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From angiotensin-converting enzyme 2 disruption to thromboinflammatory microvascular disease: A paradigm drawn from COVID- 19

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ABSTRACT

We concisely review clinical, autopsy, experimental and molecular data of 2019 coronavirus disease (COVID-19). Angiotensin-converting enzyme 2 disruption and thromboinflammatory microangiopathy emerge as distinctive features. Briefly, entry of the virus into microvessels can profoundly disrupt the local renin-angiotensin system, cause endothelial injury, activate the complement cascade and induce powerful thromboinflammatory reactions, involving, in particular, von Willebrand factor, that, if widespread, may lead to microvascular plugging, ischemia and, ultimately, organ failure. We believe the current COVID-19 data consolidate a widely unrecognised paradigm of potentially fatal thromboinflammatory microvascular disease.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is known to cause not only pulmonary and other organ/tissue damage, but also an imbalance in key elements of the renin-angiotensin system (RAS), systemic bursts of inflammatory and procoagulant mediators, and widespread microvascular obstruction that likely contribute to its fatal complications. Indeed, current global fatality rates are reported to be ~3–5%, with peaks >10% [1]. In the present article we concisely review clinical, autopsy, experimental and molecular data of SARS-CoV-2 infection and the consequences of angiotensin-converting enzyme 2 (ACE2) disruption. The emerging findings point to thromboinflammatory microvascular disease as a distinctive COVID-19 feature, involving, in particular, von Willebrand factor (VWF) overexpression and complement pathway overactivation.

2. Clinical evidence of microvascular and thromboinflammatory activation

Multiple findings link SARS-CoV-2 to microangiopathy and to thromboinflammatory hyperactivity, including angiography, histology, autopsies, in vitro experiments, antithrombotic and steroid treatment benefits, and circulating biomarkers (details in Table 1).

Briefly, immunohistology of lung, skin and other organs from patients with severe 2019 coronavirus disease (COVID-19) ('severe' defined here as hospitalised or fatal cases) show direct viral infection of capillary endothelial cells, endotheliitis and inflammatory-cell death [2–5]; additionally, widespread microthrombi, leukocyte plugs, perivascular inflammation, and intense microvascular complement deposition have been consistently reported [2–5]. COVID-19 patients hospitalised for chest symptoms and associated focal or diffuse ST-segment elevation myocardial dysfunction show frequent lack of obstructive epicardial artery disease [6,7], pointing to microvascular impairment as a likely underlying cause of acute myocardial damage. In turn, raised cardiac troponin levels (indicating myocardial injury or

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, ACE inhibitors; ANG, angiotensin; ARB, angiotensin receptor blocker; C, complement component; CCL, C-C-motif chemokine ligand; CD, cluster of differentiation; COVID-19, 2019 coronavirus disease; CRP, C-reactive protein; GCSF, granulocyte-colony stimulating factor; ICU, intensive care unit; IFN, interferon; IL, interleukin; IP, interferon-gamma inducible protein; MIP, macrophage inflammatory protein; MAC, membrane attack complex; MCP, monocyte chemoattractant protein; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PCT, procalcitonin; RAS, renin-angiotensin system; SARS-CoV, severe acute respiratory syndrome coronavirus; TF, tissue factor; TMPRSS2, transmembrane serine protease type II; TNF, tumor necrosis factor; t-PA, tissue-type plasminogen activator; VWF, von Willebrand factor.

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Table 1
Evidence of microvascular thromboinflammatory involvement in human COVID-19.

District or Pathway	Evidence	References
Microvascular	• Coronary arteries: relatively low prevalence of large artery occlusion in patients with ST-segment elevation myocardial injury suggesting microvascular involvement • Lung and skin: microvascular injury and thrombosis mediated by complement activation co-localised with SARS-CoV-2 proteins • Lung and other organs: generalised thrombotic microangiopathy despite anticoagulation; microvascular endotheliitis, severe small vessel congestion • Human capillary organoids: interaction between SARS-CoV-2 and endothelial ACE2 receptor	[2–7,14,24]
Thrombotic	• Raised plasma levels of D-dimer, fibrinogen, VWF, factor VIII • Multiorgan microthrombi and fibrin deposits • Thrombocytopenia (secondary to thrombosis) • Antithrombotic treatment benefits	[2,5,8,9,11–14,21,22,38]
Inflammatory	• Lymphopenia involving CD4+ and CD8+ T-cells; lymphocytic endotheliitis; perivascular T-cell infiltration • Microvascular C4d and C5b-9 deposits • Overexpression of plasma C5a and soluble C5b-9 • Increased circulating IL-1β, IL-2, IL-6, IL-7, IL-10, MCP-1, TNFα, GCSF, IP-10, MIP1α, IFNγ, CRP, PCT • Steroid treatment benefits	[2,4,5,9,16,20,23,38]

For abbreviations, please refer to list.

necrosis) are positively related to both inflammatory and coagulation markers and to mortality [8,9].

