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Impaired microcirculation function in COVID-19 and implications for potential therapies

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (COVID-19), is a new ribonucleic acid virus strain from the Coronaviridae family [1]. From December 2019 to June 2020, the COVID-19 pandemic included over 7.6 million confirmed cases in 216 countries, and over 427,000 deaths [2]. Acute respiratory distress syndrome (ARDS) is one of the most severe complications of COVID-19 [3]. Based on autopsy studies, the ARDS associated with COVID-19 has distinct features — lung damage is consistent with complement-mediated microvascular injury consisting of diffuse microthrombosis and hemorrhage, whereas the hallmarks of classic ARDS with alveolar damage and hyaline membranes are not prominent [4]. Microvascular injury is typically not accompanied by gross pulmonary thromboembolism and parenchymal inflammation [5]. In addition, acro-ischemia including finger/toe cyanosis, skin bullae and dry gangrene were prodromal or early symptoms of COVID-19 [6, 7], confirming skin damage patterns consistent with microvascular thrombosis. In fact, the cutaneous manifestations are present in up to 20% of patients with COVID-19 and has been classified into five clinical patterns, with pseudo-chilblain being the most, and livedo or necrosis — the least frequent [8]. Thus, microvascular thrombosis seems to be one of the main pathological findings in COVID-19 patients [9, 10].

In addition to respiratory disease, cardiovascular complications are rapidly emerging as a key threat in COVID-19 [11]. In a recent meta-analysis of 8 studies from China including 46,248 infected patients, 7% of patients experienced myocardial injury (22% of these were critically ill), as evidenced by elevated cardiac troponin [12]. Noteworthy, patients with myocardial injury had higher in-hospital mortality (37.5%) than patients with cardiovascular disease (CVD) but without myocardial injury (13.3%), or patients without CVD (7.6%). Moreover, if myocardial injury was present in patients with preexisting CVD, the mortality increased even more (69.4%) [13]. Clearly,

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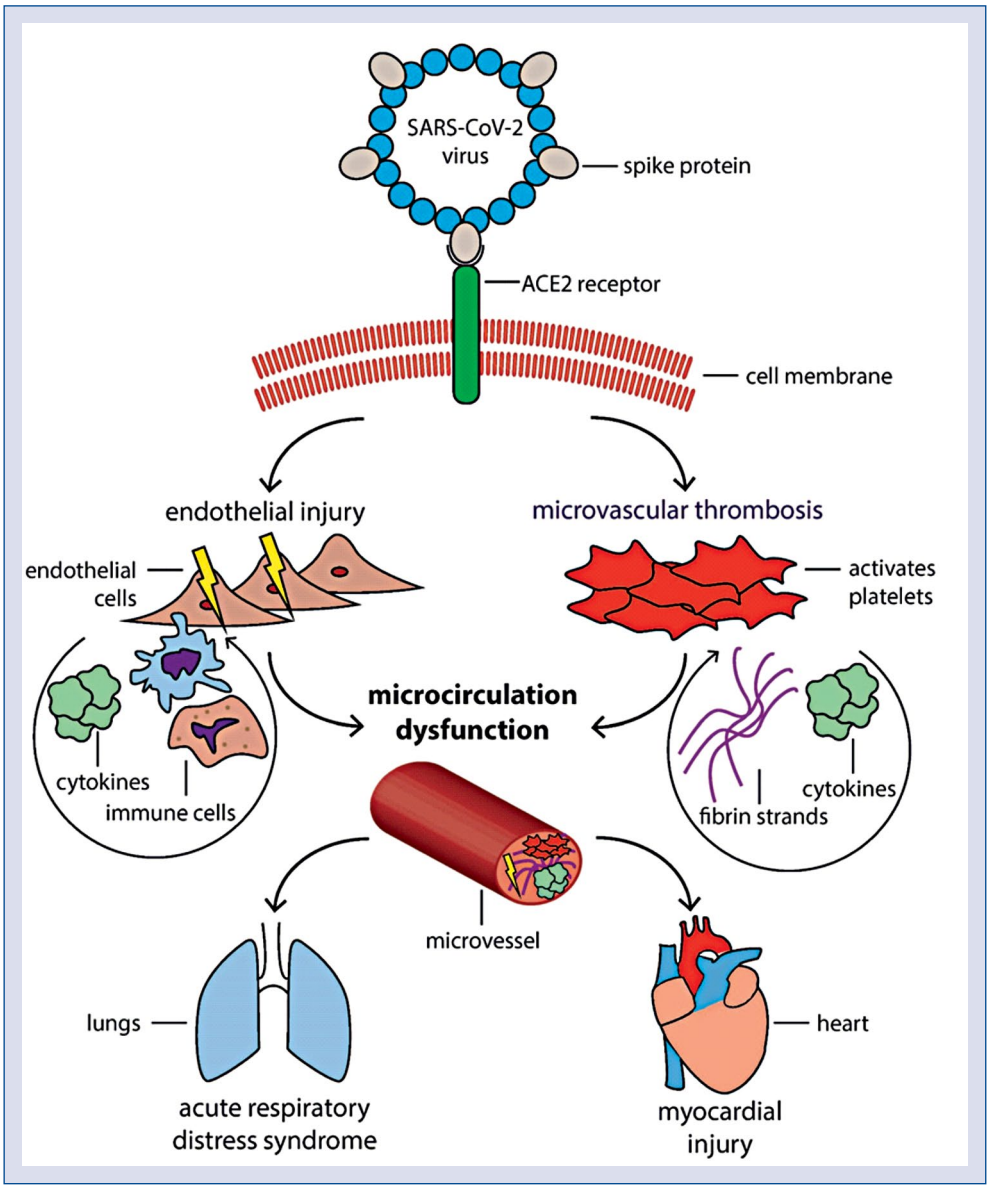

