Waves of SARS-CoV-2 Infection and Blood Coagulation—A Link and Beyond

Job Harenberg[1,2] Francesco Violi[2]

[1] Medical Faculty Mannheim, Ruprecht-Karls-University, Heidelberg, Germany
[2] DOASENSE GmbH, Heidelberg, Germany
[3] Department of Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

Address for correspondence Job Harenberg, MD, DOASENSE GmbH, Waldhofer Strasse 102, D-69123 Heidelberg, Germany (e-mail: j.harenberg@doasense.de).

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In 2020, the coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) presented a major health problem, forcing people to work from home in an effort to contain the virus. The pandemic generated opportunities for research in many areas. In the first phase of the pandemic, a great number of scientific reports were published on SARS-CoV-2. These reports generated further scientific questions, which have become even more relevant now that we are experiencing a second wave of infections. Thromboembolic events contribute to up to 20% of COVID-19-related mortality,[1] making this a highly important research topic.

Pathophysiology

COVID-19 is characterized not only by acute severe respiratory syndrome needing intensive care unit treatment but also by venous and arterial thrombosis,[2] including prolonged prothrombin time, activated partial thromboplastin time, reduced platelet count, and elevated D-dimers.[3]

There is a growing body of evidence that the SARS-CoV-2 virus infects the body via interaction of its spike protein with angiotensin-converting enzyme 2 (ACE2), which is expressed in the lung, heart, vascular system, gastrointestinal tube, kidney, and other organs.[4] The infection mechanism includes:

- Virus entry into cells upon spike protein cleavage by a serine protease transmembrane protease serine subtype 2 (TMPRSS2).[5]
- Downregulation of surface ACE2 expression and upregulation of angiotensin II (Ang II) correlating with viral load.[6]
- Ang II-induced proinflammatory changes in the arterial endothelium, vascular infiltration of monocytes, and oxidative stress-mediated vascular dysfunction.[7]
- Ang II interaction with type 1, 2, and 4 angiotensin receptors, causing leukocytes to adhere to endothelial cells, exerting a prothrombotic response and increasing fibrin and plasminogen activator inhibitor 1 production.[8]
- Activation of NADPH oxidase 2 (Nox2) by Ang II, increasing reactive oxidant species production associated with thrombotic events.[9]
- Nox2 activation promotes prothrombotic effects by biosynthesis of isoprostane and tissue factor, and inactivation of nitric oxide, a vasodilating and antiaggregating molecule.[10]
- Toll-like receptor (TLR7) activates platelets, forming platelet-neutrophil aggregates and neutrophil extracellular traps[11] (►**Fig. 1**).
- Elevated mannose-binding lectin initiates lectin-mediated complement activation correlating with D-dimer levels.[12]
- Endotoxemia enhances lipopolysaccharides, activating platelets and blood clotting via TLR4[13] (►**Fig. 1**).

Anticoagulant Treatment: Heparins

Critically ill nonbleeding patients with disseminated intravascular coagulation and virus-induced sepsis are typically treated by therapeutic doses of unfractionated heparin or low molecular weight heparin (LMWH) according to guidelines of the International Society of Thrombosis and Haemostasis. However, there is no direct evidence that this treatment is beneficial[14] for COVID-19 patients.[15]

Guidelines issued by the American Society of Hematology, American Society of Cardiology, Spanish Society of Cardiology, World Health Organization, National Institutes of Health,[16] Italian Society for Thrombosis and Haemostasis,[17] and VAS-European Independent Foundation in Angiology/Vascular Medicine[18] are based on retrospective studies only. Most guidelines agree that LMWH should be used at prophylactic