The specific cluster of plasma cytokines of COVID-19 patients admitted to intensive care units (ICU), compared to non-ICU COVID-19 patients, suggests a cytokine vicious spiral (cytokine storm) negatively affecting outcomes [9] (for complete list of cytokines see Table 1). Specifically, interleukin (IL)-6 levels are strongly related to prognosis, as in acute coronary syndromes and in classical inflammatory immune diseases such as rheumatoid arthritis [10]. Severe COVID-19 patients also develop systemic hypercoagulability, as indicated by raised plasma levels of fibrinogen, D-dimer, VWF and factor VIII [8,9,11–14].

The systemic proinflammatory response, that in extreme cases may lead to disseminated coagulopathy, is reminiscent of the cytokine plethora and kinetics of septic conditions [15], pointing to viral SARS-CoV-2 sepsis in critical forms of COVID-19 [16,17].

Inflammatory activation, lymphopenia and thrombocytopenia reported in severe COVID-19 resemble another potentially fatal syndrome triggered by viral infections, characterised by leukopenia, macrophage hyperactivity, multiorgan failure and hyperinflammation, i.e., secondary haemophagocytic lymphohistiocytosis [18]. The blood stigmata of severe COVID-19 are compatible with lymphopenia secondary to cytokine-induced complement activation and with thrombocytopenia secondary to VWF hypersecretion and microvascular thrombosis [2,8,9,18,19]. COVID-19 lymphopenia is characterised by reduced circulating CD4+ and CD8+ T-lymphocytes and is related to both cytokine levels and adverse prognosis [20]. It has been hypothesised that SARS-CoV-2 may directly infect lymphocytes, particularly T cells, promoting their death, with consequent lymphopenia and impaired antiviral responses [16].

The recent emerging benefits of dexamethasone and anticoagulant treatments, even in the absence of large artery occlusions, corroborate the pivotal role of inflammation and thrombosis in SARS-CoV-2 infection [12–14,21–23].

3. From ACE2 disruption to thromboinflammatory microangiopathy

3.1. SARS-CoV-2 and RAS imbalance

SARS-CoV-2 uses its spike 1 glycoprotein to bind to the human membrane receptor ACE2 [24,25]. Organs expressing ACE2 – including lung, intestines, kidney, myocardiocytes and endothelium - are potential SARS-CoV-2 targets [5,24,26]. Both SARS-CoV and SARS-CoV-2 bind to ACE2, but SARS-CoV-2 has a particularly snug fit and is 10–20 times more likely to bind ACE2 than SARS-CoV [25]. Fusion of SARS-CoV-2 to the host cell membrane is further facilitated by human furin or other membrane enzymes such as TMPRSS2 [25]. Viral entry causes internalisation and functional ACE2 disruption [24,25].

Under physiological conditions, ACE2 cleaves angiotensin(Ang)II to generate Ang(1–7) and, less efficiently, Ang I to generate Ang(1–9); the latter can generate further Ang(1–7) via neutral endopeptidase (neprilysin) or ACE [27]. In addition to anti-inflammatory and anti-oxidant properties (see below), Ang(1–7) boasts vasorelaxing and antithrombotic ones through the release of bioactive nitric oxide, tissue-type plasminogen activator and bradykinin (Fig. 1) [28]. These effects are mediated by Ang(1–7)'s binding to the endothelial membrane G-protein-coupled Mas receptor (MAS-R) [27]. Thus, SARS-CoV-2 binding to ACE2 not only allows the virus to invade and destroy cells [24,25], but also disrupts the vasorelaxing and antithrombotic properties of ACE2, while enhancing the harmful ones of Ang II, a potent direct vasoconstrictor and bradykinin inhibitor [28]. Ang II additionally triggers the endothelial secretion of VWF from Weibel Palade bodies [29] and the vascular expression of the fibrinolysis inhibitor, plasminogen activator inhibitor-1 (PAI-1) [30] (Fig. 1). In contrast to ACE2, ACE is a membrane receptor that converts Ang I to Ang II. ACE-inhibitors (ACEI), as well as angiotensin receptor blockers (ARB), by reducing Ang II's negative effects, are likely to act favourably in COVID-19 patients, as suggested by recent reports [31].

The alveolar-capillary membrane and pulmonary microvasculature are particularly rich in ACE2 [5,24]; they constitute a major portal for viral blood dissemination [16] and are structurally poised to suffer the full-blown thromboinflammatory effects of ACE2 disruption induced by SARS-CoV-2.

