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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 the 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...
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, myocardocytes 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(1–7) 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 0991 to tumor necrosis factor alpha (TNFα)-activated cells inhibits monocyte chemotaxis toward human perivascular adipocytes, with reduced adipocyte gene expression of chemottractant 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 chemotactrant 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 −/− mouse [36].
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 thrombo-inflammatory microangiopathy. Further insights into COVID-19 pathophysiology and
data from ongoing clinical trials will be crucial to discover targeted effec-
tive 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]. Indepen-
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