Review

Eleni Gavrilaki, Ioannis Eftychidis and Ioannis Papassotiriou*

Update on endothelial dysfunction in COVID-19: severe disease, long COVID-19 and pediatric characteristics

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Abstract

Objectives: To review current literature on the role of endothelial dysfunction in coronavirus disease-2019 (COVID-19) infection in terms of pathophysiology, laboratory features and markers, clinical phenotype in adults and children, as well as long COVID-19.

Content: We conducted a thorough assessment of the literature and critically analyzed current data, mostly utilizing the PubMed and Medline search engines to find original studies published in the previous decade.

Summary and Outlook: Accumulating evidence suggests that endothelial dysfunction may be a common denominator of severe COVID-19 in adults and children, as well as long COVID-19, implicating mutual pathophysiological pathways. This narrative review summarizes the up-to-date knowledge of endothelial dysfunction caused by COVID-19, including novel aspects of long COVID-19 and pediatric disease. This knowledge is important in order not only to understand the multisystemic attack of COVID-19, but also to improve patient management and prognosis.

Keywords: COVID-19; endothelial dysfunction; long COVID-19; pediatric; SARS-CoV-2; thrombosis.

Introduction

Coronavirus disease-2019 (COVID-19) has dramatically changed every perspective of human life worldwide, with

unprecedented morbidity and mortality [1]. Despite extensive efforts in vaccination programs, severe COVID-19 continues to represent a threat to public health, with long-term effects of the disease just being discovered [2]. Given the lack of an early prognostic model or a successful treatment regimen, better understanding of disease pathophysiology is still warranted [3].

A main pathophysiological process in severe and/or long COVID-19 involves endothelial dysfunction, which has been a key feature of several viral infections, including previous coronaviruses [4, 5]. Experimental, laboratory and clinical evidence from previous coronaviruses have triggered studies testing hypotheses on the role of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in endothelial dysfunction [6]. Indeed, endothelial dysfunction appears to be the common denominator of multiple clinical aspects of severe COVID-19 that have been challenging for treating physicians [7]. Therefore, we performed a PubMed and Medline search for original articles using the following keywords: COVID-19; endothelial dysfunction; thrombosis; long COVID-19; pediatric; SARS-CoV-2. Articles were evaluated and included in this review based on their relevance and originality.

Pathophysiology of endothelial dysfunction

Endothelium represents a continuous monolayer of endothelial cells forming the inner cellular lining of arteries, veins and capillaries. It serves as a barrier between tissues and blood with the functional capacity of an endocrine organ. Endothelium dynamically interacts with blood components and other circulating cells, participating in a number of pathophysiological processes [8, 9].

Under physiological conditions, it restores vascular integrity upon vascular injury and inhibits excessive thrombosis and clot formation by interacting with coagulation [9]. It is also involved in recruitment, adhesion and interaction of platelets and leucocytes with thrombogenic

*Corresponding author: Ioannis Papassotiriou, PhD, Department of Clinical Biochemistry, “Aghia Sophia” Children’s Hospital Athens, Greece; and IFCC Emerging Technologies Division, Emerging Technologies in Pediatric Laboratory Medicine (C-ETPLM), Milan, Italy, Phone: +30-213-2013931, E-mail: biochem@paidon-agiasofia.gr
Eleni Gavrilaki and Ioannis Eftychidis, Hematology Department – BMT Unit, G. Papanikolaou Hospital, Thessaloniki, Greece

surfaces. Furthermore, endothelium regulates vascular tone and growth by synthesizing and releasing both vasodilatory factors, such as nitric oxide (NO), and endothelium-derived contracting factors, such as endothelin and angiotensin II [8, 10]. NO biosynthesis plays the most important role for maintenance of vascular homeostasis [11].

Under conditions of increased oxidative stress, biosynthesis and availability of NO are diminished [12]. The endothelium loses its protective properties, shifting towards impaired vasodilation and expression of a pro-inflammatory, pro-atherosclerotic, and pro-thrombotic profile [13]. Endothelial dysfunction has been documented early in the course of cardiovascular disease by use of several vascular or functional markers, such as the gold-standard flow-mediated vasodilation (FMD), or by measurement of circulating biomarkers, that will be further discussed in the section on laboratory markers [14, 15].