Figure 1. Pathophysiological mechanisms underlying the most severe complications associated with COVID-19, including acute respiratory distress syndrome and myocardial injury; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2; ACE2 — angiotensin-converting enzyme 2.

myocardial injury and underlying CVD markedly deteriorates the prognosis in COVID-19 [14]. The possible mechanisms explaining this association include (i) cytokine storm, (ii) microangiopathy, (iii) viral myocarditis, (iv) stress-induced cardiomyopathy, (iv) classic myocardial infarction due to infection-induced atherosclerotic plaque instability [15, 16]. All these mechanisms have a common denominator, which is endothelial injury [17, 18].

SARS-CoV-2 enters target cells through angiotensin-converting enzyme (ACE) two receptors, which are especially widely expressed on the surface of lung epithelial cells and vascular endothelial cells in multiple organs [19, 20]. The viral infection of the endothelial cells leads to endothelial cell inflammation (endotheliitis). This triggers the immune responses responsible for a massive local release of pro-inflammatory cytokines and further aggravation of endothelial injury [21]. Since endothelium is indispensable for the maintenance of vascular homeostasis, endothelial dysfunction leads to vasoconstriction with subsequent organ ischemia and a procoagulant state. According to the previously mentioned meta-analysis, the most

prevalent comorbidities in the infected patients were those associated with preexisting endothelial dysfunction, including arterial hypertension (17 ± 7%) and diabetes mellitus (8 ± 6%), followed by coronary heart disease (5 ± 4%) [12], explaining why these patients have a predisposition to COVID-19 and worse prognosis associated with the infection [22].

Figure 1 summarizes the pathophysiological mechanisms underlying the most severe complications associated with COVID-19. Altogether, microvascular thrombosis and endotheliitis lead to impaired microcirculatory function in different vascular beds, which leads to COVID-19 related complications, including ARDS and myocardial injury. If so, therapies to improve microcirculatory function might prevent complications and subsequently improve prognosis. Established therapies to improve microcirculatory function, in patients with microvascular angina, for example, include ACE inhibitors and statins [23]. However, at this time, nearly all major societies do not recommend adding or stopping the angiotensin receptor enzyme inhibitors or other renin–angiotensin–aldosterone system antagonists in acute settings, unless done on clinical grounds independently of COVID-19, given the lack of evidence currently available on their potential benefit or harm [11]. Moreover, these therapies do not control anginal symptoms in up to 80% of patients with microvascular angina, urging the need for new treatment options [24].

The new treatment options to improve microcirculation function include ivabradine, nicorandil, ranolazine, or trimetazidine [23]. Ivabradine is a direct and selective inhibitor of the I(*f*) current in the sinus node, which reduces heart rate without affecting myocardial contractility and coronary vasomotor tone [25]. Nicorandil opens potassium channels and enhances nitric oxide production in vascular smooth muscle cells (VSMC), leading to vasodilation [26]. Ranolazine inhibits the late inward sodium channel and reduces calcium overload in cardiomyocytes, therefore improving left ventricular diastolic function and reducing the mechanical compression of microcirculation [26]. Finally, trimetazidine inhibits the reduction of adenosine triphosphate in cardiomyocytes, therefore shifting cardiac metabolism from fatty acid to glucose oxidation [27]. Out of the four novel anti-anginal agents, the combination of ranolazine and nicorandil seems to be especially promising in improving microcirculatory function due to the (i) complementary mechanisms of actions both at the cardiomyocyte and microcirculation VSMC level and (ii) promising preliminary results regarding improvement in microcirculatory function in patients with microvascular angina.

Interventional treatment of impaired microcirculatory function could be considered as an alternative to pharmacotherapy, especially for the highest risk patients, with myocardial injury and with pre-existing endothelial dysfunction. The coronary sinus Reducer is a new technology designed to reduce disabling symptoms and improve the quality of life of patients with chronic refractory angina. The Reducer is a transcatheter, a balloon-expandable metal mesh, designed to create a focal narrowing in the lumen of the coronary sinus to generate a pressure gradient across it, and thus to redistribute forces of blood flow from less ischemic to more ischemic subendocardium of the left ventricle. The procedure lasts about 20–30 min, and improved microcirculation function is achieved within 2 weeks following implantation, which is the time required for the device endothelization. In a systematic review of 6 clinical studies (n = 196), the Reducer device improved symptoms and objective indications of ischemia in 78.5% of patients [28]. In long-term follow-up of the first-in-man Reducer study (n = 14), no death or acute myocardial infarction and no device or procedure-related adverse events occurred up to 3 years following implantation [29]. Hence, implantation of the Reducer might essentially improve microcirculation function not only in patients with refractory angina but also in patients with impaired microcirculatory function in the course of COVID-19.

Altogether, we suggest that any strategy to improve microcirculatory function could prevent and/or attenuate the complications of COVID-19, especially those most severe, associated with the respiratory tract and cardiovascular system. Such strategies should be considered particularly for vulnerable patients with preexisting endothelial dysfunction, including smoking, hypertension, diabetes, and CVD, all of which are associated with adverse outcomes in COVID-19 [18, 30].

Conflict of interest: None declared

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