3.2. Angiotensin(1–7) dysfunction and inflammation

Ang(1–7), in addition to its vasorelaxing and antithrombotic effects, has major anti-inflammatory properties. This is supported by murine models of rheumatoid arthritis in which AVE 0991, an Ang(1–7) mimetic and agonist of the MAS-R [32,33], decreases the rolling, adhesion and influx of leukocytes into synovial microvascular endothelium through chemokine ligand blockade [34]. In vitro administration of AVE 00991 to tumor necrosis factor alpha (TNFα)-activated cells inhibits monocyte chemotaxis toward human perivascular adipocytes, with reduced adipocyte gene expression of chemoattractant C-C-motif chemokine ligand (CCL)2 and CCL5 molecules [35]. Stimulation of the Ang(1–7) axis in atherosclerosis prone Apo E −/− mice has profound antiatherosclerotic effects, with reduced monocyte and macrophage content in perivascular tissues [35]. Genetically ApoE-/ACE2- double knockout mice exhibit increased endothelial cell activation, increased aortic plaque burden, and enhanced expression of TNFα, IL-6, monocyte chemoattractant protein (MCP) 1, vascular-cell adhesion protein 1, junctional adhesion molecule-A, and metalloproteinases 2 and 9, when compared with the single knock-out ApoE −/− model [36].

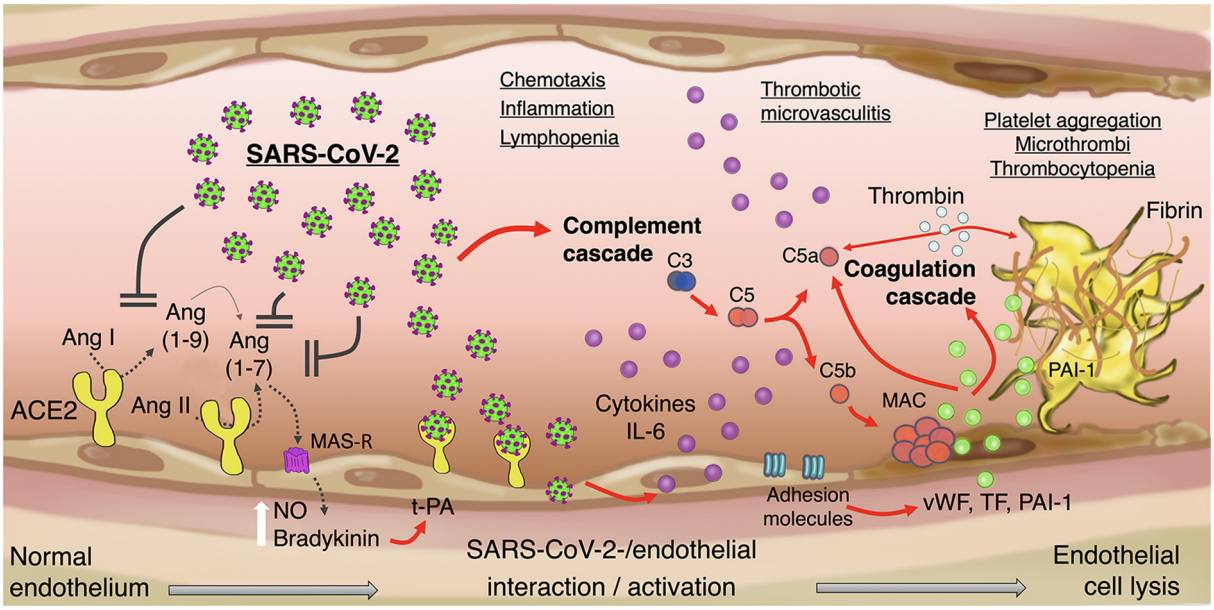

Fig. 1. Thromboinflammatory microangiopathy secondary to SARS-CoV-2 endotheliitis. Lower left: In normal microvascular endothelium, ACE2 cleaves Ang II to Ang(1–7) and, less efficiently, Ang I to Ang(1–9) which can further generate Ang(1–7); Ang(1–7), through the endothelial membrane G-protein-coupled Mas receptor (MAS-R), exerts antithrombotic, vasorelaxing and anti-inflammatory effects mediated by NO, t-PA and bradykinin. Top left and middle: SARS-CoV-2 enters the bloodstream – e.g., after crossing the alveolar-capillary membrane - and binds to endothelial ACE2, causing infectious endotheliitis, viral replication, cytokine secretion (purple circles) and VWF release. Functional ACE2 loss, induced by SARS-CoV-2, additionally inhibits the antithrombotic and anti-inflammatory properties of Ang(1–7). Chemotaxis by viral antigens, cytokines and VWF multimers all trigger complement activation culminating in cell lysis through the MAC C5b-9. Complement can induce lymphopenia and further prothrombotic, proinflammatory, chemotactic and anaphylotoxic effects. Lymphopenia may also be caused by direct viral infection of lymphocytes. Right: endothelial cell lysis, TF expression, release of VWF and PAI-1 from activated endothelium (green circles) contribute to leukocyte influx and to microthrombosis through platelet adhesion, aggregation and coagulation. Thrombocytopenia may signal widespread thrombosis. (For a colour version of this figure, the reader is referred to the web version of this article.)