In severe infectious diseases, including viral infections, endothelial dysfunction and thrombosis interact in a vicious cycle. Free radicals damage the endothelium by quenching NO and allowing toxins to pass into underlying tissues through the disrupted endothelium. Vascular leakage is a prominent feature of endothelial dysfunction in such cases, caused either directly by the viral attack or indirectly by excessive endothelial activation due to maladaptive immunological responses [9].

Previous coronaviruses and endothelial dysfunction

Two decades ago, the SARS epidemic was caused by the SARS-CoV that primarily targeting pneumocytes and enterocytes, that abundantly express angiotensin-converting enzyme 2 (ACE2), the main functional SARS-CoV receptor. Since endothelial cells express ACE2 in several organs, early studies suggested endothelial dysfunction in SARS patients [16–21].

Given the interaction between endothelial dysfunction and thrombosis, coronavirus infected patients (SARS-CoV and Middle East respiratory syndrome/MERS-CoV) have shown *in vitro* and *in vivo* a pro-coagulant profile [22–27]. In the laboratory, this interaction has been shown by increased levels of thrombopoietin, von Willebrand factor (vWF), and plasminogen activator inhibitor-1 (PAI-1) in SARS patients [28, 29]. In postmortem studies, 20 autopsies from SARS patients revealed vascular endothelial damage of both small- and medium-sized pulmonary vessels and multiple intravascular fibrin thrombi and thromboemboli

associated with pulmonary infarctions [20]. Another post-mortem analysis of an individual SARS patient documented evidence of endothelial cell inflammation and thromboemboli in the veins and microcirculation of multiple organs, thereby highlighting the thrombogenic potential of SARS-CoV in a wider spectrum of tissues, including the systemic vasculature [21].

An integral part of this vicious cycle of endothelial dysfunction and thrombosis is also complement activation [30]. Indeed, studies of previous coronaviruses have shown that blocking C3 activation significantly attenuates the lung-directed proinflammatory sequelae of infections. Both the genetic absence of C3 and blockade of downstream complement effectors, have shown therapeutic promise by containing the detrimental proinflammatory consequences of viral spread mainly via inhibition of monocyte/neutrophil activation and immune cell infiltration into the lungs [31].

Overall, these studies from previous coronaviruses have been of utmost importance for generating hypotheses and forming the background of further studies in COVID-19.

Endothelial dysfunction in COVID-19 infection

Pathophysiology

The key to understand a new complex pathophysiological process is to combine experimental and translational research applying a bench-to-bedside approach. In this context, several groups worldwide have shown evidence of complement activation in experimental and clinical studies of severe COVID-19 [32–38]. Complement activation and neutrophil extracellular traps have shaped the concept of thromboinflammation or immunothrombosis in COVID-19 [39]. Based on the paradigm of genetic susceptibility in complement-mediated disorders or complementopathies [40], our group and others have suggested genetic susceptibility identifying complement genetic variants in COVID-19 patients [3, 41, 42]. In parallel, complement inhibitors have shown safety and efficacy in severe COVID-19 during the first wave [31]. Encouraging results have been reported in case series for terminal complement inhibition with eculizumab [43], C3 inhibition with the compstatin-based inhibitor AMY-101 [44], and lectin pathway inhibition with narsoplimab [45]. Further comparative results of AMY-101 to eculizumab point toward a broader pathogenic involvement of C3-mediated pathways in thromboinflammation [46]. Given

the promising data, randomized controlled trials are ongoing for AMY-191 and eculizumab in severe COVID-19 (NCT04346797, NCT04395456).