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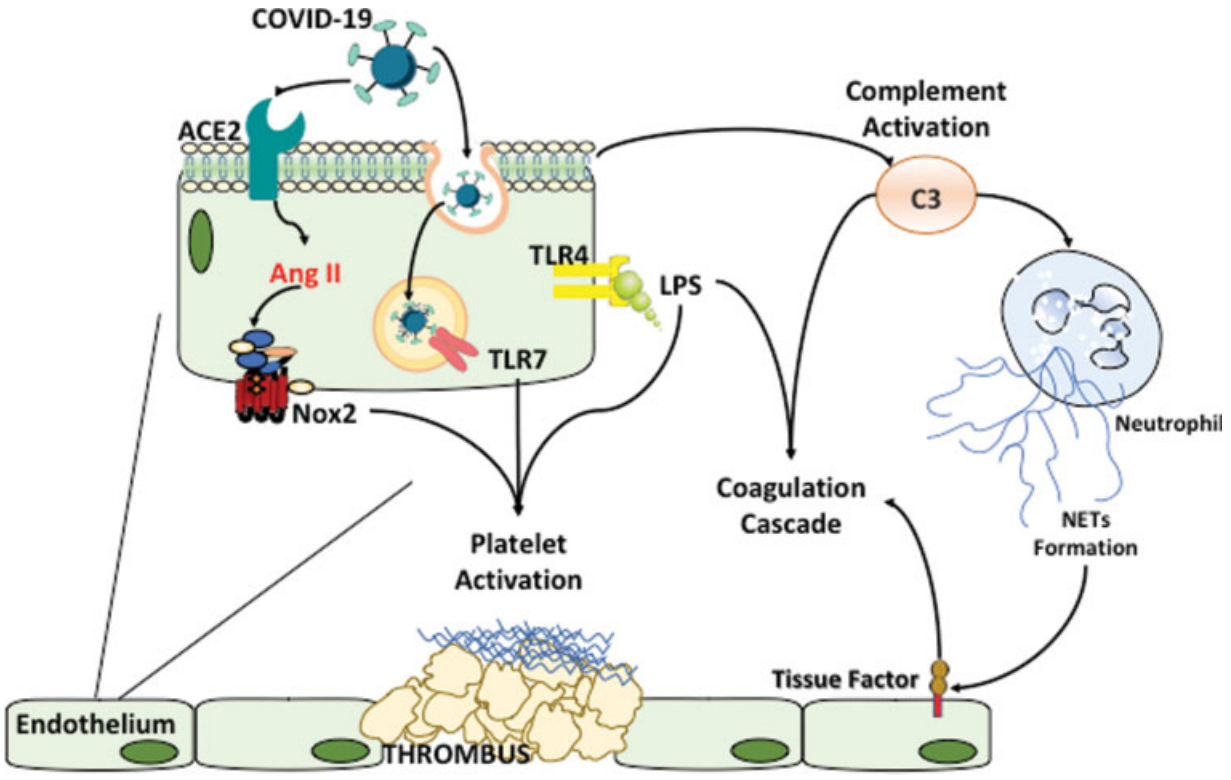

Fig. 1 COVID-19 and thrombosis: mechanisms of action. For explanation refer to Pathophysiology. COVID-19: Coronavirus disease 2019. ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; TLR4, 7, Toll-like receptor 4 or 7; Nox2, NADPH oxidase 2; LPS, lipopolysaccharides; C3, complement 3; NETs, neutrophil extracellular traps.

doses. Many of them have suggested that LMWH should be used at intermediate or therapeutic doses in high-risk COVID-19 patients.[19,20]

Anticoagulant Treatment: Direct Oral Anticoagulants

COVID-19 symptoms and thrombotic-inflammatory processes start days after initial infection with SARS-CoV-2, when patients are not hospitalized.[21] Upon hospitalization, low dose apixaban (odds ratio [OR] 0.46, $p = 0.001$), therapeutic dose apixaban (OR 0.57, $p = 0.006$), and enoxaparin prophylaxis (OR 0.49, $p = 0.001$) have all been associated with a significant decrease in mortality of hospitalized COVID-19 patients. Low and high doses of unfractionated heparin have shown no benefit. In addition, bleeding complications were not more frequent in patients receiving anticoagulant therapy compared with patients without anticoagulant therapy.[22] Upon discharge from hospital risk of venous thromboembolism (VTE) still remains. The effects of treatment with the direct oral factor Xa inhibitors apixaban, edoxaban, and rivaroxaban have been investigated during in-hospital and posthospital care of COVID-19 patients.[23] Switching from LMWH to dabigatran or edoxaban is investigated at creatinine clearances of > 30 mL/min and 30 to 15 mL/min, respectively.[24] The decision to switch from vitamin K antagonist to LMWH is determined by international normalized ratio and to direct oral anticoagulants by LMWH-independent rapid and accurate testing using patient urine samples.[25]

Currently, more than 10 studies are testing different anticoagulant regimes in thousands of hospitalized and discharged COVID-19 patients in an effort to prevent the combined outcomes of VTE and mortality.[26]

Additional Anticoagulant Treatment Options

Histones, neutrophil elastase, interleukin-8, and other toxic basic proteins are released into the pulmonary system in diseases such as asthma, cystic fibrosis, and acute respiratory distress syndrome. These and other basic proteins are toxic to the endothelium and are neutralized by the negatively charged intrapulmonary administered nebulized heparin[27] (NCT04530578, NCT04466670). Designer heparin molecules that can better interact with heparan sulfate on the surface of the SARS-CoV-2 virus have been developed to improve COVID-19 therapy.[28]

Other treatment options include administration of intravenous immunoglobulin G, tissue plasminogen, activated protein C,[29] and thrombomodulin.[30] One report has shown that administration of albumin reduces mortality in COVID-19 patients.[31]

Future Perspectives

Investigations into the pathophysiology and treatment of COVID-19 will continue into a next phase of the pandemic, when vaccination of the population will be introduced,

targeting blood coagulation, the immune system, and the occurrence of thromboembolism.

Once the ongoing prospective randomized controlled trials and other and adequately powered studies on anticoagulation in COVID-19 patients are completed, meta-analyses and indirect treatment comparisons can be performed to analyse efficacy and safety of different treatments and identify optimal risk-based antithrombotic strategies for treating COVID-19 patients, both in hospital and following discharge.

Conflict of Interest
None declared.

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