, it is best described as a multisystem vascular disease.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
ACE2: Angiotensin-converting enzyme 2
AT: Antithrombin
DAD: diffuse alveolar damage
EPCR: Endothelial protein C receptor
GAGs: Glycosaminoglycans

LMWH: low molecular weight heparin
MIS-C: Multisystem inflammatory syndrome in children
NETs: Neutrophil extracellular traps
RAAS: Renin-Angiotensin-Aldosterone System
TFPI: Tissue factor pathway inhibitor
TF-FVIIa: Tissue Factor and Factor VIIa
TM: Thrombomodulin
Tpa: Tissue-type plasminogen activator
TMPRSS2: Transmembrane protease serine 2
VWF: Von Willebrand factor
FGL2: Fibrinogen-Like Protein 2

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