Other angles of the pathophysiology of endothelial dysfunction in COVID-19 have focused on pericytes with high expression of ACE2 as target cells of COVID-19, resulting in endothelial cell and microvascular dysfunction. Given that ACE2 is highly expressed on cardiac myocytes, cardiac injury is found in COVID-19 [47]. Similarly, a coronaviral tropism for the kidney has been also suggested, since ACE2 is highly expressed on podocytes and tubular epithelial cells of the kidney [48]. What still remains puzzling, is the neuroinvasive potential of SARS-CoV-2 hypothesized by neurological signs and symptoms. Interestingly, behavioral problems, childhood tics and tic-like attacks, have been also reported [49]. ACE2 is expressed in the vasculature of the brain [50], leading to the hypothesis that endothelial injury ruptures cerebral capillaries and may be responsible for fatal intracerebral hemorrhage in COVID-19 [51]. In post-mortem studies, the first evidence of SARS-CoV-2 presence in brain tissue strongly supported this hypothesis of endothelial injury and hematogenous dissemination as the primary route of central nervous system (CNS) invasion [52]. Viral RNA has been also detected in autopsies of infected patients [53]. Alternative routes of direct nervous system invasion or an indirect immune-mediated involvement of CNS are also under consideration.

Laboratory markers

The numerous circulating inflammatory coagulation biomarkers directly implicated in clotting, with an emphasis on fibrin (ogen), D-dimer, P-selectin, and von Willebrand factor (vWF), are of special interest. Their changes cause an imbalance between procoagulant and anticoagulant factors, for example, fibrinogen induces thrombus formation, whereas decrease in high molecular vWF enhances bleeding [54].

Fibrinogen

Fibrinogen is a protein that is increased during the acute phase of inflammation [55]. Elevation in fibrinogen levels can be linked to hypercoagulability and endothelial dysfunction. On the other hand, thrombocytopenia and low levels of fibrinogen have been associated to bleeding

disorders [56]. (Measurement: *In vitro* diagnostics (IVD) available in automated platforms).

Von Willebrand factor (vWF) antigen

Endothelial cells and megakaryocytes are the only cells that produce vWF [57]. vWF plays a key role in platelet agglomeration and clot formation, and it is classed as an acute phase factor due to its importance in inflammation [58]. vWF is also known to be involved in the progression of atherosclerosis through increasing plaque creation and inflammation [59]. Furthermore, vWF binds circulating platelets to the endothelium as part of the thrombosis, inflammation, and tumor development processes [60]. vWF:antigen is both a hemorrhage (when decreased) and coagulation (when increased) indicator in normal circumstances, which is a crucial factor for COVID-19 pathology [61]. (Measurement: IVD available in automated platforms).

D-dimers

D-dimers are not typically detected unless thrombosis has occurred, therefore they can be used as a thrombosis indicator [62, 63]. D-dimer levels are normal or slightly elevated at the early stages of COVID-19, but as the patient's condition deteriorates, D-dimer levels are considerably elevated. Assessing D-dimer levels early after admission and continuing to monitor them afterward might help identify individuals with heart damage and predict further COVID-19 complications [64]. It should be noted however, that a raised troponin has been identified as a better prognostic marker of heart damage [65] (Measurement: IVD available in automated platforms).

P-selectin

P-selectin, also known as CD62P, is a protein that regulates the interactions of blood cells with endothelial cells [66]. P-selectin functions as an adhesion receptor on the cell membrane, allowing leukocytes to roll and emigrate at inflammatory areas [67]. As endothelial cells and platelets store and express P-selectin, there has been much discussion about whether elevated P-selectin levels in the blood reflect endothelial dysfunction, platelet activation, or both [66]. Soluble P-selectin (sP-selectin) is the product of spliced P-selectin, lacking the transmembrane part.

Circulating sP-selectin is considered to activate leukocyte signaling, which plays a significant role in inflammation and thrombosis. sP-selectin, on the other hand, is most likely circulating as a monomer, and *in vitro* studies suggest that sP-selectin needs to dimerize to trigger activation in leukocytes [68]. In COVID-19 patients, elevated concentrations of sP-selectin have been linked to an increased risk of thrombosis [69]. (Measurement: Research Use Only (RUO) available only enzyme-linked immunosorbent assay (ELISA))

Clinical phenotype

Thrombosis: the above-mentioned pathophysiology predisposes COVID-19 patients to a whole spectrum of thrombotic events, including microvascular thrombosis, venous thromboembolism, cardiovascular, and cerebrovascular events [40, 70].