Thus, microvascular SARS-CoV-2 induced internalisation and functional disruption of ACE2 [24,25] likely exerts powerful proinflammatory effects.

3.3. Systemic microangiopathy, complement activation and von Willebrand factor hypersecretion

The endothelium represents a rich source of ACE2 receptors [5,24]. Widespread microangiopathy with complement deposits in severe COVID-19 cases points toward systemic microvascular endothelial dysfunction [2–5,14]. Importantly, thrombotic microangiopathy is reported as a distinctive feature of COVID-19 respiratory insufficiency, being absent in influenza-related respiratory failure [5]. Activated endothelium, as well as host-defense mechanisms against viral antigens, can trigger complement activation (a crucial innate immune element) by classical, alternative or lectin pathways, through C3, C5, and generation of the C5b-9 membrane attack complex (MAC); the latter destroys target cells [2,19]; significant microvascular C5b-9 deposits have been documented in COVID-19 patients [2]. Complement activation, while attempting to neutralise infection through cell lysis, also has proinflammatory, chemotactic, anaphylotoxic and prothrombotic repercussions and can induce T-lymphopenia (Fig. 1) [2,19,37].

A systemic endothelial microangiopathy in SARS-CoV-2 infection is further supported by elevated circulating inflammatory and prothrombotic factors, particularly VWF, an established marker of endothelial dysfunction [12–14]; patients with classical thrombotic microangiopathy accumulate prothrombotic high molecular weight VWF multimers [19,37]; in COVID-19 patients requiring invasive mechanical ventilation, VWF levels 3-to-4 fold higher than the upper normal limit have been reported [38]; interestingly, nonhaemostatic functions of VWF include complement activation [37]; in turn, complement hyperactivation, which has been documented in moderate and severe COVID-19 [39], can lead to thrombotic microangiopathy [19]. The shift in RAS balance toward Ang II, likely induced by the SARS-CoV-2 interaction with vascular ACE2 [5,24,25], may be a further trigger for VWF release [29]. High plasma levels of VWF promote not only platelet rolling, adhesion and aggregation, but also leukocyte extravasation and further C5a and C5b-9 generation [37]; the latter may cause MAC-cell lysis with secondary tissue factor exposure, thrombin/fibrin formation, further platelet adhesion/aggregation, and microvascular thrombosis; PAI-1, from activated endothelium and aggregated platelets, likely contributes to consolidate the fibrin network surrounding aggregated blood elements [30] (Fig. 1).

3.4. Clinical implications

The high fatality rate of COVID-19 and the aforementioned heterogeneity of basic science and clinical reports have led to the planning of numerous drug trials, including antiviral, antithrombotic and anti-inflammatory agents [40]. To date, only the anti-inflammatory steroid, dexamethasone, has been shown to improve survival for those requiring respiratory support [23] and the antiviral agent, remdesivir, to reduce time to recovery [41]. Complement inhibition may specifically interfere with the vicious spiral of COVID-19 microvascular impairment [42,43]. ACEI, as well as ARB, are key drugs in cardiovascular diseases and in the management of hypertension [44–47]. Despite early unfavourable publicity [48], the use of ARB/ACEI in COVID-19 has been associated with promising outcomes [31] and recombinant human ACE2 protein is under evaluation as a potential supportive treatment [49]. Anticoagulant drugs are under investigation in randomised trials [50].

4. Conclusions and perspectives

Emerging distinctive features of severe SARS-CoV-2 infection include powerful ACE2 disruption and widespread thromboinflammatory microangiopathy. Further insights into COVID-19 pathophysiology and

data from ongoing clinical trials will be crucial to discover targeted effective treatments. Focusing on the similarities between human SARS-CoV-2 infection and other diseases [18,19,24,37,51], and addressing the consequences of COVID-19, especially among patients prone to chronic inflammatory conditions such as cardiovascular diseases [52,53], will contribute to overall progress and to preparedness against a virus that is expected to hang around for some years [24]. Independently from SARS-CoV-2, we believe current COVID-19 data consolidate a widely unrecognised paradigm of potentially fatal thromboinflammatory microvascular disorders.

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