Microvascular thrombosis

Microvascular thrombosis has been recognized early in the COVID-19 pandemic by post-mortem findings indicating pulmonary vascular endotheliitis, thrombosis, and angiogenesis as a unique feature of COVID-19 [33, 71]. In particular, COVID-19 has been characterized a microvascular disease [72], and some authors have suggested the terminology MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) [73].

Venous thromboembolism

Venous thromboembolism (VTE) manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE) is common in severe COVID-19 despite prophylactic anticoagulant treatment. Up to now, a plethora systematic reviews and meta-analyses have tried to summarize the data among thousands of COVID-19 patients, with the highest reported incidence of VTE at 42% in severe COVID-19 patients requiring intensive care unit hospitalization [74–90]. This very high-risk sub-group of COVID-19 patients certainly showed increased VTE incidence compared to non-COVID-19 cohorts [91]. These repeated reports of high VTE rates have necessitated relevant guidelines and recommendations of aggressive thromboprophylaxis dosing intensities, extended-duration post-discharge thromboprophylaxis and an individualized approach, considering average body

mass index, severe thrombocytopenia and drug-to-drug interactions [92–95].

Acute limb ischemia

Acute upper or lower extremity/limb ischemia (ALI) is an arterial thrombotic complication, often described as a first COVID-19 manifestation. Several cohorts have shown clinical characteristics and treatment options [96–98], suggesting that ALI occurs despite prophylactic anticoagulation and needs surgical intervention.

Cardiovascular events

From the dawn of the pandemic, acute cardiac injury was observed in 5 out of the first 41 COVID-19 patients in Wuhan, 4 of them required ICU hospitalization, suggesting that cardiac involvement was a predictor of disease severity [99]. Since then, numerous studies and several meta-analyses have tried to clarify the incidence and prognostic importance of cardiovascular events in COVID-19. Indeed, cardiovascular complications are frequent among COVID-19 patients, especially those requiring ICU hospitalization, and contribute to adverse clinical events and mortality [100–102]. Pre-existing cardiovascular comorbidities and risk factors, including diabetes mellitus [103], hypertension [104], and obesity [105], are associated with increased morbidity and mortality in COVID-19 [106]. Assessment of cardiac injury biomarkers may improve identification of those patients at the highest risk [107]. Major cardiac complications include myocardial injury and arrhythmia [108, 109]. Interestingly, a recent study from the Mayo Clinic, USA has shown that the mechanism of injury to the myocardium in 19/20 cases was not due to myocardial ischemia but hyperinflammatory process [110]. Acute cardiac injury in COVID-19 patients is more frequent than what was expected at the beginning of the outbreak, reaching an incidence of 28% [111–113].

Cerebrovascular events

Although less common than cardiovascular events, ischemic cerebrovascular events are recognized as an extra-pulmonary thromboembolic clinical feature in COVID-19. Stroke has been reported as the presenting clinical feature in COVID-19, and not simply a complication of in-hospital stay [114]. Further reviews and meta-analyses have confirmed an average incidence of stroke

ranging from 1.1 to 4.3% in COVID-19 [102, 115–121]. Mortality is also high in these patients, reaching 31.76% [115]. Interestingly, rates of cerebrovascular disease in COVID-19 patients with neurological manifestations have been reported significantly increased compared to hospitalized neurological patients without COVID-19 and associated with statistically significant worse outcomes [122]. The other side of cerebrovascular events, intracerebral haemorrhage (ICH), has also been reported COVID-19, but less frequently [123–126].

Neurological complications

Beyond cerebrovascular events, neurological manifestations are frequently reported in COVID-19 patients, including smell impairment, taste impairment, myalgia, headache, dizziness, and syncope [127]. Reported neurological complications include encephalopathy, encephalitis, seizures oculomotor nerve palsy, isolated sudden-onset anosmia, Guillain-Barré syndrome, and Miller-Fisher syndrome [128, 129]. The incidence of encephalopathy has been documented up to 9.14% [130].

Long COVID-19

A significant proportion of patients who recovered from COVID-19 continue to suffer from various complications, collectively called “long COVID-19” or post COVID-19 syndrome [131]. Although there are no established diagnostic criteria, symptoms of COVID-19 include new or persistent fatigue, dyspnea, joint pain, chest pain, cough, palpitations, anosmia, dysgeusia, alopecia, cognitive blunting, and psychological distress, which cannot be attributed to other causes in patients with preceding SARS-CoV-2 infection [132]. In a study of 287 survivors, almost 90% of patients suffered from several manifestations, with the most common symptom being fatigue (72.8%), and more critical manifestations including stroke, renal failure, myocarditis and pulmonary fibrosis [133]. Although SARS-CoV-2 infects endothelial cells resulting in autonomic dysfunction in acute infection, a recent study showed that post-COVID-19 fatigue is not associated with autonomic dysfunction [134]. Preliminary findings include extensive lung thrombosis and persistence of SARS-CoV-2 and syncytia in pneumocytes of 41 post-mortem samples, and weakened lung function and lung damage in imaging of 40 patients with persisting shortness of breath [135]. Interestingly, SARS-CoV-2 has been also detected in the penis long after the initial infection, suggesting a link between COVID-19

endothelial dysfunction and erectile dysfunction [136]. In association with long COVID-19, cardiovascular changes have been also observed through imaging modalities [137]. Lastly, little is known regarding the pathophysiology of long COVID-19, although many of the observed symptoms and syndromes may be linked to endothelial dysfunction. In a recent study of 92 patients, COVID-19 disease was an independent predictor of endothelial dysfunction detected by FMD two months after discharge [138].

Characteristics of pediatric patients

Since the early days of COVID-19, it has been reported that children had milder symptoms when compared to adult patients [139]. Despite the mildness of COVID-19 in children, severe hyperinflammatory diseases occurring 2–4 weeks after an acute infection with SARS-CoV-2 have emerged [140–145]. The symptoms of this condition, known as multisystem inflammatory syndrome in children (MIS-C), are similar to those of Kawasaki disease. In up to 25% of cases, Kawasaki manifests as an acute vasculitis (mostly affecting medium-sized arteries) in children under the age of five, with fever, lymphadenitis, and coronary artery involvement [146]. Self-reactive antibodies are produced during an acute immune response to a viral infection, most likely at mucosal surfaces and centered around IgA-producing plasma cells, according to the most popular explanation for the pathogenesis of Kawasaki disease [147]. Prior immunity to other viruses may alter their responses to SARS-CoV-2 infection and cause hyperinflammation through antibody-mediated enhancement or other mechanisms, which might explain why some children acquire MIS-C [148]. In all trials to date, the majority of children exhibited elevated markers of myocardial damage, and many had echocardiography abnormalities and/or significant echogenic coronary arteries [141, 144, 145]. Furthermore, a substantial proportion of children had elevated coagulation markers when tested and acute renal damage occurred in 22% of hospitalized children in an English cohort [142]. According to a multicenter retrospective cohort study in the United States, the rate of thrombotic complications was low in children age under 12 with COVID-19 or MIS-C, but high in children with factors such as age over 12, MIS-C, central venous catheter and cancer [149]. Lastly, data on long COVID-19 in pediatric patients are limited. Ongoing studies, such as the CLoCK one, are expected to provide additional insights [150].

Conclusions and future perspectives

Our review summarizes state-of-the-art knowledge of endothelial dysfunction caused by COVID-19, including novel aspects of long COVID-19 and pediatric disease. Our data are in agreement with previous and recently acquired knowledge that endothelial dysfunction is a common denominator of these processes. This knowledge is important in order not only to understand the multisystemic attack of COVID-19, but also to improve patient management and prognosis. Despite the lack of direct therapeutic agents for endothelial dysfunction, several treatments might affect endothelial dysfunction, with complement inhibitors being a promising strategy. Taking into account the detrimental short- and long-term effects of COVID-19, further studies are warranted to translate these data into clinical practice.

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